Stress Echocardiography

Eugenio Picano
Editor

Seventh Edition

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Eugenio Picano
Institute of Clinical Physiology of the National Research Council
Pisa, Italy

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Introduction

This book has a past. Its various editions and increasing diffusion parallel the growth of stress echocardiography within the scientific community and the clinical arena. The first edition in 1991 consisted of 100 pages, which gradually increased to 700 in the current seventh edition. Since the last 2015 edition, recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging for applications beyond ischemic heart disease were published in 2016. Guidelines on stress echo in ischemic heart disease were released by the American Society of Echocardiography in 2019. Since 2017, new information has become available regarding the methodology of stress echocardiography, including novel parameters such as B-lines, growing evidence on the prognostic value of coronary flow velocity reserve in the left anterior descending coronary artery, and updated standards for interpretation including quantitative methods of analysis such as artificial intelligence for left ventricular volumes and function. Current clinical practice guidelines of the European Society of Cardiology and the American College of Cardiology/American Heart Association have incorporated stress echo in many diverse cardiac conditions. The unsurpassed versatility allows for studying virtually all patients, and each one differently. In addition, in a societal climate of increasing demand for economic, ethical, and environmental sustainability, stress echocardiography offers the great advantages of being affordable, radiation-free, and with near-zero carbon emissions. These concepts are now endorsed by the 2023 clinical consensus statement on the clinical use of stress echocardiography of the European Society of Cardiovascular Imaging of the European Society of Cardiology.

The book was single authored in the first edition, up to the record number of 55 contributors in the present edition. They come from 22 countries spanning four continents and represent, in my opinion, some of the best available knowledge and expertise in their respective fields. I am proud and honored that they have accepted the invitation to be a part of this project. At the same time, I aimed to avoid the fragmentation, gaps, and inconsistencies of a multiauthor text. Therefore, I drafted the first version of each chapter. To all of them and to the junior and senior colleagues who have worked with me over the last 40+ years—far too many to be mentioned here—*Grazie*.

Pisa, August 30th, 2023 Eugenio Picano

The original version of this book was revised, and the MultiMedia App page has been removed.

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Contributors

Gergely Ágoston

Institute of Family Medicine, Szeged University Medical School, University of Szeged, Szeged, Hungary

Maria Grazia Andreassi

Genetics Research Unit, Clinical Physiology Institute, National Research Council of Italy, Pisa, Italy

Rosina Arbucci

Cardiodiagnosticos, Investigaciones Medicas Center, Buenos Aires, Argentina

Branko Beleslin

University Clinical Centre of Serbia, Medical School, Cardiology Clinic, University of Belgrade, Belgrade, Serbia

Tonino Bombardini

Clinic of Cardiovascular Diseases, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina

Alla Boshchenko

Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russia

Eduardo Bossone

Department of Public Health, University of Naples Federico II, Naples, Italy

Francesca Bursi

ASST Santi Paolo e Carlo Milano, Ospedale San Paolo, Dipartimento di Scienze della salute, Università degli Studi Statale di Milano, Milan, Italy

Ana Cristina Camarozano

Medicine Department, Hospital de Clinicas UFPR, Federal University of Paranà, Curitiba, Brazil

Clara Carpeggiani

CNR, Biomedicine Department, Institute of Clinical Physiology, Pisa, Italy

Jelena Čelutkienė

Faculty of Medicine, Centre of Cardiology and Angiology, Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Centre for Innovative Medicine, Vilnius, Lithuania

Quirino Ciampi

Cardiology Division, Fatebenefratelli Hospital, Benevento, Italy

Rodolfo Citro

Cardiology Department and Echocardiography Lab, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

Lauro Cortigiani

Cardiology Department, San Luca Hospital, Lucca, Italy

Carlos Cotrim

Heart Center, Departamento de Ciências Biomédicas e Medicina (UALG), (Hospital da Cruz Vermelha, UCARDIO, Hospital Particular do Algarve), Lisboa, Portugal

Maria Grazia D'Alfonso

Department of Cardiology, Careggi University Hospital, Florence, Italy

Antonello D'Andrea

Department of Cardiology, Umberto I Hospital, Nocera Inferiore (Salerno), University of Campania "Luigi Vanvitelli", Caserta, Italy

José Luis de Castro e Silva Pretto

Hospital Sao Vicente de Paulo e Hospital de Cidade, Passo Fundo, Brazil

Ana Djordjevic-Dikic

University Clinical Centre of Serbia, Cardiology Clinic, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Francesco Ferrara

Cava de' Tirreni and Amalfi Coast Division of Cardiology, University Hospital, Salerno, Italy

Nicola Gaibazzi

Cardiology Department, Parma University Hospital, Parma, Italy

Michael Henein

Department of Public Health and Clinical Medicine Units: Section of Medicine, Umeå University, Umeå, Sweden

Arnas Karuzas

Lithuanian University of Health Sciences, Institute of Cardiology, Kaunas, Lithuania

Ligence, UAB, Vilnius, Lithuania

Jaroslaw D. Kasprzak

Department of Cardiology, Medical University of Lodz, Bieganski Hospital, Lodz, Poland

Jorge Lowenstein

Cardiodiagnosticos: Investigaciones Medicas Center, Buenos Aires, Argentina

Cristina Mangia

CNR, ISAC-Institute of Sciences of Atmosphere and Climate, Lecce, Italy

Fabio Mori

Department of Cardiology, Careggi University Hospital, Florence, Italy

Aleksandra Nikolic

School of Medicine, University of Belgrade, Belgrade, Serbia

Institute for Cardiovascular Diseases “Dedinje”, Belgrade, Serbia

Iacopo Olivotto

Pediatric Cardiology Unit, Meyer Children’s Hospital IRCCS, Florence, Italy

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Miodrag Ostojic

Department of Noninvasive Cardiology, Institute for Cardiovascular Diseases Dedinje, School of Medicine, Belgrade, Serbia

School of Medicine, University of Belgrade, Belgrade, Serbia

Medical School, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Institute for Cardiovascular Diseases “Dedinje”, Belgrade, Serbia

University Clinical Center “Zvezdara”, Belgrade, Serbia

Clinical Center Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Attila Palinkas

Internal Medicine Department, Elisabeth Hospital, Hódmezővásárhely, Hungary

Eszter Dalma Pálinkás

Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary

Patricia A. Pellikka

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA

Jesus Peteiro

CHUAC-Complexo Hospitalario Universitario A Coruna, CIBER-CV, University of A Coruna, La Coruna, Spain

Eugenio Picano

Institute of Clinical Physiology of the National Research Council, Pisa, Italy

Luc A. Piérard

Medicine, University of Liège, Walloon Region, Belgium

Edyta Płońska-Gościniak

Department of Cardiology, Pomeranian Medical University, Szczecin, Poland

Bogdan A. Popescu

Cardiology Department, Institute of Cardiovascular Diseases 'Prof. Dr. C. C. Iliescu', University of Medicine and Pharmacy 'Carol Davila' Head, Bucharest, Romania

Tamara Kovacevic Preradovic

Clinic of Cardiovascular Diseases, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina

Costantina Prota

UTIC/Cardiologia, Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

Fausto Rigo

Division of Cardiology, Foundation Villa Salus Hospital/IRCCS San Camillo, Venice, Italy

Hugo Rodriguez-Zanella

Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

Monica Roşca

Cardiology Department, Emergency Institute for Cardiovascular Diseases 'Prof. Dr. C. C. Iliescu', University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania

Francesco Sabatella

Department of Cardiology, Umberto I Hospital, Nocera Inferiore (Salerno), University of Campania "Luigi Vanvitelli", Caserta, Italy

Leyla Elif Sade

Medicine, University of Pittsburgh Medical Center UPMC, Heart & Vascular Institute, Pittsburgh, PA, USA

Department of Cardiology, University of Baskent, Ankara, Turkey

Martina Samardjieva

Cardiology Clinic, Heart and Brain Center of Excellence, Pleven, Bulgaria

Medical University, Pleven, Bulgaria

Maria Chiara Scali

Campostaggia Cardiology Division, Montepulciano, Siena, Italy

Iana Simova

Cardiology Clinic, Heart and Brain Center of Excellence, Pleven, Bulgaria

Medical University, Pleven, Bulgaria

Jae-Kwan Song

Asan Medical Center Heart Institute, University of Ulsan College of Medicine, Seoul, Republic of Korea

Marco A. R. Torres

Itaipu Hospital—Unimed Leste Fluminense, Niteroi, Brazil

Caroline Van De Heyning

Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium

Albert Varga

Institute of Family Medicine, Szeged University Medical School, University of Szeged, Szeged, Hungary

Alexander Vrublevsky

Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russia

Karina Wierzbowska-Drabik

Department of Internal Disease and Clinical Pharmacology, Bieganski Hospital, Medical University of Lodz, Lodz, Poland

Angela Zagatina

Cardiology Department, Cardiocenter Medika, St. Petersburg, Russia

Olga Zhuravleva

Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russia

Michele de Nes

Image and Video editor, IT technician, Institute of Clinical Physiology, CNR Consiglio Nazionale Ricerche, Pisa, Italy

Part I

The Signs

Step A for Regional Wall Motion Abnormality in Stress Echocardiography

1

José Luis de Castro e Silva Pretto and Eugenio Picano

Keywords

Coronary artery stenosis · Ischemia · Regional thickening · Subendocardial layer · Wall motion

1.1 Classic and Alternative Ischemic Cascades

The main sign of ischemia during stress echocardiography (SE) is the transient regional wall motion abnormality (RWMA) [1] due to flow-limiting coronary artery disease (CAD). RWMA can be provoked by exercise or pharmacological stressors [2, 3]. All main SE modalities (exercise, dobutamine, vasodilators) have comparable accuracy for the diagnosis of obstructive CAD, with higher specificity and slightly lower sensitivity compared to methods based on perfusion changes, such as myocardial contrast echocardiography, stress cardiac magnetic resonance with contrast, and myocardial perfusion scintigraphy [4]. The higher sensitivity of perfusion changes compared to RWMA is easily understood based on the ischemic cascade found in patients with CAD (Fig. 1.1).

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J. L. de Castro e Silva Pretto (✉)
Hospital Sao Vicente de Paulo e Hospital de Cidade, Passo Fundo, Brazil
e-mail: jlpretto@cardiol.br

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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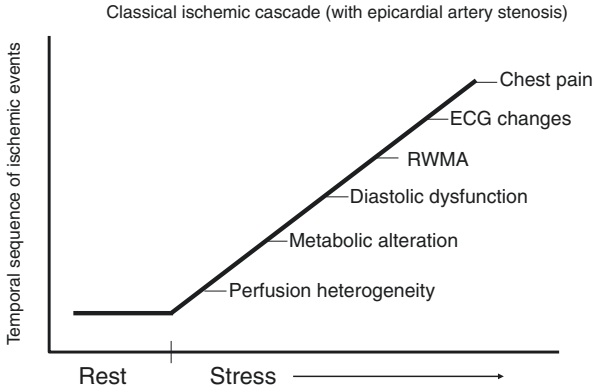

Fig. 1.1 The classic ischemic cascade. The classic ischemic cascade is triggered by stress in presence of flow-limiting coronary stenosis of epicardial arteries. The various markers are usually ranked according to a well-defined time sequence, with a reduction of coronary flow velocity reserve (or regional perfusion abnormalities) first, followed by RWMA and later appearance of ST-segment depression and chest pain. (Modified from Picano et al. [5])

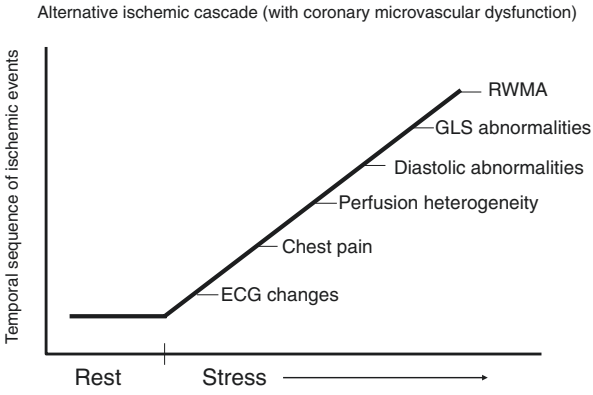

Fig. 1.2 The alternative ischemic cascade. In the model of a coronary microvascular disease characterized by a reduction in coronary flow reserve with normal epicardial arteries, anginal pain and ST-segment changes usually appear during stress in the absence of any detectable RWMA. *GLS* global longitudinal strain. (Modified from Picano et al. [5])

Regional perfusion abnormalities are the prerequisite and an earlier event than RWMA. However, in clinical practice, this reassuring one-fits-all model of the classical ischemic cascade is challenged due to the frequent occurrence of microvascular angina in patients with angina and angiographically normal coronary arteries (Fig. 1.2).

Patients with microvascular angina typically have exercise-related angina, electrocardiographic or perfusion evidence of exercise-related ischemia, and either no stenoses or mild stenoses (<50%) that are deemed functionally nonrelevant.

Coronary microvascular dysfunction can be either primary (in cardiac Syndrome X) or associated with hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease [5]. In coronary microvascular disease, stress-induced RWMA is

the exception rather than the rule and occurs in <10% of patients with perfusion changes, identifying a less favorable outcome [6]. However, deformation imaging documents a reduction, or blunted increase, of global longitudinal strain during stress in patients with reduced coronary flow velocity reserve, consistently with a truly ischemic nature of chest pain [7–10].

1.2 Left Ventricular Myocardium Segmentation Models

As with all cardiac imaging modalities, the assessment of regional left ventricular function with echocardiography is performed by artificially dividing the left ventricular myocardium into several segments. The segmentation of the left ventricle reflects coronary perfusion territories, results in segments with comparable myocardial mass, and allows standardized communication within echocardiography and with other imaging modalities [11].

The resolution of the segmental approach is a function of the number of segments; thus it can range from 20% (in the 5-segment model) to 5% (in the 20-segment model). However, increasing the number of segments, and thus reducing their size, leads to an unacceptable complication in the analysis with a greater need for approximation and interpolation. A reasonable trade-off between accuracy and feasibility is represented by the 16-segment model proposed by the American Society of Echocardiography [12]. In this model, the left ventricular myocardium is first divided into three myocardial rings (basal, mid-cavity, and apical) whose height is 1/3 of the left ventricular length. Both the basal and the mid-cavity rings account for about 35% of left ventricular myocardium mass, while the apical ring accounts for the remaining 30% [13]. The basal- and mid-cavity (papillary-muscle) rings are then divided into six segments (each segment accounts for 60° of left ventricular circumference) and the apical level into four segments. The segmentation starts at the anterior junction of the interventricular septum and the right ventricular free wall and continues counterclockwise. Basal and mid-ventricular segments are labeled as anterior, antero-septal, infero-septal, inferior, infero-lateral and antero-lateral. The corresponding apical segments will be: septal, inferior, lateral, and anterior [11, 13] (Fig. 1.3). The 16-segment model has been modified to obtain a segmentation standard applicable to all imaging modalities by adding a 17th segment (the "apical cap"), which is defined as the myocardium beyond the length of the left ventricular cavity [14].

Each segment can usually be visualized in more than one echocardiographic view and from different approaches for a more reliable and complete evaluation of wall motion.

As a rule, segmental wall motion can be reliably assessed when the endocardial contour is visualized for at least 50% of the segment length. With echocardiography, the segmental myocardial function is usually assessed subjectively by examining endocardial excursion and myocardial thickening. There are some limitations to using endocardial excursion as the sole criterion to assess segmental wall motion. The motion of any given segment of the left ventricle is influenced by the adjacent

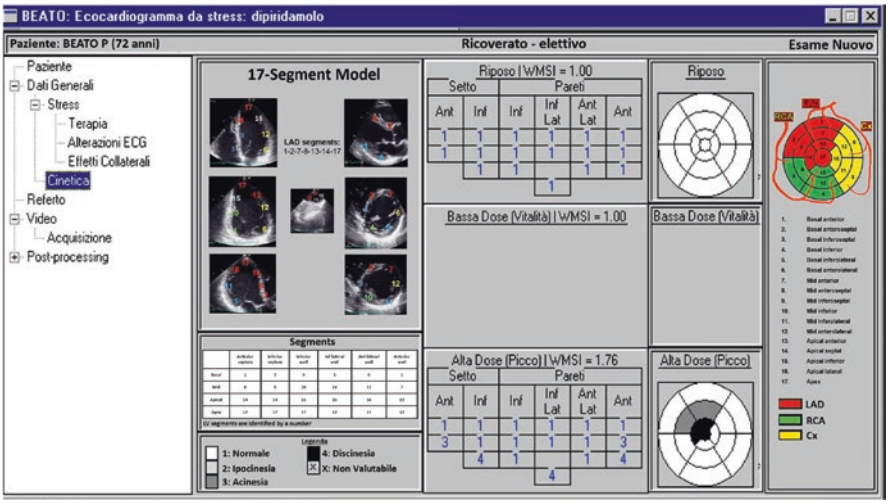

Fig. 1.3 Typical report from a positive test for severe ischemia in the left anterior descending artery (LAD) territory. *On the top left panel*: Assignment of the 17 myocardial segments to each specific projection. Segments perfused by the LAD are coded in red. Segments perfused by the left circumflex coronary artery (Cx) are coded in yellow. Segments perfused by the right coronary artery (RCA) are coded in green. *On the right panel*, the bull's eye representation of the 17-segment model of the left ventricle. The outer ring represents the basal segments, the mid-ring represents segments at the mid-cavity (papillary muscle) level, and the inner ring represents segments at the apical level. In the 17-segment model, an additional segment (apical cap) is added in the center of the bull-eye diagram. Each segment is assigned to the territories of the LAD, RCA, and Cx. *Middle panel*: The test report describes a normal left ventricular function at rest (wall motion score index, WMSI = 1) and a high-risk response with severe ischemia after the high dose of the dipyridamole stress (peak WMSI = 1.76) in the LAD territory

muscle to which it is attached. For example, in a chamber with a dyskinetic ischemic segment, some of the adjacent normal myocardium may appear hypokinetic because its motion is restricted by the attached dyskinetic muscle. The reverse phenomenon can also occur. If vigorously contracting normal muscle is next to an ischemic area, the hyperdynamic segment may pull the ischemic muscle toward the cavity, which may mask the abnormally perfused area. In general, endocardial excursion alone overestimates the degree of ischemia seen in the myocardium. A more specific finding to detect ischemic myocardium is the reduction of systolic wall thickening. Normal myocardium muscle increases in thickness during systole. Ischemia causes a reduction or absence of systolic wall thickening. Indeed, acute ischemia may also cause systolic thinning (i.e., wall thickness is greater in diastole than in systole). Clinical situations in which endocardial excursion may be abnormal with preserved wall thickening include left bundle branch block, Wolff–Parkinson–White syndrome, and paced rhythm. The presence of preserved systolic wall thickening in these conditions confirms that the wall motion abnormalities are not due to intercurrent myocardial ischemia [15].

1.3 Assignment of Segments to Coronary Arterial Territories

There is tremendous variability in the individual coronary artery blood supply to left ventricular myocardial segments. Nevertheless, it has been agreed to assign individual segments to specific coronary artery territories [16]. The assignment of the 17 segments to one of the three major coronary arteries with the bull's eye format is shown in Fig. 1.3.

The greatest variability in myocardial blood supply occurs at the apical cap (segment 17) which can be supplied by any of the three arteries. If the basal segment of the anterior wall (segment number 1) is affected, high-grade proximal stenosis of the left anterior descending artery before the origin of the first septal perforator can be suspected. The anatomical relationships described above, although frequent, are by no means uniform: different anatomical patterns may be found in different patients [16]. In particular, the assignment of myocardial regions to coronary artery territories may change substantially with a dominant right coronary artery or with a less frequent dominant left circumflex artery.

1.4 Tips and Tricks

A regional dysfunction can be artifactually "created" by incorrect positioning of the transducer. Therefore, the presence of an RWMA should be assessed by visualizing the same left ventricular segment from different acoustic windows using different echocardiographic views. The long-axis parasternal view allows optimal visualization of the anterior septum and the inferior-lateral wall since the endocardium is perpendicular to the ultrasonic beam. However, this view can be limited by the susceptibility to translational motion of the heart due to respiratory interference induced by the hyperventilation associated with some stressors. A foreshortened long axis view may create false hyperkinesis (masking true hypokinesia) of apical segments and create a false hypokinesis of the basal septal and inferior-lateral segments. The parasternal short-axis view at the papillary muscle level allows a simultaneous assessment of the left ventricular segments belonging to the distribution territories of all three coronary arteries. This view is particularly suited for quantitative wall motion analysis, although it may be challenging to obtain in patients with relatively advanced age, such as those with CAD. Even less frequently utilized is the parasternal short-axis view at the mitral level, where a spurious transient wall motion abnormality of the basal inferior segment is commonly seen. The cause of this artifactual dysfunction is the physiological systolic shortening of the left ventricle in a base-to-apex direction so that in diastole the left ventricular wall is imaged whereas, in systole, it is the left atrium that enters the image plane. A further drawback is that with many stressors the extent of the base-to-apex shortening of the left ventricle is increased compared to resting conditions. Accordingly, if a wall motion abnormality in the inferior-lateral basal segment is visualized in the parasternal short-axis view at the mitral level, it

should be reported with caution unless the inferior-lateral basal segment can be visualized in another apical view.

The perfect short-axis view must be round. An elliptic shape of the short axis view can mask a wall motion abnormality of the anterior segments and mimic a hypokinesis of inferior-lateral ones (Fig. 1.4).

The apical (4- 3-, and 2-chamber) views are the most frequently used and most useful views in SE. Inducible ischemia affects the subendocardial layer of the left ventricular wall first. Since myocardial fibers in the subendocardial layer are oriented longitudinally, the first function lost by the ischemic myocardium is the ability to shorten longitudinally (in the basal-apex direction) and this abnormality can be visually appreciated using the apical views. To properly acquire the apical views of the left ventricle, particular care should be taken to properly orient the view and avoid the foreshortening of the cavity [17, 18]. A properly oriented 4-chamber view will maximize the right ventricular cavity area and will not show the aortic root. A foreshortened 4-chamber view can mask hypokinesia of the apex (which will appear falsely hyperkinetic) and can mimic hypokinesia of the basal lateral and basal anteroseptal segments. The apical 2-chamber view, if properly acquired, should not show either the aortic root or the right ventricular cavity. It is analogous to the right anterior oblique projection employed in ventriculography and clearly shows the

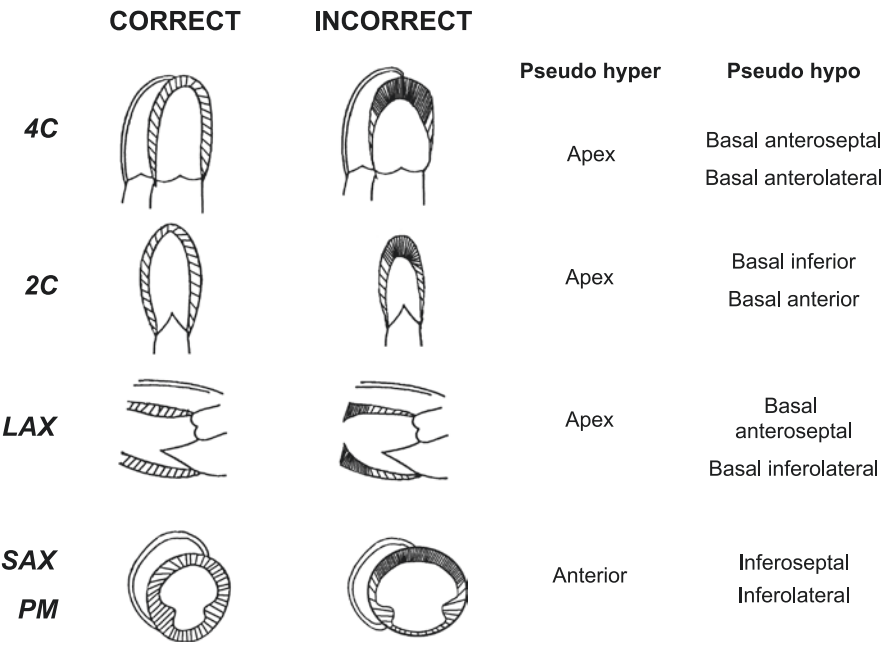

Fig. 1.4 SE artifacts. The *left panel* shows the correct imaging for each of the main views; the *right panel* shows the incorrect imaging which may mask or mimic regional dysfunction during stress

inferior and anterior walls. A foreshortened 2-chamber view can mask hypokinesia of the apex and mimic hypokinesia of the basal inferior wall.

A properly acquired apical long-axis view will show the aortic root. It is analogous to the left anterior oblique projection employed in ventriculography and clearly shows the inferolateral wall and anterior septum. A foreshortened apical long-axis view can mask hypokinesia of the apex and mimic hypokinesia of the basal inferolateral wall.

The 4-chamber subxiphoid view closely parallels the image obtained with the apical 4-chamber view, and subcostal short-axis views are similar to the short-axis parasternal ones. The main advantage is that this acoustic window remains feasible in patients in whom the ultrasonic study would otherwise be difficult, such as those who are obese or with severe lung disease. This view is certainly useful for assessing right ventricular ischemia, which is usually accompanied by acute dilation of the right ventricle.

1.5 Matching Between Transthoracic and Transesophageal Segments

Transesophageal SE can be performed in patients with limited transthoracic echocardiography image quality. The semi-invasive nature of the technique makes it more unpleasant for the patient [19, 20]. Excellent results have been obtained with pharmacological transesophageal SE for the assessment of myocardial ischemia (with dobutamine or dipyridamole) [21–23], myocardial viability (with dobutamine) [24], coronary flow velocity reserve (with dipyridamole or adenosine) [25–29], and prognostic stratification based on inducible RWMA [30, 31]. The segmental analysis is generally performed using the 17-segment model modified for transesophageal echocardiography [19, 20]. Despite its undisputed accuracy, the clinical role of transesophageal SE is decreasing because patients with difficult acoustic windows are rare with current ultrasound technology and ultrasound-enhancing agents when needed. Transesophageal SE remains a reasonable option in patients in the operating room (for early assessment of functional results of revascularization) or the intensive care unit (for instance, for recruitment of heart donors with SE).

1.6 Methodology for Assessment of Regional Wall Motion Abnormalities

Regional wall motion must be assessed at rest, intermediate stages, peak stress, and recovery phase. All standard projections are obtained at each stage (Fig. 1.5).

The time sequence of acquisition and recordings is shown in Table 1.1.

The response of left ventricular function to ischemia is monotonous and independent of the stress employed. Normal myocardium shows systolic thickening and endocardial movement toward the center of the cavity. The normal hyperkinetic response during stress indicates an increase in normal movement and thickening.

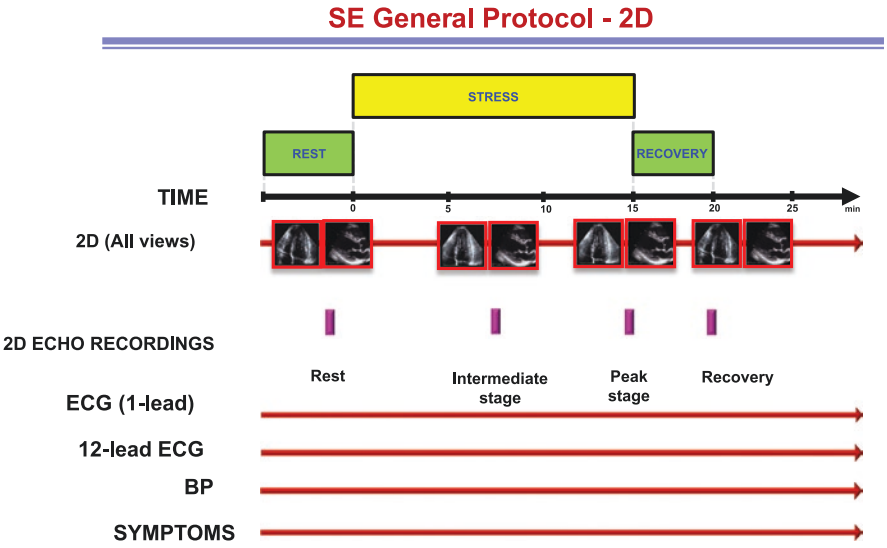

Fig. 1.5 The protocol for SE. The apical views (4-chamber, 2-chamber, and 3-chamber) and the parasternal views (long-axis and short-axis) are ideally required. Digital recordings are required at rest, intermediate stage, peak stress, and also in the recovery phase (after antidote administration for dipyridamole or dobutamine). *BP* blood pressure, *ECG* electrocardiogram

Table 1.1 Acquisition in SE for regional wall motion analysis

		Rest	Stress-intermediate	Stress-peak	Recovery
	Time (min)	TTE	0–10	11–15	15–20
2D	All views	v	v	v	v
ECG, 1-lead	Echo monitor	v	v	v	v
ECG,12-lead	ECG monitor	v	v	v	v
BP	Sphygmomanometer	v	v	v	v
Symptoms	Patient	v	v	v	v

BP blood pressure, *2D* 2-dimensional echocardiography, *ECG* electrocardiogram, *TTE* transthoracic echocardiography

The hallmark of transient, stress-induced myocardial ischemia is the RWMA, in its three degrees of increasing severity [2, 11]: hypokinesia (decreased systolic thickening and endocardial motion); akinesia (absent or negligible thickening and endocardial motion); dyskinesia (stretching, with paradoxical thinning and/or outward endocardial motion during systole) (Table 1.2).

The severity of RWMA mirrors the severity of the regional subendocardial hypoperfusion. A reduction in subendocardial blood flow of about 20% produces a 20% decrease in wall thickening; a 50% reduction in subendocardial blood flow decreases regional wall thickening by about 40%, and when subendocardial blood flow is

Table 1.2 Wall motion and thickening

Score	Status	Wall thickening
1	Hyperkinesis	>60%
1	Normal	40–60%
2	Hypokinesis	10–39%
3	Akinesis (=severe hypokinesis)	0–10%
4	Dyskinesis	<0% (Wall thinning)

reduced by 80%, akinesia occurs. Dyskinesia appears appears when the flow deficit is extended to the subepicardial layer and ischemia is transmural [32].

The 17- or 16-segment model of the left ventricle represents the anatomical background for rapid (real-time) semiquantitative assessment of wall motion (from 1 = normal to 4 = dyskinesis). The difference between rest and stress wall motion score index provides a simple assessment of the induced ischemia, combining the horizontal extent (the number of involved segments) with the vertical depth of ischemia (the severity of abnormality of each segment, from hypo- to dyskinesia). The definition of risk is important since patients at high risk will benefit from revascularization with better survival and amelioration of symptoms. High risk is defined as a cardiac mortality rate >3% per year and low risk as a cardiac mortality rate <1% per year. The high risk is defined as stress-induced RWMA (hypokinesia, akinesia, or dyskinesia) ≥3 segments out of 16 [32]. The low risk is defined by the absence of RWMA during stress. The degree of RWMA also predicts the symptomatic benefit after myocardial revascularization. The greater the downstream SE abnormality caused by the stenosis, the greater the reduction in symptoms post-percutaneous coronary intervention [33].

1.7 Response Patterns

All SE diagnoses can be easily summarized in four equations centered on regional wall function and describing the fundamental response patterns: normal, ischemic, viable, and necrotic (Table 1.3).

The possible mechanical patterns are schematically shown in Fig. 1.6 along with their myocardial and coronary correlates.

In the normal response, a segment is normal at rest with hyperkinesis during stress (Fig. 1.7, Video 1.1).

In the abnormal response, a segment shows normokinesis at rest with hypo-, a-, or dyskinesis during stress (Fig. 1.8, Video 1.2).

Resting akinesia that becomes dyskinesis during stress reflects a purely passive, mechanical phenomenon of increased intraventricular pressure developed by normally contracting walls and should not be considered true active ischemia [3]. It is conceptually similar to the increase in ST-segment elevation during exercise in patients with resting Q waves and ST-segment elevation on a resting electrocardiogram.

Table 1.3 SE in four patterns

Rest	Stress	Pattern	Diagnosis
Normokinesis (1)	Normal-hyperkinesis (1)	Hyperfunction	Normal
Normokinesis (1)	Hypo-, a-, dyskinesis (≥2)	Worsening	Ischemia
Akinesis (3)	Hypo-, normokinesis (1 or 2)	Improving	Viable
A-, dyskinesis (3–4)	A-, dyskinesis (3–4)	Fixed	Necrosis

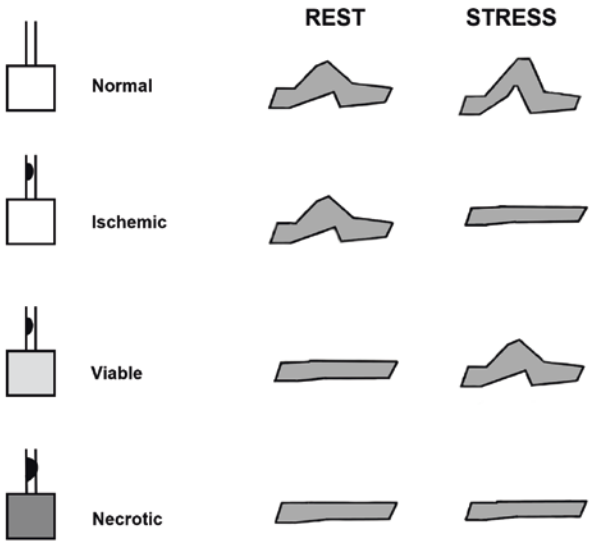

Fig. 1.6 SE patterns of normal (*upper row*), ischemic (*second row*), viable (*third row*), and necrotic (*fourth row*) responses are schematically represented. On the *left side*, the corresponding schemes of the coronary artery (*parallel lines*) and the myocardium (*box*) are shown. A normal myocardium is represented as a *white box*; a necrotic myocardium as a *black box*; a viable myocardium as a *gray box*. In a normal segment fed by a normal coronary artery, the segment is normal at rest with normal–hyperkinesis during stress (*upper row*). In a normal myocardium fed by a critically stenosed coronary artery, the segment is normal at rest and shows hypo-, a-, or dyskinesis during stress (*second row*). A viable segment (*third row*) with akinesis at rest is normal during stress. A necrotic segment shows an abnormal, fixed wall motion abnormality at rest and during stress (*lower row*)

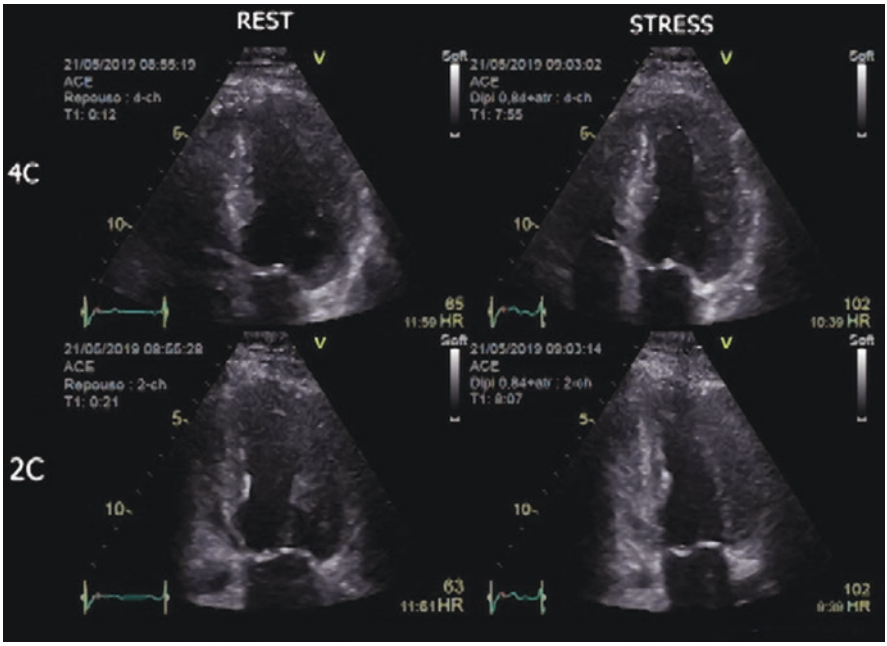

Fig. 1.7 A normal wall thickening at rest (left panel) with hyperkinetic wall motion and reduced left ventricular cavity during stress (right panel). End-systolic frames are shown. Left panels: rest. Right panels: stress. Upper panels: Apical 4-chamber view (4C). Lower panels: Apical 2-chamber view (2C). See accompanying Video 1.1. (Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

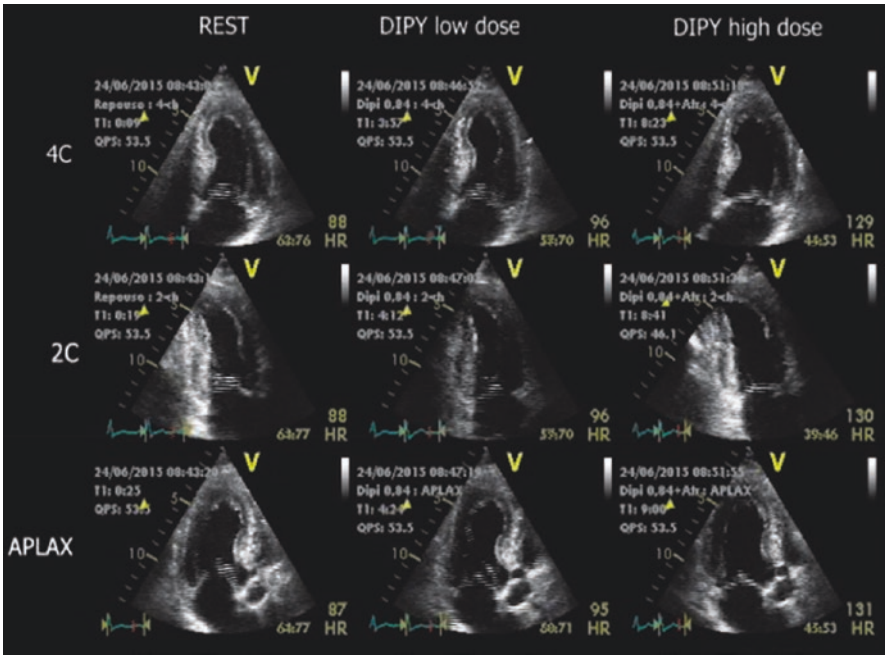

Fig. 1.8 End-systolic frames showing normal wall thickening at rest (left panel) with mild RWMA at a low dose (middle panel) and marked RWMA involving the lateral and inferior walls at the high dose of dipyridamole stress (right panel). Left panels: rest. Middle panels: Low dose. Right panels: peak stress. Upper panels: Apical 4-chamber view (4C). Intermediate panels: Apical 2-chamber view (2C). Lower panels: Apical long-axis view (APLAX). See accompanying Video 1.2. (Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

1.8 Diagnostic Results and Accuracy

The diagnostic accuracy for noninvasive diagnosis of obstructive epicardial CAD is similar to other imaging functional testing techniques, with excellent specificity (around 90%) and good sensitivity (around 80%). In individual studies, the reported accuracy varies widely, as can be expected due to the many factors modulating the capability of any stress to increase diagnostic sensitivity (and, symmetrically, to reduce specificity). Higher sensitivity is observed in patients with extensive (multivessel), severe (≥90% diameter reduction) disease involving the left anterior descending artery, with complex-type morphology, compared to patients with limited (single-vessel) disease of intermediate (50 to 80% diameter reduction) severity and simple-type morphology located in left circumflex or right coronary artery. Higher values of sensitivity balanced by a drop-off in specificity can be achieved with the assessment of myocardial perfusion [34] or coronary flow velocity reserve in the left anterior descending artery [35], allowing to detect a lower grade coronary

atherosclerosis and/or coronary microvascular dysfunction not linked with ischemia which goes undetected with wall motion abnormalities and still contributes to prognostic vulnerability [36].

SE data can be usefully combined with a carotid scan to rule out anatomic carotid disease [37] and with resting transthoracic echocardiography to assess cardiac calcification, based on calcification of mitral annulus, aortic valve leaflets, and ascending aorta. Both carotid disease and inappropriate cardiac calcification are a marker of subclinical atherosclerosis, a predictor of subsequent events, and allow a refined risk stratification based on SE [38]. In the echocardiography and vascular ultrasound laboratory, the detection of cardiac calcification or carotid plaque allows us to image atherosclerotic disease at a very early stage, decades before the coronary flow-limiting plaque which determines stress-induced RWMA during SE.

1.9 False-Negative Results

Despite the high diagnostic accuracy of SE in predicting obstructive epicardial CAD, anatomically significant CAD can be present in absence of inducible RWMA ("false negative response") and stress-induced RWMA may occur in the absence of significant CAD ("false positive response"). A SE false-negative result may occur for patient-, stress-, angiography-, myocardium-, reader- and image-related reasons (Table 1.4).

False-negative results with maximal tests performed off therapy are associated with a good prognosis, almost comparable to true negative results [4]. Antianginal therapy with beta-blockers, calcium antagonists, and nitrates lowers the sensitivity of SE and prevents stress-induced RWMA with all forms of testing. The outcome associated with a negative test performed under anti-ischemic medical therapy is less benign than a negative test-off therapy [4]. Submaximal stresses do not test the coronary circulation efficiently, and a second-choice test (for instance, pharmacological after a nondiagnostic exercise test) should be employed to have a diagnostic maximal result. It is more important for the patient to have maximal stress rather

Table 1.4 Main Sources of false-negative and false-positive results

	Reason of false-negative	Reason of false-positive
Patient-related	Under antianginal therapy	True ischemia in HCM or AS
Stress-related	Submaximal stress	Vasospasm, standing position
Angiography-related	Anatomically mild-intermediate (40 to 70%) or functionally nonsignificant, LCx and RCA distal location	Angiographically non-significant but flow-limiting with FFR, or anatomically significant with ICUS, LAD proximal location
Myocardium-related	Not critical ischemic mass	Occult cardiomyopathy
Image-related	Inadequate segmental imaging	Inadequate segmental imaging
Reader-related	Conservative reading	Aggressive reading

AS aortic stenosis, *HCM* hypertrophic cardiomyopathy, *ICUS* intracoronary ultrasound, *FFR* fractional flow reserve, *LAD* left anterior descending coronary artery, *LCx* left circumflex, *RCA* right coronary artery

than which stress is used. Not all coronary stenoses were created equal and—when maximal stress is administered—patients with a negative SE response more often show lesions of intermediate severity (50 to 80 % diameter reduction) and with preserved fractional flow reserve, indicating that the hemodynamic severity of the lesion is more important than its anatomic severity in determining stress-induced RWMA. Conservative underreading can be a cause of low sensitivity. In some cases, true ischemia occurs but may go undetected by SE, especially in less well-imaged segments, such as the inferior or lateral walls, because of the inherent limitations of subjective analysis and lack of quantitative criteria or images of borderline quality during stress.

1.10 False-Positive Results

False-positive results in SE may indicate true induced ischemia and absolute subendocardial under perfusion despite angiographically non-significant CAD. A false-positive response can be due to patient-, stress-, angiography-, myocardium-, reader- and image-related reasons (Table 1.4).

False-positive results are associated with a poor prognosis, comparable to true positive results [39]. The main stress-related cause is epicardial coronary artery vasospasm, which may unpredictably occur superimposed to any degree of coronary artery stenosis (from absent to severe) during or soon after exercise, dobutamine (during or also after beta-blockers administration), or dipyridamole (more frequently following the antidote aminophylline). It is a diagnosis by serendipity: coronary vasospasm is found when looking for coronary artery stenosis during testing. It is an easy diagnosis if you think of it, and an important one, since coronary vasospasm is a possible cause of chest pain, sudden cardiac death, syncope, and lack of response to medical therapy with beta-blockers and coronary revascularization. It is not infrequent, since 10–20% of dobutamine SE positivity without coronary lesions is due to coronary vasospasm [40, 41]. Although ignored by guidelines, specific noninvasive testing for coronary vasospasm with ergonovine or hyperventilation can be safely performed in properly selected patients in the SE lab [42]. Another cause of stress-related false-positive findings is the inferior-basal pseudo-dyskinesia occurring when the patient is in a standing position, possibly for the changing interaction of the inferior wall with the posterior leaflet of the mitral valve and diaphragm [43]. The main angiography-related cause is stenosis of intermediate, subcritical severity at angiography that is, in reality, anatomically and functionally severe when verified by more accurate intracoronary ultrasound or functional assessment with fractional flow reserve during invasive coronary angiography [44]. These patients should be considered as true positive, belong to a high-risk subset, and should be treated accordingly. The myocardial revascularization cures the stress-induced RWMA and improves anginal symptoms. The main myocardium-related cause of a “false-positive” response is hidden cardiomyopathy or regional scar. The incipient muscle disease may not be overt at rest, but a chronotropic, afterload, and arteriolar vasodilatory challenge with excessive heart rate and systolic blood pressure rise associated with

stress can unmask a true regional dysfunction. In all these conditions, RWMA has an excellent prognostic value. Aggressive over-reading can be a cause of low specificity in images of low or borderline quality.

1.11 Towards Quantitative SE

The current state-of-the-art diagnosis remains subjective by visual eyeballing, but it might be possible to corroborate the current naked eye diagnosis with a quantitative assessment with myocardial deformation indices and/or artificial intelligence. The rationale behind strain SE is its quantitative nature, ability to differentiate tethering from surrounding segments, earlier onset than RWMA during the ischemic cascade (leading to higher diagnostic sensitivity), and longer persistence after stress interruption. At present, it cannot be used routinely in clinical practice due to limited feasibility (around 80%), noisy data in high heart rate states (>100 bpm), lack of standardization of parameters and software, and missing effectiveness studies [45]. Artificial intelligence elaboration of images and data may be more automated and operator-independent [46].

1.12 Clinical Guidelines and Recommendations

According to the 2019 European Society of Cardiology guidelines for the diagnosis of chronic coronary syndromes, SE based on RWMA is recommended instead of exercise ECG as the initial test to diagnose obstructive CAD for a symptomatic patient (with angina and/or dyspnea) [1]. SE is the functional test of choice in patients with suspected or known CAD due to its widespread availability, possibility to be combined with exercise, radiation-free nature, no need to use contrast based on iodine and gadolinium, and versatility of information [47]. Similar recommendations were issued in 2021 by the American College of Cardiology/ American Heart Association guidelines on chest pain [48], although in patients with a low pretest probability of disease who can exercise and with an interpretable electrocardiogram, a simple exercise-electrocardiogram is recommended. SE based on inducible RWMA is also recommended before high-risk noncardiac surgery [49], heart failure with reduced ejection fraction and CAD suitable for revascularization [50], heart transplant for rejection surveillance [51], congenital heart disease (coronary congenital anomalies, status post-switch operation) [52, 53], Kawasaki disease [54], status post-chest radiotherapy for cancer [55], and sports eligibility in asymptomatic subjects>35 years at high risk before high-intensity activity [56] (Table 1.5).

The test is not recommended in asymptomatic patients. The test is also not recommended in low-risk patients with either acute chest pain in the emergency department evaluation or with stable chest pain in the outpatient evaluation [48]. SE based on RWMA is also not recommended for the diagnosis of CAD in patients with valvular heart disease [57] and hypertrophic cardiomyopathy [58] due to the high rate of false positive responses.

Table 1.5 The place of SE with RWMA in the guidelines

Condition	COR	Source
CCS-initial test in symptomatic patient[a]	1	ESC 2019 [1] and ACC/AHA 2021 [48]
CCS-second test after uncertain stenosis at CCTA	1	ESC 2019 [1]
CCS-risk stratification in suspected or known CAD	1	ESC 2019 [47]
Before noncardiac high-risk elective noncardiac surgery in patients with poor functional capacity and a high likelihood of CAD or high clinical risk	1	ESC 2022 [49]
Before noncardiac high-risk elective noncardiac surgery in asymptomatic patients with poor functional capacity and previous PCI or CABG	2a	ESC 2022 [49]
Before noncardiac intermediate-risk elective noncardiac surgery in asymptomatic patients when ischemia is of concern in patients with clinical risk factors and poor functional capacity	2b	ESC 2022 [49]
Heart failure with reduced ejection fraction and CAD	2b	ESC 2021 [50]
Heart transplant for rejection surveillance	2a	ISHLT 2010 [51]
Coronary anomalies, TGA post-switch operation	1	ESC 2019 [52] and ACC/AHA 2021 [53]
Kawasaki disease	2a[b]	ACC/AHA 2017 [54]
Status post-chest radiotherapy for cancer	2a[c]	ACC/AHA 2017 [55]
Sport eligibility	2b[d]	ESC 2020 [56]

ACC/AHA American College of Cardiology/American Heart Association, *CABG* coronary artery bypass surgery, *CCTA* coronary computed tomography angiography, *CCS* chronic coronary syndromes, *COR* class of recommendation: 1: is recommended; 2a: should be considered; 2b: may be considered, *ESC* European Society of Cardiology, *ISHLT* International Society Heart and Lung Transplantation, *METS* metabolic equivalents, *PCI* percutaneous coronary intervention, *TGA* transposition of great arteries

[a]Preferentially considered over CCTA in case of high clinical likelihood, revascularization likely, viability assessment also required

[b]Symptomatic with chest pain or asymptomatic LV dysfunction; surveillance in asymptomatic every year (large aneurysm), 3 years (medium aneurysm), and 5 years (small aneurysm)

[c]Every 5–10 years in asymptomatic pts. who received >15 Gray mean heart dose

[d]Asymptomatic >35 years with high risk (>5%) before high-intensity activity

For both European and American guidelines, SE may be preferred as a first-line test in patients at the higher end of a range of clinical likelihood if revascularization is likely or when the patient has previously diagnosed CAD, or viability assessment is also required. The recommended stress is any (exercise, dobutamine, vasodilator) for induction of RWMA [1, 3], dobutamine for viability [1–3], and a vasodilator for simultaneous coronary flow velocity reserve evaluation [1, 48]. The warranty period lasts 1 year after a normal functional stress test in absence of change in symptoms [48].

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Step B for B-Lines in Stress Echocardiography

2

Maria Chiara Scali and Eugenio Picano

Keywords

Alveolar-capillary barrier · Extravascular lung water · Left ventricular filling pressure · Pulmonary congestion · Venous pressure

2.1 History and Pathophysiology

Lung ultrasound (LUS) was first proposed for the diagnosis of interstitial pulmonary syndrome by the French intensivist Daniel Lichtenstein in 1997 [1]. B-lines (also known as ultrasound lung comets) were introduced for the detection of extravascular lung water in heart failure patients in 2004 [2–4]. In one-third of coronary artery disease or heart failure patients, B-lines are absent at rest and appear only during exercise [5, 6] emphasizing the need for a dynamic assessment to assess a subclinical vulnerability to develop pulmonary edema [7, 8]. B-lines appear during interstitial pneumonia and were soon adopted by the echocardiographic community as a first-line tool for the diagnosis of COVID-19 pneumonia [9–11].

LUS has rapidly changed our understanding of pulmonary congestion in heart failure, much in the same way as stress echocardiography (SE) had changed the

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M. C. Scali (✉)
Campostaggia Cardiology Division, Montepulciano, Siena, Italy
e-mail: mariachiara.scali@uslsudest.toscana.it

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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understanding of the ischemic cascade with regional wall motion abnormalities [12, 13]. The sequence of events leading to acute pulmonary edema during heart failure can be conceptualized as a cascade—the so-called "lung water cascade"[14]. The initiating hemodynamic event of the cascade is the increase in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (hemodynamic congestion), eventually leading to the rupture of Starling's equilibrium in the alveolar-capillary barrier, which is the precondition for interstitial accumulation of lung water (Fig. 2.1).

Lung water is detectable initially only during stress, and at a later stage, also at rest. In between hemodynamic and clinical pulmonary congestion, the intermediate event is the interstitial pulmonary congestion detectable by LUS as multiple B-lines, linked to an increased water-to-air ratio per unit of lung volume tissue in the subpleural interlobular septa [15]. Pulmonary congestion is the key manifestation of impending acute heart failure but the clinical, auscultatory, and chest X-rays findings are all late, insensitive, and unspecific signs of pulmonary congestion (Fig. 2.2) [16]. Lung water accumulation is linearly related to the number of B-lines in experimental and clinical conditions [17, 18].

The conceptual similarities and differences between the ischemic cascade and the lung water cascade are summarized in Table 2.1.

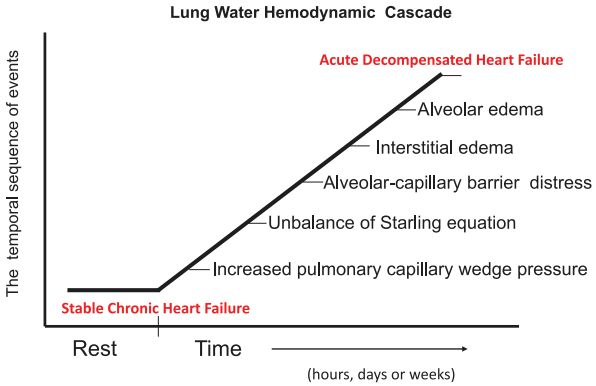

Fig. 2.1 The lung water hemodynamic cascade. Hemodynamic congestion is the early event before the development of unbalance of Starling forces in the alveolar-capillary barrier and the development of interstitial and later alveolar pulmonary edema. (Adapted and modified from Picano et al. [3, 12])

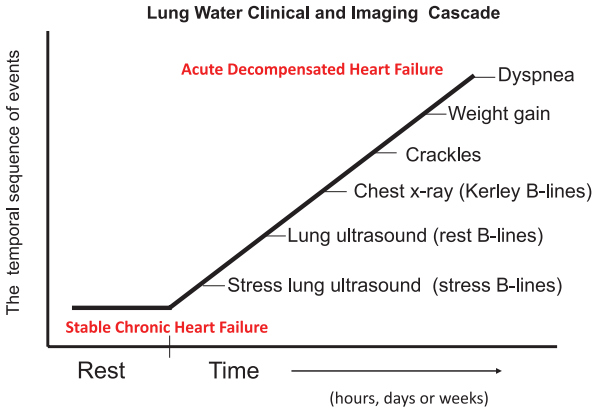

Fig. 2.2 The lung water clinical cascade. Stress B-lines are an earlier event than resting B-lines. Only after hours, days, or weeks is the clinical congestion apparent. Therapeutic countermeasures are likely more effective when initiated at the early, presymptomatic, and pre-radiologic silent stages of the cascade. (Adapted and modified from Picano et al. [3, 12])

B-lines do not identify a disease, but a condition associated with multiple causes such as cardiogenic acute pulmonary edema, acute respiratory distress syndrome, pneumonia, or any chronic interstitial disease. Despite these caveats, the technique is now the best one available for bedside detection of pulmonary congestion (Table 2.2).

For any given capillary wedge pressure, the permeability of the alveolar-capillary barrier may change acutely (over minutes) or chronically (over days or months) for several extra-hemodynamic factors. These factors may "pull" water within the vessel such as oncotic and osmotic forces (albumin or sodium), or "push" water extraluminally for enhanced permeability due to inflammation [19] or reducing lymphatic drainage (chest radiotherapy) (Table 2.3).

Even in the absence of left heart failure, pulmonary congestion may occur through an entirely venous, right-sided mechanism. The increase in systemic venous pressure is determined by postcapillary, but also by purely precapillary pulmonary hypertension, with normal left heart function. The dominant mechanism of lung water accumulation in left heart failure is increased fluid filtration. The prevailing mechanism for right heart failure is decreased fluid efflux due to impaired lymphatic

Table 2.1 Classical ischemic and lung water cascades

	Myocardial ischemia	Lung water
Underlying disease	Coronary artery disease	Heart failure
Target organ	Myocardium	Lung
Proximal imaging biomarker	RWMA	B-lines
Distal clinical symptom	Chest pain	Dyspnea
Imaging tool	Echocardiography	LUS
Advanced stage	Unstable angina	Acute heart failure

LUS lung ultrasound, *RWMA* regional wall motion abnormality

Table 2.2 Pulmonary congestion hemodynamic, radiologic, and LUS correlates

	PCWP (mmHg)	Chest X-ray	LUS
Normal	<12	Normal	A-lines
Initial congestion	12–17	Kerley B-lines	Mild B-lines
Interstitial edema	17–25	Hazy hila	Moderate B-lines
Alveolar edema	>25	Butterfly lung	Severe B-lines

PCWP pulmonary capillary wedge pressure

Table 2.3 Modulators of lung water accumulation for any given capillary wedge pressure

Lung water	Increases	Decreases
Plasma albumin	Low	High
Plasma sodium	Low	High
Plasma CRP and IL-6	High	Low
Air fine particulate matter	High	Low
ACB permeability	High	Low
PCWP rise	Acute, steep	Chronic, slow
Central venous pressure	High	Low

ACB alveolar-capillary barrier, *CRP* C-reactive protein, *IL*-6 interleukin-6, *PCWP* pulmonary capillary wedge pressure

drainage caused by high resistances due to the increased systemic venous pressure in the inferior vena cava accepting lymphatic flow from the lung [20]. B-lines are detectable also with a normal left heart, in presence of systemic venous hypertension [21].

2.2 The Main Signs of Pulmonary Congestion: B-Lines

The normal lung shows lung sliding with A-lines, which are artifactual horizontal reverberations, equidistant from one another below the pleura, at exact multiples of the transducer-pleural line (Fig. 2.3).

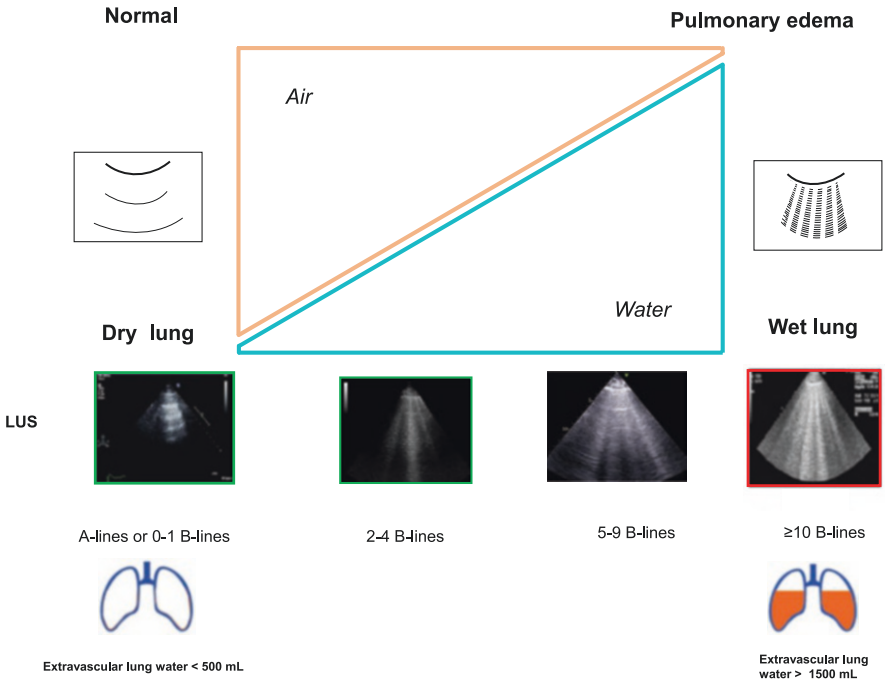

Fig. 2.3 Normal dry and abnormal wet lung. *Left panel*. Normal lung surface. The pleural line is thin, and the interstitial tissue does not generate any signal, so all that is seen using ultrasound is the repetition of the pleural line (A-lines). The A-line indicates air below the pleural line. The conceptual correlate is a dry lung (normal air, without water). The morphologic correlate is normal alveoli filled with air and thin interstitial space. *Right panel*. The pulmonary congestion pattern. There is a perfectly visible normal pleural line and multiple B-lines. The B-line indicates water below the pleural line. The conceptual correlate is a wet lung (abnormal water, reduced air). The morphologic correlate is a thickened interstitial space filled with water which may eventually fill the alveoli in pulmonary edema. *Lower panel*: The normal lung is "black" (no signal). The abnormal wet lung is "*black and white*" (with *white rockets* departing from the pleural line). The lung with overt pulmonary edema is "*white*" with an increase of coalescing comets. (Adapted and modified from Picano et al. [3, 12])

Table 2.4 Normal A-lines vs. abnormal B-lines

	A-lines	B-lines
Main reflector	Parietal pleura	Lung parenchyma
Direction	Horizontal	Vertical
Shape	Curvilinear	Linear
Interline spacing	Regular multiples	Irregular
Respiration (sliding)	Asynchronous	Synchronous
Biochemistry of lung	100% air	From 5 to 100% water
Lung at first-glance	Black lung	White lung

Table 2.5 Wet versus Dry B-lines

	Dry B-lines	Wet B-lines
Main component	Connective tissue	Edema, inflammation
Diuretics	No effect	Decrease
Orthostatic position	No effect	Decrease
Underlying disease	Systemic sclerosis	Heart failure

B-lines arise vertically and linearly from the pleural line, extend towards the edge of the screen, and move synchronously with lung sliding and respiration.

B-lines are among the easiest and most reproducible signs to recognize in cardiovascular ultrasound, considered to be "kindergarten" for trainees, while the identification of regional wall motion abnormalities is the more challenging "university" [22]. B-lines can be absent at rest with LUS showing the normal A-lines pattern (Table 2.4).

A-lines indicate that there is air below the pleural line: either 99.5% air, that is, normal lung below, which contains a trace amount of water; or it can be 100% air, in pneumothorax [22]. A-lines can be present in a patient at rest and are replaced by B-lines during stress. At each site, the number of B-lines mirrors the amount of extravascular lung water.

Wet B-lines made of water are dynamic variables and they may change over minutes, increasing with exercise, volume overload, or supine decubitus and decreasing with appropriate decongestion therapy or volume depletion or upright position. On the contrary, dry B-lines made of connective tissue stay fixed with all these maneuvers and tend to have greater echogenicity and restricted motion, usually exploited by artificial intelligence algorithms for automatic detection and quantification [22] (Table 2.5).

2.3 Methodology: The 4-Site Simplified Scan

For a cardiologist, LUS is an add-on to transthoracic echocardiography, just as lung auscultation is part of cardiac physical examination. A cardiac 2.5–5.0 MHz transducer is generally suitable since the small footprint makes it ideal for scanning intercostal spaces. Patients are examined in the supine or semi-recumbent position with the cardiac transducer at an imaging depth of 16 or 18 cm in sagittal orientation (perpendicular to the ribs).

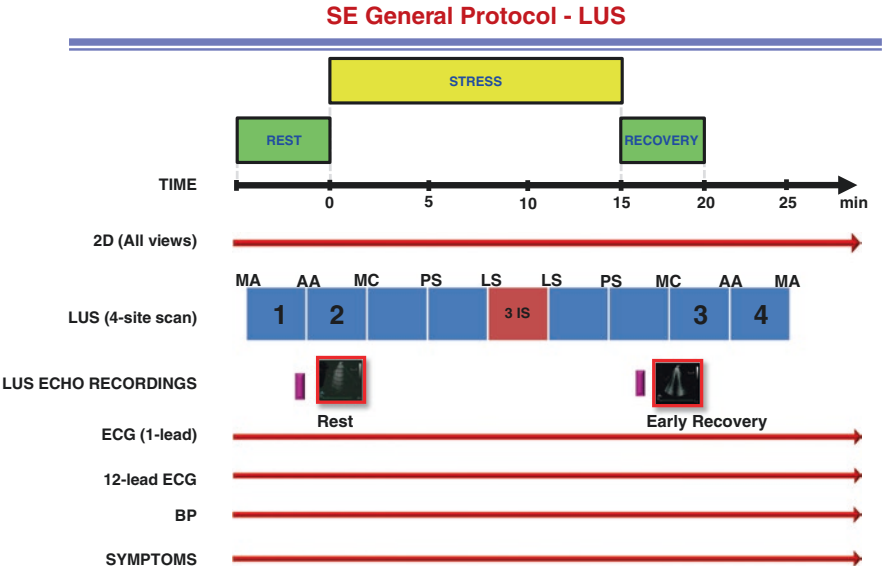

Fig. 2.4 The LUS 4-site simplified scan. *MA* mid-axillary, *AA* anterior axillary, *MC* mid-clavicular, *PS* parasternal lines, *3 IS* third intercostal space. Adapted and modified from Scali et al. [6, 7]. See accompanying Video 2.1. (Video images courtesy of Maria Chiara Scali, MD, Campostaggia hospital, Siena, Italy. The video is available under the chapter's "Supplementary Material" on Springer Link)

A 4-site simplified scan is adopted, including only the "wet spots" with most B-lines, in the third intercostal space, symmetrically in the right and left hemithorax (Fig. 2.4): from mid-axillary to the anterior axillary line, and from anterior axillary to the midclavicular line (*Ma'am* as a memory trick).

For each of the 4 sites, a six-second clip is recorded and analyzed online or offline. LUS mapping does not interfere with EKG leads and takes only <1 min to be completed in the early recovery phase, when B-lines are even more obvious than at peak exercise. The highest number of B-lines in a single intercostal space is counted and then summed across all four spaces. Each site has a possible score from 0 (black lung) to 10 (white lung), generating a total score of all 4 chest zones from 0 (all 4 sites with 0 individual site scores) to 40 (all 4 sites with individual site scores of 10). The cumulative number of stress B-lines are categorized as absent (score points 0–1); mild (2 to 4); moderate (5 to 9); and severe (≥10 points). LUS remains 100% feasible during stress [23].

The time sequence of acquisition and recordings is shown in Table 2.6. The time window for B-lines acquisition during stress is the early recovery phase, and therefore, it does not interfere with two-dimensional imaging at peak stress.

The global lung water score combines the horizontal extension of pulmonary congestion (the number of involved spaces) and the vertical depth of congestion (how deep is the water in each site) (Table 2.7) [23].

Table 2.6 Acquisition in LUS SE

		Rest	Stress-intermediate	Stress- peak	Early recovery	Recovery
	Time (min)	TTE	0–10	11–15	16	17–20
LUS	4-site scan	v			v	

Table 2.7 B-lines scoring with 4-site simplified scan

	Number of B-lines	Extravascular lung water (mL)	Prognosis
Absent	0–1	<500	Excellent
Mild	2–4	500–1000	Good
Moderate	5–9	1000–1500	Fair
Severe	10–40	>1500	Poor

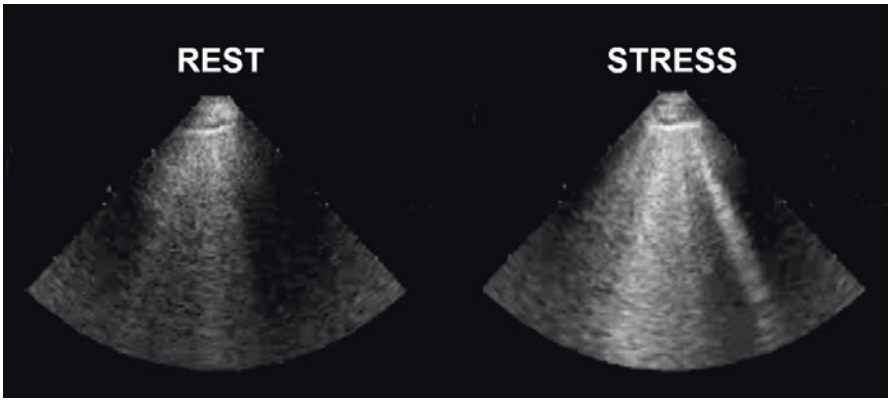

Fig. 2.5 LUS is abnormal at rest (B-lines) and more abnormal during stress (coalescent B-lines. In the corresponding video: a rest-stress LUS study shows lung sliding with 4 B-lines at rest and 9 B-lines after exercise stress, in the left third intercostal space between the mid-axillary and anterior axillary line. This worsening B-profile can be also described as septal rockets at rest becoming glass rockets during stress. See accompanying Video 2.2. (Video images courtesy of Maria Chiara Scali, MD, Campostaggia Hospital, Siena, Italy. Adapted and modified from Picano et al. [12, 22]. The video is available under the chapter's "Supplementary Material" on Springer Link)

2.4 LUS Response Patterns

The normal pattern is represented by A-lines at rest and at peak stress. The abnormal pattern is represented by A-lines at rest with B-lines in the early recovery phase.

Another abnormal, worsening pattern is represented by B-lines at rest with an increasing number of B-lines at peak stress (Fig. 2.5).

2.5 Coronary Anatomy and Functional Correlates

In an unhealthy cardiovascular response to stress, left ventricular end-diastolic pressure and pulmonary capillary wedge pressure increase, and B-lines may appear or worsen during exercise [24], dobutamine, or vasodilator stress [25]. Patients with stress B-lines have more severe and extensive coronary artery disease [25]. In patients with heart failure and reduced ejection fraction, the number of peak stress B-lines is tightly correlated with indices of functional severity such as peak oxygen consumption ($R = -0.90$) or resting cardiac natriuretic peptide values ($R = 0.88$) [6]. Patients with more stress B-lines also show more frequently severe mitral insufficiency, pulmonary hypertension, abnormal increase in systolic blood pressure during stress, and left ventricular systolic or diastolic dysfunction [25, 26].

In patients with valvular heart disease, more stress B-lines indicate a higher valvular gradient during exercise in presence of resting mild-to-moderate mitral stenosis [27] or higher end-systolic volumes during stress in patients with valvular regurgitation [28]. B-lines during stress appear more often in presence of increased values of E/e' in hypertrophic cardiomyopathy [29] or with left atrial volume dilation in heart failure with preserved ejection fraction [30] (Table 2.8).

B-lines can be absent during stress in patients with good exercise tolerance and indicate a lack of pulmonary congestion, for instance, in a patient with dilated cardiomyopathy or non-compacted myocardium (Fig. 2.6).

In general, B-lines can appear during stress for increased pulmonary pressure and/or for a primary change in alveolar-capillary barrier permeability which may occur in apnea divers [31], extreme physiology in high altitude settings [32, 33], or exposure to air pollutants such as fine particulate matter or nitrogen dioxide [34], even in the absence of marked changes in pulmonary wedge pressure.

B-lines are also present in precapillary pulmonary hypertension, with a normal left heart [35]. The increase in systemic venous pressure secondary to right heart failure is a barrier to efficient lymphatic drainage of interstitial lung water which is a normal protection mechanism to keep the interstitium dry, in presence of a small but continuous leak of fluid from the capillary vessel in the alveolar-capillary barrier (see Chap. 10, Fig. 10.2).

Table 2.8 Stress B-lines and their pathophysiological substrate

Coronary artery disease	Myocardial ischemia
Heart failure reduced EF	Global systolic dysfunction (reduced contractile reserve)
Heart failure preserved EF	Increase E/e' (reduced diastolic reserve)
Aortic valve disease	Increased gradient/regurgitation
Mitral valve disease	Increased gradient regurgitation
Extreme physiology	Pulmonary hypertension in high-flow states
High altitude pulmonary edema	Alveolar-capillary barrier disruption
Hypertrophic cardiomyopathy	Increase E/e' and MR, reduced preload reserve
Arterial hypertension	Afterload mismatch for excessive blood pressure rise
Right heart failure	Systemic venous congestion reduces lymphatic drainage

EF ejection fraction, *MR* mitral regurgitation

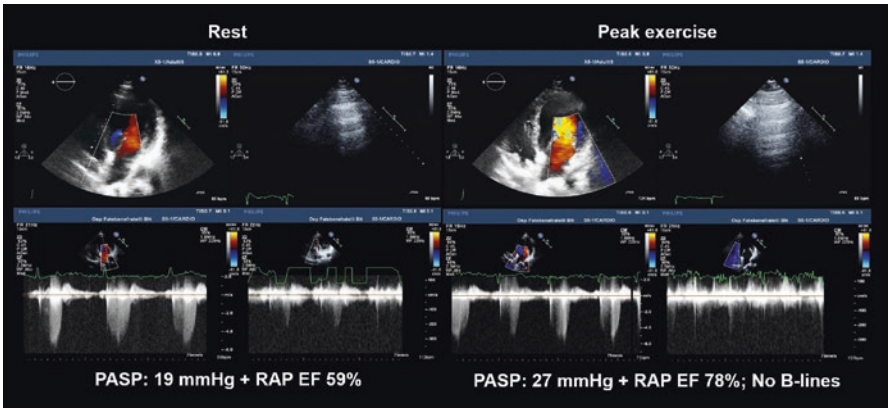

Fig. 2.6 A 32-year-old woman with a non-compacted left ventricle with New York Heart Association class 1. At rest (left panel), normal ejection fraction and normal pulmonary artery systolic pressure. During exercise stress (right panel), the patient shows a normal increase in ejection fraction, normal pulmonary artery systolic pressure rise, and A-lines at rest and during stress. (Courtesy of Quirino Ciampi, MD, Benevento, Italy)

2.6 Outcome Data and Implications for Therapy

The prognostic value of stress B-lines is superior to rest B-lines in predicting all-cause death. Stress B-lines are predictors of outcome independent and incremental to ejection fraction and regional wall motion abnormalities [4, 36–41]. Their prognostic value has been shown in patients with chronic coronary syndromes, heart failure with depressed or preserved ejection fraction, and ischemic mitral regurgitation [6, 20, 30, 42].

The efficacy of a diuretic therapy driven by resting B-lines has been demonstrated in three randomized trials with the number needed to treat five to seven in the setting of heart failure patients [43–47]. In patients with end-stage renal failure in dialysis, therapy driven by B-lines was associated at 24 months of follow-up with a progressive reduction of pulmonary congestion with also a decrease in the hypotensive episodes during dialysis [48]. With diuretics or dialysis in heart failure, B-lines-driven therapy is better than conventional therapy in squeezing the lung softly, with the improvement of outcome. The benefit of B-lines-driven therapy remains to be proven for stress B-lines, which show the theoretical advantage over rest B-lines of mirroring more closely pulmonary congestion during daily activities.

2.7 Tips and Tricks

For the cardiologist, an LUS study must be focused, fast, and factual without imposing excessive additional time, separate reporting, and supplementary billing. We can easily add one more minute to a standard exam to scan the lung for pleural effusion or pulmonary edema.

B-lines reflect the presence of extravascular lung water (for hemodynamic or inflammatory causes) or interstitial fibrosis, but the integration with clinical data and transthoracic echocardiography allows to identify the underlying etiologies and answer the clinical question most of the time [11].

LUS has spread from cardiology to intensive care, from pneumology to nephrology, and from rheumatology to sports medicine. This adds appeal to the technique, but may pose communication difficulties due to heterogeneity of terminology, execution, and reporting, and a better harmonization is needed [7]. In cardiology, the 4-site simplified scan is recommended in SE for time constraints and can be fruitfully applied to resting LUS as a convenient alternative to the 8-zone protocol [11, 15].

B-lines must not be mixed up with Z-lines, which are frequently observed as bundle-shaped reflections arising from the pleural line, but—differently from true B-lines—are ill-defined, less echogenic than the pleural line, short, and do not move in synchrony with respiration [15]. B-lines are not affected by chest wall thickness (the difference between the transducer and the pleural line), which increases the number of A-lines [49]. The image depth can affect the resolution of the image and is usually kept at 16 cm.

B-lines typically originate from the pleural line and are detected by LUS. However, they originate from a high impedance mismatch between a specular reflector like the pleural line and a low impedance reflector like water in the lung. This same biophysical condition can occur, in resting conditions or during stress, with the high impedance pericardial interface and the neighboring lung which becomes full of water replacing air. In this case, B-lines arise from the epicardium and go deeply into the edge of the screen in the surrounding lung. Also, in this case, it is a sign of lung water, which may appear in a few seconds during an ischemic stress test or after a complication such as ventricular fibrillation [50, 51]. Experimentally, pericardial B-lines are sensitive and specific for cardiogenic pulmonary edema in dogs [52].

The detection of the number, size, and shape of B-lines can be affected by many possible factors, from the vendor, imaging technology (native or tissue harmonic), transducer type and frequency, focus level setting, and depth [53]. The same transducer with the same settings should be used at rest and during stress.

2.8 Clinical Guidelines and Recommendations

European Association of Cardiovascular Imaging recommendations for use of pocket-size devices explicitly lists "*semi-quantification of extra-vascular lung water*" with B-lines among the top eight indications [54]. The 2016 guidelines of the European Society of Cardiology on heart failure recommend LUS among diagnostic tests in heart failure (class of evidence 2b, level of recommendation C) as a test that may be considered in patients with acute heart failure for the confirmation of pulmonary congestion and pleural transudate [55]. In patients with suspected acute heart failure, in 2015 it was recommended by the European Society of

Cardiology as a first-line diagnostic test to assess pulmonary congestion, since "*in reasonably expert hands it can be equally or more informative than chest X-ray allowing also an important time-saving*" [56]. The 2017 expert consensus of the acute heart failure group of the European Society of Cardiology concluded that "*transthoracic echocardiography and LUS can assist in the rapid assessment of patients with acute dyspnea and hypotension and have the potential to transform how the clinicians assess and manage critically ill patients with acute heart failure and cardiogenic shock*" [57].

According to the 2017 joint European Association of Cardiovascular Imaging and American Society of Echocardiography recommendations, during exercise SE the acute increase in B-lines detected by LUS is a feasible way of demonstrating that the symptom "*dyspnea when exercising*" is related to pulmonary congestion due to heart failure [57].

According to the universal definition of heart failure proposed by the European Society of Cardiology in 2021, the diagnosis is based on the presence of symptoms and signs of heart failure corroborated by (elevated natriuretic peptides or) objective evidence of cardiogenic pulmonary (or systemic) congestion [58]. B-lines assessed at rest and (at an earlier stage) during stress can therefore become essential for the diagnosis of heart failure, titrate severity, assess the effects of therapy, and refine risk stratification. Today no SE will be considered complete without a short but efficient assessment of the lung B-lines during stress [59]. With Sharon Mulvagh, "*Stress LUS provides us with an immense opportunity to prognosticate and phenotype our patients with heart failure, valvular disease, and coronary artery disease by using their hemodynamic response to exercise. LUS is making a splash in the incoming tidal wave of heart failure. And as this tide of lung water rises, we are now ready and vigilant, with a probe in hand!"* [60]. Assessment of B-lines with the 4-site simplified scan is now the recommended standard of practice in all patients referred to SE according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [61].

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Step C for Cardiac Reserve in Stress Echocardiography

3

Tonino Bombardini and Eugenio Picano

Keywords

Contractile reserve · End-diastolic volume · End-systolic volume · Preload reserve

3.1 Pathophysiology: From Cardiac Molecules to Ventricular Volumes

Left ventricular (LV) contractility is "the inherent capacity of the myocardium to contract independently of changes in the preload or afterload" according to the definition by Lionel Opie [1]. The assessment of contractility remains important to identify a primary defect of the intrinsic myocardial force of contraction from an extrinsic change in loading conditions producing the same effect on cardiac performance [2]. At the molecular level, cardiac calcium handling is essential for the normal cardiac excitation-contraction coupling, and the failing heart shows a profound derangement of intracellular calcium handling through altered kinase activity [3] with impairment in cardiac contractility and arrhythmogenesis (Fig. 3.1).

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T. Bombardini (✉)
Clinic of Cardiovascular Diseases, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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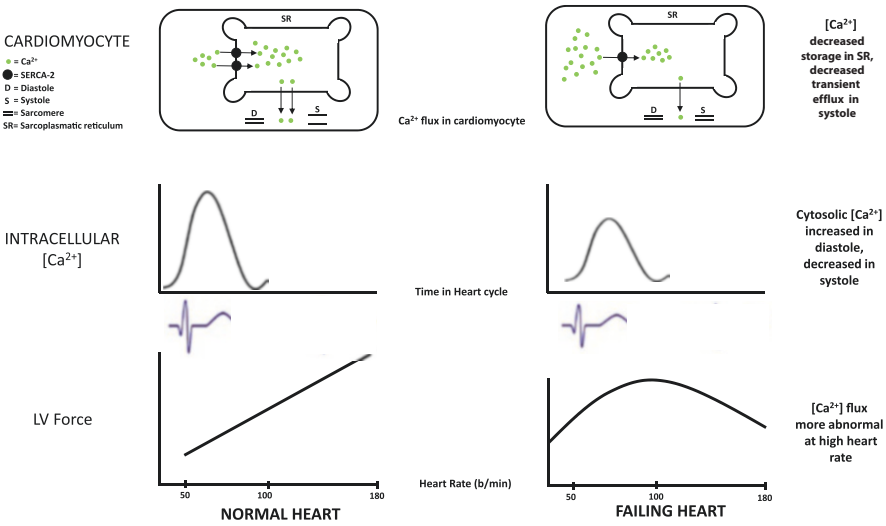

Fig. 3.1 Left: normal heart. Right: failing heart. Upper panels: the myocytes of the failing heart show depressed SERCA activity with diminished calcium reuptake and storage in the sarcoplasmic reticulum in diastole and diminished release in systole. Middle panels: the intracellular calcium transients are markedly abnormal in myocytes from the failing heart (right). Lower panels. The relationship between heart rate (x-axis) and force (y-axis) in vivo. The force-frequency relationship peaks at a high heart rate in normal conditions, but falls at a low heart rate in the failing heart. (Adapted from Bombardini T, US patent 6859, 662 B2, February 22, 2005. See corresponding Video 3.1, Courtesy of Dr. Tonino Bombardini and Monica Zoppè, B Sc [2]. The video is available under the chapter's "Supplementary Material" on Springer Link)

In the transition from the normal heart to the failing heart, gene expression changes from the adult pattern to that of fetal life. The sarcoplasmic reticulum calcium ATPase (SERCA) is depressed in function and expression. The sarcolemmal sodium-calcium (Na^+/Ca^{2+}) exchanger is increased, but enhanced Na^+/ Ca^{2+} exchange instead of sarcoplasmic reticulum Ca^{2+} reuptake is an energy-wasting process. This molecular process takes place for each contraction unit of the cardiac myocyte, the sarcomere [4]. The sarcomere length in diastole is around 2 mm and shortens in systole to 1.80 mm. The initial sarcomere length is linked to cardiac performance through the Starling mechanism. The increased sarcomere length leads to an increased force generation of sarcomeres, and therefore to increased LV pressure in the normal, not in the failing, heart.

In vivo, we cannot measure sarcomere length at end-diastole and SERCA activity in the myocyte. As a surrogate of sarcomere length and preload, we measure the end-diastolic volume (EDV) of the left ventricle. As a surrogate of SERCA activity and intrinsic contractility, we measure force as systolic blood pressure (SBP)/end-systolic volume (ESV). The relationship between cardiac performance and EDV is linear, and the slope of this line represents contractility.

In this simplified framework, volumetric echocardiography, a cuff sphygmomanometer, and a one-lead electrocardiogram are the simple way for assessing preload reserve, myocardial contractility, and chronotropic response during stress.

Two-dimensional quantitative volumetric echocardiography allows measurement of LV EDV and ESV, and related indices of LV function such as ejection fraction (EF) and stroke volume. The information supplied by these volumetric indices is complementary and partially independent. EF is a chimeric index, a hybrid of form and function, being the ratio between stroke volume that measures function and EDV that measures form [5]. EF is also dependent on afterload, preload, and heart rate. Simultaneous values of SBP, EDV, and heart rate should be reported to place EF values in context. Volumetric echocardiography during stress provides an integrated view of preload reserve through EDV recruitment and contractile reserve as the reduction in ESV. The cardiac reserve is defined as an adequate increase in cardiac output during stress and requires adequate contractile reserve, preload reserve, and chronotropic reserve. Sarcomere contraction leads to shortening of the left ventricle along its long axis and around its circumference, which then results in radial thickening. Strain quantifies the deformation in the longitudinal, circumferential, and radial directions. Since the EF is more affected by circumferential (radial) than longitudinal (long-axis) strain, a normal EF can be observed when the longitudinal function (global longitudinal strain) is already abnormal but the circumferential strain is normal or even supranormal.

ESV is a functional parameter, linked to calcium uptake and reuptake during contraction, and mirrors the activity of the SERCA-2 molecule [6]. EDV is more a morphologic parameter, linked to the ideal sarcomere length [7].

Together, LV EDV and ESV allow separation of the mechanisms of reduced preload and reduced contractile reserve and may complement an index of global function such as EF or global longitudinal strain (Table 3.1).

A critical reduction in cardiac output during stress is due to any possible combination of reduction in heart rate, preload reserve, or contractile reserve. The normal heart progressively increases heart rate and decreases ESV during stress, with an increase in force, EF, and EDV (Fig. 3.2).

Table 3.1 The information on volumetric SE beyond EF

	ESV	EDV
Physiologic parameter	Contractile reserve	Preload reserve
Conceptual value	Function	Form
Cell view	SERCA-2 activity	Sarcomere length
Normal stress response	Decrease	Increase (at low HR)
Physiology companion	Cuff SBP (for LV force)	B-lines (for LVEDP)
Abnormal response	Increase	Unchanged
Decreases variability	UEA, RT3D, AI	UEA, RT3D, AI

AI artificial intelligence, *EDV* end-diastolic volume, *ESV* end-systolic volume, *HR* heart rate, *LVEDP* LV end-diastolic pressure, *RT3D* real-time 3-dimensional echocardiography, *SBP* systolic blood pressure, *SV* stroke volume, *UEA* ultrasound-enhancing agents

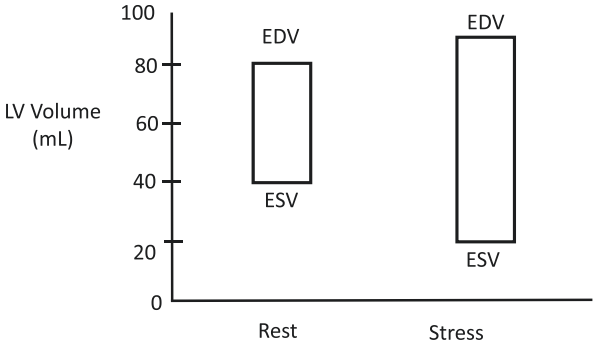

Fig. 3.2 The physiologic response of EDV and ESV during stress. EDV increases, ESV decreases, and stroke volume increases during stress

Table 3.2 The information on volumetric SE beyond EF

Parameter	Definition	Normal range, units
Stroke volume (SV)	EDV–ESV	60–100 mL/beat
Cardiac output (CO) rest	SV * HR	4.0–8.0 L/min
Cardiac output (CO) peak	SV * HR	13.2 ± 3.5 L/min
Cardiac index (CI)	CO/BSA	2.5–4.0 L/min/m^2
Cardiac index reserve (CIR)	CI stress – CI rest	3.9 ± 1.4 L/min/m^2
Cardiac power output I (CPOI)	CI*MAP* 451^{-1}	0.5–0.7 Watts/m^2
Force (elastance)	SBP/ESV	3–5 mmHg/mL

EDV end-diastolic volume, *ESV* end-systolic volume, *HR* heart rate, *MAP* mean arterial pressure, *SBP* systolic blood pressure

The diseased heart reaches a critical heart rate during stress when ESV and force decline after an initial rise. The lower the critical heart rate, the more severe the disease. A very diseased heart shows a blunted response with no reduction in ESV and no increase in force during the stress. From raw measurements of EDV and ESV coupled with elementary parameters such as heart rate and SBP, stress echocardiography (SE) allows a more profound insight into the cardiac pump than the simple regional wall motion abnormality (RWMA) and EF. The main parameters useful for noninvasive hemodynamics are summarized in Table 3.2. All these parameters can be easily collected at rest and during stress. ESV depends on the contractile state of the left ventricle and, when combined with SBP, is termed elastance or force, which is a load-independent index of contractility [4, 5].

LV contractile reserve can also be obtained as the increase from rest to stress in EF or quantitative, geometry-independent global longitudinal strain [8, 9]. According to Marwick 2022, "perhaps the best way to integrate the role of loading in the evaluation of LV function is to ensure that the measurement of blood pressure should be included in imaging studies that could be used clinically to estimate contractility" [10]. Force does that.

The assessment of global LV function at rest and during stress may also identify a hypercontractile phenotype, with an increased LV EF at rest, which is associated with an unfavorable outcome in the long term [11, 12].

3.2 Methodology

LV volumes are obtained at rest and during stress to assess LV function, preload, and contractile reserve (Fig. 3.3).

The time sequence of acquisition and recordings is shown in Table 3.3.

The method of disks requires biplane views, which are feasible and of good quality in most but not all patients [13]. Simpler methods are less accurate for absolute measurements, but equally accurate for the evaluation of relative changes; when the Simpson method is not feasible, an apical single-plane or even the linear

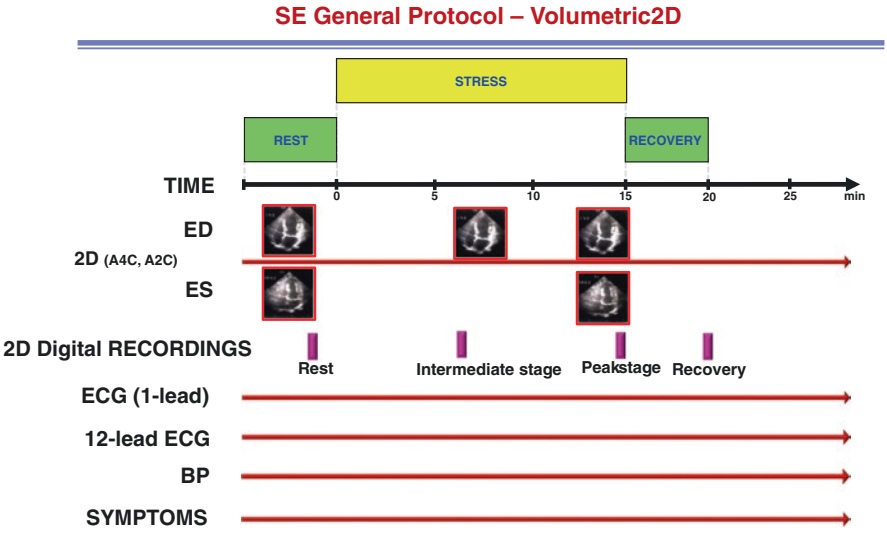

Fig. 3.3 The protocol for volumetric SE. Step A (regional wall motion) and step C (global LV function) require the very same images, and for LV volume measurements, the apical views (4-chamber and 2-chamber) are ideally required, although in selected cases with suboptimal imaging a single plane apical four-chamber view or a parasternal view (with the linear method) is sufficient. Digital recordings are required at rest and peak stress, and also at intermediate stages when the LV dilation is highest (around 10 to 15%) before diastole shortens substantially at higher heart rates and LV filling decreases. *BP* blood pressure, *ECG* electrocardiogram, *SE* stress echocardiography

Table 3.3 Acquisition in volumetric SE

		Rest	Stress-intermediate	Stress-peak	Recovery
	Time (min)	TTE	0–10	11–15	16–20
2D	A4C, 2C	v	v	v	v
ECG, 1-lead	Echo monitor	v	v	v	v
ECG, 12-lead	ECG monitor	v	v	v	v
BP	Sphygmo	v	v	v	v
Symptoms	Patient	v	v	v	v

A4C apical 4-chamber, *A2C* apical 2-chamber, *TTE* transthoracic echocardiography

Teichholz method can be employed. This increase allows the assessment of LV volumes in virtually all patients even when image quality is suboptimal. After volumes are measured, EF or force can be derived. The identification of the endocardial contour of the left ventricle can be easier, faster, and more precise with ultrasound-enhancing agents [14]. As technology evolves allowing high frames rates during stress, volumetric SE will become routine with real-time three-dimensional echocardiography, especially with vasodilator stress which only mildly increases the heart rate and therefore does not degrade image quality too much due to the low frame rate of three-dimensional echocardiography, as it may happen during exercise or high dose dobutamine [15–21]. Artificial intelligence allows operator-independent assessment of LV volume changes during stress [22] (Fig. 3.4). All three methods can be combined with contrast real-time three-dimensional echocardiography images elaborated with artificial intelligence to reach better accuracy and operator independence.

The physiologic companion of ESV is SBP by cuff sphygmomanometer (or arterial tonometer) used to calculate force as the ratio of SBP divided by ESV [23]. The physiologic companion of EDV is *E*/*e′* (a proxy of LV end-diastolic pressure) used to calculate LV stiffness as the ratio of *E*/*e′* divided by EDV. The values identifying a normal response are stress-specific since exercise and dobutamine (normal value of force-based LV contractile reserve >2.0) are stronger inotropic stresses than vasodilators (normal value of force-based LV contractile reserve >1.1). LV contractile reserve can be assessed with stress-rest variation in EF or more quantitative global longitudinal strain, or more load-independent LV force (Fig. 3.5).

During exercise, EDV initially increases to sustain the increase in stroke volume through the Frank-Starling mechanism [24], and later falls at high heart rates.

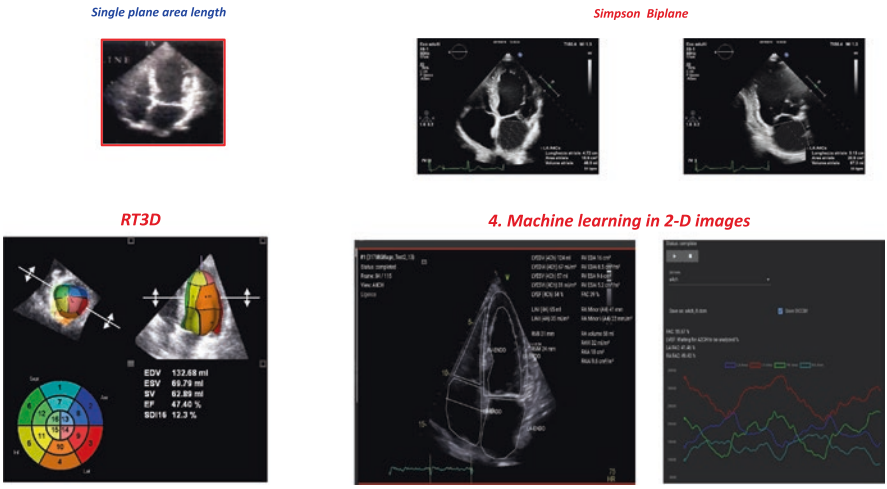

Fig. 3.4 Methodology of measurement of EDV and ESV. Single plane (upper left), biplane (upper right), real-time three-dimensional echocardiography (lower left), and artificial intelligence with two-dimensional images (lower right, courtesy of Ligence Heart, dr. Arnas Karuzas, Kaunas, Lithuania)

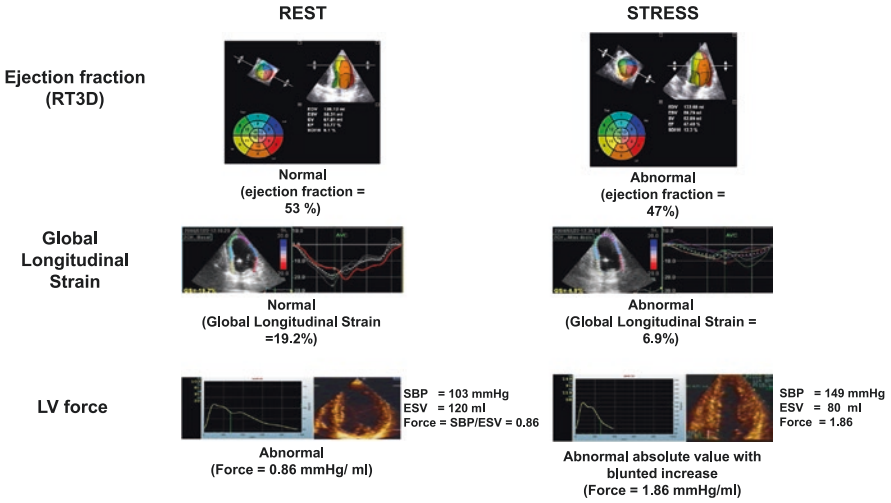

Fig. 3.5 The assessment of LV contractile reserve at rest (left side) and during stress (right side) with EF by real-time three-dimensional echocardiography (upper panel), global longitudinal strain (middle panel), and force (lower panel) in three different patients. The upper panel shows a normal EF at rest and an abnormal value during stress. The middle panel is a normal global longitudinal strain at rest with abnormal values during stress. The lower panel illustrates a patient with abnormal force at rest and a blunted increase during stress

3.3 The Main Signs of Normal and Abnormal Contractile Reserve

The volumetric response to stress is remarkably consistent with all stresses, with the normal pattern characterized by an increase in EDV and a reduction in ESV during stress, with an increase in EF and stroke volume. The abnormal pattern is characterized by unchanged EDV and unchanged-decreased ESV, with a blunted increase or even decrease in EF and stroke volume (Table 3.4). Changes in EDV are better assessed at the intermediate stage with exercise and dobutamine, when less tachycardia is present.

The contractile response can be combined with the regional wall motion response for the identification of different response patterns.

The normal pattern is characterized by the absence of ischemic RWMA and ESV reduction during stress. ESV decrease is more marked with exercise and dobutamine and less marked with vasodilators (Fig. 3.6).

The global response is clinically more important in patients with moderate-to-severe resting LV dysfunction. The responder pattern is characterized by an increase in EF, Force, and usually a reduction in LV volumes associated, during vasodilator stress, with an increase in coronary flow velocity reserve (Fig. 3.7).

The nonresponder pattern is characterized by the lack of increase in EF and Force. LV volumes remain unchanged. The contractile reserve can be evoked by

Table 3.4 Left ventricle volumetric, contractile, and chronotropic responses during stress

	EDV	ESV	EF	SV
Normal	Increase	Decrease	Increase	Increase
Abnormal	Unchanged	Increase	Decrease	Decrease

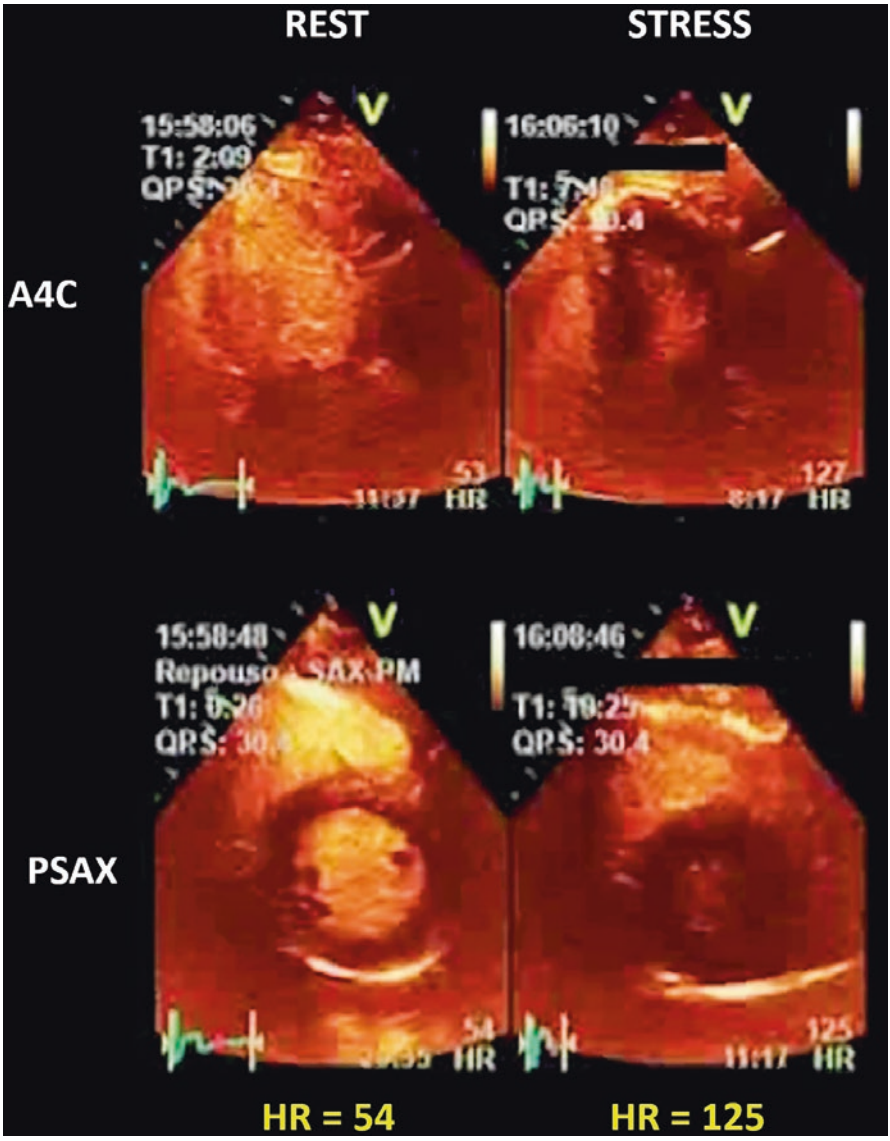

Fig. 3.6 The normal response of a nonischemic and strong heart. Apical 4-chamber (upper panels) and parasternal short-axis view at the mid-papillary level (lower panels) showing normal wall motion at rest and marked reduction of the end-systolic area at peak dobutamine stress with an ultrasound-enhancing agent. See corresponding Video 3.2. (By courtesy of Dr. Josè Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

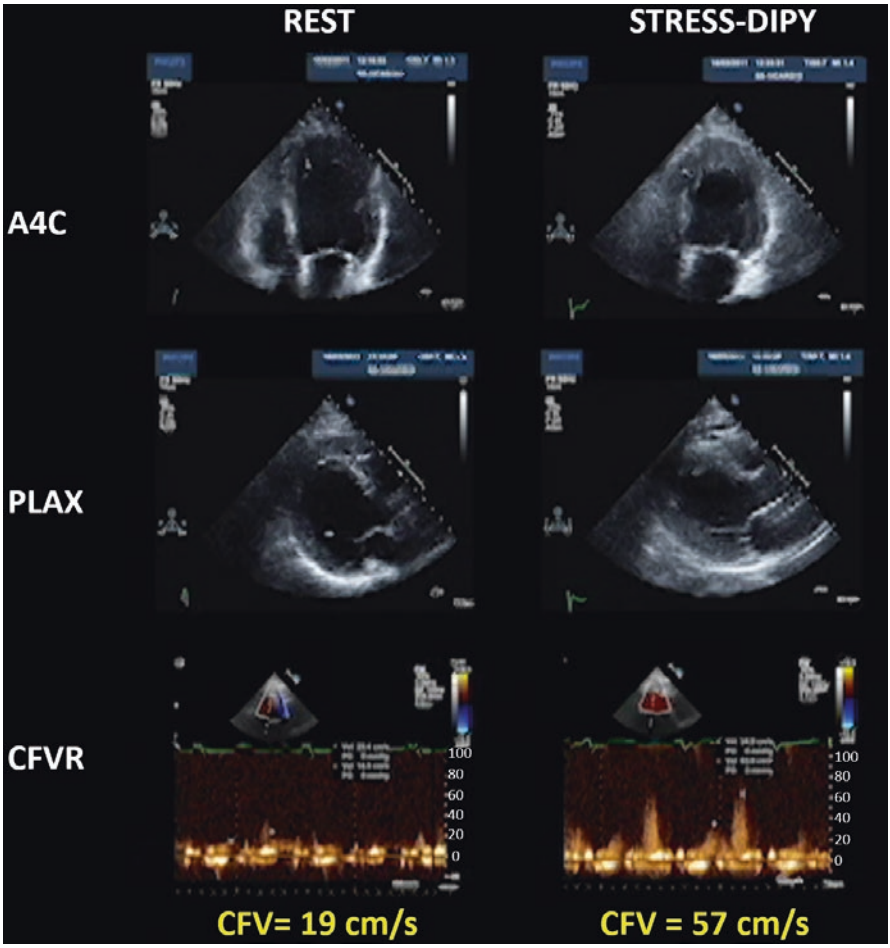

Fig. 3.7 The responder pattern of a nonischemic heart with severe LV dysfunction at rest. Apical 4-chamber view showing the end-systolic frames of a dilated left ventricle at rest (left panel) which increases function and reduces ESV during dipyridamole stress (right panel). The corresponding coronary flow pattern shows a normal coronary flow velocity reserve in the left anterior descending coronary artery. See corresponding Video 3.3. (By courtesy of Dr. Quirino Ciampi, Benevento, Italy. The video is available under the chapter's "Supplementary Material" on Springer Link)

dobutamine or vasodilator stress. During vasodilator stress, the lack of contractile reserve is usually matched by a blunted coronary flow velocity reserve (Fig. 3.8).

Another abnormal pattern found in presence of myocardial scar or necrosis, in absence of inducible ischemia, is a normal regional wall motion with ESV dilation during stress [24]. The most abnormal pattern is characterized by an ischemic and weak heart, with stress-induced RWMA and marked ESV dilation during stress. The global response of the left ventricle is best assessed at all steps of exercise or pacing, or other stresses by identifying the critical heart rate, i.e., the heart rate when force starts to drop. The force-frequency relationship is steep and upsloping in normal, biphasic (with a peak at critical heart rate) in diseased, and flat in very diseased failing hearts [25].

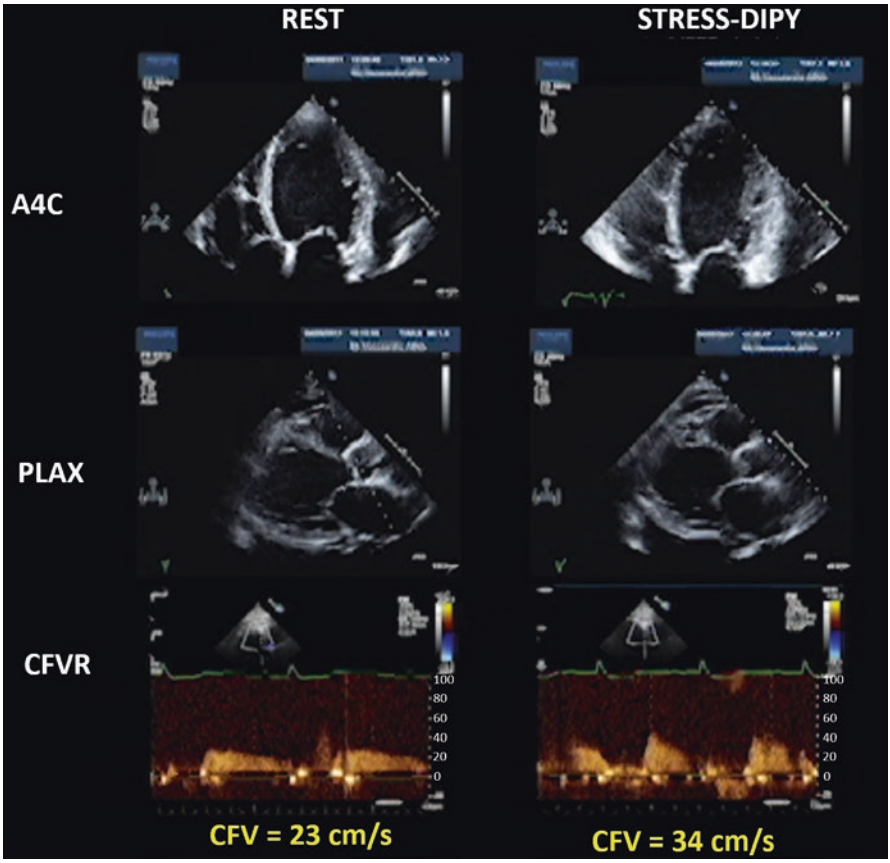

Fig. 3.8 The nonresponder pattern of a nonischemic heart with severe LV dysfunction at rest. Apical 4-chamber view showing the end-systolic frames of a dilated left ventricle at rest (left panel), with unchanged function and ESV during dipyridamole stress (right panel). The corresponding coronary flow pattern shows a reduced coronary flow velocity reserve in the left anterior descending coronary artery. See corresponding Video 3.4. (By courtesy of Dr. Quirino Ciampi, Benevento, Italy. The video is available under the chapter's "Supplementary Material" on Springer Link)

3.4 Coronary Anatomic, Functional, and Prognostic Correlates

In a healthy cardiovascular response, LV ESV decreases, EDV increases at least during the early stages of stress, and stroke volume increases. In an unhealthy cardiovascular condition, LV ESV increases, EDV remains unchanged or decreases, and stroke volume fails to increase adequately [24].

In presence of inducible RWMA, the mere LV cavity dilatation during SE will be pointing towards multivessel disease and/or left main disease and worse prognosis [25–30]. However, LV dilation during stress can occur independently of underlying

coronary artery disease and inducible ischemia and may reflect a myocardial disease [31, 32].

In patients who were studied in brain death as potential heart donors and subsequently underwent cardio-autopsy verification, the impaired LV contractile reserve even in absence of RWMA was associated with severe coronary artery disease or extensive fibrosis or necrosis of the left ventricle [33].

The prognostic value of LV contractile reserve is independent of RWMA and EF [34–40]. There is more than RWMA in the LV response for phenotypic characterization of the stress response. The information beyond RWMA and wall motion score index can be captured with the evaluation of cardiac power (cardiac output and SBP) or cardiac power mass (cardiac output normalized for LV mass) or cardiac reserve index (stress to rest variation in cardiac index). Whatever the preferred approach, the prognostic information of the global LV mechanics is independent and incremental to RWMA and EF [41].

The combination of LV contractile (ESV), preload (EDV), and chronotropic (heart rate) reserve allows the hemodynamic phenotyping in the individual patient, identifying the specific hemodynamic alteration in cardiac output which may occur even in absence of inducible myocardial ischemia [42]. Every heart with abnormal cardiac reserve is abnormal in its way, and this hemodynamic phenotyping could be useful to tailor a specific therapy (Fig. 3.9).

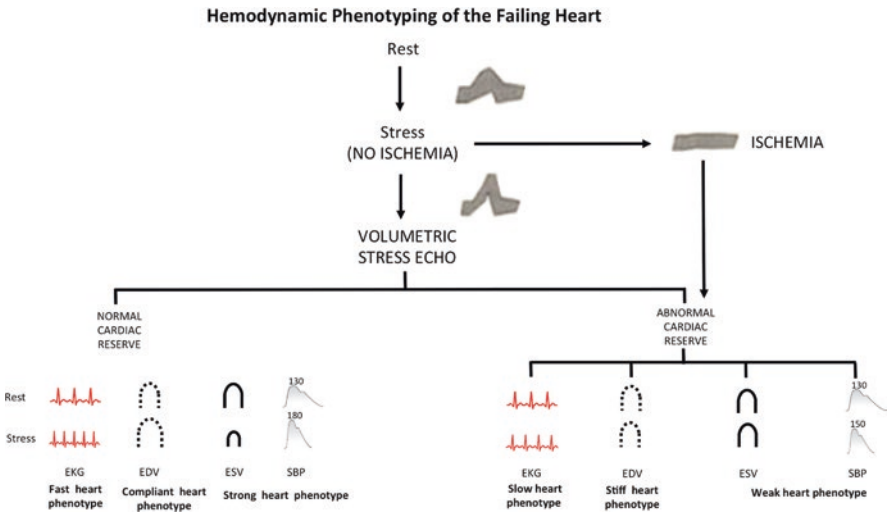

Fig. 3.9 Hemodynamic phenotyping of the failing heart by SE. SE easily allows identifying myocardial ischemia as RWMA often associated with abnormal cardiac reserve (upper panel). However, a normal response of regional wall motion can also be associated with abnormal cardiac reserve, possibly due to the isolated or combined presence of distinct phenotypes: "slow heart" with chronotropic incompetence; "stiff heart" with impaired preload reserve; "weak heart" with blunted LV contractile reserve. Each phenotype might be identified for an effective personalized treatment. (Adapted from original data of Prof. Tonino Bombardini, Banja Luka, Bosnia-Herzegovina, Journal Clinical medicine 2021 [42])

3.5 Tips and Tricks

Only representative cycles with optimal endocardial visualization are measured for EDV and ESV. The endocardial border is traced, excluding the papillary muscles. The frame captured at the R wave of the electrocardiogram is considered to be the end-diastolic frame, and the frame with the smallest LV silhouette is the end-systolic frame. Images are obtained in the same position (semi-supine or upright) for each patient at baseline at peak stress. Cuff SBP is recorded at the time of volume measurements. In principle, the concept of force can be applied to the right ventricle, with volumes measured by three-dimensional echo and pulmonary artery systolic pressure from tricuspid regurgitant jet velocity or acceleration time [41].

3.6 Clinical Guidelines and Recommendations

EDV, ESV, and EF are part of the minimum data set recommended during SE for the detection of coronary artery disease and outside coronary artery disease [43]. However, analysis is usually qualitative with side-by-side comparison, without measurement. As a result, mostly qualitative patterns have been identified, with the normal response characterized by an increase in EDV and a decrease in ESV during stress, with an increase of EF. The degree of these changes varies with individual stresses, with the reduction in ESV and increase in EF more marked with dobutamine and exercise (with an abnormal cutoff <5%) than with vasodilators and atrial pacing. The abnormal pattern during stress is the lack of increase in EDV, dilation (rather than reduction) of ESV, and a blunted increase in EF leading to a reduction of cardiac functional reserve. More quantitative information is needed to provide stronger support to phenotyping based on volumetric SE and this can be easily done with hand-made measurements of Simpson's rule or with measurements based on artificial intelligence on two-dimensional or three-dimensional images. In the normal response, the increase in EDV is considered by 2020 American Society of Echocardiography recommendations as more marked in treadmill compared to the small increase in supine bicycle and the decrease observed with dobutamine, vasodilator, and pacing [43]. The change in EDV during exercise is about 10 to 20% in early, intermediate steps of supine exercise and therefore comparable to a treadmill. EDV also increases or remains unchanged after dipyridamole or early stages of dobutamine and pacing. When high heart rates are reached, the time for LV filling is critically reduced, and EDV is reduced.

The pattern of changes is more homogeneous with ESV which consistently decreases with all stresses, although more markedly with stronger inotropic stresses (exercise and dobutamine). The abnormal pattern can occur independently of ischemia since changes in volumetric global response can be due to myocardial scar (fibrosis) or necrosis, or even limited ischemia or infarction not reaching the critical myocardial mass necessary to induce regional dysfunction. With or without a concomitant RWMA, the preserved cardiac reserve is associated with a more benign prognosis. Assessment of EDV and ESV with quantitative volumetric

echocardiography is now the recommended standard of practice in all patients referred to SE according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [44].

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Step D for Doppler-Based Coronary Flow Velocity Reserve in Stress Echocardiography

4

Fausto Rigo and Eugenio Picano

Keywords

Adenosine · Coronary flow reserve · Dipyridamole · Endothelial function · Left anterior descending artery · Microcirculation

4.1 Pathophysiology

The seminal concept of coronary flow reserve (CFR) was proposed experimentally by Gould in 1974 [1]. Under normal conditions, in the absence of stenosis, coronary blood flow can increase approximately four- to sixfold to meet increasing myocardial oxygen demands. This effect is mediated by vasodilation at the arteriolar bed, which reduces vascular resistance, thereby augmenting coronary flow and flow velocity. The CFR is the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demand and can be expressed by the difference between the hyperemic flow and the resting flow curve. In most clinical applications, hyperemia is induced pharmacologically, not via an increase in oxygen demand, and coronary flow velocity reserve (CFVR) is measured as a proxy of true CFR. A combined anatomical and physiological classification can ideally identify four separate segments

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F. Rigo (✉)
Division of Cardiology, Foundation Villa Salus Hospital/IRCCS San Camillo, Venice, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

E. Picano (ed.), *Stress Echocardiography*,
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in the hyperemic curve (Fig. 4.1): (1) The hemodynamically silent range of 0–40% stenosis, which does not affect CFR (>2.5) to any detectable extent. (2) The clinically silent zone, where stenosis ranging from 40 to 70% may marginally reduce the CFR without reaching the critical threshold required to provoke ischemia with the usual stresses. (3) The severe stenosis range (70–90%), where critical stenosis reduces CFR to less than 2.0, and myocardial ischemia is usually elicited when stress is applied. (4) The very severe stenosis range (>90%), producing a marked trans-stenotic pressure drop at rest, with a reduction of baseline myocardial blood flow and a CFR close to 1, or even less; in these patients, the administration of a coronary vasodilator decreases the post-stenotic flow for steal phenomena.

This experimental paradigm can be accurately reproduced clinically in a highly selected series of patients with single-vessel disease, no myocardial infarction, no coronary collateral circulation, normal baseline function, no left ventricular hypertrophy, no evidence of coronary vasospasm, and who are off therapy at the time of testing. In these patients, the more severe the stenosis, the more profound the impairment in CFR. The correction of the stenosis improves CFR, and perfect dilation normalizes the CFR. The predictable relationship found in the experimental animal and a very selected patient population [2] is not found in the clinical arena [3], where many variables can modulate the imperfect match between epicardial coronary artery stenosis and CFR. Among others, these variables include factors related to coronary stenosis (geometric characteristics, length of stenosis), factors related to coronary circulation (coronary collaterals), factors related to the myocardium (left ventricular hypertrophy, left ventricular scar or necrosis, extravascular compressive forces), and factors related to microvascular (organic or functional) disease, from coronary small vessel stenosis (with increased wall to lumen ratio or vessel rarefaction) to coronary small vessel vasospasm.

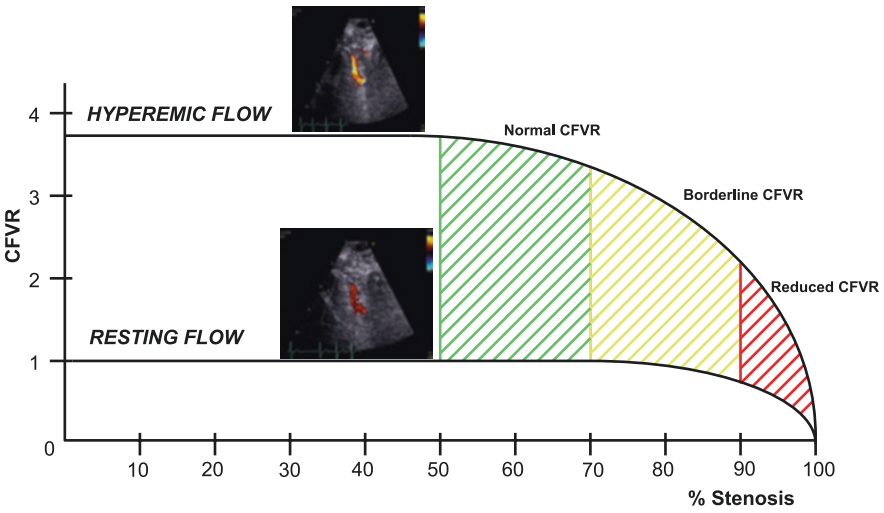

Fig. 4.1 The curve of CFR with the four segments: hemodynamically silent (0–40% stenosis); clinically silent (40–70% stenosis); hemodynamically significant (70–90% with CFVR<2.0); and very severe stenosis (>90%, with CFVR<1.0). (Redrawn and adapted from Gould [1])

The coronary microvascular function can be abnormal in absence of coronary artery disease (CAD) and even in absence of heart disease. The derangement of microvascular function is possibly due to low-grade inflammation and increased systemic oxyradical stress. Coronary microvascular dysfunction is highly prevalent and associated with adverse clinical outcomes. It is a common mechanism of disease initiation and progression, involved in coronary, myocardial, and valvular heart disease, chronic and acute transplant rejection, and systemic rheumatologic disease [4]. The pathophysiological mechanisms of coronary microvascular disease are multiple and heterogeneous. Coronary microvascular dysfunction is an intermediate end-point, a long-term prognostic predictor, and a potential therapeutic target in many cardiac and extracardiac conditions, from CAD to nonischemic heart failure (Table 4.1).

More than one mechanism can be present in several conditions, including CAD or hypertrophic cardiomyopathy. The finely autoregulated coronary microvascular function is also impaired at an early stage in several extra-cardiac conditions, from cancer to dementia, possibly as the sign of an early derangement of low-grade chronic systemic inflammation and unbalance of the redox equilibrium impairing the vasodilatory capacity of the coronary small vessels. The usual index vessel to assess the health of the endothelium is the forearm, but changes in the forearm are only loosely related to the condition of the endothelium in the coronary bed, which can be directly assessed during stress echocardiography (SE). It is usually stated that the endothelial bed covers an area as large as a soccer pitch. With CFVR in the index vessel of the left anterior descending (LAD) artery, we assess the health of the microcirculation in the critically important penalty box of the vascular soccer field, affected by many different conditions (Fig. 4.2).

Coronary flow velocity (CFV) by Doppler is biphasic, with a lower peak during systole due to the effect of myocardial contraction which increases extravascular resistances (Fig. 4.3).

The flow velocity variations are proportional to the total blood flow if the diameter of the vessel lumen is kept constant. CFV can be used not only to assess vasodilation,

Table 4.1 Mechanisms of coronary microvascular disease

	Structural	Functional	Intravascular	Extravascular
AS	Rarefaction			
Systemic sclerosis	Perivascular fibrosis			
Hypertension	Remodeling			
INOCA-microvascular		Reduced vasodilation		
INOCA-vasospastic		Increased vasoconstriction		
Acute heart rejection		Reduced vasodilation		
ACS			Embolization	
LVH				Increased extraluminal resistances

ACS acute coronary syndromes, *AS* aortic stenosis, *INOCA* ischemia with angiographically normal coronary arteries, *LVH* left ventricular hypertrophy. Microvascular remodeling for the increased wall-to-lumen ratio of coronary arterioles

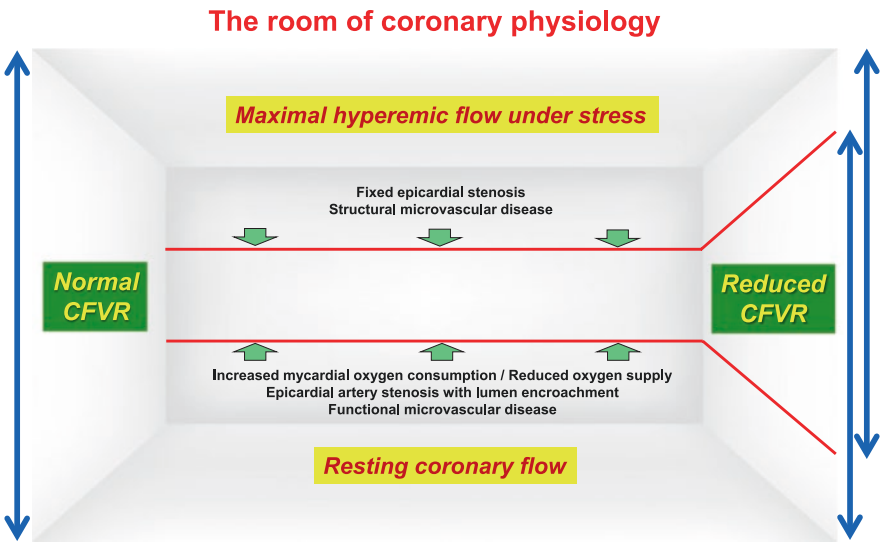

Fig. 4.2 Common causes of CFVR reduction. The many possible causes of CFVR reduction, also beyond coronary artery stenosis. The same reduction of CFVR can be due to reduced peak stress flow or increased resting flow. The reduction of peak stress flow is suggestive of structural coronary microvascular disease and/or fixed organic coronary stenosis. The increased resting flow is suggestive of functional coronary microvascular disease and/or increased myocardial oxygen demand and/or epicardial artery stenosis encroaching coronary lumen

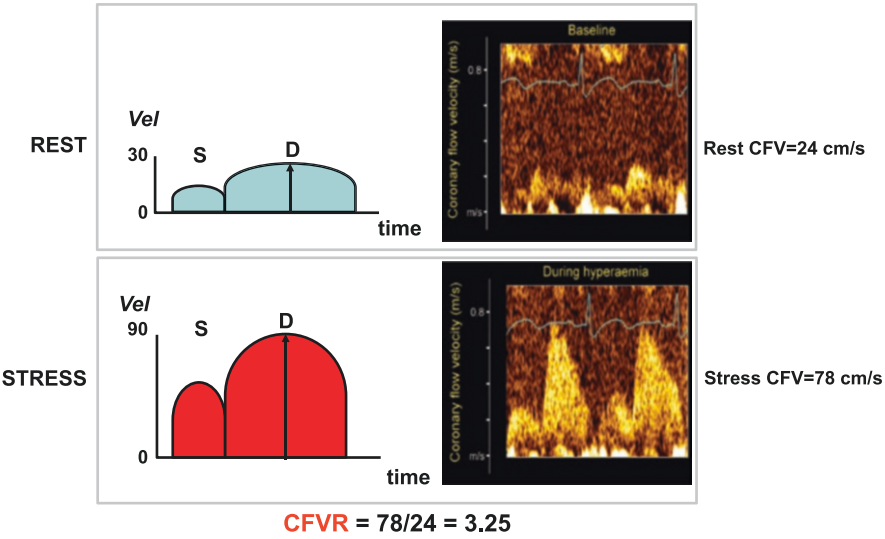

Fig. 4.3 Left panel: schematic representation of CFV profile obtained with transthoracic Doppler of the mid-distal LAD and measurement of the CFVR through peak diastolic flow velocity. The coronary blood flow velocity is higher in diastole. Right panel: the pulsed Doppler tracing obtained at rest and peak vasodilator stress. CFVR is the ratio of peak-to-rest values. (By courtesy of dr. Lauro Cortigiani, Lucca, Italy)

but also coronary vasoconstrictive reactivity at the microvascular level after appropriate stimuli such as hyperventilation, ergonovine, or cold pressor test [5].

4.2 Methodology

CFVR can be obtained with semi-invasive transesophageal [6, 7] or, more conveniently, with noninvasive transthoracic echocardiography (TTE), which shows an excellent correlation with invasive Doppler methods [8] or noninvasive quantitative methods such as positron emission tomography [9]. A high-frequency pediatric probe or broadband transducer (2–7 MHz) is used [10].

Besides the classic projections for SE testing, specific projections for LAD coronary artery imaging are integrated into the cardiac imaging sequence [11]. The mid-distal LAD is searched from the low parasternal long-axis view and/or modified apical 4-, 3-, or 2-chamber view under the guidance of color-Doppler (Fig. 4.4).

The posterior descending artery can be imaged with dedicated imaging projections, but with greater difficulty and a lower success rate, around 85% at rest (Fig. 4.5).

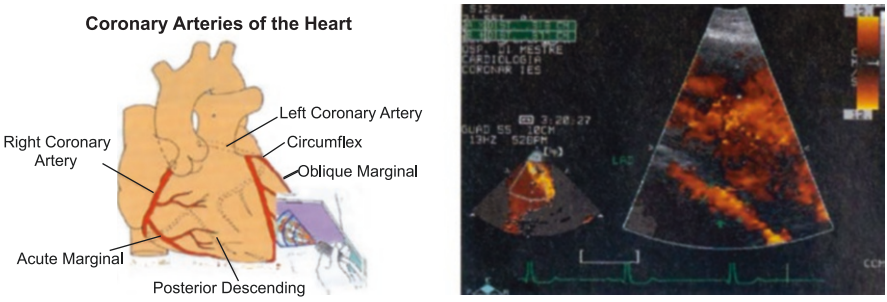

Fig. 4.4 *Left panel*: Artist's drawing illustrating transducer beam orientation to the LAD coronary artery. The mid-distal tract is imaged from a modified apical 2-chamber view. *Right panel*: The corresponding echocardiographic image of LAD color flow

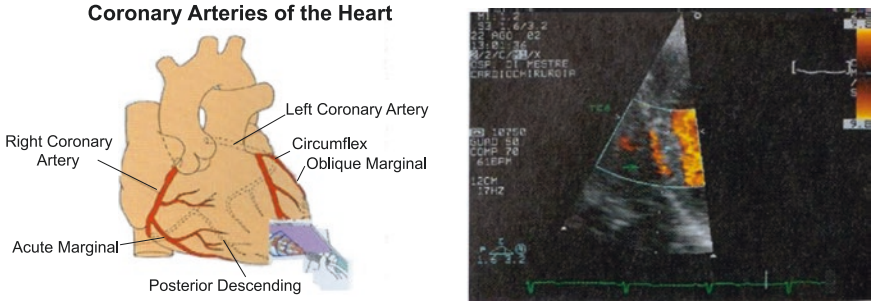

Fig. 4.5 *Left panel*: Artist's drawing illustrating transducer beam orientation to the posterior descending coronary artery. The mid-distal tract is imaged from a modified apical 2-chamber view with counterclockwise rotation and anterior angulation of the probe. *Right panel*: The corresponding echocardiographic image of posterior descending color flow

The success rate is lower for the left circumflex artery, around 80% at rest (Fig. 4.6).

Color Doppler flow mapping is therefore the first step for LAD imaging (Fig. 4.7).

In the best scenario, LAD is visualized throughout the cardiac cycle (Fig. 4.8).

In the usual scenario, LAD is intermittently visualized during diastole (Fig. 4.9).

With the evolution of technology and the use of multifrequency transducers combined with ultrasound-enhancing agents when needed, color-Doppler imaging of

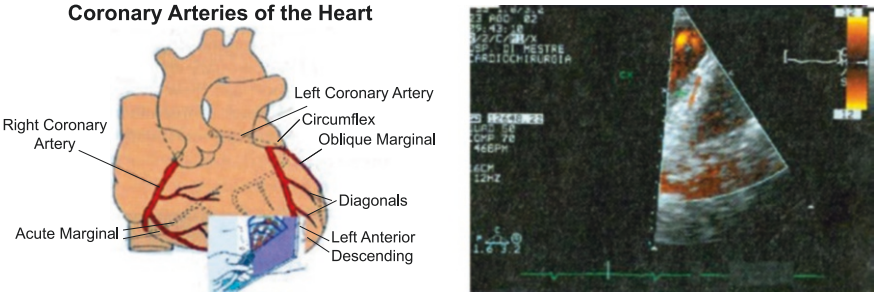

Fig. 4.6 *Left panel*: Artist's drawing illustrating transducer beam orientation to the left circumflex coronary artery. The mid-proximal tract of the left circumflex artery is imaged from a modified apical 4-chamber view with 50–80°clockwise rotation and posterior angulation of the probe. *Right panel*: The corresponding echocardiographic image of left circumflex color flow

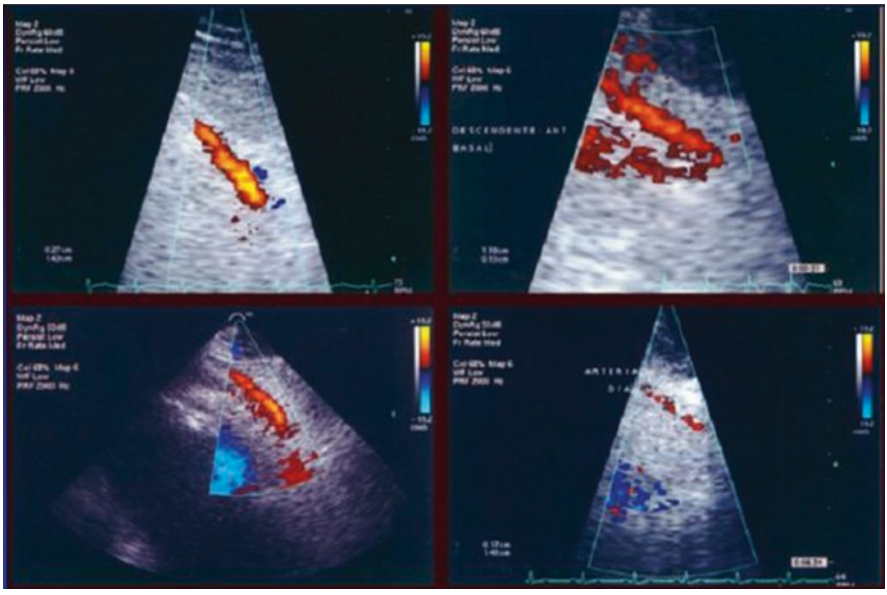

Fig. 4.7 Color Doppler flow imaging of the LAD artery, visualized in its middle-to-distal portion to a variable extent in four different patients. (Courtesy of Dr. Jorge Lowenstein, Buenos Aires, Argentina)

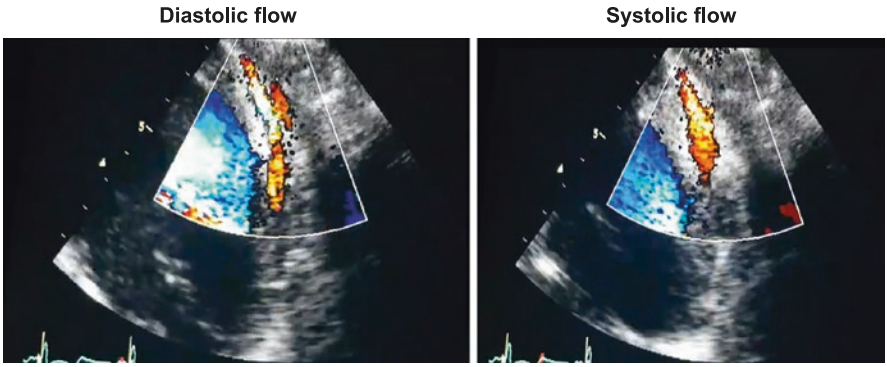

Fig. 4.8 Color Doppler flow imaging of the LAD at end-diastole (left panel) and end-systole (right panel). (See Video 4.1, courtesy of Dr. Lauro Cortigiani, Lucca, Italy). The video is available under the chapter's "Supplementary Material" on Springer Link

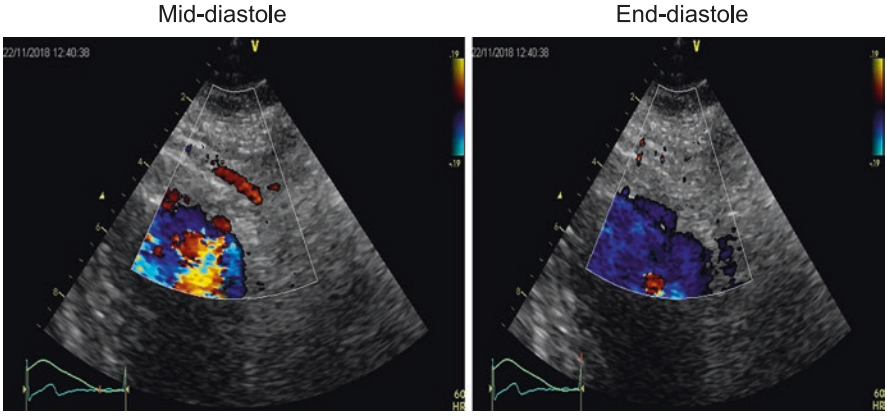

Fig. 4.9 Color Doppler flow imaging of the LAD at mid-diastole (left panel) and end-diastole (right panel). Coronary flow is only detectable at mid-diastole. Video 4.2 shows the corresponding cine-loop. (See Video 4.2, courtesy of Dr. Karina Wierzsbovska-Drabik, Lodz, Poland). The video is available under the chapter's "Supplementary Material" on Springer Link

coronary flow is becoming easier and faster. Several parameters might be measured from Doppler tracings of LAD artery flow, including systolic flows, time–velocity integrals, and mean flows. However, peak diastolic flow is not only the simplest parameter to be measured and the easiest to obtain, but also the most reproducible [12].

All stresses can be employed for measuring CFVR, but with different success rates. The success rate is acceptable (>70%) with semi-supine exercise, good (>80%) with dobutamine or pacing, and excellent (>90%) with vasodilators [13]. The abnormality cut-off is stress-independent, although dipyridamole and adenosine elicit a more profound coronary vasodilation (Fig. 4.10) and are therefore the first choice for assessing CFVR [14].

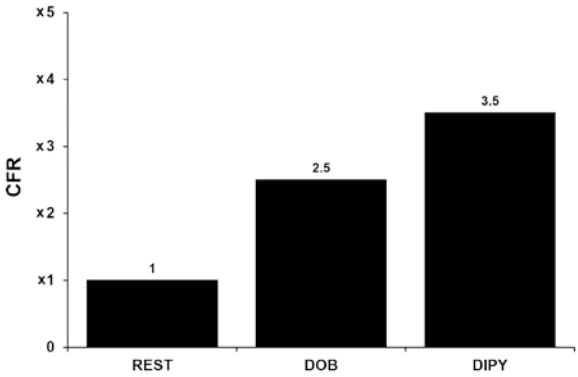

Fig. 4.10 CFR and stresses: Vasodilator stress with dipyridamole (*DIPY*) evokes a greater recruitment of CFR, than dobutamine (*DOB*). Vasodilators (dipyridamole, adenosine, and regadenoson) are more appropriate stressors than dobutamine for testing CFR, also due to the higher feasibility

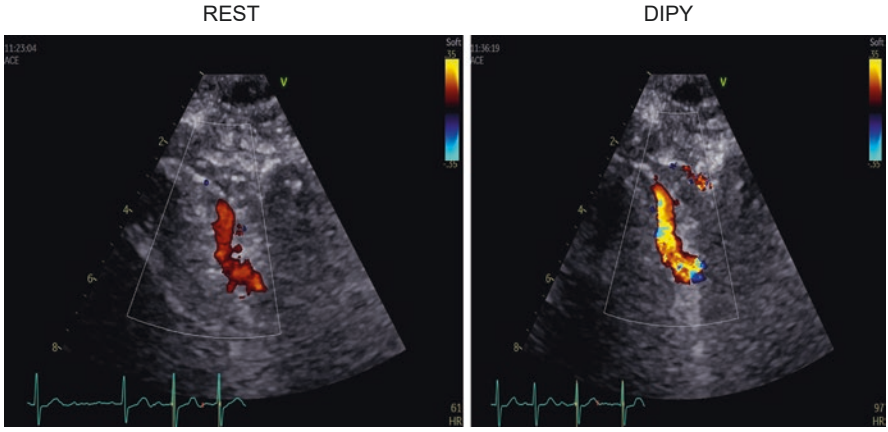

Fig. 4.11 The color Doppler signal at rest (left panel) and peak vasodilatory stress with dipyridamole (right panel). The flow velocity signal is brighter and larger following dipyridamole (DIPY), with only a minimal increase in heart rate. (Courtesy of Dr. Lauro Cortigiani, Lucca, Italy)

Not infrequently, the signal-to-noise ratio improves during vasodilator stress, since the flow velocity is higher, the coronary lumen outlined by the color signal is larger, and the heart rate only mildly increases. A barely readable signal at rest can become larger and brighter during vasodilator stress (Fig. 4.11).

The quality of the Doppler spectrum is of unchanged quality at rest and during dipyridamole, or another vasodilator, stress (Fig. 4.12).

When the same patient undergoes two different stresses, for instance, with dobutamine or exercise and vasodilator, CFVR is usually higher with vasodilator stress (Fig. 4.13).

CFVR by Doppler has a unique temporal resolution, and it is easy to assess the rate of vasodilation, its peak effect 4–6 min after the end of the infusion with dipyridamole, the immediate reversal after administration of antidote (Fig. 4.14), and

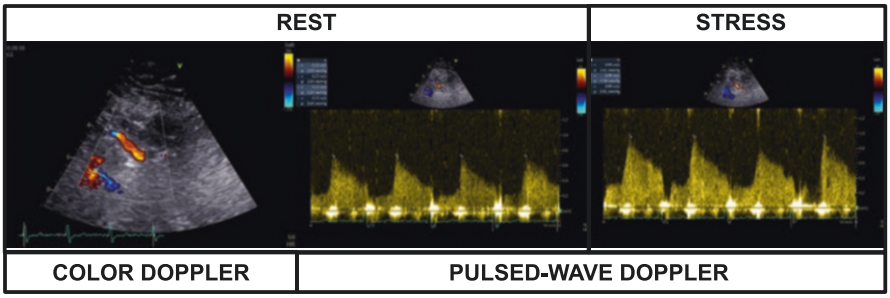

Fig. 4.12 The color Doppler signal at rest (left panel) and pulsed Doppler signal at rest (middle panel) and peak vasodilatory stress with dipyridamole (right panel). The resting flow velocity is 72 cm/s at rest, and 95 cm/s at peak stress, with a CFVR = 95/72 = 1.34. The resting flow velocity is abnormally high. (Courtesy of Dr. Lauro Cortigiani, Lucca, Italy)

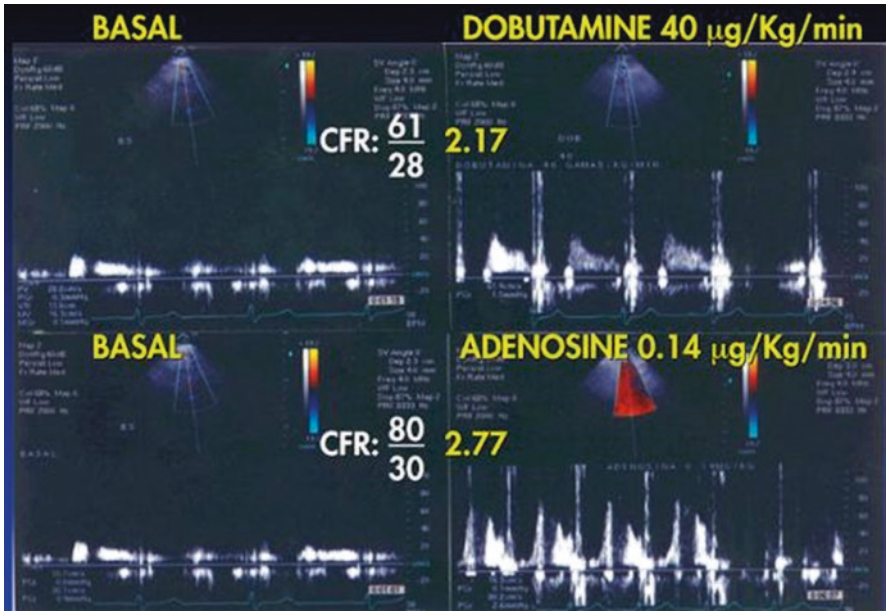

Fig. 4.13 CFVR was assessed in the same patient with TTE with dobutamine (*upper panels*) and adenosine (*lower panels*). *Left panels*, baseline signal. *Right panels*, peak stress signals. The increase in CFVR is substantially higher with adenosine than with dobutamine. (Courtesy of Dr. Jorge Lowenstein, Buenos Aires, Argentina)

possibly falling of vasodilation during stress for the occurrence of steal phenomena determining flow reversal when steal occurs [15].

The injection of ultrasound-enhancing agents reinforces the color-Doppler signal and is sometimes needed to rescue an otherwise uninterpretable examination [16].

The recommended methodology is shown in Fig. 4.15.

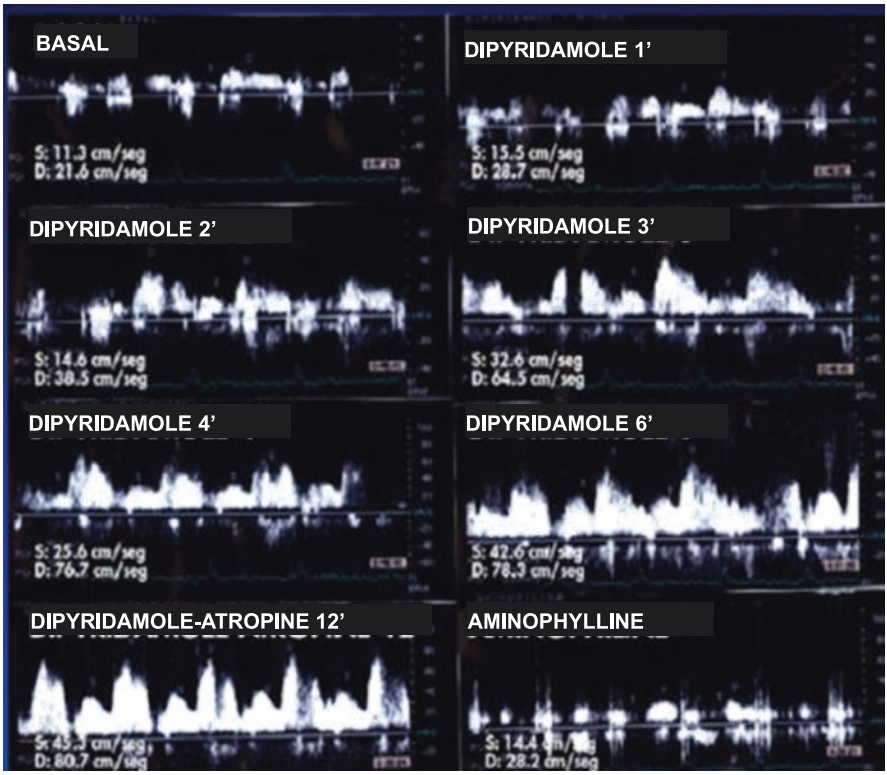

Fig. 4.14 The temporal sampling of CFVR by TTE. There is a progressive, stepwise increase in CFVR peaking after the high dose and immediately reversed upon administration of aminophylline. (Courtesy of Dr. Jorge Lowenstein, Buenos Aires, Argentina)

The sequence of acquisition is shown in Table 4.2. In the sequence of image acquisition at peak stress, step D for CFVR comes first, step A with C for regional wall motion and volumetric imaging second at peak stress, and step B last, in the early recovery phase.

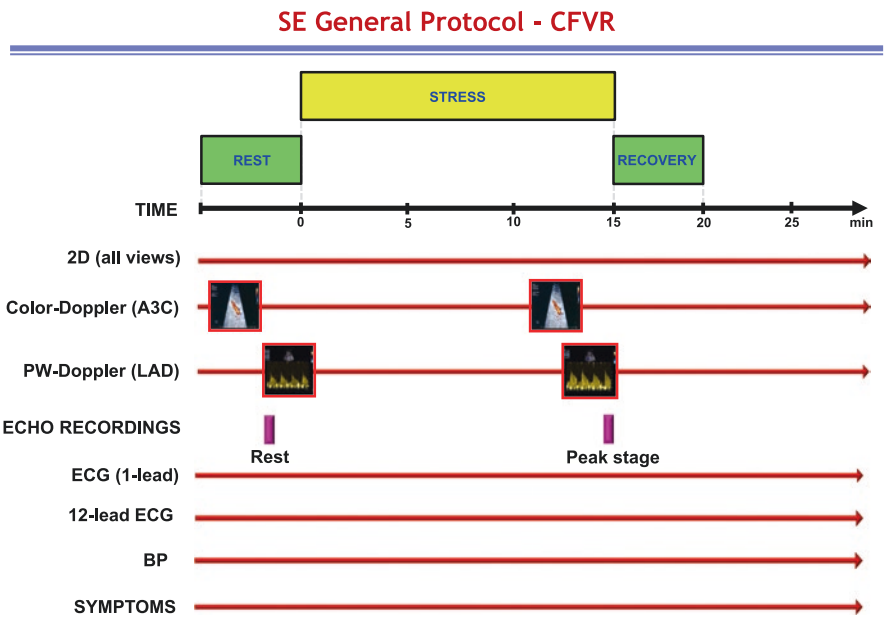

Fig. 4.15 The protocol for CFVR. Intermittent imaging of the LAD artery flow is performed at rest and peak stress. *BP* blood pressure, *CFVR* coronary flow velocity reserve, *ECG* electrocardiogram, *RWMA* regional wall motion abnormalities, *SE* stress echocardiography

Table 4.2 Acquisition during stress: general protocol

		Rest	Stress-intermediate	Stress-peak	Recovery
	Time (min)	TTE	0–10	11–15	15–20
2D-all views	A4C, 2C, 3C	v	v	v	v
Doppler-LAD	A3C, PLAX	v		v	
ECG, 1-lead	Echo monitor	v	v	v	v
ECG,12-lead	ECG monitor	v	v	v	v
BP	Sphygmo	v	v	v	v
Symptoms	Patient	v	v	v	v

A3C apical 3-chamber, *A4C* apical 4-chamber, *BP* blood pressure, *LAD* left anterior descending, *PLAX* parasternal long-axis, *TTE* transthoracic echocardiography

4.3 Response Patterns

In the normal response, a normal CFVR (>2.0) indicates a preserved coronary microcirculatory function (Fig. 4.16). The concomitant normal wall motion is usually associated with normal epicardial coronary arteries.

In the abnormal response, CFVR is reduced (≤2.0) (Fig. 4.17). The concomitant regional wall motion abnormality (RWMA) is associated with obstructive stenosis of epicardial coronary arteries.

The wall motion and CFVR response can be integrated with the heart rate response. An example of a completely normal wall motion, CFVR, and heart rate response indicative of angiographically normal coronary arteries, normal coronary microcirculation, and preserved sympathetic reserve is shown (Fig. 4.18). This response is associated with an excellent outcome.

A normal CFVR in the territory of the LAD coronary artery can also coexist with ischemia due to epicardial coronary artery stenosis in a different artery, such as the left circumflex artery (Fig. 4.19).

The myocardium increases function, thickness [17], stiffness [18], and also temperature with increased coronary flow [19]. The heart with a preserved CFVR can be referred to as a "warm" heart, as opposed to the "cold" heart with reduced CFVR [20].

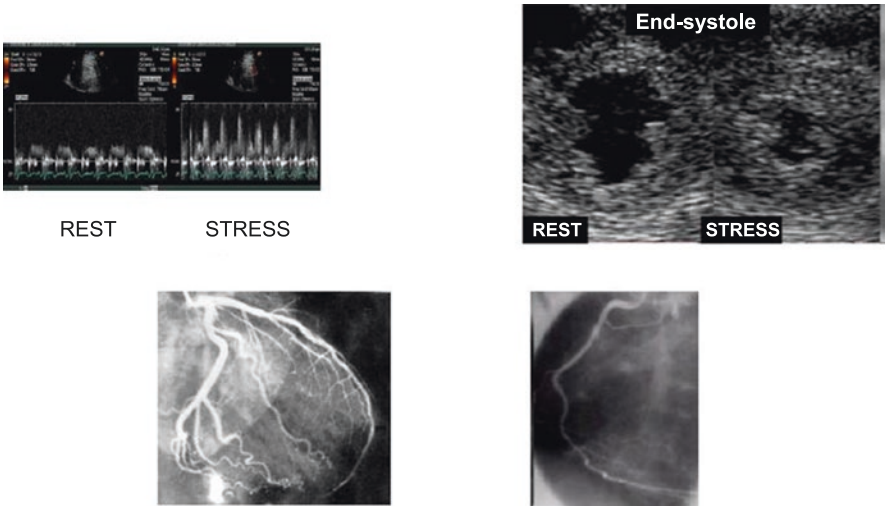

Fig. 4.16 A typical example of a normal regional wall motion and CFVR pattern from a patient with normal coronary arteries (shown in the lower panels). The end-systolic frames from the parasternal short-axis view show a normal thickening at rest and during stress (*right upper panel*). On the *left* upper panel, pulsed Doppler shows a threefold increase in Doppler peak diastolic flow velocity from baseline to peak dipyridamole

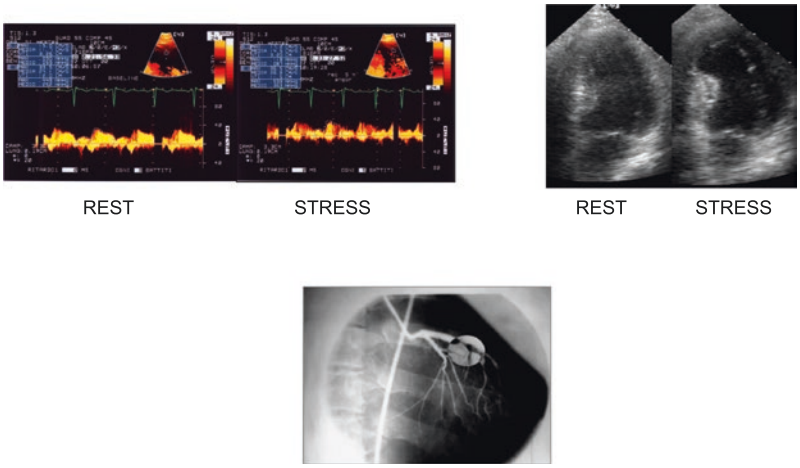

Fig. 4.17 A typical example of a regional wall motion (*right upper panel*) and CFVR (*left upper panel*) pattern from a patient with tight proximal stenosis of the LAD artery (*lower panel*). On the *right*, the end-systolic frames from the apical 4-chamber view show a normal thickening at rest and akinesia of the apex during stress. On the *left*, pulsed Doppler shows no significant increase in Doppler peak diastolic flow velocity from baseline (*left*) to peak dipyridamole (*right*)

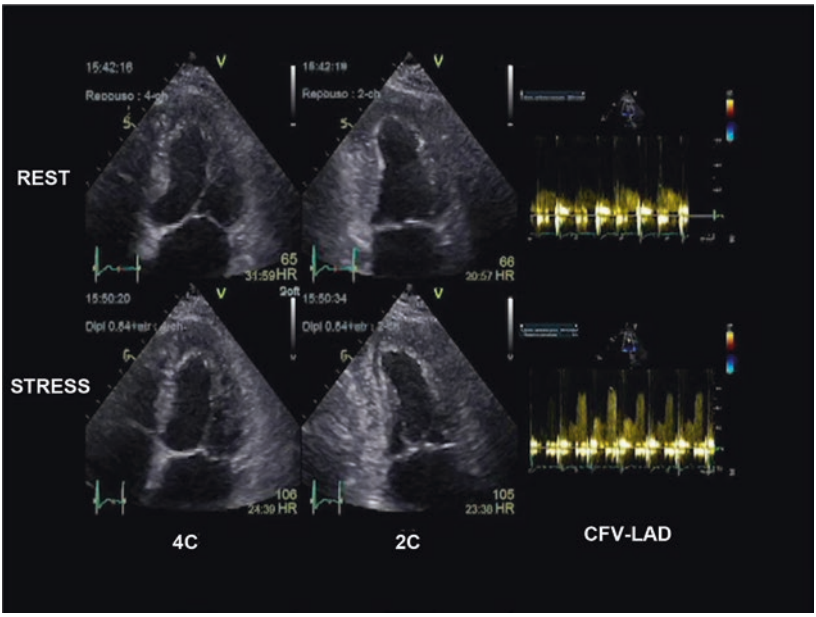

Fig. 4.18 The normal response of a nonischemic and warm heart. *Upper panels*, rest. *Lower panels*, peak dipyridamole stress. *Left panels*: apical 4-chamber (4C) view; *Middle panels*: apical 2-chamber view (2C); *Right panels*: pulsed-wave Doppler of peak flow velocity in LAD. (See Video 4.3, courtesy of Dr. Josè Luis Pretto, Passo Fundo, Brazil). The video is available under "Supplementary Material" on Springer Link

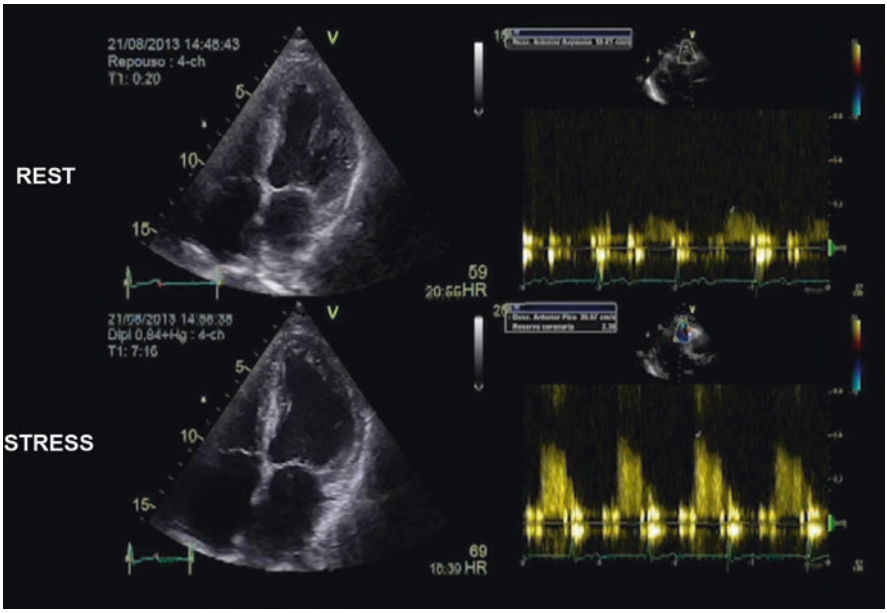

Fig. 4.19 The abnormal response with ischemic wall motion in a non-LAD territory and normal CFVR in the LAD territory. Ischemia occurs in the territory of the left circumflex artery, with RWMA of the basal and mid segments of the anterolateral wall. *Upper panels*, rest. *Lower panels*, peak dipyridamole stress. *Left panels*: apical 4-chamber (4C) view; *Right panels*: pulsed-wave Doppler of peak flow velocity in LAD. (See Video 4.4, courtesy of Dr. Josè Luis Pretto, Passo Fundo, Brazil). The video is available under the chapter's "Supplementary Material" on Springer Link

4.4 Coronary Anatomy and Functional Correlates

The use of CFVR as a stand alone diagnostic criterion suffers from major pitfalls since only the LAD coronary artery is easily sampled, but in a limited tract, and CFVR cannot distinguish between microvascular and macrovascular epicardial coronary disease [21]. Therefore, it is more clinically useful to evaluate the additive value over conventional wall motion for LAD coronary artery detection. The assessment of CFVR adds sensitivity for LAD disease [22–26], with a modest loss of specificity (Fig. 4.20).

CFVR and wall motion analysis offer complementary information during SE (Table 4.3).

From the pathophysiological viewpoint, wall motion positivity requires ischemia as a necessary prerequisite, whereas CFVR can be impaired in the absence of induced ischemia. Wall motion is easy to acquire but can be difficult to analyze. CFVR can be more difficult to acquire, but the analysis is usually straightforward and quantitative. An RWMA has a higher positive predictive value for predicting the presence of epicardial coronary artery stenosis. A normal CFVR has a higher

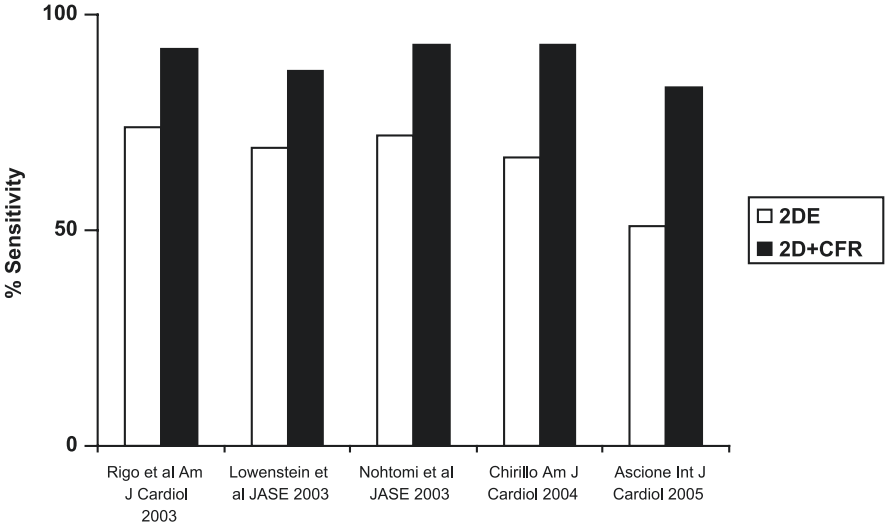

Fig. 4.20 The sensitivity for noninvasive detection of anatomic disease of the LAD coronary artery based on wall motion (2D echocardiography) and CFVR criteria (CFR) in five different studies, all consistently showing the higher sensitivity achieved with the contribution of 2D echocardiography and CFVR criterion versus 2D echocardiography alone. (Redrawn and adapted from original data of [22–26])

Table 4.3 The two sides of SE testing

	RWMA	CFVR
Specificity for CAD	Higher	Lower
Sensitivity for CAD	Lower	Higher
Image acquisition difficulty	Lower	Higher
Image interpretation difficulty	Higher	Lower
Prognostic value	High	Incremental over RWMA
Antiischemic therapy	Masks ischemia	Neutral effect
Coronary arteries explored	All territories	Mostly LAD
Prognostic value beyond CAD	Modest	Excellent

CAD coronary artery disease, *LAD* left anterior descending artery, *RWMA* regional wall motion abnormality

negative predictive value. Therefore, flow and function can complement each other since a wall motion abnormality is highly specific and a normal CFVR is highly sensitive to CAD [22–26]. In addition, the flow information is relatively unaffected by concomitant antianginal therapy, which markedly reduces the sensitivity of ischemia-dependent RWMA [27] and does not influence CFVR except to a limited extent, if at all [28].

In patients with hypertrophic cardiomyopathy, the reduction in CFR is not correlated to the maximal septal thickness and is also detectable in non-hypertrophic segments for the structural and functional impairment of coronary microcirculation [29]. In heart failure, the reduction in CFR precedes and portends the left ventricular

cavity dilation in the early stages of the disease and is not correlated to ejection fraction [30]. CFR is therefore an additional pathophysiologic vulnerability likely due to a low-grade inflammation targeting coronary small vessels and contributing to the progression of several cardiac and even noncardiac diseases. As a consequence, CFVR provides valuable prognostic information also outside of CAD.

4.5 Outcome Data

With the advent of CFVR in the SE laboratory, in a few years, a striking amount of information became available through large-scale multicenter studies, showing the impressive prognostic value of CFVR within and beyond CAD. This value has been proven in patients with stable angina [31], patients with intermediate stenosis of single-vessel disease [32, 33], and several other challenging subsets characterized by negative wall motion response during SE, such as patients with diabetes [34, 35] or hypertension [36], under antianginal therapy at the time of testing [37], with left bundle branch block [38], dilated cardiomyopathy [39], hypertrophic cardiomyopathy [40], or heart transplant [41]. The prognostic value has also been shown for hard endpoints only and all-cause death.

The prognostic value of CFVR adds incremental information over the value of inducible wall motion abnormalities. A reduction in CFR is an established predictor of adverse outcomes and death as now established by meta-analysis including 79 studies with 59,740 patients across multiple modalities of CFR measurements [42]. The relative risk of a reduced CFR is 3.78 for all-cause death, with a linear increase of risk of 16% for each 0.1 unit reduction in CFR.

The CFVR response is not dichotomous (black or white) but can be usefully titrated with different shades of gray, allowing a more effective stratification of severity. The usual, stress-independent, cut-off value between normal (>2.0) and abnormal (<2.0) response can be enriched with a score of mild, moderate, and severe abnormal response (Table 4.4). There is a spectrum of prognostic information and CFVR <2.6 is associated with a progressive decline in survival [43].

Table 4.4 CFVR response in LAD

	CFVR	Prognosis
Normal	> 2.60	Excellent
Mildly abnormal	2.17–2.60	Good
Moderately abnormal	1.81–2.16	Fair
Severely abnormal	<1.81	Poor

4.6 Tips and Tricks

CFVR can be now routinely added to SE with excellent feasibility across a wide range of body mass indexes. In patients in whom the flow signal is not obtainable or the quality of the envelope is considered inadequate or incomplete, an ultrasound-enhancing agent enhances both the color Doppler delineation of the LAD and the outer edge of pulsed-Doppler flow tracing. Color flow velocity is best set at 20–30 cm/s, with wall motion filters off. The sample volume is around 5 mm, with an adult multifrequency or, when needed, a pediatric probe with better resolution in the near field of interest for LAD imaging. With proper settings, almost any vendor can work [44], although success rate and image quality vary (Table 4.5).

Mapping of the Doppler signal from different angles can lead to spurious variations in peak diastolic flow velocity affecting measurements. Sometimes, a nice flow signal is obtained from noncoronary arteries, for instance, intercostal arteries which can be recognized from the dominant systolic component. A coronary artery different from the LAD artery can be sampled, such as a diagonal or intermediate branch. Occasionally, wall noise such as atrioventricular diastolic flow can be misinterpreted as a coronary Doppler flow signal. Resting CFV is slightly higher in the proximal tract of the LAD coronary artery than in the distal tract, and the same site must be sampled at rest and peak stress to avoid this potential source of variability.

As is true for all echocardiographic techniques, also CFVR does not tolerate improvisation and some basic training and technology requirements should be met before starting (Table 4.6).

The feasibility and clinical impact are highest for the mid-distal native LAD coronary artery and the left internal mammary artery graft, while It Is lowest (albeit still feasible) for posterior descending and left circumflex arteries. CFVR can be altered by changes in resting and hyperemic flows, which are influenced by hemodynamics, loading conditions, and contractility. For example, tachycardia increases basal flow and decreases hyperemic flow, thus reducing CFVR by 10% for each 15-beat increase in heart rate. The main problem with CFVR in clinical practice

Table 4.5 Vendor-specific optimal settings for imaging flow in the LAD artery

Vendor	GE	Philips	Siemens
Transducer	M5 (4,3)S	S5–1/X5–1	4Vic
Color-Doppler			
Frequency (MHz)	2.7–2.6		3.5
Scale (cm/s)	20–24	15–25	12–22
Gain	0 dB	80%	
Persistence	3.6	2 or 3	2
PW Doppler			
Sample volume (mm)	4	3	3
Gain (% or dB)	−10 dB	60%	
Filter	4.5/2.9 cm[a]	Low or min	4 or 5
Power (MI)	**0.5**	**0.4**	

MI mechanical index, *PW* pulsed-wave

[a] It corresponds to low-velocity rejection in the GE setting

Table 4.6 Requirements and techniques for CFVR assessment in mid-distal LAD

Variable	Requirement
Training 1— The prerequisite	ASE training level III (familiar with SE)
Training 2—Learning curve	100 studies with an experienced supervisor
Transducer	Second harmonic, multifrequency, broadband
Technology	High-end desirable
Acoustic window	Mod PLAX, mod A5C, A3C
What to measure	Peak diastolic flow velocity
How to measure	Perpendicular to baseline
Ultrasound-enhancing agents	When tracings are uninterpretable (5%)

A3C apical 3-chamber view, *A5C* apical 5-chamber view, *ASE* American Society of Echocardiography, *LAD* left anterior descending coronary artery, *mod* modified, *PLAX* parasternal long-axis view, *PSAX* parasternal short-axis view

resides in its lack of specificity for the epicardial vessel: an abnormal CFVR value does not determine whether this abnormal flow velocity relates to epicardial stenosis, microvascular disease, or both.

There are many assumptions and approximations behind the assessment of CFVR as a proxy for CFR. The 'maximal' vasodilatory stimulus is not truly maximal, although high doses of dipyridamole and adenosine are more effective than pacing and dobutamine in recruiting the flow reserve. The flow velocity variations are proportional to the total blood flow if the diameter of the vessel lumen is kept constant. In reality, the diameter of epicardial coronary arteries increases by an average of 30% in healthy subjects following adenosine infusion [45] and may dilate or constrict with dobutamine or exercise. The true coronary flow is the product of CFV times coronary vessel area. Failure to take into account epicardial coronary artery vasodilation during hyperemia may cause a non-systematic underestimation of volumetric CFR of 30–40% [46]. We measure peak diastolic flow velocity, by far the easiest and most reproducible parameter, but flow dynamics are more complex and the time integral of diastolic and systolic flow velocities would probably be more informative. Flow velocity is angle-dependent, and the angle of interrogation should be the same at rest and during stress, but this is not always easy under high heart rate conditions and especially with stresses such as exercise or dobutamine, although this theoretical error is reduced by maintaining a large Pulsed Wave sample volume (at least 10 mm). All coronary arteries can be interrogated, but only the mid-distal LAD artery is easy to find after a short search time, and up to now CFVR in other coronary arteries is not ready for clinical use. The binary cut-off of abnormality set at 2.0 is useful, but in reality, there is a continuum of risk across all values of CFVR, and the prognosis worsens progressively with values of CFVR <3.0. Despite these theoretical and practical limitations, the technique works. With second-harmonic technology, broadband multi-frequency or high-frequency probes, pre-adjusted coronary flow settings, and sometimes the use of ultrasound-enhancing agents, CFVR in a mid-distal LAD coronary artery has stood the stress test of large-scale multicenter trials.

Most centers do it in a one-stop-shop (with high dose dipyridamole), others (without access to a semi-supine bike) prefer to have treadmill exercise and, at the

end of the recovery phase in the same stress session, to use a shot of adenosine for isolated CFVR assessment in a hybrid form of exercise + pharmacological testing. Coronary vasodilation usually induced with exogenous adenosine or endogenous adenosine accumulation with dipyridamole is a mixed stimulus, with both a dominant endothelium-independent and also endothelium-dependent vasodilation [47].

It can be affected by a variety of extrinsic factors, and a transient decrease in CFVR is observed after a high-fat meal or exposure to high levels of air pollution and fine particulate matter. An acute improvement is observed after LDL-pheresis in subjects with familial hypercholesterolemia or after fasting in diabetes. Measurements of CFVR should be performed in a fasting state, in a quiet room, and in stable hemodynamic conditions, and probably the air pollution levels should be noted since extreme variations can affect CFVR conditions, with more polluted air quality lowering the observed values [48].

The cutoff value of 2.0 is valid for diagnostic and prognostic purposes, for exercise and dobutamine, dipyridamole and adenosine, regadenoson and pacing, for women and men, and young and aged subjects, and all coronary arteries, including right anterior mammary artery graft, left anterior mammary artery graft, and right coronary and left circumflex coronary artery [49–53].

4.7 The Value of Resting CFV

CFV at rest also counts, and not only as a prerequisite for CFR assessment. The resting flow velocity tends to be higher when the CFVR is lower [54]. Increased heart rate, myocardial contractility, and systolic blood pressure will all increase myocardial oxygen consumption and increase resting CFV. Diffuse nonobstructive CAD, anemia, and hypoxia will reduce oxygen supply and increase resting CFV. Higher values of CFV at rest are associated with progressively worse outcomes [55–59]. Coronary flow is good and essential for adequate myocardial function, but too much of a good thing can be dangerous and in the long run maladaptive. Patients with increased resting CFV have a worse outcome, and this information can be obtained with no stress, no risk, and with a simple resting echocardiogram [60]. The absence of resting coronary flow is associated with obesity, occlusion of a LAD coronary artery, and high resting heart rate. At rest, the flow direction can be inverted, and this finding is highly suggestive of coronary collateral circulation from the donor's right coronary artery to a chronically occluded LAD [61]. Typically, this retrograde flow will disappear during vasodilator stress, allowing direct documentation of horizontal steal phenomena concomitant with the development of stress-induced RWMA in the LAD territory [62].

There is more information in the resting coronary flow profile than peak diastolic velocity since a steep diastolic CFV reflects elevated left ventricular end-diastolic pressure [63] and an increased systolic to diastolic flow ratio is altered in patients with severe CAD or with Myocardial Bridge [64]. The choice to go with peak diastolic flow velocity has 2 main reasons: first, it is the parameter better correlated with coronary flow invasively measured, and second, it is by far the simplest and

more reproducible to be measured. However, there is little doubt that there is more information than the peak diastolic flow profile in the resting coronary flow, and this information can now be realistically extracted in an operator-independent way by artificial intelligence algorithms simplifying the analysis time and increasing the number of extracted variables, in an efficient and operator-independent fashion [65].

4.8 Clinical Guidelines and Recommendations

ESC guidelines 2019 recognize that invasive measurements of CFR using a Doppler wire are complex, time-consuming, and carry a small risk. Therefore, in angina with normal coronary arteries, objective evidence of microvascular disease may be alternatively obtained by measuring diastolic coronary blood flow in the LAD artery using TTE Doppler recordings [66]. A CFVR <2.0 strongly suggests coronary microvascular disease. Specialist guidelines endorse a more extensive application of CFVR in the SE lab, suggesting that "*whenever possible, it is recommended to perform dual imaging (flow and function) vasodilator SE*" [67]. Joint recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging suggest that the evaluation of CFVR is optimally performed with vasodilatory SE and can provide prognostically relevant information in hypertrophic and dilated cardiomyopathy [68]. The large-scale validation of CFVR in the LAD artery within the framework of the SE 2020 study has established the independent and incremental prognostic value of CFVR over RWMA [69] and is promoting a larger use of the technique. Only large primary vessels can be reliably imaged, and "*difficulty in imaging all three major coronary arteries is a significant limitation, preventing the wide clinical use of this technique*", but this limitation applies to diagnostic applications of the technique, which are clearly out of reach for the technique [70]. In the words of Valentin Fuster, "*knowing that the technology is quite feasible, I can see a future by which the use of the quadruple imaging (ABCD) protocol may provide a lot of information"*, allowing the old concept of CFVR to "*go back to the future with the fullest speed in Europe and United States*" [71]. In an editorial comment, an eminent Canadian cardiologist, Sharon Mulvagh, commented that "*The current shift toward using SE protocols with both known and novel parameters is a new frontier. It will be interesting to observe the impact of SE 2020 in shifting practice. There has been a reluctance to "go with the flow" on this North-American side of the Atlantic, but perhaps this will change with a clear demonstration of the feasibility and incremental value of a multiparametric SE approach, especially in women, who could benefit greatly from a noninvasive, nonionizing assessment of myocardial microvascular integrity*" [72]. This approach is especially appealing since coronary microvascular dysfunction can represent a potential selective therapeutic target [73]. In the 2021 cardiology guidelines of the American College of Cardiology/American Heart Association for the diagnosis of chest pain, CFVR received a class 2b recommendation ("*may be useful*") in patients with ischemia and normal coronary arteries, and its role is acknowledged also in patients with known or suspected CAD for refining risk stratification [74]. CFVR in

mid-distal LAD is now the recommended standard of practice in all patients referred to SE according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [75].

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Step E for EKG-Based Heart Rate Reserve in Stress Echocardiography

5

Lauro Cortigiani and Eugenio Picano

Keywords

Arrhythmic risk · Neurons · Noradrenaline · Sympathetic reserve · Sudden cardiac death

5.1 Cardiac Autonomic Function

Cardiac autonomic dysregulation is pivotal to the development and progression of most cardiovascular diseases, from heart failure to coronary artery disease, characterized by the negative prognostic implications of enhanced sympathetic activity and impaired parasympathetic responsiveness [1]. The possibility to gain the elusive dimension of cardiac autonomic function and balance with a parameter of striking simplicity such as heart rate reserve (HRR) is appealing. HRR is calculated as the ratio of peak/stress heart rate values [2]. The approach is applied in the same way to physical [3] and pharmacological [4] stresses, although the cutoff point can be different since exercise and dobutamine are stronger chronotropic stress than vasodilators.

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L. Cortigiani (✉)
Cardiology Department, San Luca Hospital, Lucca, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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At rest, heart rate is mostly due to baseline sympathetic tone, which increases during exercise determining the rise in heart rate and chronotropic competence. When exercise stops, the parasympathetic tone starts increasing and the speed of recovery of resting heart rate measures parasympathetic reserve, whereas the increase in heart rate during exercise measures sympathetic reserve. The mediator of sympathetic increase during exercise is cardiac noradrenaline produced by cardiac afferent nerve endings going from baroreceptors and the intrinsic nervous system of the heart to the lower brain stem and stimulating cardiac efferent nerves projecting on the cardiac sinus node via beta-1 receptor stimulation. The same stimulation of the sinus node can be achieved by exogenous catecholamines such as dobutamine [5].

A similar but softer and indirect sympathetic stimulation is achieved with adenosine, either exogenously administered or accumulated via dipyridamole as endogenous adenosine. Plasma adenosine increases two-to-three fold during dipyridamole infusion at the dose employed in stress echocardiography (SE) due to inhibition of cellular reuptake by the drug [6]. Dipyridamole infusion is also accompanied by a 70% increase in plasma noradrenaline of neuronal origin which can be detected even in absence of inducible myocardial ischemia and is not related to blood pressure changes [7]. Adenosine directly stimulates A2A adenosine receptors present on afferent nerve endings in the carotid body, skeletal muscle, heart, and kidney [8]. The increase in noradrenaline determines a rise in heart rate via stimulation of beta1-receptors present on the sinus node. The activation of specific excitatory reflexes of sympathetic tone and simultaneous withdrawal of vagal tone usually override the direct A1-receptor-mediated negative chronotropic effect of adenosine on sinus node cells [9]. The blunted increase in heart rate may reflect the reduced responsiveness to adrenergic stimuli, which can be due to increased baseline activity (mirrored by higher resting heart rate) or reduced adrenergic responsiveness, both associated with autonomic dysfunction and a higher level of risk. This interpretation is also consistent with previous early experiences with dipyridamole stress, reporting that the HRR (calculated retrospectively from the reported rest and peak values) was 1.20 to 1.50 in patients with or without ischemia [10] and almost abolished in patients with transplanted and denervated hearts [11].

Cardiac autonomic dysfunction is an early sign of disease in several cardiovascular conditions, including heart failure. As the disease progresses, cardiac noradrenaline increases, and tissue noradrenaline, nerve density, and nerve function decrease [5]. This determines a progressive decline in HRR (Fig. 5.1), exploitable as an early diagnostic marker, a prognostic risk factor, and a potential therapeutic target.

Many conditions of disease in their early phase affect cardiac autonomic balance. These conditions include diabetes, hypertension, renal failure, and Chagas disease. Sympathetic activation is universally present and contributes to disease progression in coronary artery disease, heart failure, or valvular heart disease (Table 5.1).

In all conditions with early involvement of the cardiac autonomic system, the reduction of HRR can be the earliest and for a long time the only sign of abnormality during SE.

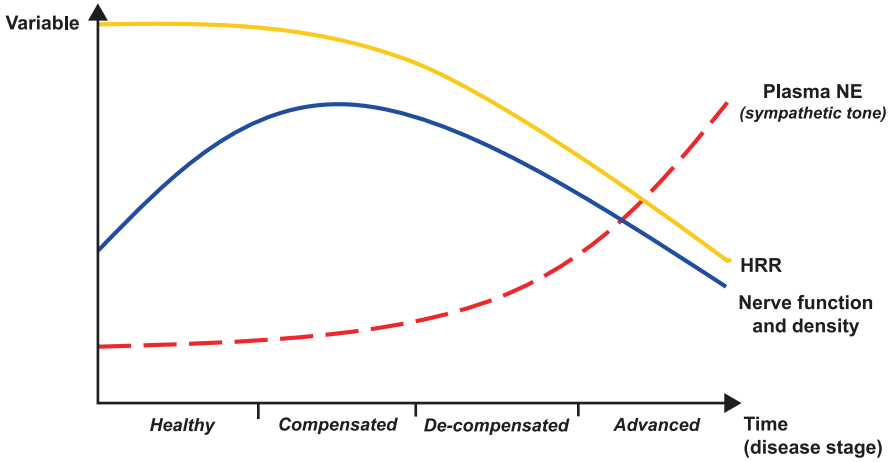

Fig. 5.1 The conceptual model of HRR as a universal mechanism of disease. After the initial compensatory phase, HRR progressively declines. (Modified and adapted from reference [5])

Table 5.1 Main conditions with cardiac autonomic dysfunction

	Early sign	Late sign
Coronary artery disease		v
Heart failure reduced EF		v
Heart failure preserved EF	v	
Hypertension	v	
Diabetes	v	
Hypertrophic cardiomyopathy	v	
Kidney disease	v	
Chagas disease	v	

EF ejection fraction

5.2 How to Measure Heart Rate Reserve

Heart rate is recorded from a one-lead electrocardiogram displayed in the echo monitor 1–5 min before (rest heart rate), each minute during, and 1–5 min after stress (Fig. 5.2).

The maximal variation of heart rate from rest to stress is considered. HRR is defined as the peak/rest ratio of heart rate (Fig. 5.3).

The abnormal cutoff value is <1.80 for exercise, but lower in patients studied on beta-blockers (<1.62) and in patients with advanced age since the peak heart rate declines by 10 beats every decade beyond the age of 50. In elderly patients, an age-normalized index is more appropriate: 220-age. The abnormal cutoff is <1.80 in dobutamine-atropine (independently of age and beta-blockers) and ≤ 1.22 for dipyridamole [12–14]. The information can be extracted also from patients with permanent atrial fibrillation, although heart rate values should be averaged over at least 5 rather than the usual 3 beats and the abnormality cutoff is lower than in patients with sinus rhythm. With dipyridamole, the abnormal cut-off is <1.17 instead of 1.22 [15].

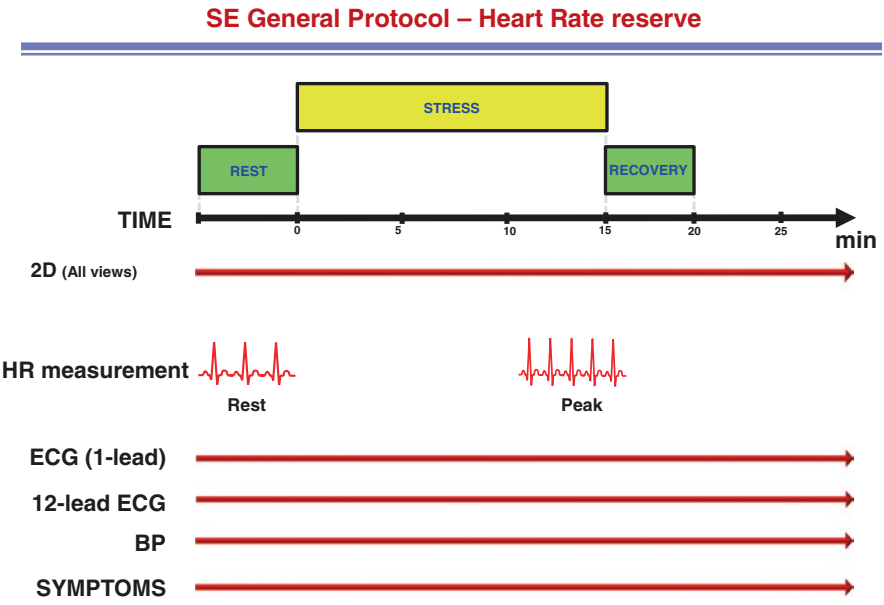

Fig. 5.2 The protocol to assess heart rate at baseline and peak stress. One-lead electrocardiogram present in the echo monitor is sufficient to assess heart rate reserve as a peak/rest ratio

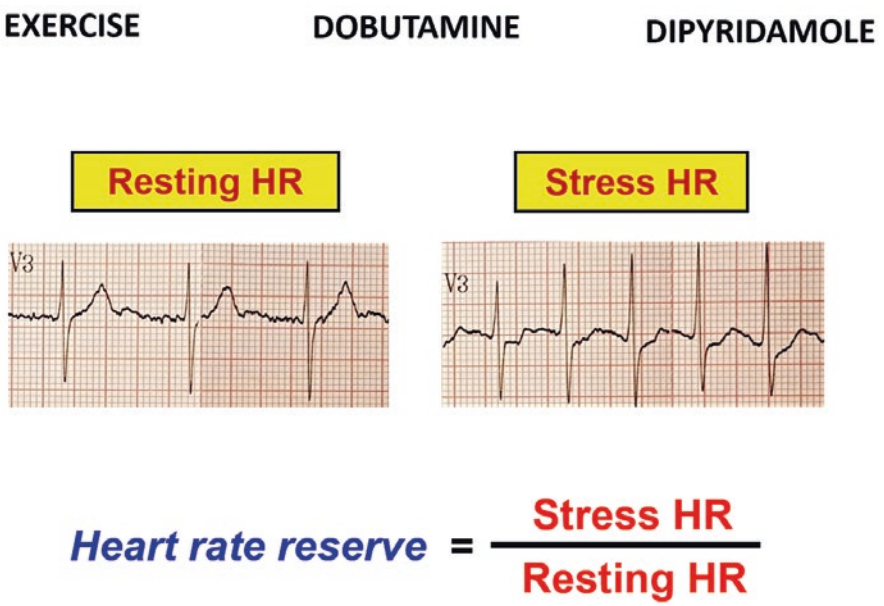

Fig. 5.3 The methodology of HRR measurement. With all stresses, the peak-to-rest ratio of heart rate is calculated from the automatic display of the one-lead electrocardiogram present in the echo monitor

5.3 Heart Rate Reserve Response Patterns

A normal heart rate response can be present with abnormal regional wall motion (Fig. 5.4).

An abnormal heart rate response can be associated with normal regional wall motion (Fig. 5.5).

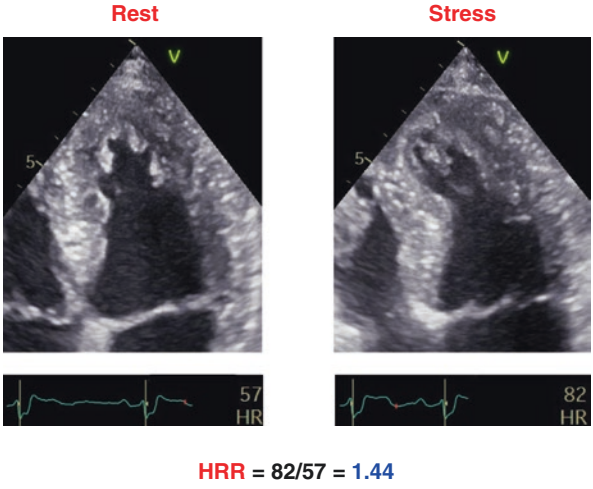

Fig. 5.4 The response of an ischemic and fast heart. Heart rate at rest (left lower panel, = 57 beats per minute) and after dipyridamole test (right lower panel = 82 beats per minute). Heart rate reserve (peak/rest, 82/57 = 1.44) is reduced. End-systolic frames from the apical 4-chamber view show normal wall thickening at rest (left upper panel) with apical akinesia during stress (right upper panel). (See Video 5.1, courtesy of Dr. Lauro Cortigiani)

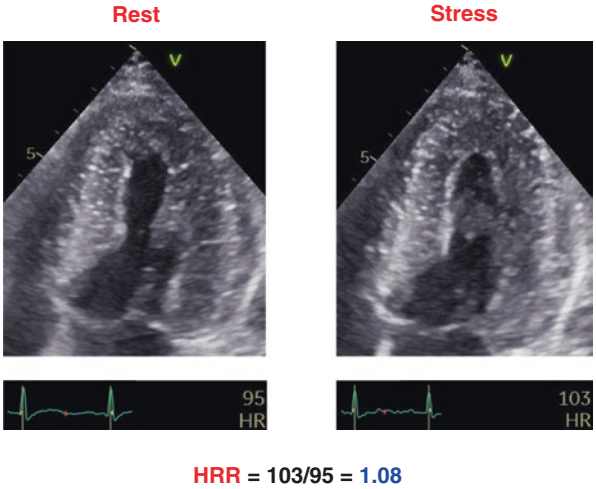

Fig. 5.5 The response of a nonischemic and slow heart. Heart rate at rest (left lower panel = 95 beats per minute) and after dipyridamole test (right lower panel = 103 beats per minute). Heart rate reserve (peak/rest, 103/95 = 1.08) is reduced. End-systolic frames from the apical 4-chamber view show normal wall thickening at rest (left upper panel) and during stress (right upper panel). (See Video 5.2, courtesy of Dr. Lauro Cortigiani)

Table 5.2 The severity of HRR response

	HRR-Exercise and dob	HRR-Dipyridamole	Prognosis
Normal	> 1.8	>1.41	Excellent
Mild	1.5–1.8	1.27–1.40	Good
Moderate	1.25–1.49	1.16–1.26	Fair
Severe	<1.25	<1.16	Poor

The conceptual model is therefore very simple: a normal sympathetic reserve is associated with a fast heart, and an abnormal sympathetic reserve vulnerable to electrical instability and sudden death is associated with a slow heart. The abnormal response can be considered in a binary fashion (normal or abnormal) or titrated in mild, moderate, and severely abnormal responses (Table 5.2).

5.4 Anatomic and Functional Correlates

All conditions characterized by alterations of cardiac autonomic function and activation of resting sympathetic tone are associated with an increased probability of a reduced HRR. Cardiac autonomic dysfunction is associated with loss of cardiac sympathetic integrity and may contribute to impaired coronary flow reserve and reduced left ventricular contractile reserve, as shown in patients with diabetes or hypertrophic cardiomyopathy [16–20].

5.5 Outcome Data

Patients with known or suspected coronary artery disease and/or heart failure are at increased risk of events in the presence of reduced HRR during exercise [12], dobutamine [13], or dipyridamole SE [14]. The prognostic value of a blunted HRR is independent of regional wall motion abnormalities and is observed in populations tested off or on concomitant beta-blocker therapy. It is not a binary response but rather a continuum, with less heart rate increase associated with a worse prognosis. This stratification of response can be observed in all patients and all stresses. Patients with chronic coronary artery disease studied with dipyridamole stress have a worse prognosis when HRR falls in the lowest quartile [14]. The five-year hard event rate increased from 8% to 24% from the highest (≥1.41) to the lowest (≤1.14) quartile.

In asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy studied with exercise [21], the 8-year mortality rate increased from 2% to 11% from the highest (≥2.14) to the lowest (≤1.61) quartile.

The prognostic value of HRR is independent and incremental over regional wall motion abnormalities, B-lines, contractile reserve, and coronary flow velocity reserve in patients with abnormal chronotropic response to exercise, ischemia with normal coronary arteries, chronic coronary syndromes, and nonischemic heart failure [22–27].

5.6 Tips and Tricks

If atropine is added with dipyridamole, cutoff values are higher and not validated. During pharmacological testing, the value of HRR is not affected by physical conditioning and deconditioning, which affect the value of chronotropic incompetence during exercise and dilute the prognostic impact of a reduced HRR [17]. The peak heart rate can be recorded at a fixed time corresponding to the end of exercise and dobutamine stress, but with dipyridamole infusion endogenous adenosine accumulates by reuptake inhibition, and the peak chronotropic effect occurs some minutes after the end of infusion [14]. The highest change in heart rate (measured each minute) is observed in the time interval from 0 to 6 min after dipyridamole infusion [14]. It is important to record the peak value, since there is minimal interpatient variability, whereas the peak value always corresponds with peak stress during exercise. Beta-blockers reduce the absolute rest and peak value of heart rate during dipyridamole, but the relative rest-stress changes mirrored in HRR are essentially the same. Clinical physiology studies demonstrate that beta-blockers do not abolish the increase in heart rate elicited by adenosine, suggesting that vagal withdrawal (enhanced by beta-blockers) is also important in determining the increase in HR during dipyridamole [14]. HRR during stress is, at least in principle, a simple cardiac autonomic function test. The heart with a preserved HRR can be referred to as a "fast" heart, as opposed to the "slow" heart with a reduced HRR.

5.7 Clinical Guidelines

Different cardiac autonomic tests have been proposed to identify patients at risk for sudden death, such as heart rate variability, baroreflex sensitivity, and T wave alternans, but they are time-consuming, complex, and did not gain widespread acceptance in the clinical arena. Despite all difficulties, knowledge of the tests assessing autonomic function would be extremely important in clinical practice [28]. HRR keeps the vital information and deletes all methodological complications. It is a simple, quantitative, operator-independent, and nonimaging parameter that expands the risk stratification potential of SE. It provides insight into autonomic imbalance, which is important in determining vulnerability to arrhythmias and sudden death and is usually missed by cardiac functional testing. With pharmacological stresses, it is not affected by physical conditioning and deconditioning, concomitant therapy, or extra-cardiac conditions such as orthopedic disease, which heavily influence the value of reduced chronotropic incompetence during exercise [29]. Assessment of chronotropic incompetence is established during stress testing with exercise in general cardiology guidelines and a part of the minimum data set obligatory during SE with either exercise or pharmacological SE [30]. Clinicians may consider chronotropic incompetence as an easily accessible biomarker of cardiac autonomic dysfunction useful for the overall assessment of individual vulnerability in a particular patient (Fig. 5.6). Assessment of HRR with one-lead electrocardiogram present in

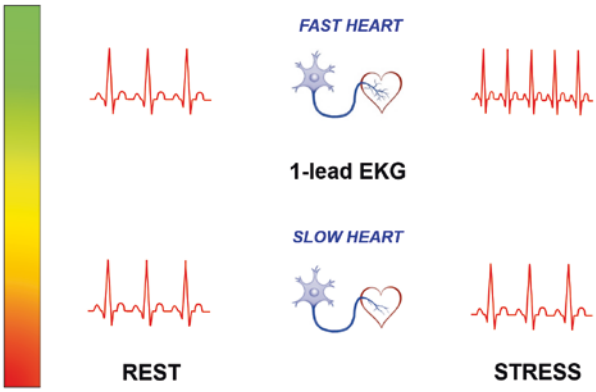

Fig. 5.6 The incorporation of HRR expands the spectrum of prognostic stratification, with the lower risk associated with a fast heart with preserved HRR (green in the risk bar) and the higher risk associated with reduced HRR (red in the risk bar). The functional correlate of a slow heart is a reduction in density and function of sympathetic nerve endings in the sinus node

the echo monitor is now the recommended standard of practice in all patients referred to SE according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [31].

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Step F for Mitral Regurgitant Flow in Stress Echocardiography

6

Angela Zagatina and Eugenio Picano

Keywords

Dilated cardiomyopathy · Heart failure · Hypertrophic cardiomyopathy · Left ventricular function · Pulmonary artery systolic pressure

6.1 Mitral Regurgitation as a Disease and as a Syndrome

The mitral valve closure in systole requires the coordination of several functionally interdependent, yet anatomically distinct, components, from left ventricular cavity dimension to wall function and synchrony, papillary muscles, chordae tendineae, mitral valve leaflets, mitral annulus, and left atrium (Fig. 6.1) [1].

Each link of this complex physiological chain can be altered by disease, and therefore, mitral regurgitation (MR) is a common condition, causing morbidity and mortality with increasing trends with an aging population [2]. The main separation is usually between primary, degenerative MR with abnormal leaflets and secondary, functional MR with structurally normal mitral valve leaflets with altered (restricted or redundant) motion, as can be observed for instance in coronary artery disease, heart failure, or hypertrophic cardiomyopathy (Table 6.1).

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A. Zagatina (✉)
Cardiology Department, Cardiocenter Medika, St. Petersburg, Russia

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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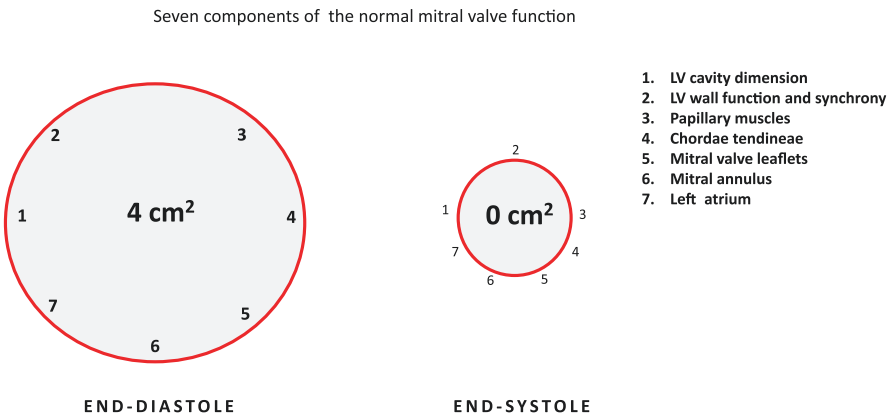

Fig. 6.1 Mitral valve area at end diastole and end systole. The normal end-diastolic (ED) area of the mitral valve orifice of 4 cm^2 becomes zero at end systole (ES) for the coordinated action of seven anatomic and functional players: left ventricular cavity; left ventricular wall function and synchrony; papillary muscles; chordae tendineae; mitral leaflets; mitral annulus; and left atrium

Table 6.1 Cardiovascular diseases associated with mitral regurgitation

	Involved structure
Primary MR	Valve leaflets
CAD	LV function and synchrony
HFrEF (proportionate MR)	LV cavity
HFrEF (disproportionate MR)	LV dyssynchrony
HCM	Redundant papillary muscles
MAC	Mitral annulus
HFpEF	Left atrium

CAD coronary artery disease, *HCM* hypertrophic cardiomyopathy, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LV* left ventricle, *MAC* mitral annulus calcification

When a significant mitral regurgitation develops, it may have important implications as a determinant of patient symptoms and as a potentially treatable condition with different repair transcatheter or surgical techniques with leaflets and chordal or annular solutions.

Stress echocardiography has a unique potential for several reasons: objective testing of symptom status is crucial in "asymptomatic" primary severe MR; the functional and prognostic impact of MR is more clearly assessed dynamically with an exercise rather than with a resting evaluation; the behavior of all rings of the physiological chain supporting mitral valve function is separately assessed, from the left ventricular cavity, wall function, and synchrony to left atrium [3, 4]; the technique offers unique data on all other conditions modulating the functional and prognostic impact of MR, from pulmonary hemodynamics to right ventricular function and cardiac, coronary, and sympathetic reserve [5].

6.2 How to Measure MR

Mitral regurgitation is characterized by a retrograde flow from the left ventricle to the left atrium in systole, and the presence, spatial extent, velocity, and shape of this flow are characterized by color Doppler with the integration of continuous-wave and pulsed-wave Doppler and allow to characterize the severity of mitral regurgitation. The basic measurements and formulas used to derive qualitative, semiquantitative, and quantitative indices of MR severity are summarized in Table 6.2. The color flow display depends on many technical and hemodynamic factors and is not recommended to quantify the severity of MR. In some cases without important changes during stress, a semiquantitative assessment with vena contracta width is sufficient. A vena contracta <3 mm indicates mild MR, whereas a width ≥ 7 mm defines severe MR. Intermediate values are not accurate at distinguishing moderate from mild or severe MR and require the use of cardiac magnetic resonance for confirmation. In other cases when qualitative and quantitative parameters give discordant or indeterminate results and MR is a critical clinical variable, a quantitative assessment with effective regurgitant orifice area (EROA) and regurgitant volume is recommended provided that the quality of images and the specific experience of the operator are adequate.

Current recommendations identify grades of chronic MR severity based on the integrated use of vena contracta width, EROA, and regurgitant volume [6]. The value of these cutoffs is limited by the technical difficulty of obtaining consistent results, relatively wide variability, non-systematic underestimation in the case of eccentric jets, and overestimation in non-holosystolic jets (for EROA), which reduced feasibility and reliability in the case of calcific mitral valve or annulus (for regurgitant volume). These limitations cause frequent discordance between quantitative parameters and/or clinical data leading to the diagnosis of indeterminate severity and further testing with transesophageal echocardiography or cardiac magnetic resonance [6]. A commonly used score titrates MR as absent or trivial (score 0), mild (score 1), moderate (score 2), moderate–severe (score 3), or severe (score 4). On practical grounds, minor, questionable, or uncertain changes are not clinically relevant, but obvious changes with different indices pointing in the same direction can be pivotal for driving a clinical decision.

Table 6.2 MR severity score at rest and during stress

	Absent (trivial)	Mild	Moderate	Moderate–severe	Severe
ASE grade	0	1	2	3	4
VC width (mm)	Na	<3	3–6.9	3–6.9	≥7.0
PISA radius (mm)	Na	<4	4–10	4–10	≥10
R F (%)	Na	<30	30–39	40–49	≥50
EROA (cm2)	Na	<0.2	0.2–0.4	0.2–0.4	≥0.4
R Vol (ml)	Na	<30	30–44	45–59	≥60

ASE American Society of Echocardiography, *EROA* effective regurgitant orifice area, *Na* not available, *PISA* proximal isovelocity surface area, *RF* regurgitant fraction, *R Vol* regurgitant volume, *VC* vena contracta

The general protocol for a stress echo focused on MR should obligatorily include the color flow Doppler of MR, the continuous-wave Doppler of MR, and the 2-dimensional apical views of the left ventricle (Fig. 6.2). The color flow regurgitant jet of MR is essential for the qualitative (regurgitant jet), semiquantitative (vena contracta width), and quantitative (flow convergence) assessment.

However, the study of MR is not enough, and a complete assessment of the cardiovascular response during stress should include the evaluation of left and right ventricular function, pulmonary pressures, pulmonary congestion, and, when possible, left atrial volume and function [7]. The sequence of acquisition in cases of MR-focused stress echo is summarized in Table 6.3. The imaging sequence usually follows a standardized approach, starting from 2-dimensional 4-, 2-, and 3-chamber

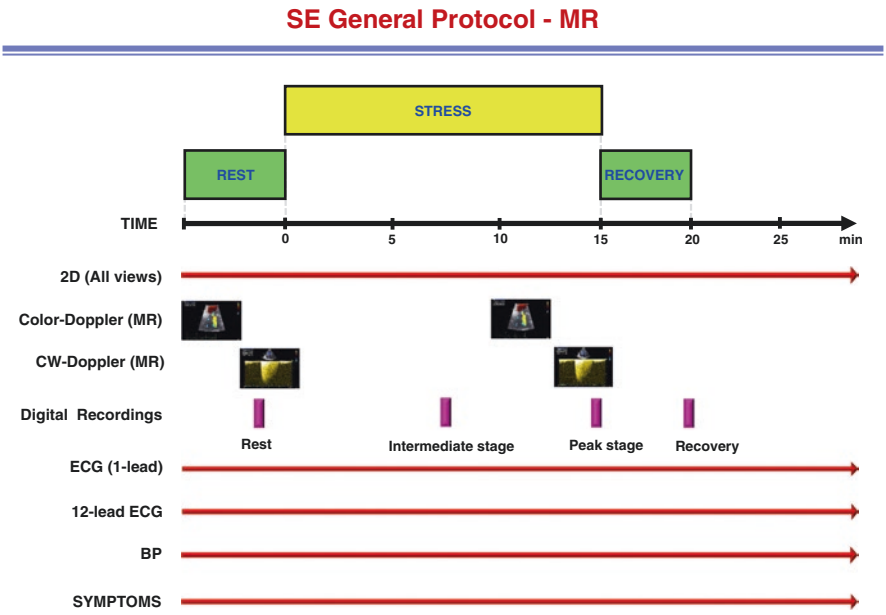

Fig. 6.2 General stress echo protocol focused on MR

Table 6.3 Protocol recommended for symptomatic non-severe primary mitral insufficiency

Suggested sequence of acquisition:	Rest	First stages	Peak stress	Recovery <2 min
1 2D (EF, WMSI, GLS, LAV)	v		v	
2 Color flow Doppler MR	v		v	
3 CW Doppler of MR	v		v	
4 TR CW Doppler	v	v	v	
5 LUS B-lines (and E/e')	v			v
6 M-mode (TAPSE)	v		v	

1. 2D LV apical views (4-, 2-, and 3-chamber views) 2. Color flow Doppler of MR (PISA, vena contracta, regurgitant jet) 3. CW Doppler of MR for PISA 4. TR CW or ACT PW Doppler for PASP estimation 5. Lung ultrasound 4-site scan for B-lines 6. M-mode for TAPSE
Adapted and modified from Garbi M et al. [7]

views for assessment of regional and global left ventricular function. Color flow Doppler is necessary for the quantification of severity by the proximal isovelocity surface area (PISA) method and vena contracta and continuous-wave Doppler of the MR for quantification of severity by the PISA method. Continuous-wave Doppler of the tricuspid regurgitant jet assesses the transtricuspid pressure gradient and estimates the systolic pulmonary artery pressure at the first stages of the exercise. Additional parameters are E/e', B-lines, and left atrial volume and strain. E/e' and B-lines can be easily acquired in the early recovery phase since B-lines show their peak value in the first minute of the recovery, and E/e' can be measured only when E and A waves are unfused, at heart rate < 110 typically present at rest and in the recovery phase. At peak, if PISA is not feasible, MR vena contracta is obtained.

6.3 Response Patterns During Stress

During stress, the three patterns of negligible (mild at rest–mild during stress), fixed (moderate rest–moderate during stress), and worsening (mild/moderate at rest–severe during stress) response can be found and cannot be predicted by resting findings.

The most frequent and benign response is a mild MR at rest, which remains mild during stress (Fig. 6.3, Video). MR quantification is not recommended.

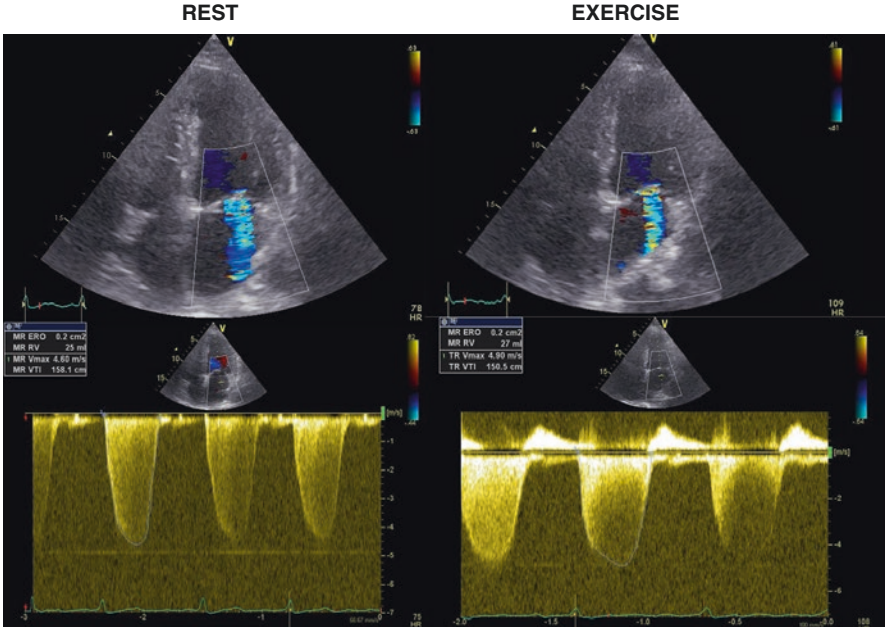

Fig. 6.3 Mild MR severity is unchanged during stress. Apical 4-chamber view showing color flow Doppler at rest and during exercise in a patient with MR of mild severity at rest (left panel) and during stress (right panel). (Video 6.1 courtesy of Dr. Angela Zagatina, Saint Petersburg, Russia). The video is available under the chapter's "Supplementary Material" on Springer Link

The moderate MR can remain unchanged during stress but quantification is recommended (Fig. 6.4, Video).

Moderate MR can worsen during stress, and in this case, the quantification of MR is mandatory since it can have a profound impact on the management of the patient (Fig. 6.5).

For clinical purposes, a semiquantitative estimation of MR severity is usually more than enough for absent and trivial MR (score 0), or mild MR in the case of a single, small, narrow, central, brief jet (score 1). An integration of semiquantitative and quantitative assessment is necessary in all remaining cases since a significant MR is increasingly recognized as an important prognostic factor and a potential therapeutic target, and its assessment, albeit not perfect, cannot be left to approximation and should be aligned with the best possible methodology. Semiquantitative assessment is based on vena contracta width obtained from the apical 4-chamber and 2-chamber views. Quantitative assessment requires the use of the PISA method. Regurgitant volume and EROA are measured using standard formulas. When there is a significant

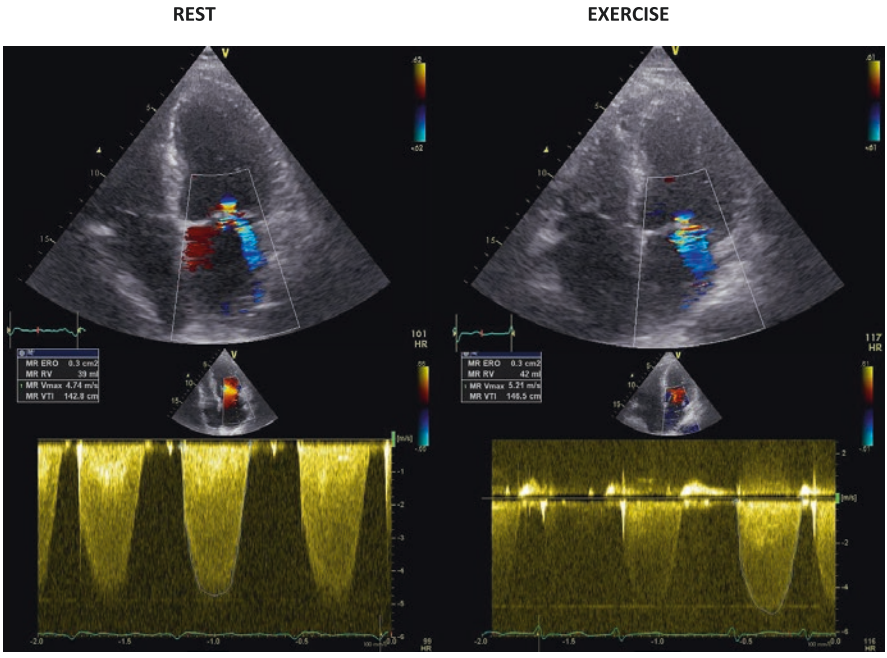

Fig. 6.4 Moderate MR severity is unchanged during stress. Apical 4-chamber view showing color flow Doppler at rest and during exercise in a patient with mitral regurgitation of moderate severity at rest (left panel) and during stress (right panel). (Video 6.2 courtesy of Dr. Angela Zagatina, Saint Petersburg, Russia)

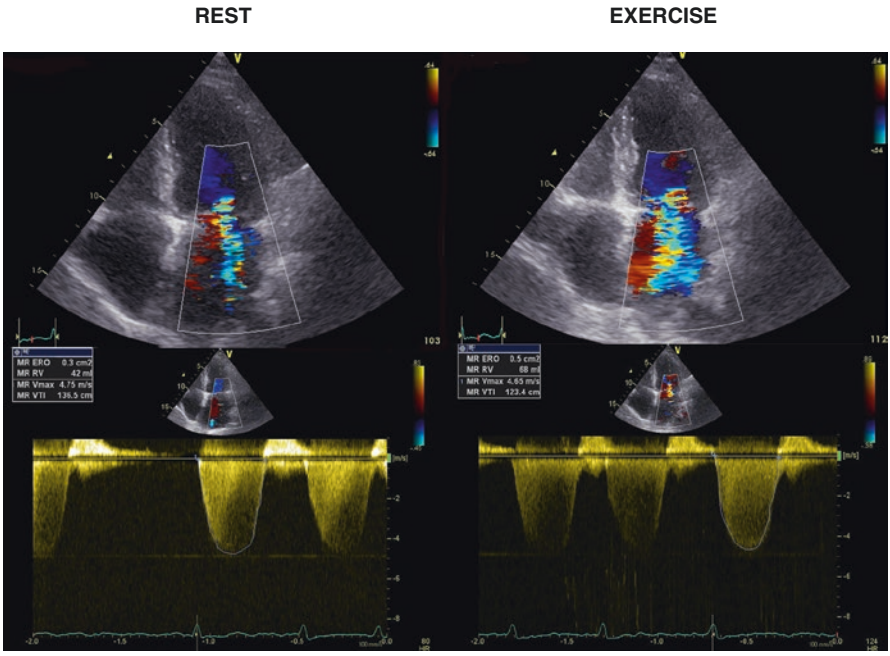

Fig. 6.5 Worsening MR pattern during stress. Apical 4-chamber view showing color flow Doppler and the proximal flow convergence region at rest (left panel) and during exercise (right panel) in a patient with a large exercise-induced increase in mitral regurgitation. ERO, effective regurgitant orifice; RVol, regurgitant volume. (Video 6.3 courtesy of Dr. Angela Zagatina, Saint Petersburg, Russia). The video is available under the chapter's "Supplementary Material" on Springer Link

MR, it is important to put the MR in the context of all other variables that can be explored with stress echo and are the causes or the consequences of MR, from left ventricular wall motion to left atrium dilation and pulmonary congestion. A mild MR at rest can worsen with severe ischemic MR at peak exercise in presence of extensive regional wall motion abnormalities (Fig. 6.6).

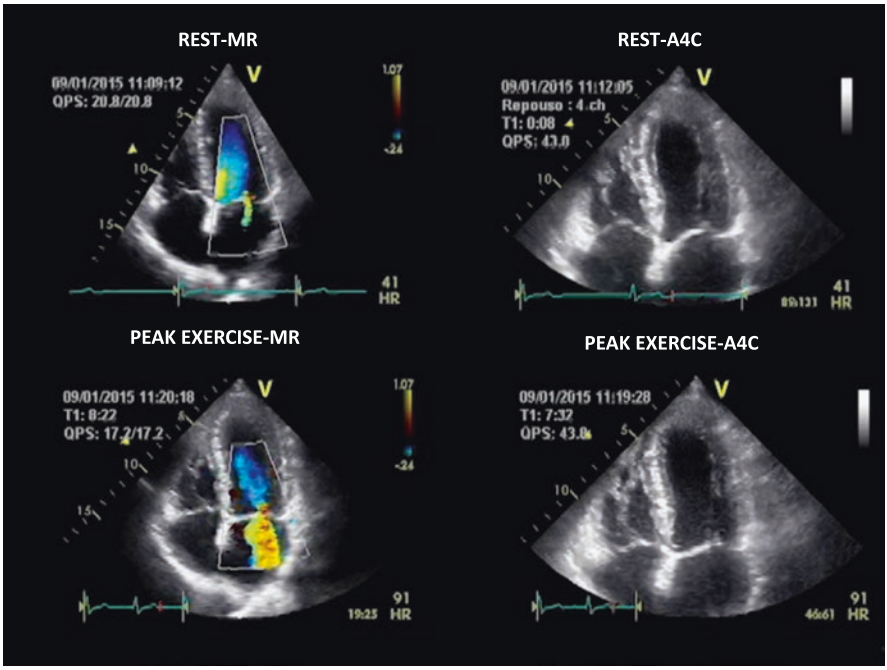

Fig. 6.6 Worsening ischemic MR pattern during stress. Apical 4-chamber view showing regional wall motion from apical 4-chamber view (right panels) and color flow Doppler (left panels) at rest (upper panels) and during exercise (lower panels) in a patient with a large exercise-induced increase in mitral regurgitation associated with a normal wall motion at rest and akinesis of the lateral and lateral–apical segments at peak exercise, with dilation of the end-systolic volume of the left ventricle. (Video 6.4 courtesy of Dr. Josè Luis Pretto, Passo Fundo, Brazil). The video is available under the chapter's "Supplementary Material" on Springer Link

6.4 Anatomic and Functional Correlates

In patients with chronic coronary syndromes, a stress-induced severe MR correlates with more severe and extensive underlying coronary artery disease [8]. In heart failure, severe MR during exercise is associated with left atrial enlargement and dysfunction, pulmonary hypertension, lung congestion, and right ventricular dysfunction with reduced anaerobic threshold during spiroergometry testing [9].

6.5 Outcome Data

The worsening of MR during exercise is a negative prognostic predictor during primary [10, 11] and secondary MR [12–14] due to heart failure [15] or hypertrophic cardiomyopathy [16].

6.6 Tips and Tricks

The precise assessment of the severity of MR with ultrasound is complex, time-consuming, and prone to uncertainties, approximations, and artifacts [17]. Accurate quantitative examinations take a significant extra-imaging and analysis time of a few minutes, and it cannot be done in a hurry, since the implications of a small calculation mistake can be large. Transthoracic echocardiography is the most used imaging technique to assess the presence and severity of MR, but even in expert hands in dedicated laboratories, the assessment of severity is neither simple nor precise. No single parameter is sufficiently reliable and a panel of parameters is used, but they are numerous, complex, and often give discordant results.

Even in dedicated settings, the reproducibility of MR quantification by transthoracic echocardiography remains only fair at rest. The interobserver agreement for EROA (0.61) and regurgitant volume (0.50) is suboptimal even between senior cardiologists specialized in echocardiography and valvular heart disease and assessing baseline conditions [18].

During stress, loading conditions and heart rate changes, and therefore, also the changing severity of MR must be evaluated with caution. In fact, for any given MR severity, the increase in systolic blood pressure will increase MR and the increase in heart rate will reduce the Doppler sampling rate per beat and therefore the reliability of the severity assessment [19]. The rise in systolic blood pressure during stress can also provoke an increase in MR area with color flow Doppler without a true increase in MR volume since color displays velocity and not flow. Stress may induce worsening or improvement of regional and global left ventricular function, and this may affect the severity of MR, which has a valvular and a myocardial component. When the left ventricle gets smaller and stronger during stress, the MR will decrease, and when the left ventricle gets larger and weaker, MR will increase. Therefore, changes in MR must always be put in the context of stress-induced changes in systemic hemodynamics and left ventricular function [20].

MR is usually reported at baseline and peak stress. Post-stress imaging in the recovery phase after exercise can be less useful since hemodynamic alterations normalize rapidly after stress. Minor shifts in severity within the same severity class or between adjacent severity classes or with discordant findings between different indices can be ignored to avoid clinical confusion to the referring physician. MR assessment by echocardiography will be easier and more reproducible with artificial intelligence techniques [21].

6.7 Clinical Guidelines and Recommendations

According to the 2017 recommendation of the American Society of Echocardiography and the European Association of Echocardiography and Cardiovascular Imaging on stress echo beyond coronary artery disease, MR must be reported according to specific diagnostic questions, since not everything can be looked for in all patients [22]. The preferred and only stress to test the mitral valve is exercise [23]. Dobutamine

increases stroke volume similarly to exercise, but changes in loading conditions are non-physiological and changes in MR during stress do not mirror those occurring with exercise. Vasodilators may induce informative changes in MR during stress in coronary artery disease patients only.

There is a limited place for exercise stress echocardiography in evidence-based guidelines on MR of major scientific cardiology societies [24, 25]. In chronic secondary MR, exercise stress echo is useful (class of recommendation 1, level of evidence C) to establish the etiology of MR and to assess myocardial viability since there is a subset of patients with viable myocardium in whom the ischemic MR will improve after revascularization [25]. In chronic primary MR, exercise stress echo can be reasonable (class of recommendation 2a, level of evidence B) to document that MR of increasing severity or with increased filling pressures can be the cause of symptoms [25]. The severity and functional impact of MR at rest can change dramatically during exercise and it is the hemodynamic burden during daily life activities that will likely impact functional status and prognosis [26]. Event-free survival is lower in those asymptomatic patients with severe primary MR who have a reduced exercise capacity despite good left ventricular function and normal left ventricular dimensions at rest and during exercise [27]. Left ventricular global longitudinal strain and changing global longitudinal strain $\leq 2\%$ during exercise emerged as useful in the risk stratification of asymptomatic patients with primary MR, which is independently associated with a more than twofold increase in the risk of a cardiac event during the follow-up [28]. The increase in MR severity and dynamic pulmonary hypertension (systolic pulmonary arterial pressure > 60 mmHg) also are predictors of a worse prognosis. Asymptomatic patients with primary MR presenting an abrupt increase in systolic pulmonary arterial pressure > 15 mmHg at the first step of exercise have a twofold increase in the risk of cardiac events [29]. Conversely, a decrease in MR severity, often related to recruited left ventricular contractile reserve, is a marker of better outcomes with medical treatment.

The dynamic changes in MR can be reliably assessed by stress echocardiography, and this may potentially influence revascularization strategies and interventional treatment, including cardiac resynchronization therapy and mitral valve repair in secondary MR [30]. With or without regional wall motion abnormality, the absence of a severe MR during stress is associated with a more benign prognosis.

Prospective large-scale and randomized outcome studies are needed to support more evidence-based, stress echo-driven treatment strategies in the evidence-poor field of primary and secondary MR [31]. In addition, a comprehensive stress echo evaluation may include important determinants of mortality such as pulmonary congestion, left ventricular contractile reserve, chronotropic response, and heart rate reserve, when possible coronary flow reserve in the left anterior descending coronary artery. This is the plan of the stress echo 2030 study, in the subproject on stress echo in secondary ischemic MR (project 10, SEMIR, stress echo in mitral ischemic regurgitation) and primary MR (part of project 11, SEVA, stress echo in valvular heart disease) (Fig. 6.7).

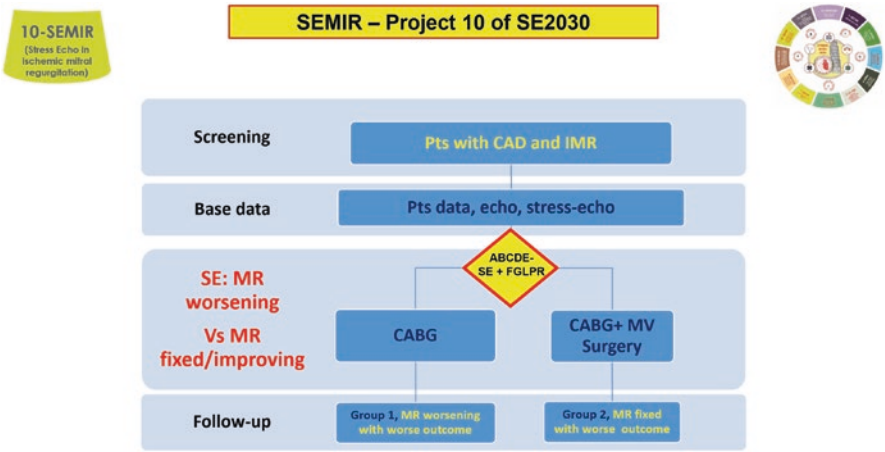

Fig. 6.7 Study protocol of the SEMIR study (subproject 10 of Stress Echo 2030). Another subproject (subproject 11) addresses the value of comprehensive stress echo in non-ischemic MR as a part of the SEVA (stress echo in valvular disease) subproject. MV Surgery, mitral valve surgery

About 500 patients will be recruited until 2025 and followed up until 2030, to establish the much-needed evidence-based framework for the clinical use of exercise stress echo in MR [32].

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Step G for Gradients in Stress Echocardiography

7

Carlos Cotrim and Eugenio Picano

Keywords

Athletes · Heart failure with preserved ejection fraction · Hypertrophic cardiomyopathy · Standing · Systolic anterior motion · Upright position

7.1 Preload, Contractility, and Dynamic Gradients

The aortic valve opening in systole requires the coordination of several functionally interdependent, yet anatomically distinct, components, from left ventricular (LV) cavity dimension to wall function and synchrony, papillary muscles, chordae tendineae, and mitral valve leaflets, all contributing to an efficient ejection with an adequate stroke volume and developed arterial pressure in an unobstructed LV outflow tract (LVOT) with a non-critical LV outflow tract gradient (LVOTG) [1]. LVOTG disproportionately increases, at rest or dynamically during exercise stress echocardiography (SE) or other forms of hemodynamic stress, when the LVOT is obstructed by anatomic or functional components. Septal hypertrophy, small and/or hyperkinetic left ventricle, elongated anterior mitral leaflet, anteriorly displaced or

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C. Cotrim (✉)
Heart Center, Departamento de Ciências Biomédicas e Medicina (UALG), (Hospital da Cruz Vermelha, UCARDIO, Hospital Particular do Algarve), Lisboa, Portugal

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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bifid anterior hypermobile papillary muscle, and mitral annulus calcification represent the anatomic or functional background triggering left ventricular outflow tract obstruction (LVOTO) in the presence of reduced LV filling and increased contractility (Fig. 7.1).

High flow in LVOT generates the Venturi effect and dynamic LVOTO or midventricular obstruction (MVO), possibly causing symptoms such as hypotension, dyspnea, angina, and syncope. The obstruction is dynamic but favoring factors can be structural and treatable, from the hypertrophic septum to elongated anterior mitral valve leaflets to bifid anteriorly misplaced anterior papillary muscle. Dynamic LVOTO or MVO (also called obstructive phenotype) is a common condition in a variety of different cardiovascular diseases, and it may contribute to causing symptoms (Table 7.1): hypertrophic cardiomyopathy (HCM) [2]; aborted sudden death in hearts without structural alterations also in athletes [3]; hypertensive LV hypertrophy especially with a sigmoid septum in the elderly [4]; a subset of patients with ischemia and angiographically normal coronary arteries [5, 6] or myocardial infarction with hyperdynamic-type hemodynamic phenotype [7]; hyperkinetic left

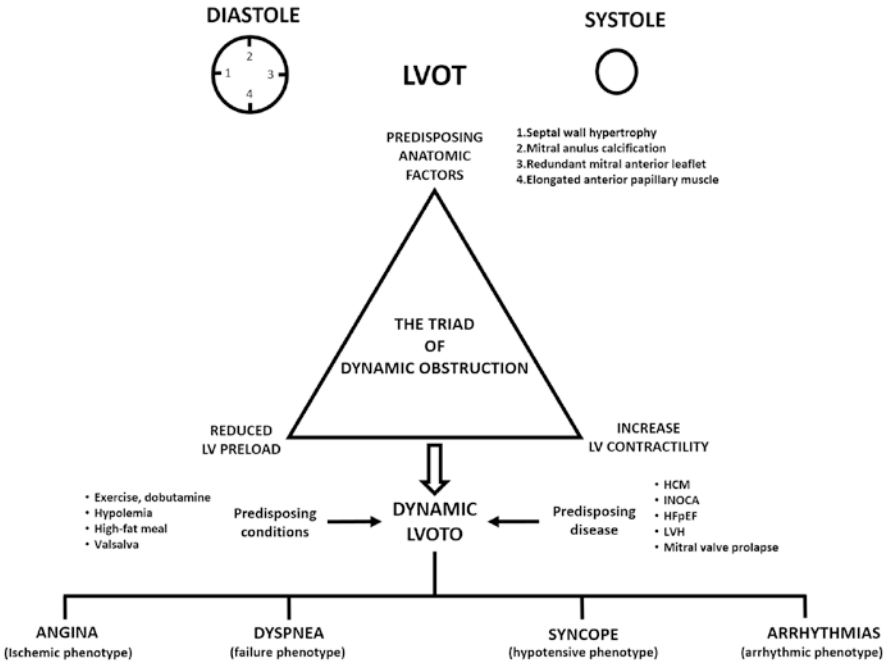

Fig. 7.1 LV outflow area at end diastole and end systole. The normal end-diastolic (ED) area of the LV outflow tract of 3 cm^2 becomes only mildly reduced to 2.0 cm^2 at end systole (ES) for the coordinated action of anatomic and functional components: LV septal wall thickness; LV cavity dimension; LV wall function and synchrony; papillary muscles; chordae tendineae; and mitral leaflets. The triad favoring dynamic obstruction is made by predisposing anatomic factors reducing LVOT in systole, increased LV contractility, and reduced LV preload

Table 7.1 LV gradients at rest or during stress in different clinical conditions

	Location of gradient	Presenting symptom
VHD	Transvalvular gradient	Dyspnea
CHD	Transvalvular gradient	Dyspnea
HFpEF	Intraventricular gradient	Dyspnea
HCM	Intraventricular gradient	Dyspnea or chest pain
Genotype-positive HCM	Intraventricular gradient	Dyspnea or syncope
Aborted sudden death	Intraventricular gradient	Syncope
Athletes	Intraventricular gradient	Syncope or chest pain
Hypertensive LVH	Intraventricular gradient	Dyspnea or syncope
INOCA	Intraventricular gradient	Chest pain
Sigmoid septum	Intraventricular gradient	Dyspnea or syncope
Hyperkinetic LV	Intraventricular gradient	Dyspnea or syncope
Takotsubo	Intraventricular gradient	Dyspnea or syncope
Post-MV interventions	Intraventricular gradient	Dyspnea or syncope
Liver failure	Intraventricular gradient	Dyspnea or syncope

CHD congenital heart disease, *HCM* hypertrophic cardiomyopathy, *HFpEF* heart failure with preserved ejection fraction, *INOCA* ischemia with angiographically normal coronary arteries, *LVH* left ventricular hypertrophy, *MV* mitral valve, *VHD* valvular heart disease

ventricle [8]; Takotsubo cardiomyopathy [9]; and end-stage liver disease [10]. Sometimes, a dynamic obstruction can coexist with a structural cause such as aortic stenosis [11], mitral annulus calcification or after mitral valve interventions reducing native LVOT area [12], and anterior mitral valve leaflet elongation [13] or hypermobile anteriorly positioned papillary muscle frequently coexisting with HCM [14]. LVOTO is present in some forms of congenital heart disease for structural causes such as membranous subaortic stenosis and tunnel aortic stenosis but also for purely functional causes such as LVOTO related to atrioventricular septal defects [15].

The prototype of dynamic LVOTO or MVO is the one found in HCM, but not all patients with HCM have the obstructive phenotype, and not all patients showing LVOTO or MVO have HCM. Dynamic LVOTO is more difficult to recognize than fixed obstruction since it can be absent at rest and still be the cause of clinical symptoms occurring in daily life activities. A high flow in a narrow LVOT generates a Venturi effect in the LVOT, which results in the attraction of the anterior mitral leaflet toward the interventricular septum causing LVOTO. It can be the cause of hypotension and dyspnea through a reduction in forwarding aortic flow due to mid-systole or late-systole obstruction. LVOTO increases the vulnerability to ischemia and arrhythmias since it rises myocardial oxygen demand with the increase in wall stress and reduces oxygen supply through systemic hypotension and increase in extravascular resistances.

LVOTO can worsen with the administration of inotropes or diuretics. When recognized, it can be effectively treated with fluid administration, weaning of adrenergic agents, and whenever possible beta-blockers or interventions targeted to the morphologic substrate favoring obstruction, which is not always only one.

The obstructive phenotype is frequently ignored, but is a relatively frequent and complex entity that deserves attention and may offer unique, therapeutically relevant information in disparate clinical settings, from the intensive care unit [16, 17] to the SE laboratory [18]. The evaluation at rest and in the supine position is the standard way in everyday practice but may not reflect the real impact of this mechanism in daily life activities that may trigger symptoms such as dyspnea or angina or syncope [19]. The standing position and the administration of stress are needed to unmask a suspected occult LVOTO [20]. In the majority of cases, these alterations remain latent and borderline at rest and can be elicited during stress, especially with exercise [21, 22] and dobutamine [23, 24]. The gradient induced by dobutamine in this context is possibly meaningless from the clinical point of view.

7.2 Methodology

Two-dimensional echocardiography and color Doppler are a guide to the definitive assessment of flow velocity with continuous-wave Doppler. Imaging is best done in the standard left lateral decubitus and again in the orthostatic position (Fig. 7.2).

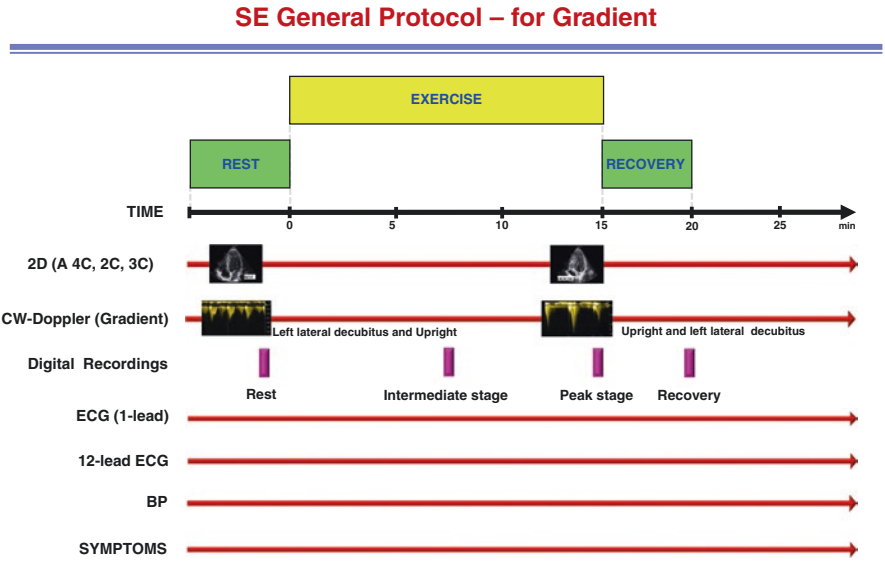

Fig. 7.2 Methodology for assessment of LVOTG. Two-dimensional echocardiography, color Doppler, and continuous-wave Doppler are performed at rest and peak stress, when possible both in the left lateral decubitus and upright position. The best stress is a treadmill with peak imaging acquisition; the second best is the upright bicycle. If the semi-supine bike is used, the patient can be imaged while standing immediately at the exercise stop. Hypercontractility with a small cavity and systolic anterior motion of the mitral valve is imaged by 2-dimensional echocardiography, mosaic pattern with flow turbulence in LVOT by color Doppler, and the quantification of gradients is made possible with measurement of flow velocity by continuous-wave Doppler

7.3 The Main Signs of Obstruction and Response Patterns

A red flag for dynamic obstruction is a hypertrophic, hyperkinetic, small left ventricle during stress, with a systolic anterior motion of the mitral valve and color Doppler turbulence in the LV outflow tract leading to the assessment of late-peaking increased flow velocity with continuous-wave Doppler allowing to establish the diagnosis and severity of intraventricular dynamic obstruction (peak flow velocity > 3.0 m/s). LVOTO can be found in 5% of patients referred for SE and without HCM and is more likely with smaller end-systolic LV, higher systolic blood pressure, increased septal wall thickness at rest, and chordal systolic anterior motion at rest or during stress [25] (Table 7.2).

An example of an increase in dynamic obstruction in a patient without HCM is shown in Fig. 7.3 The peak flow velocity is increased, and the flow profile has a peculiar late-peaking dagger-shaped profile. The obstruction occurs in the LVOT.

Another example of an increase in dynamic obstruction in a patient without HCM is shown in Fig. 7.4 In this case, the obstruction occurs in the MVO.

An example of an increase in dynamic obstruction in a patient with HCM is shown in Fig. 7.5.

The degree of flow increases during stress, the type of exercise, and the underlying clinical conditions are essential to put these hemodynamic data in context. It is especially important to reproduce the conditions leading to symptoms in that particular patient. LVOTO or MVO can be absent at rest or even during stress, yet it can represent the underlying cause of life-threatening conditions in daily life. The stress can be adapted and tailored to the individual patient rather than standardized with a one-fits-all approach, which sometimes can be deceptively reassuring (Fig. 7.6).

The cutoff value for LVOTO is usually set at late-peaking Doppler velocity values ≥3.0 m/s [25]. However, values of LVOTO with peak jet velocity ≥ 3 m/s can occur in one of three healthy young normals with upright exercise and are simply the expression of the physiologic increase in LV contractility and increased flow with reduced preload [26]. Conditions transiently reducing venous return and LV preload such as de-hydration, high-fat meal, anemia, and high room temperature may increase LVOTO at rest and during stress [27]. Any decision based mainly or only on resting LVOTO in HCM should consider the many factors modulating the

Table 7.2 Echocardiographic findings associated with LVOTO

	Rest 2D	Stress 2D	Stress color Doppler	Stress CW Doppler
Septal wall	Too thick			
Anterior leaflet MV	Too long			
Anterior papillary muscle	Too anterior			
LV ESV		Too small		
LV EF		Too high		
Mitral valve		SAM		
Peak flow velocity			Turbulence	>3.0 m/s
Flow shape				Late peak

CW Continuous wave, *EF* ejection fraction, *ESV* end-systolic volume, *MV* mitral valve, *SAM* systolic anterior motion

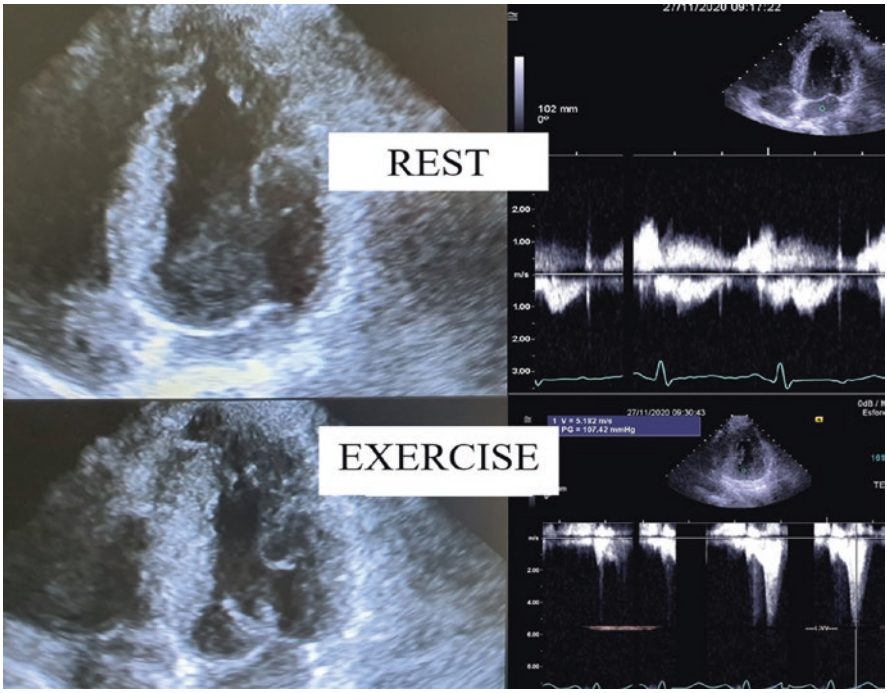

Fig. 7.3 Obstructive phenotype with LVOTO in a young patient with exercise-related syncope and without HCM. Upper panel: rest, lower panel: exercise. LVOTG is normal at rest (right upper panel) and at peak exercise is 107 mmHg (right lower panel), with systolic anterior motion (left lower panel)

gradient independently of LVOTO severity, from postprandial state to anemia [28, 29]. In HCM, a greater increase in dynamic gradients predicts a higher risk for sudden death and heart failure in the long term and better response to obstruction-relieving therapy with surgical, interventional, or pharmacological means. Also in patients with angina and angiographically normal coronary arteries, the attenuation of LVOTO with beta-blockers during exercise predicts symptomatic improvement [30].

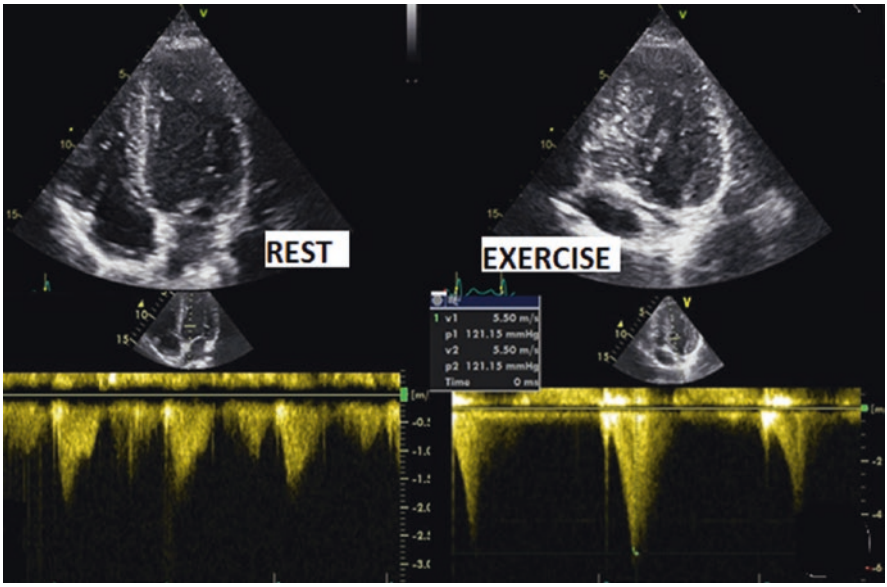

Fig. 7.4 Obstructive phenotype with MVO in a young triathlon athlete with aborted sudden death without HCM. Left panel: rest, right panel: exercise. There is no wall hypertrophy. During exercise, there is a reduction in the end-systolic volume of the left ventricle with an increased velocity with continuous-wave Doppler. The intraventricular gradient at peak exercise is 121 mmHg. See the accompanying video (Video 7.1). (Video image courtesy of Carlos Cotrim, Lisbon, Portugal). The video is available under the chapter's "Supplementary Material" on Springer Link

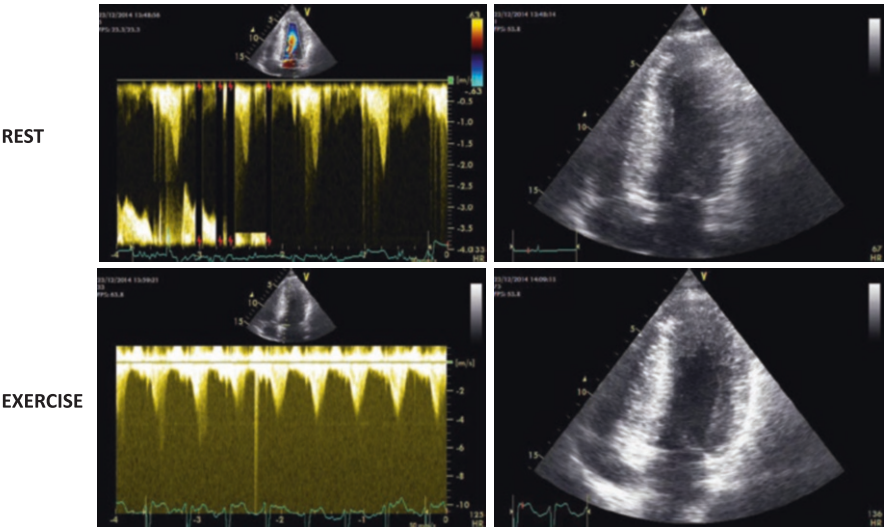

Fig. 7.5 Obstructive HCM before exercise became severely obstructive during and after exercise in an orthostatic position during ESE on a treadmill. Upper panel: rest, lower panel: exercise. See the accompanying video (Video 7.2). (Video image courtesy of Carlos Cotrim, Lisbon, Portugal). The video is available under the chapter's "Supplementary Material" on Springer Link

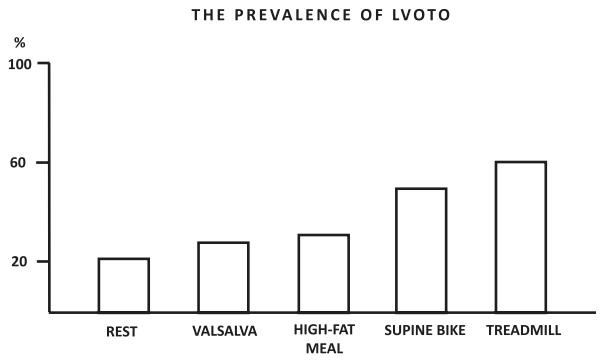

Fig. 7.6 Prevalence of dynamic gradients during stress in HCM. The prevalence of dynamic obstruction is low at rest, higher during Valsalva (which mildly reduces preload), increases during exercise (increasing contractility) with imaging in the supine position, and further increases with post-exercise imaging in the orthostatic position (reducing preload). The unmasking of dynamic gradients can be further potentiated with exercise after 2 h of high-fat meal ingestion with splanchnic vasodilation reducing venous return

7.4 Tips and Tricks

The antegrade systolic velocity across the narrowed aortic valve, or aortic jet velocity, is measured using continuous-wave Doppler ultrasound. Aortic stenosis jet velocity is defined as the highest velocity signal obtained from any window after a careful examination; lower values from other views are not reported. The acoustic window that provides the highest aortic jet velocity is noted in the report and usually remains constant in sequential studies in an individual patient. The apical window is usually the preferred approach [31].

Usually, three or more beats are averaged in sinus rhythm, and averaging more beats is mandatory with irregular rhythms (at least five consecutive beats). Special care must be taken to select representative sequences of beats and to avoid post-extrasystolic beats.

The shape of the continuous-wave Doppler velocity curve is helpful in distinguishing the level and severity of obstruction. Although the time course of the velocity curve is similar for fixed obstruction at any level (valvular, sub-valvular, or supra-valvular), the maximum velocity occurs later in systole and the curve is more rounded in shape with more severe obstruction. With mild obstruction, the peak is in early systole with a triangular shape of the velocity curve, compared with the rounded curve with the peak moving toward mid-systole in severe stenosis, reflecting a high gradient throughout systole. The shape of the continuous-wave Doppler velocity curve also can be helpful in determining whether the obstruction is fixed or dynamic. Dynamic subaortic obstruction shows a characteristic late-peaking velocity curve, often with a concave upward curve in early systole.

There are recognized sources of error that must be minimized when measuring gradients: malalignment of jet and ultrasound beam, recording of mitral regurgitation jet, effects of flow, and posture. In general, the measurement of gradients is accurate and quantitative, repeatable, highly feasible, and simple.

The best way to detect LVOTO with exercise is to image the heart with the patient maintaining or assuming the orthostatic position immediately after cessation of exercise. This approach differs from the standard imaging with semi-supine exercise, with the patient lying in semi-supine decubitus before, during, and after exercise. The standard approach with treadmill exercise may also miss a significant dynamic LVOTO since the patient is imaged in semi-supine decubitus immediately after exercise for echocardiographic imaging. The value of orthostatic imaging is not surprising for the clinical cardiologist familiar with cardiac auscultation. Since the pre-imaging era, it is known that the systolic murmur of HCM increases with standing (reducing preload) and Valsalva (reducing venous return with increasing intrathoracic pressure) and decreases with squatting and passive leg lift (increasing preload). SE follows the footsteps of semiology since both are guided by simple pathophysiology principles.

An example of the interaction between preload, contractility, and gradients is given by the prevalence of obstruction (<30 mmHg at rest and > 50 mmHg during provocative maneuver) in HCM. The prevalence rate is 20% at rest, rises to 30% after the Valsalva maneuver (reducing venous return and LV preload), to 60% during treadmill with echo imaging in the post-exercise phase in the supine position, and to 75% if the patient is kept standing after treadmill, with the persistent increase in LV contractility coupled with the marked fall in venous return and LV filling. Lower preload and increased contraction both contribute to the smaller cavity and the increased gradient (Fig. 7.7). Upright exercise imaging should be the standard approach in patients with an elusive cause of potentially life-threatening symptoms such as syncope or near syncope or aborted sudden death on exercise with or without HCM.

The assessment of dynamic gradients in the orthostatic position is especially recommended in HCM, since dynamic gradients have important therapeutic implications. A non-obstructive form of HCM at rest can become obstructive during exercise and show a severe obstruction during orthostatic recovery after exercise (Fig. 7.8).

In other cases of HCM, the critical threshold of 50 mm Hg of the gradient can only be unmasked by the orthostatic position soon after exercise (Fig. 7.9).

Two-dimensional images may focus on the systolic anterior motion of the mitral valve at rest, absent at rest, present at peak exercise, and severe after exercise in the orthostatic position (Fig. 7.10).

The search for LVOTO or MVO as an explanation for symptoms of our patients is also important in children [30] or old age [31] and is easy to do, carefully adapting exercise protocol to each patient.

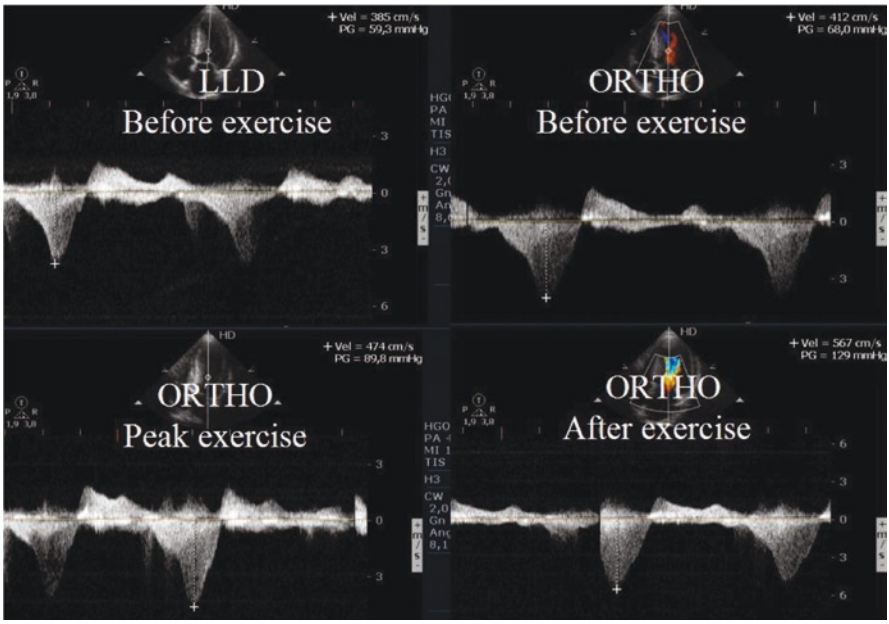

Fig. 7.7 LV outflow peak gradient during exercise in a symptomatic athlete. At rest, in left lateral decubitus, the peak velocity is 385 cm/s corresponding to a gradient of 59 mmHg (left upper panel). In the orthostatic position at rest, the peak velocity slightly rises to 412 cm/s corresponding to a peak gradient of 68 mmHg (right upper panel). At peak treadmill exercise, with the patient in the orthostatic position, the peak velocity is 474 cm/s corresponding to a gradient of 89 mmHg (left lower panel). At the exercise stop, with the patient in the orthostatic position, the peak velocity is 567 cm/s corresponding to a gradient of 129 mmHg (right lower panel) (from Cotrim et al., [31])

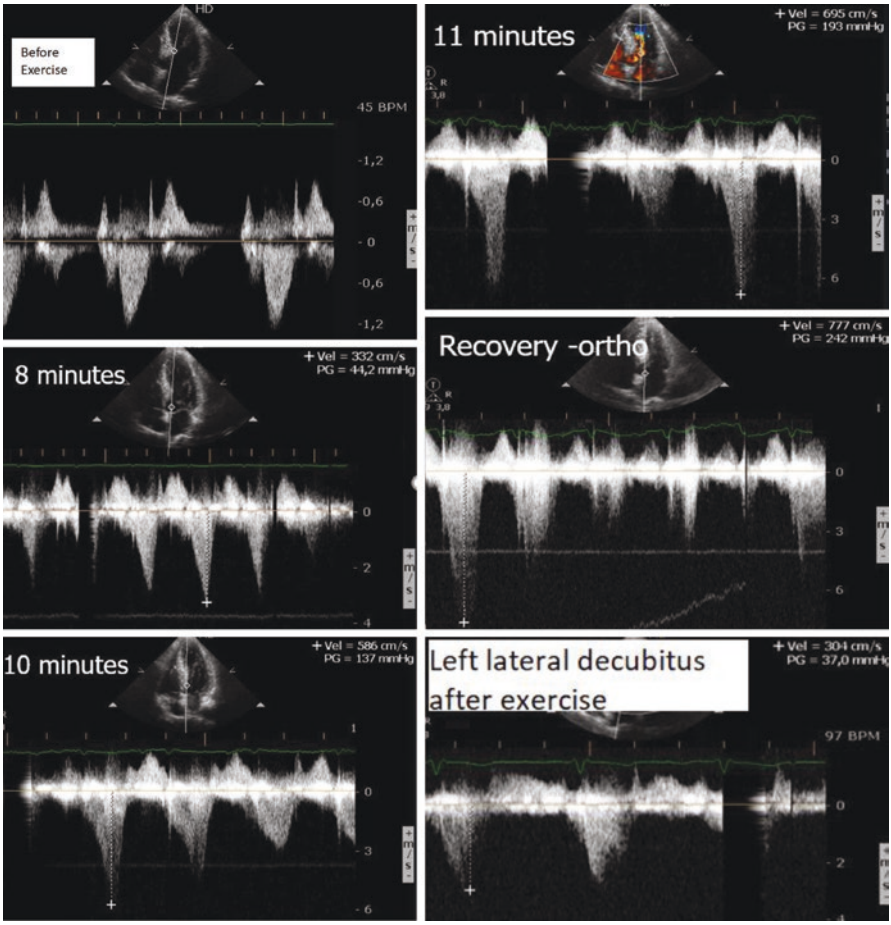

Fig. 7.8 LV outflow peak gradient during exercise in a patient with HCM. At rest, in left lateral decubitus, the peak velocity is <100 cm/s corresponding to a nonsignificant gradient. During exercise, the peak velocity gradually increases to 332 cm/s, peak gradient of 44 mmHg at 8 min of exercise (left middle panel), 586 cm/s (peak gradient of 137 mmHg) at 10 min of exercise (left lower panel), and 695 cm/s (peak gradient of 193 mmHg) at 11 min of exercise (right upper panel). In the early recovery phase, with the patient in an orthostatic position, the peak velocity is 777 cm/s corresponding to a gradient of 242 mmHg (right middle panel). At the exercise stop, with the patient again in the left lateral decubitus position, the peak velocity is 304 cm/s corresponding to a gradient of 37 mmHg (right lower panel) (by courtesy of Carlos Cotrim, Lisbon, Portugal)

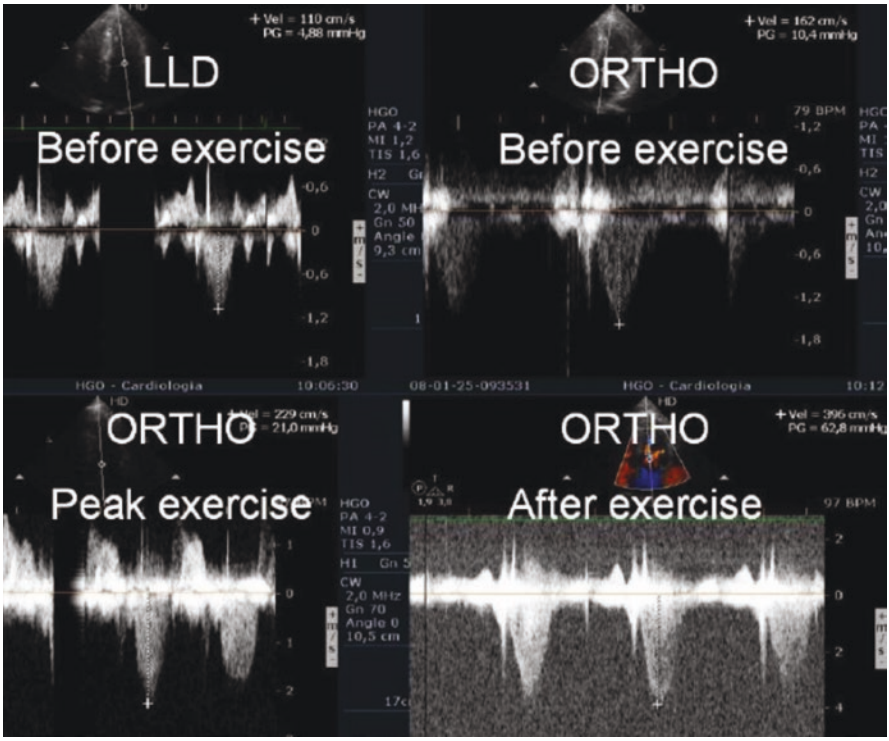

Fig. 7.9 LV outflow peak gradient during exercise in a symptomatic patient with HCM. At rest, in left lateral decubitus (LLD), the peak velocity is 110 cm/s corresponding to a gradient of 4.9 mmHg (left upper panel). In the orthostatic position at rest, the peak velocity slightly rises to 162 cm/s corresponding to a peak gradient of 10.4 mmHg (right upper panel). At peak treadmill exercise, with the patient in an orthostatic position, the peak velocity is 229 cm/s corresponding to a gradient of 21 mmHg (left lower panel). At the exercise stop, with the patient still in the orthostatic position, the peak velocity is 396 cm/s corresponding to a gradient of 62 mmHg (right lower panel) (by courtesy of Carlos Cotrim, Lisbon, Portugal)

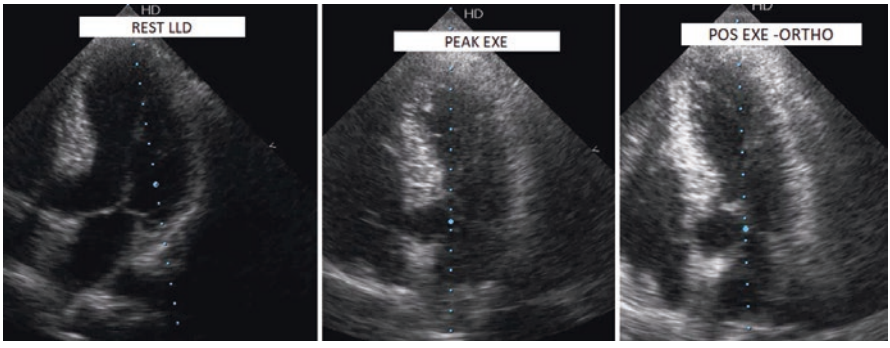

Fig. 7.10 Systolic anterior motion of the mitral valve in a patient with HCM: absent at rest (left panel), present at peak exercise (middle panel), and severe at post-exercise in the orthostatic position (right panel). See the accompanying video (Video 7.3). (Video images courtesy of Carlos Cotrim, Lisbon, Portugal). The video is available under the chapter's "Supplementary Material" on Springer Link

Table 7.3 Cutoff values of significant stress gradients

Condition	Parameter	Cutoff	Stenosis
Aortic stenosis	Mean gradient	≥40 mmHg	Fixed
Aortic prosthesis	Mean gradient	Δ > 20 mmHg	Fixed
Aortic coarctation	Peak gradient	>30 mmHg	Fixed
HFpEF	Peak LVOTG	>30 mmHg	Dynamic
HCM	Peak LVOTG	>50 mmHg	Dynamic
Athletes	Peak LVOTG	> 50 mmHg	Dynamic

Δ stress to rest change, *HCM* hypertrophic cardiomyopathy, *HFpEF* heart failure with preserved ejection fraction, *LVOTG* left ventricular outflow tract gradient

7.5 Clinical Guidelines and Recommendations

As suggested by the 2017 recommendations on SE beyond coronary artery disease released by the American Society of Echocardiography and the European Association of Cardiovascular Imaging, transvalvular and intraventricular pressure gradients should be reported according to specific diagnostic questions, since not everything can be looked for in all patients [32]. The clinical conditions, the main parameter, and the diagnostic cutoff values are reported in Table 7.3.

Exercise represents the only physiological and most effective form of gradient provocation. In symptomatic patients with HCM who do not exhibit an LVOTG of ≥50 mm Hg during standard echocardiographic evaluation, an exercise SE assessment should be performed to detect and quantify LVOTO (class of recommendation 1). For asymptomatic individuals, the class of recommendation is 2b considering that exercise SE provides a comprehensive understanding of their individual pathophysiology [33]. Regardless of symptomatic status, LVOTG assessment during exercise should be performed (class of recommendation 1) in every HCM patient without resting obstruction who has a positive history of syncope [34]. According to the recent European Society of Cardiology guidelines on sports cardiology, all individuals with HCM who wish to participate in sports activity should have the LVOTG assessed after light exercise [35]. Moreover, outside HCM, the assessment of LVOTG can elucidate the hidden cause of unexplained dyspnea, exertional fatigue, post-exercise dizziness, or syncope in athletes or in patients with suspected heart failure with preserved ejection fraction [32] or congenital heart disease [36].

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Step L for Left Atrium Stress Echocardiography

8

Costantina Prota and Eugenio Picano

Keywords

Atrial strain · Diastole · Preload reserve · Reservoir function

8.1 The Physiology of the Left Atrium

The left atrium (LA) is a highly dynamic chamber and plays an active part in the physiology of the entire cardiovascular system [1]. Left atrial volume (LAV) by two-dimensional echocardiography is an accurate measure of LA size. It is an integral part of the standard assessment of left heart function. An increase in the LA volume index (LAVI) is considered a hallmark of diastolic dysfunction and chronically elevated left ventricular (LV) filling pressures [2]. Moreover, LA dilation at rest has an important prognostic value, since it is associated with a higher risk of adverse events in many cardiovascular conditions, including coronary artery disease, hypertension, atrial fibrillation, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, hypertrophic cardiomyopathy, sleep apnea, renal failure, stroke, and valvular or congenital heart disease [3]. Experts agree that measurements of LA should be performed not only in the resting state but also during stress echocardiography (SE) [4].

The LA has a pivotal role in the sequence of events that modulate LV filling. During LV diastole, LA and LV are interdependent and complementary. Preserved

C. Prota (✉)
UTIC/Cardiologia, Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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LA function could prevent patients with impaired LV diastolic function from developing symptoms of heart failure; on the contrary, an underperforming LA can, at least partially, influence the LV function [5].

Experimental studies demonstrate that LAV may change over seconds or minutes when the hemodynamic conditions are modified. It can acutely either decrease in the presence of LV unloading [6] or augment for increased LA preload [7]. A Frank–Starling mechanism similar to the left ventricle exists also for LA, with increased function for increasing volumes up to a point when increasing LAV leads to a fall in atrial performance. LA structural, electrical, and functional remodeling leads to future LA cardiomyopathy with LA fibrosis and LA failure [8]. In theory, a stress-induced dilation can identify an early stage in the classic cascade of events of atrial disease based upon resting LAVI, with the possibility to identify incipient atrial failure when resting LAVI is still normal or near-normal [9].

The physiologic response to the stress of a healthy heart, of young subjects with small resting LAVI and trained athletes, is a reduction or mild increase in LAV and an increase in LA function, but no net changes are detectable at cumulative analysis in coronary artery disease, heart failure, and valvular or hypertrophic cardiomyopathy patients [10–16]. There are profound differences in individual responses. Patients with normal resting LAVI can dilate during stress, and patients with dilated resting LAVI are capable to decrease during stress. Indeed, reversible damage of LA may be more likely when resting LAVI is dilated but capable to decrease during stress (Fig. 8.1).

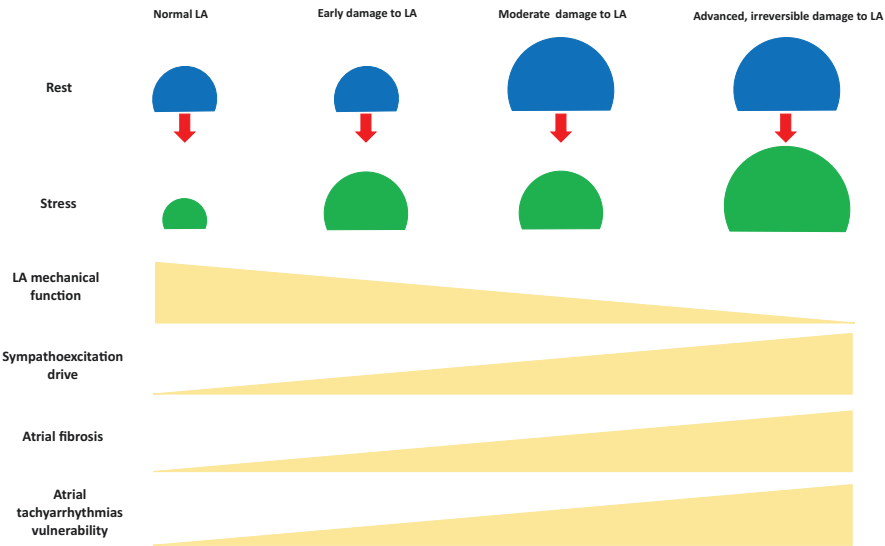

Fig. 8.1 Natural history of LA dysfunction. LAV and function are normal at rest with stress-induced volume reduction and function increase in normal healthy conditions. At an initial stage of disease, the left atrial functional reserve can be impaired with a lack of volume reduction during stress due to the need to recruit preload reserve to face the increased left atrial filling pressures. At an advanced stage of the disease, LAV is increased at rest and decreases during stress for recruitment of left atrial contractile reserve. At a further irreversible stage, LA is dilated at rest and further dilates during stress. Throughout all these stages, atrial fibrosis progressively increases and so do the sympathetic drive and the vulnerability to develop atrial tachyarrhythmias

LAV measurement evaluates LA size but misses potentially important information on the complex LA global function, usually divided into a reservoir, conduit, and contractile (booster pump) function, which requires an integration of volumetric two-dimensional echocardiography, spectral Doppler, tissue Doppler, and deformation indices [17]. LA acts as a reservoir for pulmonary venous return during ventricular systole, a conduit for pulmonary venous return during early ventricular diastole, and a booster pump for ventricular filling during late ventricular diastole. In a normal subject, the atrial contribution to ventricular stroke volume by the reservoir, conduit, and booster function is 40%, 35%, and 25%, respectively.

The volumetric analysis of LA using LAVI remains an adequate approach to estimate the cumulative effect of increased LV filling pressures over time, but with limitations in detecting early LV diastolic alterations, considering this volumetric parameter reflects mainly the chronic effect of increased LV filling pressures. Recent findings have found that a new LA functional parameter, LA strain, has a strong correlation to invasive gold standard diastolic measurements and LV filling pressures, even better than LAVI [18]. In particular, the LA reservoir peak atrial longitudinal strain (PALS) is the most important and easiest parameter to measure LA function. The physiologic stress response is an increase in LA strain, especially in LA reservoir function (Fig. 8.2).

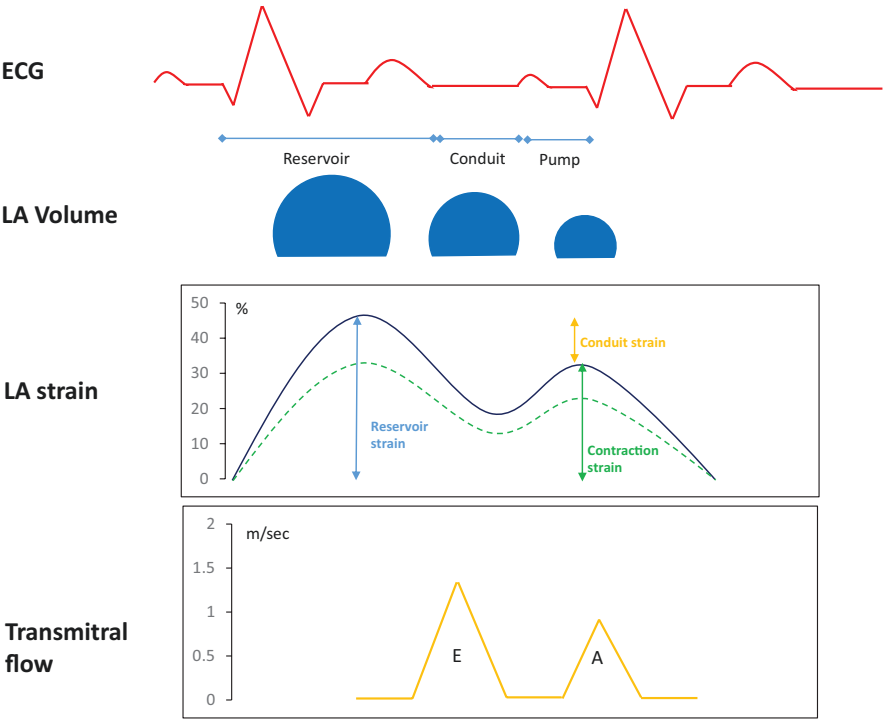

Fig. 8.2 LA functions. Left atrial functions: reservoir, conduit, and booster pump synchronized with electrocardiographic (top row), volumetric (second row), atrial strain (third row), and transmitral flow (last row) events. The booster pump corresponds to the P wave of the electrocardiogram and A wave of mitral inflow and contributes 25% to the overall LV stroke volume

Table 8.1 Main descriptors of LA size and function and their response during stress

Parameter	Imaging	Meaning	Normal response	Abnormal response
LAVI	2D-ES	Morphology	Decrease—unchanged	Marked increase
LA EF	2D, ED/ES	Global function	Increase	Blunted increase
PALS	2D strain	Reservoir function	Increase	Decrease

Due to its important diagnostic and prognostic impact and thanks to its high feasibility and simplicity to acquire, a complete LA study should be part of SE in conditions when LA is suspected to play a role, from heart failure with preserved ejection fraction to valvular heart disease. Indeed, anatomy and functional parameters can be combined at rest and during stress to have a comprehensive description of LA anatomy and function, summarized in Table 8.1.

8.2 How to Measure LAV and Function

Echocardiographic measurements of the LA are obtained offline from the apical 4- and 2- chamber views, with the biplane disk summation method for LAV [17] and through speckle tracking echocardiography for LA function [19]. All measurements are recorded at rest and peak stress (Fig. 8.3).

Left atrial size is measured at ventricular end systole (when the LA chamber is at diastole) in the frame preceding the mitral valve opening at the end of the T wave on the electrocardiogram. The LA planimetry is traced and the volume is computed by the online software package and indexed to body surface area to obtain LAVI, according to current guidelines [17]. While tracing the endocardium, care is taken to exclude the LA appendage and ostia of pulmonary veins. The length of the LA is the shortest distance between the midline of the plane of the mitral annulus to the roof or opposite the superior side of the LA measured in either the 4- or 2-chamber views. The definition of LAV dilation is based on a well-validated statistic called reference change value. One of the main advantages of this statistic is that it includes biological, analytical, and observer variability. On this basis, a LAVI change of $\geq$6.8 mL/m^2 between rest and stress is considered a real change above background variation and is used as a cutoff to identify a LAVI "dilator" cohort [16].

LA ejection fraction is calculated from volumetric indices as LA max (at end systole, just before mitral valve opening)—LA min (at end diastole, when the mitral valve closes)/LA max. Its normal value at rest is 50–70% and usually increases during stress in a healthy response.

LAVI measurement is simple and informative, and a universally accepted barometer of time-integrated left atrial pressure. It is used as a surrogate of left atrial remodeling and dysfunction also with other imaging techniques such as cardiovascular magnetic resonance or cardiac computed tomography. Yet, there is evidence that LAVI is an insensitive marker of LA dysfunction, which may be assessed more directly with other indices. A normal LA response to stress is also characterized by an increase in LA ejection fraction. One-third of patients with heart failure with preserved ejection fraction show normal LAVI with an impaired LA ejection

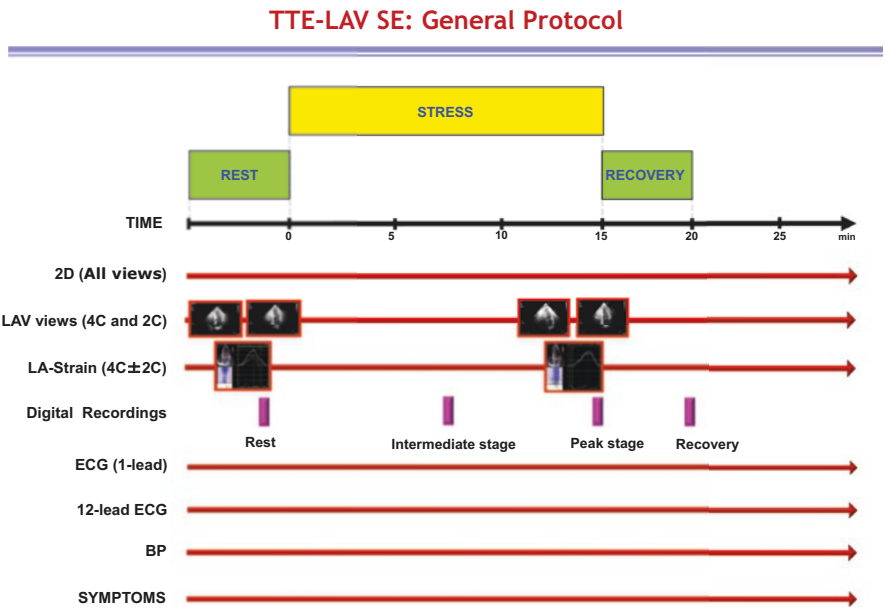

Fig. 8.3 LA-SE: volume and function. The LAV acquisition is performed at rest and peak stress with the apical 4-chamber (4C) and 2-chamber (2C) views. The measurement of LAV is completed with the assessment of LA peak atrial longitudinal strain from the same views to assess the reservoir function. The normal response during stress is characterized by a reduction in LAV and an increase in PALS. The abnormal response during stress is characterized by an increase in LAV and a decrease in peak atrial longitudinal strain

fraction consistently with the well-established concept that LA dysfunction likely precedes LA remodeling. In general, there is an inverse relationship between LAVI and LA ejection fraction, with LA ejection fraction reduction at higher volumes as contractile reserve becomes exhausted.

More recent studies have focused on the LA reservoir function by 2D speckle tracking echocardiography. Good image quality is needed to obtain meaningful data. LA reservoir strain is assessed according to recommendations for the standardization of LA deformation imaging [20, 21], with a frame rate of 60–70 at rest and 80–90 during stress. Furthermore, the Taskforce of the American Society of Echocardiography/European Association of Cardiovascular Imaging recommends reporting LA strain from an optimized LA-focused apical 4-chamber view, to obtain non-foreshortened images of the LA. Biplane LA strain can be performed, but it is not mandatory.

Images are analyzed offline, using the QRS as the reference point and tracing the LA endocardial borders in the apical 4- and 2-chamber views at rest and peak stress. Particularly, the region of interest definition usually starts with delineating the endocardial contour, which should be drawn from the mitral annulus, across the pulmonary vein and/or LA appendage orifices until the mitral annulus on the opposite side. A region of interest of 3 mm has been recommended, but might require

individual adaptation. LA strain is measured as GLS of the entire wall, not considering segmental strain; moreover, given the limited thickness of the LA wall, a distinction between endocardial strain and full wall strain is not needed. Zero reference is end diastole, defined by mitral valve closure and obtained in the clinical routine through the ECG R-trigger. Some studies have used a zero reference at the beginning of atrial contraction (ECG P-trigger), which, however, results in different strain values, has otherwise no advantages, and is not feasible in atrial fibrillation; a feasible and easiest approach is to simply refer to the nadir of the atrial strain curve. The deformation of the atrial wall reflects the three atrial phases: (1) reservoir strain: It encompasses the time of LV isovolumic contraction, ejection, and isovolumic relaxation and is calculated as the difference in the strain value at the strain curve peak minus end diastole; always positive; (2) conduit strain: It occurs from the time of mitral valve opening through until the onset of LA contraction, calculated in sinus rhythm as the difference in the strain value at the onset of atrial contraction minus the peak value of the curve; always negative; (3) contraction strain: It occurs from the onset of LA contraction until end diastole in patients with sinus rhythm and is therefore calculated as the difference in the strain value at end diastole (by definition zero) minus the value at the onset of atrial contraction; always negative [21].

Among these parameters, global PALS reflecting the LA reservoir function is the most reproducible. PALS is assessed at rest and peak stress and expressed in % values. During stress, the normal response is an increase in reservoir function more obvious for stresses associated with increased contractile reserve such as exercise and dobutamine, and milder for modalities associated with lower inotropic increase such as vasodilators. Any increase <15% is considered likely abnormal, although the available data are limited.

8.3 Response Patterns in SE

SE is increasingly used for diagnosis, risk stratification, and prognosis of patients with known or suspected coronary artery disease and other cardiac diseases. However, in this contest, the role of LA in patients referred for SE is not well-defined yet. To summarize, the profiling of LA response to stress can ideally include both LAV (volume) and PALS (function). The normal response pattern to stress is a LAV reduction with PALS increase, whereas the abnormal pattern is a LAV dilation with strain decrease**.** An example of a normal LAV-reducer response is shown in Fig. 8.4.

The normal functional response, in this case, is the increase in PALS (Fig. 8.5).

As it happens for LV, the dilation of LA is a physiological response and a compensatory mechanism to increase LV filling up to a certain point, but a pathological response when it exceeds given limits that incorporate the adaptation to stress, methodological measurement variability, and biological variability. An example of an abnormal dilator response is shown in Fig. 8.6.

The abnormal functional response is the decrease in PALS (Fig. 8.7).

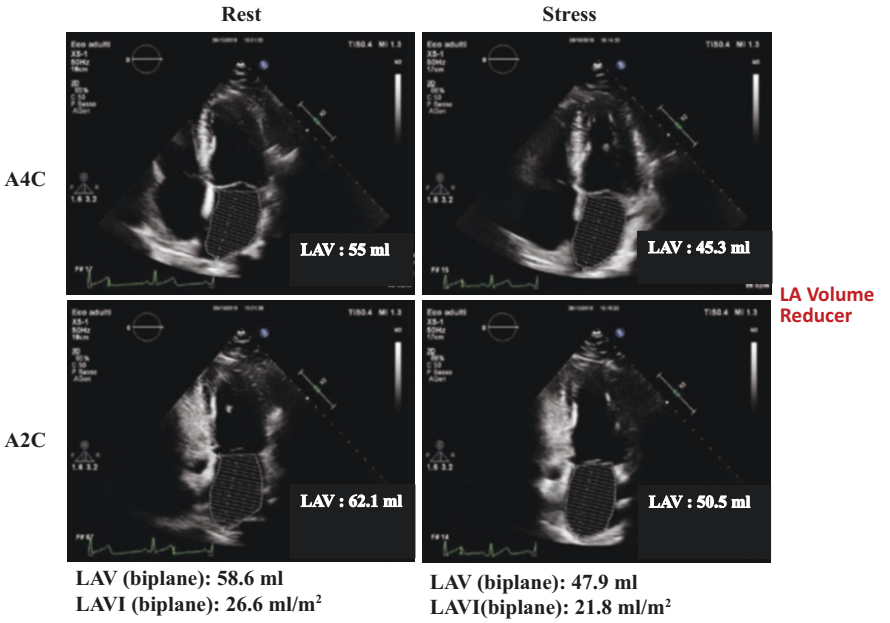

Fig. 8.4 An example of LAV reduction during stress. Apical 4-chamber (upper panels) and 2-chamber (lower panels) views of a patient at rest (left panels) and peak dobutamine stress (right panels). LAVI volume decreases >20% at peak stress. *LAV* left atrial volume, *LAVI* left atrial volume index

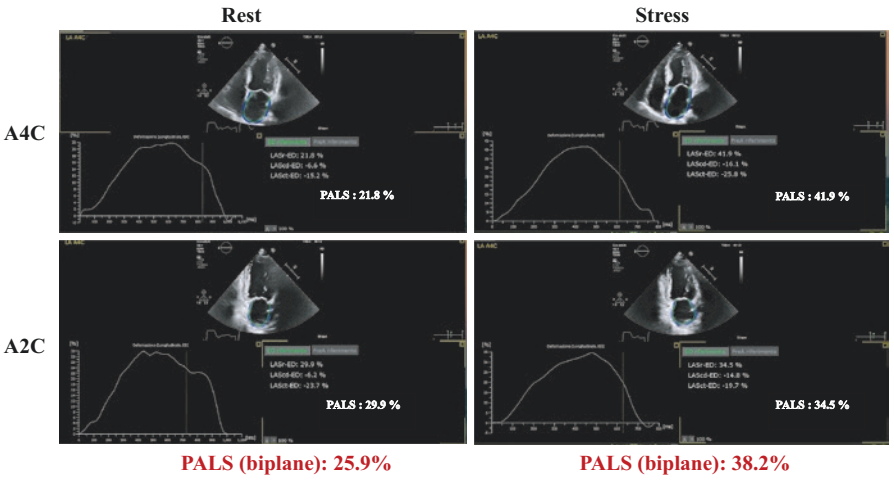

Fig. 8.5 An example of PALS increase during stress. Apical 4-chamber (upper panels) and 2-chamber (lower panels) views of a patient at rest (left panels) and peak dobutamine stress (right panels). PALS increases >20% at peak stress. *LAV* left atrial volume, *LAVI* left atrial volume index

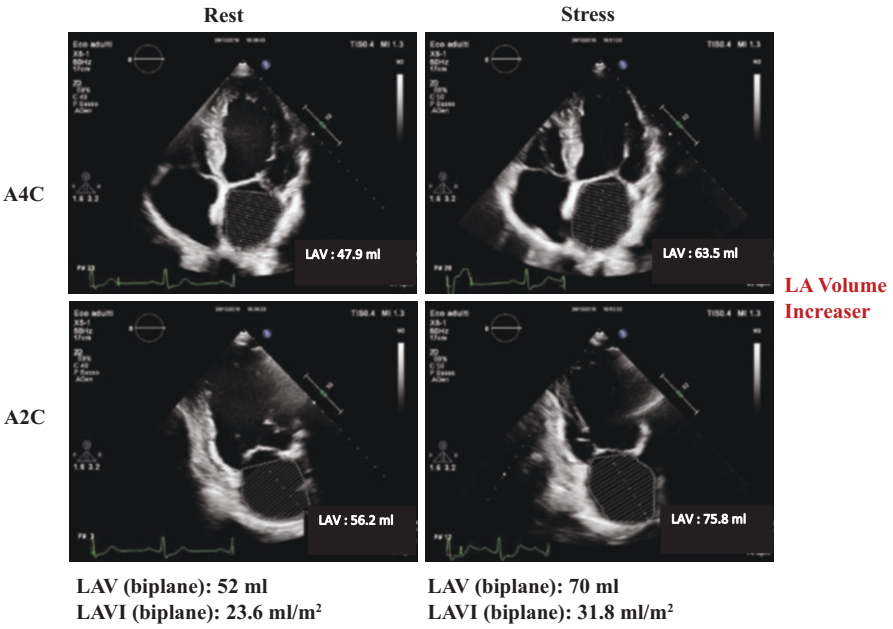

Fig. 8.6 An example of increased LAV during stress. Apical 4-chamber (upper panels) and 2-chamber (lower panels) views of a patient at rest (left panels) and peak dipyridamole stress (right panels). LAVI volume increases >20% at peak stress. *LAV* left atrial volume, *LAVI* left atrial volume index

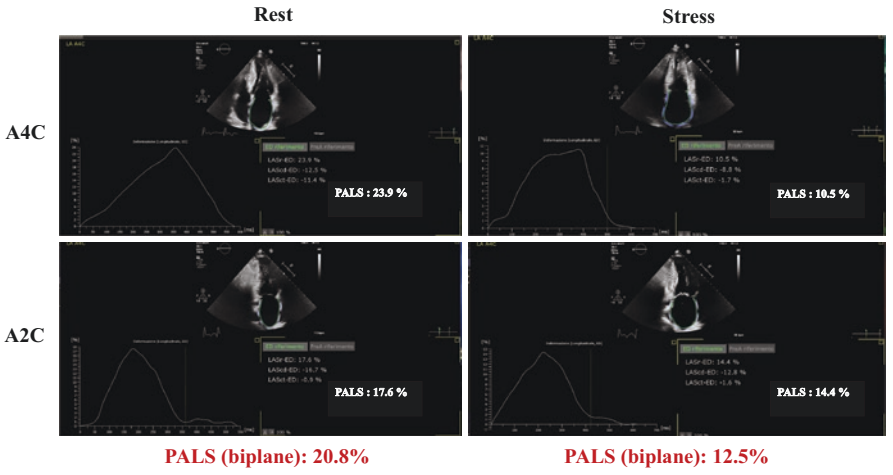

Fig. 8.7 An example of PALS decrease during stress. Apical 4-chamber (upper panels) and 2-chamber (lower panels) views of a patient at rest (left panels) and peak dipyridamole stress (right panels). PALS decreases at peak stress. *PALS* peak atrial longitudinal strain

8.4 Coronary Anatomic and Functional Correlates

In patients with stress-induced regional wall motion abnormalities, LAVI dilation is more frequently associated with more severe and extensive coronary artery disease [16]. In patients with and without regional wall motion abnormalities, LAVI dilation is more often accompanied by pulmonary congestion (B-lines), hemodynamic congestion (high systolic pulmonary arterial pressure), and reduced LV contractile and heart rate reserve. There is a minority of patients with LAV dilation without increment in pulmonary congestion, in whom probably the atrial Frank–Starling mechanism is sufficient to protect the lung from congestion. Another smaller subset of patients develops pulmonary congestion without LAV increase, probably for a stiff LA unable to compensate with dilation during stress. LAVI dilation during stress is predicted by high resting *E*/*e*', reduced LV ejection fraction, and small LAVI at rest. Exercise-induced LAVI dilation is three times more frequent in patients with hypertrophic cardiomyopathy or heart failure with reduced ejection fraction when compared to patients with heart failure and preserved ejection fraction [22].

8.5 Outcome Data

A wealth of data demonstrates that a dilated resting LAVI is a predictor of adverse outcomes in many conditions from coronary artery disease to hypertrophic cardiomyopathy, from heart failure to valvular or congenital heart disease [23–25]. Data are conspicuously missing to date for stress LAVI. In a recent study, it has been reported that stress LAVI shows a stronger association with the surrogate outcome endpoint of atrial arrhythmias detected by Holter ECG than rest LAVI [26]. In the same study, it has been demonstrated that also LA strain represents more powerful markers of new-onset atrial fibrillation compared with LA diameter. The finding that LA strain has shown an added prognostic value in several diseases is nowadays well-known. For example, in the current evaluation of diastolic dysfunction an abnormal LA strain was significantly associated with a worse New York Heart Association functional class, even when LAVI was normal. Moreover, in a retrospective post hoc analysis, an abnormal LA strain had a significant association with the risk of heart failure hospitalization at 2 years [18]. More data are needed to support stress LA strain as a diagnostic and prognostic tool.

8.6 Tips and Tricks

The LA assessment must face its far-field location, thin walls, and the presence of pulmonary veins and left atrial appendage. Any change in LA size and function may derive from an intrinsic atrial abnormality, altered load, or compensatory response. The major feasibility limitation is that image acquisition during stress is usually focused on zoomed LV and regional wall motion, with image depth too small to include LA boundaries and sometimes with foreshortening of LA precluding a

correct data analysis. The apical views to optimize LA may not be the same as to optimize the left ventricle, and LA may be foreshortened in the standard apical 4-chamber view optimized for the left ventricle. LAV measurement based on standard views may underestimate LAV derived from atrial-focused views.

The technique of LAVI measurement from 2-dimensional echocardiography is well standardized and shows limited variability at rest and during stress, although LA enlargement does not occur uniformly in all directions. In perspective, SE can benefit from advanced imaging with real-time three-dimensional echocardiography, offering a more accurate assessment of LAVI, independent of geometric assumptions although more dependent on image quality and patient cooperation [27]. The measurement of LAV with artificial intelligence is non-inferior to a human observer, more reproducible, and less time-consuming.

PALS is a measure of left atrial but also indirectly of LV function, germane to global longitudinal strain (GLS). LV GLS captures the systolic deformation of the base toward the apex, whereas PALS quantifies the maximum elongation of the LA during LV systole. The LA roof is anchored to the great veins, and therefore, the major determinant of LA expansion is the LV systolic contraction with downward displacement of the LV base toward the apex. Therefore, any condition lowering GLS will also symmetrically lower PALS. The normal value of PALS is 42% and the normal value of GLS is 21% corresponding to the left ventricle to LA length ratio in normal subjects. LA and LV can rarely be considered separate entities and affect each other exactly as it happens for LV systolic and diastolic functions [20].

LA size is assessed at the maximal atrial dimension based on current recommendations, but the minimal size of LA may be a more important prognostic indicator [28].

8.7 Clinical Guidelines and Recommendations

LAV and LA function dynamic assessment during SE finds no place in current recommendations and guidelines [29–32]. However, LA can be easily measured during stress, with an excellent success rate and good reproducibility, and there is clear potential since the technique is highly feasible and the observed behavior is highly heterogeneous during stress for any given resting LA volume and function. In perspective, the acceptance and utilization of LAVI during stress can be made easier by several facilitating factors. Cardiologists already know that LAVI is an important biomarker of LV diastolic dysfunction and know how to measure it at rest. The parameter is easy to measure in virtually all patients with an acceptable echocardiographic window. It can be obtained by all cardiologists with all machines. It requires very little extra imaging and analysis time. Feasibility and reproducibility are optimal with new software based on artificial intelligence and already commercially available. It is simple to understand and apply. LAV imaging is usually not degraded by stress, and the success rate is very high.

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Step P for Pulmonary Hemodynamics in Stress Echocardiography

9

Karina Wierzbowska-Drabik and Eugenio Picano

Keywords

Acceleration time · Cardiac output · Pulmonary hypertension · Pulmonary vascular resistances · Tricuspid regurgitant jet velocity

9.1 Physiology of Pulmonary Circulation

Pulmonary circulation is a key pathophysiology variable and a potential therapeutic target in several conditions characterized by pulmonary hypertension. However, the isolated assessment of resting pulmonary pressure is largely inadequate for several reasons.

Absolute values of pressure depend on the flow [1]. According to Ohm's law in an electrical circuit applied to the circulation, the electrical potential between two points (pressure gradient) is equivalent to the product of flow and resistance. Flow shows wide variations at rest. High-output states contribute to increases in pulmonary artery systolic pressure (PASP) in pulmonary circulation. On average, each liter per minute of the increase in flow is accompanied by a 1 mmHg increase in mean pulmonary artery pressure in young healthy subjects, but the pressure increase can double in healthy adults aged >60 years and can be up to 5 times higher in disease states, due to increased vascular stiffness and pulmonary capillary bed

K. Wierzbowska-Drabik (✉)
Department of Internal Disease and Clinical Pharmacology, Bieganski Hospital, Medical University of Lodz, Lodz, Poland
e-mail: wierzbowska@ptkardio.pl

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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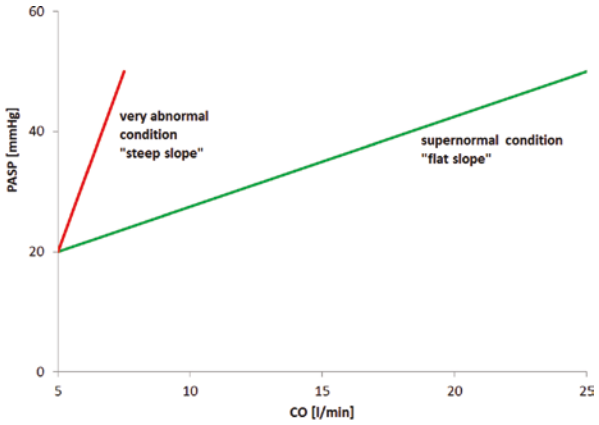

Fig. 9.1 Exercise-induced increase in pulmonary pressure is a long-term predictor of pulmonary hypertension at rest, but the very same value of PASP can be obtained with a supernormal (green line) and very abnormal (red line) condition due to left heart disease or pulmonary vascular disease. The simultaneous assessment of cardiac output or its proxy exercise time allows separating the two conditions since the same value is achieved with a fivefold increase in cardiac output in a healthy subject and with a 1.5 increase in cardiac output in a diseased subject

rarefaction or impaired functional vasodilatory capacity. Cardiac output can increase 2, 5, or 10 times during exercise, and therefore, the characterization of pulmonary hemodynamics only with pressure changes ignores the essential determinant of flow. The same rest and stress PASP can be found in very different health and disease states (Fig. 9.1).

The dependence of pressure upon flow emphasizes the potential and limitations of exercise stress echocardiography (SE) in the characterization of pulmonary hemodynamics.

Patients develop symptoms on exercise and only later at rest. Resting pulmonary pressure rises when >50% of the pulmonary microcirculation has been lost. The changes in PASP during exercise precede the occurrence of resting alteration diagnostic of pulmonary hypertension [2]. Any therapeutic effort is more likely to be successful at an early, reversible stage rather than when fixed changes evident at rest occurred. Exercise-induced pulmonary hypertension (PH) is an early biomarker, an intermediate endpoint, and a long-term predictor of PH.

In addition, the changes in pulmonary pressure are important for the diagnosis, but several other variables should be systematically assessed, such as right ventricular and left ventricular function, pulmonary congestion, cardiac autonomic balance, and systemic venous pressure [3]. It is the simultaneous evaluation of all these variables, which allows the identification of individual phenotypes, integrated risk stratification, and possibly a tailored personalized therapy.

PH is a chronic disease, and a single, isolated assessment is not sufficient to monitor its natural history [4]. A widely available test can be repeated without restrictions of access, risk, and cumulative damage from nephrotoxic contrast. Moreover, right heart catheterization during exercise is technically challenging of

the difficulties in wedging the balloon catheter during intense exercise and for the exaggerated respiratory oscillations in pulmonary artery wedge pressure.

Despite the strong rationale, exercise assessment of pulmonary hemodynamics is still not endorsed in the guidelines, for several reasons. The slope of the mean pulmonary pressure/cardiac output relationship is steeper in older normals of 60–80 years compared to healthy young adults, and the same increase in cardiac output is accompanied by a twofold higher rise in pulmonary pressure. The increase in body mass index also makes the pressure rise steeper, and again, this makes more difficult the identification of abnormal cutoff values of pulmonary pressure during exercise. The increase in PASP does not separate the left heart disease from pulmonary vascular disease, but only the latter is accompanied by a normal pulmonary artery wedge pressure, which requires right heart catheterization, although *E*/*e*′ may provide some information on left ventricular filling pressure changes during exercise [4].

9.2 How to Measure Pulmonary Artery Pressure

Echocardiography can derive simple and reasonably accurate estimates of pulmonary hemodynamics, although with some approximations, assumptions, and simplifications. The *E*/*e*′ ratio has been shown to have a reasonably accurate correlation with invasive left ventricular filling pressure and pulmonary capillary wedge pressure at rest but is less accurate with exercise (*see* Chap. 26).

PASP is estimated from peak tricuspid regurgitant velocity (TRV) jet (in m/s) according to the well-validated modified Bernoulli's equation [5]: PASP = 4(TRV)^2 + right atrial pressure (Table 9.1).

Right atrial pressure can be estimated from the inferior vena cava diameter and respiratory collapse (Table 9.2). The diameter is measured perpendicularly to the long axis of the inferior vena cava at end expiration, just proximal to the junction of the hepatic veins that lie approximately 0.5–3.0 cm proximal to the ostium of the right atrium.

Technically adequate signals of TRV have complete envelopes with well-defined borders, a sweep velocity of at least 100–200 mm/s, and can be obtained (without the need for contrast) at baseline and peak exercise stress in about 50% of patients.

Table 9.1 Noninvasive assessment of pulmonary pressure by Doppler echocardiography

		Normal values (rest)
PASP	4 × TRV^2 + RAP	TRV <2.8 m/s
mPAP	79–0.45 (ACT)	ACT >130 ms
PEDP	4 × (pulmonary regurgitation end-diastolic velocity) + RAP	<15 mmHg
PVR	10 × TR velocity/RVOT$_{VTI}$	<2.0 Wood units

ACT acceleration time, *PASP* pulmonary artery systolic pressures, *PVR* pulmonary vascular resistances, *PEDP* pulmonary end-diastolic pressure, *mPAP* mean pulmonary artery pressure, *RVOT* right ventricular outflow tract, *TRV* tricuspid regurgitant velocity, *VTI* velocity-time integral, *RAP* right atrial pressure

Table 9.2 Estimation of RAP based on IVC diameter and collapse

IVC diameter (cm)	Respiratory collapse (%)	RAP (mmHg)
<2.1	≥50	3
>2.1	≥50	8
<2.1	<50	8
>2.1	<50	15

IVC inferior vena cava, *RAP* right atrial pressure

Table 9.3 Estimation of PASP based on ACT values

ACT values (ms)	PASP (mmHg)
50	80
80	60
100	50
120	42
140	35
160	29

Acceleration time (ACT) is obtained in almost all patients both at rest and during stress and is used to estimate the mean pulmonary artery pressure and also PASP [6]. Pulsed-wave Doppler is used with the sample positioned at the annulus of the pulmonary artery, in the parasternal short axis, or the subcostal view. ACT is measured as the time (in milliseconds) from the beginning of pulmonary ejection until the peak value of systolic velocity [7]. The normal value is >130 ms, the abnormal is <105, and the indeterminate is between 105 and 130 ms [8]. Generally, the shorter the ACT the higher the pulmonary vascular resistance and hence the pulmonary arterial pressure.

From the raw data of ACT, PASP was derived based on the correlation linking ACT to TRV as follows: log10 PASP = −0.004 (ACT) + 2.1 [9] (Table 9.3).

Heart rate increase physiologically shortens ACT, but no corrections are needed in the range of 70–110 beats/min.

The suggested protocol for the study of pulmonary hemodynamics should include TRV and, when TRV is not feasible, ACT. Right ventricular function is assessed at least with a tricuspid annular plane systolic excursion (TAPSE) and optimally supplemented by the S' value of tricuspid annulus motion and fractional area change calculation. The cardiac output is measured, or at least the exercise time is recorded (Fig. 9.2).

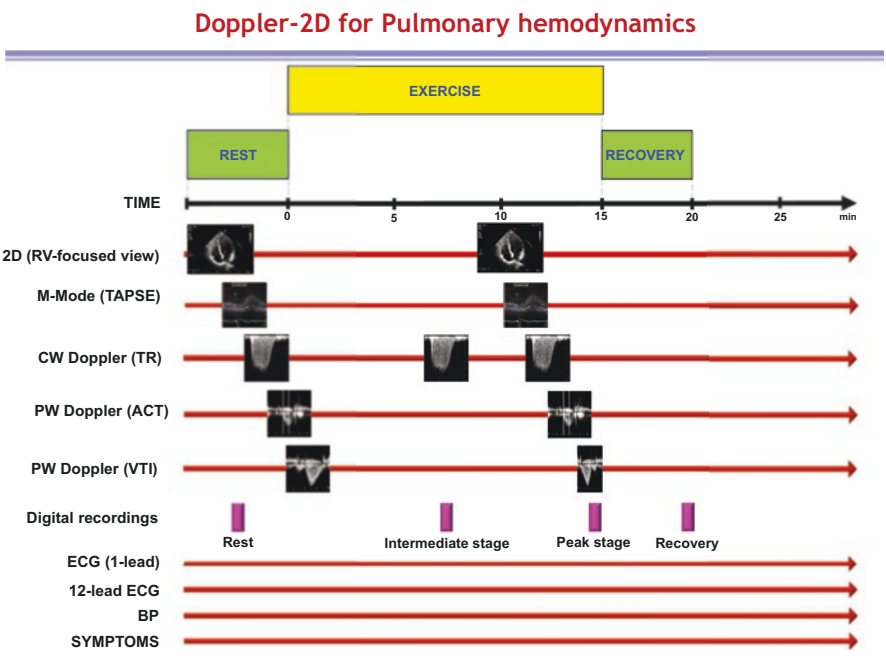

Fig. 9.2 SE for pulmonary hemodynamics. The combination of TRV and ACT allows an estimate of pulmonary pressures and their changes during exercise in virtually all patients. Right ventricular function is simultaneously assessed with 2-dimensional echo-targeted M-mode tracing. Stroke volume can be measured from volumetric echocardiography of the left ventricle or from pulsed-wave Doppler of the time–velocity integral of flow in the left ventricular outflow tract multiplied by the cross-sectional area derived from the raw measure of diameter. The assessment of right ventricular function with at least M-mode (TAPSE), optimally integrated with 2-dimensional echo (fractional area change %), and tissue Doppler S' integrate the study to evaluate the right ventricular–pulmonary pressure coupling

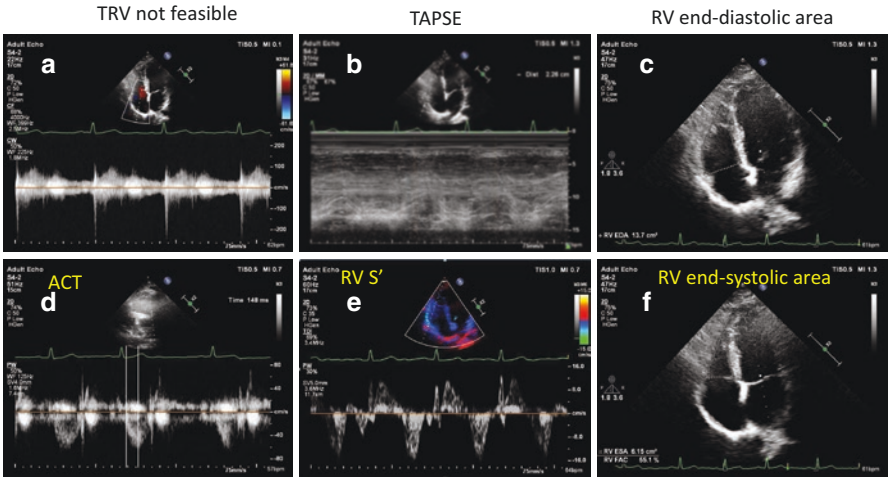

Fig. 9.3 Echocardiographic study of pulmonary hemodynamics and right ventricular function in healthy control. Panel (**a**): TRV not feasible—lack of full spectrum of TR. Panel (**b**): TAPSE = 23 mm. Panel (**c**): RV end-diastolic area (EDA). Panel (**d**): ACT 148 ms. Panel (**e**): RV *S* = 12 cm/s. Panel (**f**): RV end-systolic area (ESA). EDA and ESA are needed for the calculation of fractional area change (FAC) = 55%

The raw measurements needed for a complete echocardiographic study are summarized in Fig. 9.3.

9.3 Response Patterns of Pulmonary Hemodynamics During Exercise

An example of a normal response, with a mild increase in TRV during exercise, is shown in Fig. 9.4.

An example of an abnormal response, with a marked increase in TRV during exercise, is shown in Fig. 9.5.

An example of a normal response, with mild shortening of ACT during exercise, is shown in Fig. 9.6.

An example of an abnormal response, with severe shortening of ACT during exercise, is shown in Fig. 9.7.

The profile of ACT during a pulmonary hypertensive response changes from a smooth, dome-like shape at rest [10] to a steep slope during stress (Fig. 9.8).

The combination of TRV with ACT is useful to achieve an interpretable estimation of PASP in almost all patients during stress with a combined TRACT (tricuspid regurgitation + ACT) approach [11].

Once we have PASP (derived from TRV or ACT), a measurement corrected for flow can be obtained by measuring cardiac output (heart rate × stroke volume) by

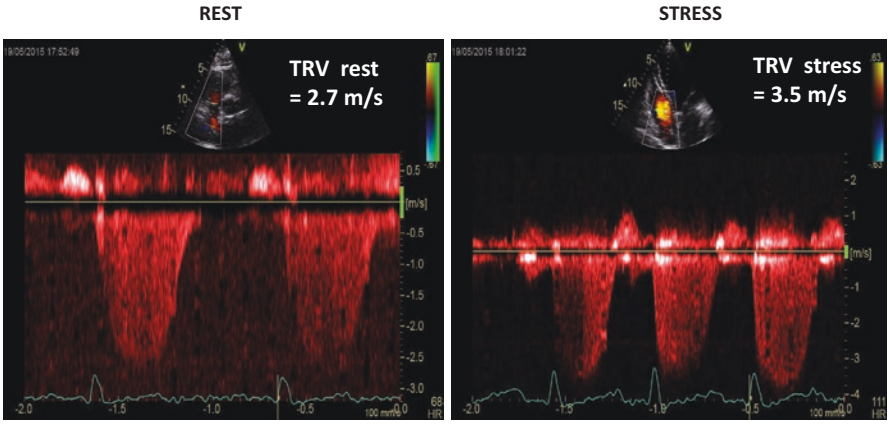

Fig. 9.4 Patient with resting PASP (estimated from the jet velocity of tricuspid regurgitation) of 32 mmHg. During exercise, the patient experiences a mild rise in PASP without symptoms

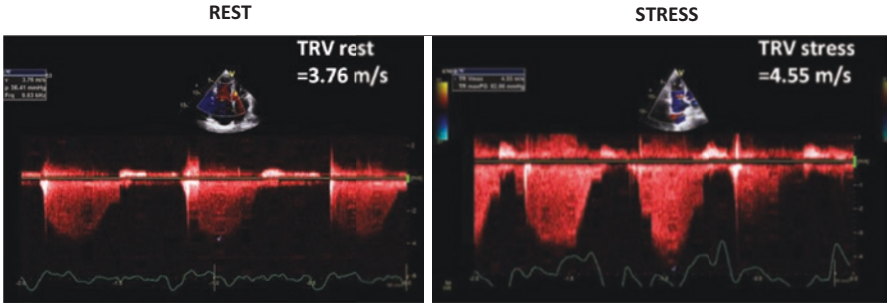

Fig. 9.5 Patient with resting PASP (estimated from the jet velocity of tricuspid regurgitation) of 65 mmHg. During mild exercise, the patient experiences severe dyspnea and a marked rise in PASP

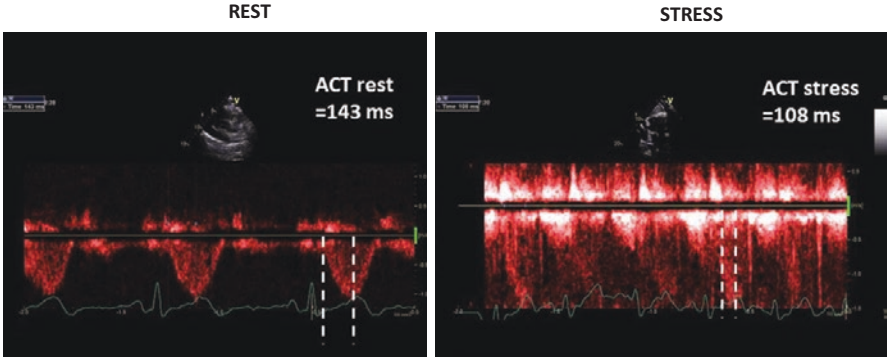

Fig. 9.6 Patient with resting PASP (estimated from ACT of systolic pulmonary flow velocity) of 34 mmHg. During exercise, the patient experiences a mild shortening of ACT without symptoms, and PASP increases to 47 mmHg

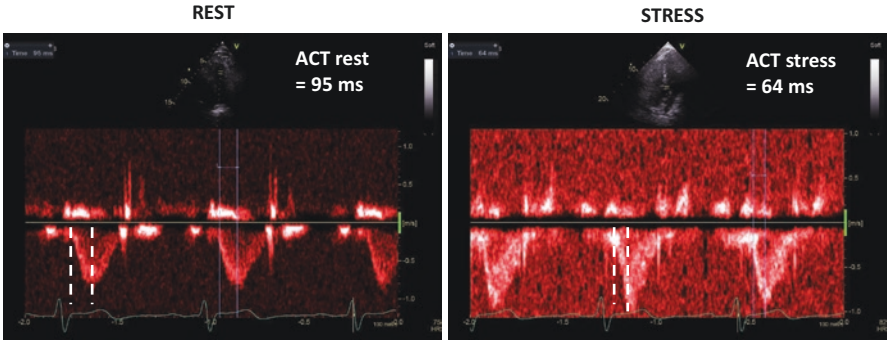

Fig. 9.7 Patient with resting PASP (estimated from ACT of systolic pulmonary flow velocity) of 52 mmHg. During exercise, the patient experiences severe dyspnea and a marked rise in PASP to 70 mmHg with a shortening of ACT <80 ms

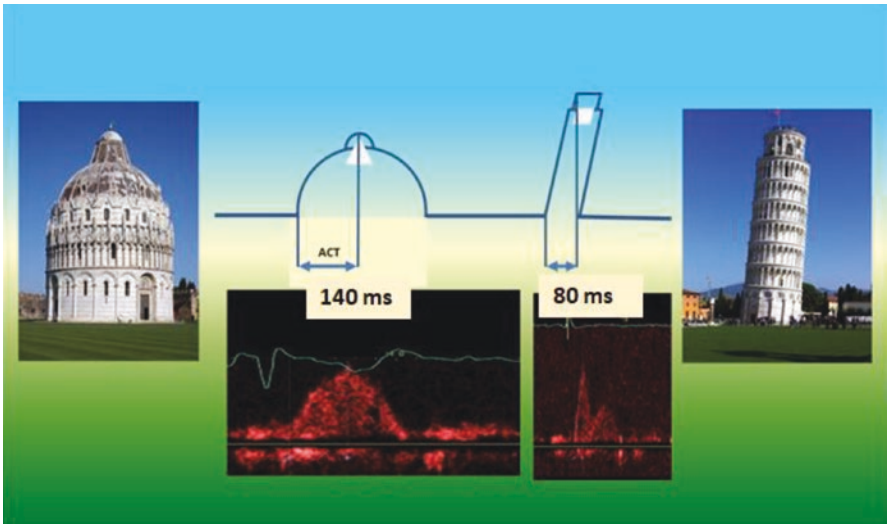

Fig. 9.8 Pulmonary hypertensive response pattern with ACT with side-by-side comparison or rest and stress pulmonary systolic flow profile changes from a smooth, rounded, dome-like shape with long ACT (left side, rest) to a peaked, steep, tower-like shape with short ACT (right side, stress) somewhat similar to the skyline of Place of Miracles in Pisa

measuring stroke volume with one of two possible methods [12]: velocity–time integral from pulsed-wave Doppler and volumetric 2-dimensional echocardiography (end-diastolic volume minus end-systolic volume). A reasonable proxy is the minutes of exercise, which are imaging-independent and in the same range linearly related to the change in cardiac output. The slope of PASP/cardiac output (or exercise time) during exercise is a methodologically sound approach and allows to integration pressure values with flow [12]. The slope of the relationship between PASP/

cardiac output (and exercise time) offers a measure of the severity of pulmonary circulation impairment more reliable than a simple peak PASP [13].

Notably, the pulmonary artery diastolic pressure can be estimated at rest from the velocity of the end-diastolic pulmonary regurgitant jet, using the modified Bernoulli's equation [pulmonary artery diastolic pressure = 4 * (velocity of the end-diastolic pulmonary regurgitant jet)^2 + right atrial pressure] [14]. This approach is especially useful in patients with congenital heart disease [15].

With a complete assessment of relatively simple parameters, echocardiography allows the rest and stress estimate of PASP (with TRV or ACT when TRV is not feasible), pulmonary vascular resistances (flow increase/pressure increase), right ventricular function (TAPSE, *S′* from tissue Doppler imaging and fractional area change from 2-dimensional echocardiography), or right ventricular function/pulmonary pressure coupling (TAPSE/PASP). Each parameter can be titrated with normal and abnormal ranges with mild, moderate, or severe abnormality [16–20], but these values have been mostly validated at rest. For TRV, one can estimate the probability of PH as low (≤2.8 m/s or not measurable), intermediate (2.9–3.4 m/s), or high (>3.4 m/s). For ACT, one can estimate PH as absent (>130 ms), borderline (100–130 ms), mild (80–100 ms), or severe (<80 ms with systolic notch). For ACT, the increase in heart rate >110 during exercise needs a correction for heart rate. Normal pulmonary vascular resistance values are <2.0 and normal TAPSE/PASP, as well as pulmonary vascular reserve, values are >2.0.

9.4 Functional Correlates of PH

Exercise PH has been associated with worse functional capacity and abnormal right ventricular contractile reserve in patients with dyspnea [21, 22]. Heart failure patients with exercise-induced PH have lowered left ventricular contractile reserve, greater severity of dynamic mitral regurgitation, dilated left atrium, and—in patients with preserved ejection fraction—diastolic dysfunction [23–25].

9.5 Outcome Data

The prognostic meaning of an exercise-induced increase in PASP varies radically depending on the clinical context. In patients with left heart failure or significant mitral valve disease, PASP increase reflects an increase in left atrial pressure and impaired left ventricular diastolic reserve and is a predictor of poorer prognosis. Instead, patients with severe PH and right heart failure indicate a preserved right ventricular contractile reserve and indicate a better prognosis [26–28]. The prognostic value of right ventricular/pulmonary artery pressure coupling is an independent and incremental predictor of outcome compared to PASP only [29].

9.6 Tips and Tricks

The assessment of PASP depends on the presence of at least trivial tricuspid regurgitation, which is found in about 40–85% of normal subjects and 80–90% of patients with PH [30]. To optimize the reproducibility of the measurement of tricuspid regurgitation maximum continuous-wave velocity, the dense signal ("the chin") rather than the fluffy higher velocity ("the beard") is measured [31]. Furthermore, training is required to be able to assess TRV during the exercise. Over- and underestimation of TRV are a frequent problem. The quality of the TRV recording may be improved by injecting an agitated saline solution or other ultrasound-enhancing agents intravenously [32].

The assumption made by measuring PASP with TRV is that blood flow velocity depends on pressure. In reality, the blood flow velocity is also inversely related to the cross-sectional area through which the blood flows. With a dilated tricuspid annulus and severe tricuspid regurgitation, for a given pressure gradient the flow velocity decreases, and PASP is underestimated. PASP corresponds to right ventricular systolic pressure in the absence of flow obstruction between the right ventricle and pulmonary artery. When this obstruction is present in the right ventricular outflow tract or the pulmonary valve, the PASP is estimated as the right ventricular systolic pressure minus the pressure gradient.

Up to now, there is no firm consensus on which PASP threshold is diagnostic for exercise-induced PH, particularly if SE is applied. There are only a few invasive and noninvasive studies analyzing the normal values for pulmonary artery pressures during exercise. Usually, in healthy subjects, the systolic pressures do not exceed 40 mmHg even during heavy exercise. However, in well-trained athletes and those older than 55 years, systolic pressures as high as 55–60 mmHg are encountered [32].

From the pathophysiological viewpoint, based on the fundamental equation of flow (flow = pressure gradient/resistance), the abnormal exercise-induced increase in pressure can be linked to a supernormal flow increase (e.g., in athletes), or a normal increase in flow but with a subnormal fall in resistances due to a limited capability of pulmonary vessel recruitment and vasodilation (e.g., in chronic obstructive pulmonary disease with parenchymal PH or congenital heart disease).

The Doppler assessment of PASP has an imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in at least 15% of patients with inadequate tricuspid regurgitation jet, and is unreliable in massive tricuspid regurgitation. The combination of TRV with ACT increases the feasibility, although a modest shortening of ACT with a marked increase in heart rate must be interpreted with caution due to the physiologic shortening of ACT with increasing heart rates. The orientation of the beam is rarely parallel to flow in the right ventricular outflow tract, and the pulsed-wave Doppler signal of systolic flow for ACT measurement is best assessed with a sample positioned at the annulus of the pulmonary artery, in the parasternal short axis, or the subcostal view.

During stress, accepted cutoff values of normal and abnormal responses are still lacking. PASP values are linearly dependent on cardiac output, and the multi-point pulmonary artery pressure–flow relationship is more meaningful than a single PASP

value. Post-exercise measurements are unreliable because of the rapid return to the baseline of pulmonary hemodynamics.

Usually, the same right atrial pressure calculated at rest is added to PASP values calculated at rest and peak stress, but it changes during stress and should not be considered a constant. Right atrial pressure can increase two- or threefold during exercise and even in normal subjects, and it contributes to 40% of invasively recorded PASP. In theory, it should be reassessed at rest and peak stress to avoid introducing another significant source of error in the estimation of pulmonary pressures during exercise. In practice, this is rarely done.

A report of pulmonary hemodynamics should include the following: TRV whenever feasible at rest and peak stress (or submaximal stress when the signal is lost at peak exercise since most changes occur in early stages of exercise); when TRV is not feasible, ACT; always, heart rate at rest and peak stress (since ACT values may shorten with an increase in heart rate independently of pressure changes); exercise time (which is a surrogate of cardiac output increase during stress); and if possible, rest and stress cardiac output (from 2-dimensional or Doppler measurements). In this way, a widely used but flow-dependent measure of PASP (from TRV or ACT) can be used, and a flow-independent index of pulmonary resistance or reserve can be measured, which is more conceptually robust and possibly more effective in outcome stratification. Measurement of right ventricular function at least with TAPSE and right ventricular function/pulmonary pressure coupling (with TAPSE/PASP) is also recommended.

9.7 Clinical Guidelines and Recommendations

The practice of exercise Doppler echocardiography measurements of the pulmonary pressures in PH was discouraged by the 2022 European Society of Cardiology guidelines on PH because of the lack of validated criteria and prospective confirmatory data questionable plausibility of flow-dependent parameters with low feasibility during stress [33]. As a consequence, right heart catheterization is still considered the diagnostic gold standard despite invasiveness, cost, risk, iodine contrast nephrotoxicity, and challenging technical difficulties during exercise. Exercise Doppler SE is indicated in symptomatic patients with suspected chronic thromboembolic PH with resting TTE showing an intermediate or high probability of PH [33].

At present, the application endorsed by joint recommendation of the American Society of Echocardiography and the European Association of Echocardiography and Cardiovascular Imaging is the exercise Doppler study in symptomatic individuals with left heart disease, including mild mitral stenosis, asymptomatic severe aortic insufficiency, and asymptomatic severe mitral regurgitation [34] (Table 9.4).

Exercise SE with a noninvasive assessment of pulmonary pressure, resistance, and right ventricular function should be considered in patients at high risk for pulmonary arterial hypertension development as the adjunct tool exceeding the diagnostic potential of rest-only examination.

Table 9.4 Clinical applications of SE in known or suspected PH

Disease	Appropriate	Uncertain
Symptomatic, mild mitral stenosis	√	
Asymptomatic, severe mitral insufficiency	√	
Valvular heart disease (other)	√	
Heart failure with a preserved ejection fraction	√	
Heart failure with a reduced ejection fraction	√	
Congenital heart disease (ASD)	√	
HCM	√	
Symptomatic or asymptomatic athletes	√	
Pre-liver transplant	√	
Chronic CTEPH	√	
Suspected PAH in normal resting TTE		√
Re-evaluation of exercise-induced PH on therapy		√
Proven resting PH		√

ASD atrial septal defect, *CTEPH* chronic thrombo-embolic PH with intermediate-to-high probability on resting TTE, *HCM* hypertrophic cardiomyopathy, *PASP* pulmonary artery systolic pressure, *PH* pulmonary hypertension, *PAH* pulmonary arterial hypertension, *TTE* transthoracic echocardiography

Similarly, in patients with an established diagnosis of PH, not showing the contraindications to exercise, noninvasive but quantitative assessment could improve the monitoring of treatment and help further in prognostic stratification. In this setting, SE will enhance the functional status evaluation beyond the 6-min walking test results and cardiac natriuretic peptides assessment in patients with World Health Organization classes I to III.

The assessment of the parameters of PH is also an integral part of the so-called diastolic SE (Table 9.4) [35].

In all these conditions, the disproportionate increase in PASP during exercise can be useful as an ancillary marker of diastolic dysfunction, to regrade disease severity based on resting findings and to refine risk stratification.

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Step R for Right Ventricular Function in Stress Echocardiography

10

Hugo Rodriguez-Zanella and Eugenio Picano

Keywords

Congenital heart disease · Fractional area change · Right ventricular ejection fraction · Three-dimensional echocardiography · Tricuspid annular plane systolic excursion

10.1 Right Ventricle Anatomy and Function

The behavior of the right side of the heart during stress has been underemphasized and sparsely investigated by cardiologists and pulmonologists. Reasons vary, but the right ventricle (RV) has traditionally been considered a passive conduit between the venous system and the lungs largely because of early animal experiments showing no increase in central venous pressure after the free wall of the RV had been destroyed [1]. In addition, echocardiography of the right heart is less well-standardized than imaging of the left ventricle (LV). Recent pathophysiological, clinical, and prognostic data have defined the important role of the RV in many conditions, including ischemic heart disease and heart failure. Given that the RV and the LV share a common septum, have an overlapping blood supply, and are

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H. Rodriguez-Zanella (✉)
Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Table 10.1 Information on RV function (baseline and stress)

	Essential	Important
CHD (repaired TOF)	✓	
Right heart VHD	✓	
Left heart VHD	✓	
Athletes	✓	
Heart failure	✓	
COPD	✓	
PH	✓	
COVID-19	✓	
ARVC	✓	
CAD		✓
Post-radiotherapy		✓
HCM		✓

ARVC arrhythmogenic right ventricular cardiomyopathy, *CAD* coronary artery disease, *CHD* congenital heart disease, *COPD* chronic obstructive pulmonary disease, *HCM* hypertrophic cardiomyopathy, *PH* pulmonary hypertension, *TOF* tetralogy of Fallot, *VHD* valvular heart disease

bound together by the pericardium, changes induced by myocardial ischemia and/or heart failure are reflected in pulmonary hemodynamics and right ventricular function [2]. Modern echocardiography allows a systematic evaluation of regional and global systolic RV function during stress, which is essential or important in several conditions (Table 10.1). Pulmonary hemodynamics and RV function are tightly interconnected in the right heart-pulmonary circulation unit [3].

10.2 How to Measure Global RV Function

The evaluation of right ventricular size and function is made difficult by the retrosternal position, complex geometry, and heavy trabeculation of the RV, which also partially overlaps with the silhouette of the LV. The global RV function is more used than the segmental RV function and is a part of the minimum data set at rest and during stress (Fig. 10.1).

There are several approaches to measure global RV function: tricuspid annular plane systolic excursion (TAPSE) with M-mode; fractional area change (FAC) from 2-dimensional echocardiography (%); ejection fraction (EF) from real-time three-dimensional echocardiography (RT3D); RV peak systolic S-wave velocity of Doppler tissue imaging of the lateral tricuspid annular motion; and free wall longitudinal strain from deformation imaging (STEFWLS) (Table 10.2). In the normal response of healthy subjects, resting values increase during stress.

TAPSE is the simplest and the most reproducible index. TAPSE measures the descent of the right ventricular base from the apical 4-chamber view. 2D-targeted M-mode tracings record the free wall long-axis amplitude of movement (normally 15–20 mm). A good relationship has been reported between TAPSE and the RV EF measured by radionuclide ventriculography in a manner independent of geometric assumptions [5]. Conceptually, TAPSE assesses the longitudinal function of the

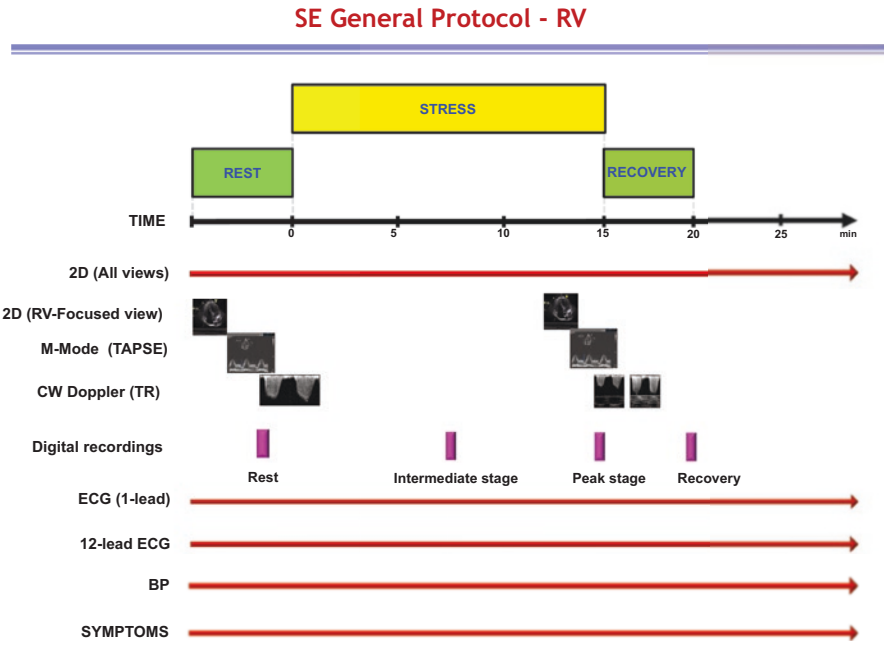

Fig. 10.1 RV protocol. An RV-focused apical 4-chamber view is integrated by the assessment of TAPSE with M-mode and systolic pulmonary artery pressure with continuous-wave Doppler of tricuspid regurgitant jet velocity for the assessment of right ventricular to pulmonary circulation coupling

Table 10.2 Values of RV systolic function

	TAPSE (mm)	FAC (%)	RT3D-EF (%)	TDI-s′ (cm/s)	STEFWLS (%)
Normal	≥16	≥35	≥45	>10	>20%

Values of normality from Rudski [4]
FAC fractional area change, *RT3D* real-time 3-dimensional echocardiography, *STEFWLS* Strain echocardiography free wall longitudinal strain, *TAPSE* tricuspid annular plane systolic excursion, *TDI* tissue Doppler imaging

RV. The assessment of TAPSE avoids the approximation, mistakes, and computational burden inherent to the calculation of EF in the RV, whose crescentic and irregular shape eludes any geometric modeling, although RT3D has the potential to solve or at least limit this problem [6]. Artificial intelligence-based objective measurements may help to increase the robustness of FAC or RV EF [6]. In the normal response, the increase in RV function during exercise is matched by a mild increase in pulmonary artery systolic pressure (PASP) with preserved TAPSE/PASP ventriculoarterial coupling [3, 4, 6].

It is also possible to assess global diastolic right ventricular function (Table 10.3) [7], and this can be important in restrictive cardiomyopathy.

Table 10.3 Values of RV diastolic function

Parameter	Normal	Abnormal
E/*A* ratio (units)	>0.8	<0.8
e′ (cm/s)	>8	<8
E/*e′* (units)	<6	>6
E deceleration time (ms)	>119	<119

Values of normality from Rudski [4] and Kossaifi [8]

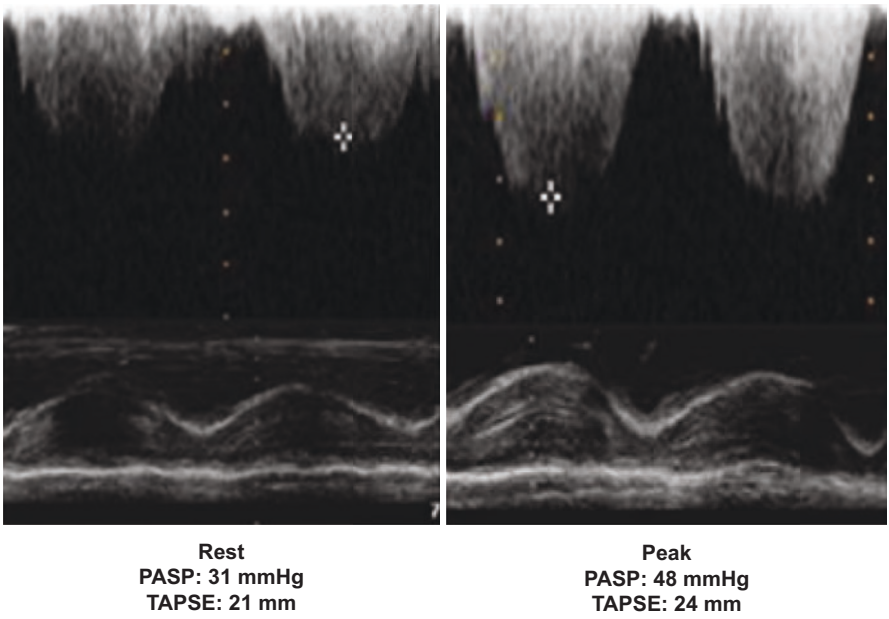

Fig. 10.2 Normal RV global reserve during exercise with preserved RV to pulmonary pressure coupling. See accompanying Video 10.1. (Video image courtesy of Carlos Cotrim, MD, Lisbon, Portugal. The video is available under the chapter's "Supplementary Material" on Springer Link) (Modified from Borghi-Silva et al. [7])

10.3 Right Ventricular Response Patterns During Stress

An example of a normal global RV response during exercise with preserved right ventricular-pulmonary circulation coupling [7] is shown in Fig. 10.2.

An example of an abnormal global RV response during exercise is shown in Fig. 10.3.

With 2-dimensional echocardiography, the normal response of the RV to stress is a reduction in size and an increase in function, while the abnormal response is an RV dilation with septal wall flattening and paradoxical motion during systole (Fig. 10.4).

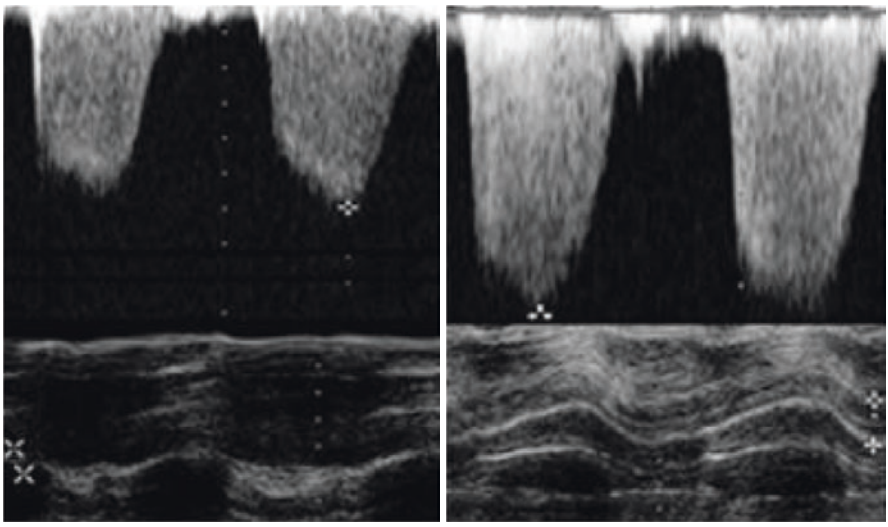

Fig. 10.3 Abnormal RV global reserve during exercise with abnormal RV to pulmonary pressure coupling with a modest increase in TAPSE and excessive rise in PASP. (Modified from Borghi-Silva et al. [7])

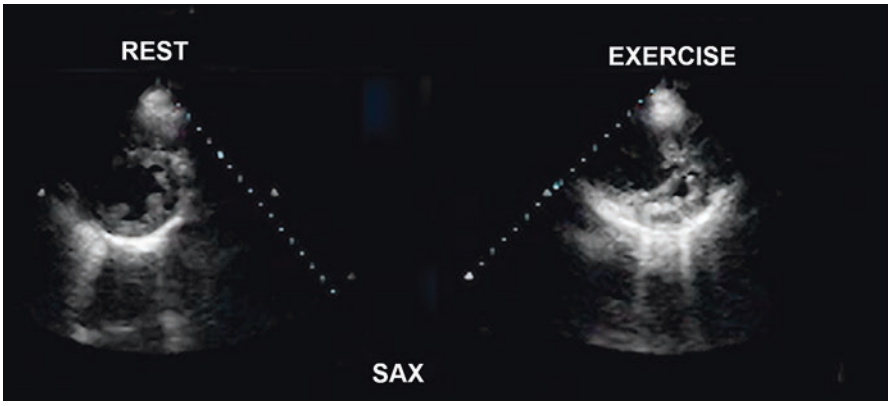

Fig. 10.4 Short-axis view of the left and RV showing a normal RV size at rest (left panel) and an abnormal RV response during exercise with dilated RV at peak exercise with a flattened interventricular septum in a patient with pulmonary hypertension (right panel). Note also B-lines departing from the pericardium into the lung field. They are present at rest (n = 2) and increase in number (n = 4) during exercise, possibly due to greater transcapillary fluid transudation in the lung interstitium for hypertension of central venous pressure leading to inadequate lymphatic clearance

10.4 Coronary Anatomic and Functional Correlates of Regional RV Function

The assessment of regional RV function is important for the detection of stress-induced RV ischemia. In right coronary dominant hearts (85% of cases), the RV is nourished by the right coronary artery. In patients with coronary artery disease, a segmental RV dysfunction is associated with a critically stenotic dominant right coronary artery. The RV is less vulnerable to ischemia than the LV for several anatomic and functional factors, including the rich system of Thebesian veins in the RV (allowing perfusion of the papillary muscles of the RV), the dual anatomic supply system (in which the left coronary branches perfuse almost one-third of the RV), the rapid development of collateral vessels to the RV given the lower resistance that favors a left-to-right transcoronary pressure gradient, and the relatively thin walls and lower stroke work and wall tension (with lower oxygen demand and less vulnerability to transmural perfusion heterogeneity during stress) [9]. The blood supply of the RV is characterized by a rich collateral system and perfusion during diastole and systole. The perfusion rate of the RV at rest is 50 mL/min/100 g, much lower than that of the LV (120 mL/min/100 g). However, right ventricular ischemia may occur during stress and is difficult to capture, if not specifically looked for. It requires additional projections (subcostal view) to image RV ischemia and more experience to recognize it. There is not one single echocardiographic view in which the complete RV can be seen. For purposes of echocardiographic analysis, the RV can be divided into four segments: anterior wall, lateral wall, inferior wall, and wall of the outflow tract [4, 10].

The inferior (or diaphragmatic) wall is in contact with the diaphragm with underlying echoes from the liver and is the most frequent target of ischemia. Regional RV wall motion analysis is most useful in detecting RV ischemia or infarction in coronary artery disease patients [10–15]. The development of stress-induced contraction abnormalities of the RV (more often lateral and inferior segments) is a hallmark of tight right coronary artery stenosis [10] (Table 10.4).

These alterations appear later than in the LV, are best recognized from a modified parasternal and subcostal long-axis view, and can be accompanied by severe right ventricular and right atrial enlargement.

Table 10.4 Differences between right ventricular ischemia and left ventricular ischemia during stress echocardiography

	Right	Left
Prevalence in RCA disease	40–60%	70–90%
Prevalence in LCA disease	0–20%	70–90%
ECG abnormalities	Right precordial leads	Standard leads
Isolated presentation	Rare	Frequent
Technical success rate	60–80%	90–98%
Prognostic value	Possible	Established

LCA left coronary artery, *RCA* right coronary artery

Isolated right ventricular ischemia occurs in 2% of patients with right coronary artery stenosis when assessed by wall motion abnormalities [14], but increases to 5–10% if assessed by the failure of TAPSE to increase >2 mm or other indices of RV longitudinal function [15, 16].

The assessment of coronary flow velocity reserve in the posterior descending coronary artery is important also beyond coronary artery disease. Similar to what happens to the left anterior descending coronary artery, any alteration in right ventricular hypertrophy or right coronary artery microcirculation can affect the posterior descending artery coronary flow velocity reserve. The posterior descending artery of the right coronary artery has been consistently imaged, with a success rate of around 75% [17, 18], usually from a modified apical 2-chamber view with counterclockwise rotation and anterior angulations of the probe [19]. The information on the right coronary artery flow reserve is derived as the ratio of peak diastolic flow velocity during stress over rest. A concordant reduction in both left anterior descending and posterior descending arteries is associated with a worse prognosis than a reduction in either one coronary artery—both in coronary artery disease [20, 21] and in dilated cardiomyopathy patients [22]. In addition, a reduction in right coronary artery reserve is associated with conditions of right ventricular pressure overload and may help in the functional characterization, for instance, of congenital heart disease patients [23].

10.5 Outcome Data

The reduction in RV contractile reserve during exercise or dobutamine is associated with a worse outcome in left and right heart failure [24, 25], pulmonary hypertension [26], and arterial pulmonary hypertension [27]. For any given right ventricular contractile reserve, the prognosis is worse in the presence of reduced TAPSE/PASP values during stress [28]. In patients with congenital heart disease such as repaired tetralogy of Fallot, a reduced RV reserve is associated with worse baseline functional indices and worse outcomes [29]. Early alterations in RV contractile reserve can be detected during exercise in patients with arrhythmogenic right ventricular cardiomyopathy [30, 31] and in athletes [32, 33] and associated with ventricular arrhythmias.

10.6 Tips and Tricks

The standard apical 4-chamber view of the LV may miss portions of the RV and is important to have an RV-focused view to avoid foreshortening of the RV and underestimation of the RV cavity. From the standard apical 4-chamber view focused on the LV, the transducer is rotated counterclockwise to obtain the maximal diameter of the RV.

The report of rest and stress data should include TAPSE values. The meaning of TAPSE changes is better understood if put in the context of PASP changes, and the ratio of TAPSE/PASP is a simple index of RV-pulmonary artery coupling.

10.7 Clinical Guidelines and Recommendations

The evaluation of RV or, better, right heart-pulmonary circulation unit is recommended in several conditions [34]: athletes, congenital or valvular heart disease, dilated or hypertrophic cardiomyopathy, coronary artery disease, heart failure with preserved EF, arrhythmogenic right ventricular cardiomyopathy, and status post-COVID-19 in symptomatic patients.

In all these conditions, stress echo of the RV provides an estimate of the right ventricular contractile reserve, allows better phenotyping of the patient, regrades disease severity based on resting findings, and refines risk stratification [35].

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ABCDE Protocol for Stress Echocardiography in Chronic Coronary Syndromes

11

Quirino Ciampi and Eugenio Picano

Keywords

B-lines · Contractile reserve · Heart rate reserve · Preload reserve · Wall motion

11.1 From Coronary Stenosis to Patient Vulnerability

Stress echocardiography (SE) based on the assessment of inducible regional wall motion abnormality (RWMA) for functional evaluation of patients with known or suspected coronary artery disease (CAD) has a well-established clinical role recognized in guidelines [1, 2] and recommendations [3]. The unique versatility of SE also allows applications outside coronary artery disease in conditions such as valvular heart disease, congenital heart disease, dilated or hypertrophic cardiomyopathy, extreme physiology, and post-heart transplant rejection [4, 5]. The utilization rate of SE rose five- to tenfold in the last 20 years in risk- and cost-sensitive environments, due to increasing awareness from patients, doctors, and payers of considering economic costs and long-term radiation risks [6]. SE is considered a mature technique and its strength is also its major limitation, since it remained conceptually and methodologically unchanged from its birth 40 years ago and evaluates only the

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Q. Ciampi (✉)
Cardiology Division, Fatebenefratelli Hospital, Benevento, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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hemodynamic vulnerability of the epicardial coronary artery stenosis (Fig. 11.1, *left panel*). However, coronary stenosis is neither the only nor the most important source of the clinical vulnerability of the ischemic patient [8]. The state-of-the-art ABCDE-SE evaluates not only the coronary plaque but the comprehensive patient vulnerability taking advantage of the versatility of the technique (Fig. 11.1, *right panel*) [7].

In the standard SE approach, the methodology is a naked-eye assessment of RWMA, the technology is 2-dimensional echocardiography, and the main patient is the one with known or suspected CAD. This approach has obvious merits, since it provides a highly specific marker of myocardial ischemia and underlying epicardial CAD, with excellent risk stratification capability, an outstanding safety record, and an unsurpassed cost–benefit profile. Yet, there are limitations. The SE positivity rate based on RWMA fell from 70% in the eighties to 10% in the last decade for all tests based on myocardial ischemia, likely due to the increased use of anti-ischemic therapy at the time of testing [9, 10]. The diagnostic sensitivity and prognostic negative predictive value are suboptimal, lower than the predictive value of a test based on perfusion imaging [11, 12], and declined over the last 40 years [13]. All these limitations of the technique can now be fixed or minimized with the use of the state-of-art ABCDE protocol. In a one-stop shop, we can assess five different functional reserves and phenotypes, all known to affect outcomes: the epicardial artery reserve with step A [13]; the diastolic reserve through pulmonary congestion [14] with step

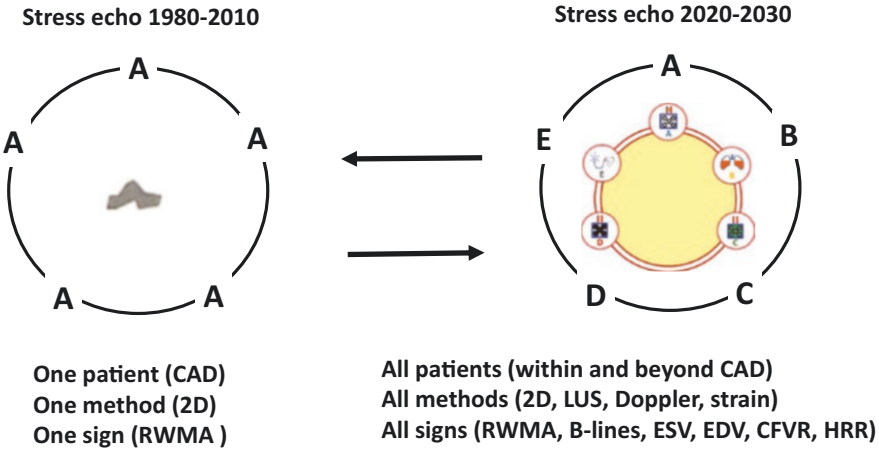

Fig. 11.1 Conceptual approach of advanced SE: from vulnerable stenosis to vulnerable patient. *Left panel*. In the classical or conventional approach used for 40 years and in first-generation multicenter studies such as Echo-Persantine Cooperative (EPIC) and Echo-Dobutamine Cooperative (EDIC) studies, SE was only focused on the hemodynamic significance of the coronary stenosis. *Right panel*. The advanced ABCDE protocol was used in the last 5 years in the second-generation SE2020 and SE2030 multicenter studies. The focus is shifted on the patient as a whole rather than the patient as a mere collection of coronary stenosis, with the assessment of vulnerability to ischemia (step A with RWMA now corroborated with artificial intelligence), pulmonary congestion (step B), left ventricular contractile and preload reserve (step C), coronary microcirculation (step D), and chronotropic reserve (step E). (Modified from Picano et al. [7])

B; the left ventricular contractile reserve [15] with step C; the coronary microcirculatory reserve [16] with step D; and the cardiac autonomic dysfunction [17] with step E. The old landline telephone is now a mobile smartphone with a variety of applications, which makes it ideally suited to tailor the right test at the right time on the right patient [18].

11.2 How to Do ABCDE-SE

In the novel state-of-the-art ABCDE-SE protocol, RWMA remains the first step A, corroborated by quantitative deformation imaging with global and regional strain. B-lines are assessed in step B; left ventricular contractile and preload reserve in step C; Doppler-based coronary flow velocity reserve in the left anterior descending coronary artery in step D, and ECG-based heart rate reserve in non-imaging step E. The five parameters converge conceptually, logistically, and methodologically in the ABCDE protocol, which can be applied to all stresses and all patients and allows comprehensive color-coded risk stratification of the vulnerable patient beyond coronary artery stenosis [19]. Conceptually, ABCDE-SE targets five complementary pathophysiological targets each independently contributing to the overall vulnerability profile of the patient and each weakly, if at all, related to the other steps (Fig. 11.2).

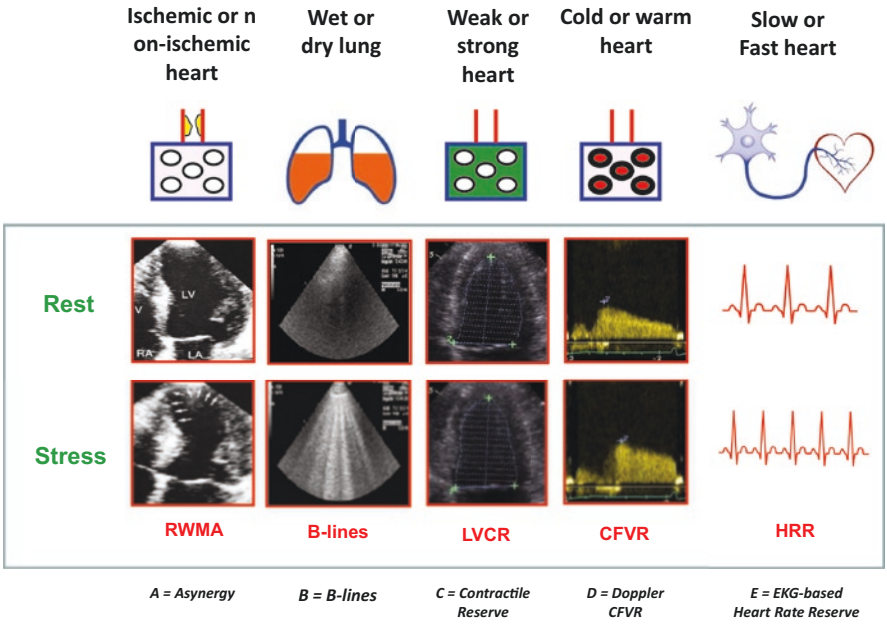

Fig. 11.2 Targets of integrated ABCDE-SE. The five pathophysiological targets of ABCDE-SE: epicardial coronary artery stenosis (with RWMA), step A; lung water (with B-lines), step B; myocardial function (with the left ventricular end-systolic area), step C; small vessels (with CFVR), step D; cardiac autonomic balance (with HRR), step E. (Modified and adapted from Picano [18])

Methodologically, all five steps are unified under the same ABCDE protocol that uses the known versatility of the technique: 2-dimensional echocardiography for regional wall motion analysis; lung ultrasound for B-lines; volumetric echocardiography for preload and contractile reserve; color- and pulsed-wave Doppler for coronary flow velocity reserve in the left anterior descending coronary artery; and ECG for heart rate reserve. Logistically, the five steps are used following a strict sequence to optimize the timing of the examination with no loss of information, with B-lines acquired in the early recovery phase and flow and motion acquired first since they recover in a few seconds (Fig. 11.3) [20].

The five steps of the ABCDE protocol are as follows: (1) step A: RWMA by 2D; (2) step B: B-lines by lung ultrasound (with the 4-site simplified scan of third intercostal space) assessing the shape of lung water [21]; (3) step C: left ventricular

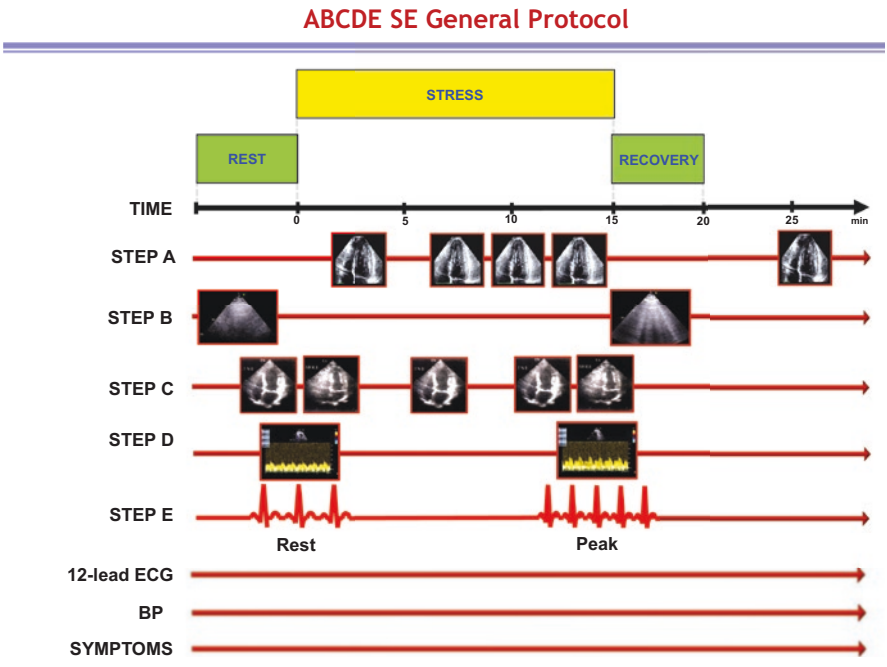

Fig. 11.3 ABCDE-SE protocol. The completion of the test from the preparation phase to the written response takes about 30 minutes. The recovery phase is optional and advised in the presence of test positivity. Step A and step C require the very same images. Step E requires only one ECG lead. Step B can be completed in the early (<30 s) recovery phase. Intermittent imaging of the left anterior descending artery (LAD) flow is performed at rest and peak stress with the same transducer used for continuous 2-dimensional imaging (2DE) of wall motion. *BP* blood pressure, *CFVR* coronary flow velocity reserve, *ECG* electrocardiogram, *LUS* lung ultrasound, *RWMA* regional wall motion abnormalities, *SE* stress echocardiography. See the accompanying Video 11.1. (Courtesy of Dr. Quirino Ciampi. The video is available under the chapter's "Supplementary Material" on Springer Link)

Table 11.1 Imaging and non-imaging parameters for ABCDE stress echo protocol

	RWMA	B-lines	LVCR	CFVR	HRR
ABCDE	A, asynergy	B, B-lines	C, contractility	D, Doppler	E, EKG
Variable	Ischemia	Water	Force	Reserve	ANS
Reserve	Epicardial	Diastolic	Contractile	Microcirc	Sympathetic
Imaging time	Minutes	Seconds	Seconds	Minutes	None
Analysis time	Seconds	Seconds	Minutes	Seconds	Seconds
Feasibility	>95%	Almost 100%	>95%	>80%	100%

Modified and adapted from Picano 2020 [7], http://creativecommons.org/licenses/by/4.0/
ANS autonomic nervous system, *CFVR* coronary flow velocity reserve, *HRR* heart rate reserve, *LUS* lung ultrasound, *LVCR* left ventricular contractile reserve, *PWD* pulsed-wave Doppler
Microcirc: coronary microcirculation

contractile reserve assessed as the stress/rest ratio of force (systolic arterial pressure by cuff sphygmomanometer/end-systolic volume from 2-dimensional echocardiography) or more simply as left ventricular cavity dilation during stress [22]; (4) step D: Doppler-based assessment of coronary flow velocity reserve in left anterior descending coronary with pulsed-wave Doppler [23]; and (5) step E: imaging-independent EKG-based assessment of heart rate reserve (peak/rest heart rate) [24] (Table 11.1).

The same transducer is used for cardiac and lung ultrasound scans.

11.3 Response Patterns of ABCDE-SE

The fully normal response of ABCDE-SE is shown in Fig. 11.4. A fully normal ABCDE-SE response identifies a "non-ischemic," "dry," "strong," "warm," and "fast" heart at very low risk.

The fully abnormal response of ABCDE-SE is shown in Fig. 11.5. A fully abnormal ABCDE-SE response identifies an "ischemic," "wet," "weak," "cold," and "slow" heart, at very high risk.

An example of a normal response is shown in Fig. 11.6.

An example of an abnormal response is shown in Fig. 11.7.

Each step has its positivity and severity titration criteria, which can be summarized with a score from 0 (all parameters normal) to 5 (all parameters abnormal). When a single parameter is not feasible or not available, it is scored as zero.

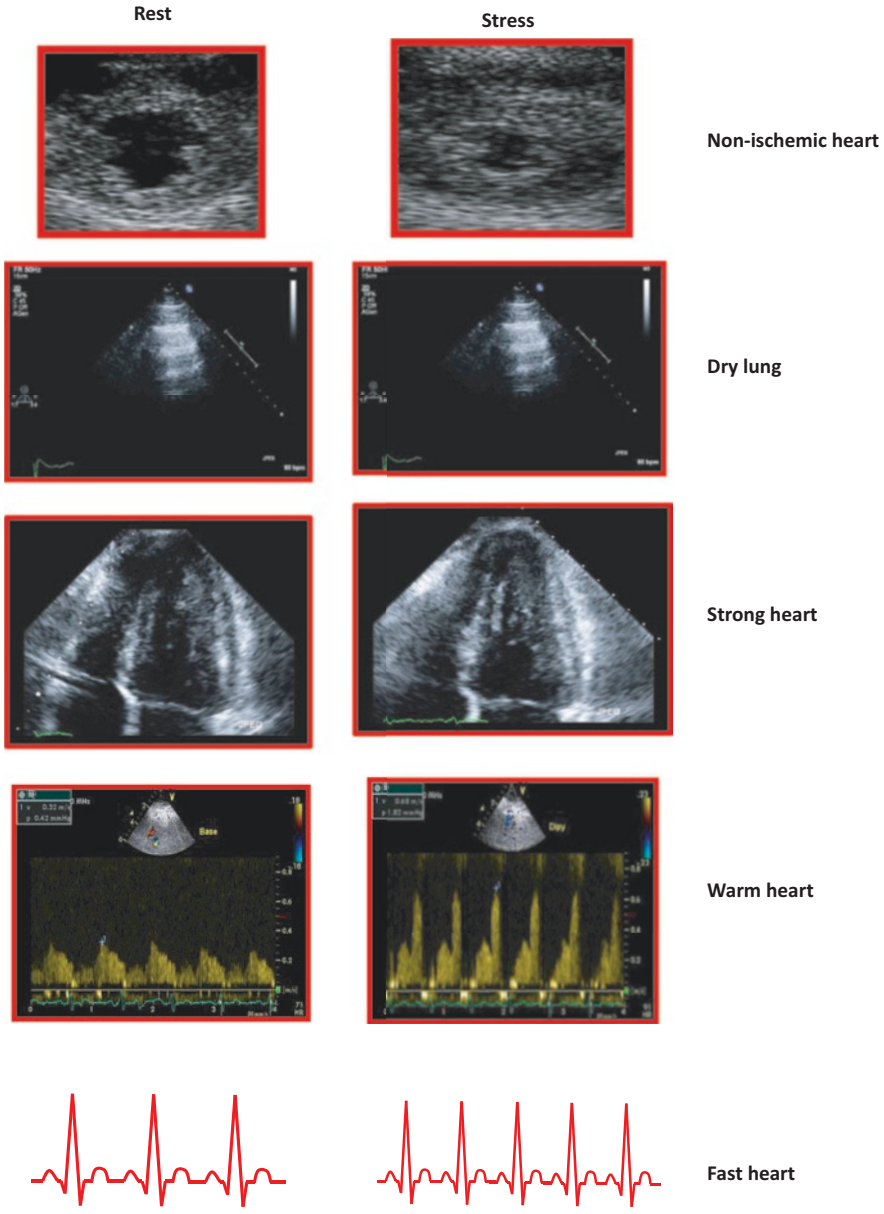

Fig. 11.4 Fully normal ABCDE-SE response. From top to bottom, the five different ABCDE steps of SE with a fully normal response from rest (left column) to stress (right column) are shown. The normal response is shown for a non-ischemic (step A), dry (step B), strong (step C), warm (step D), and fast (step E) heart. (Modified and adapted from Picano et al. [20], http://creativecommons.org/licenses/by/4.0/)

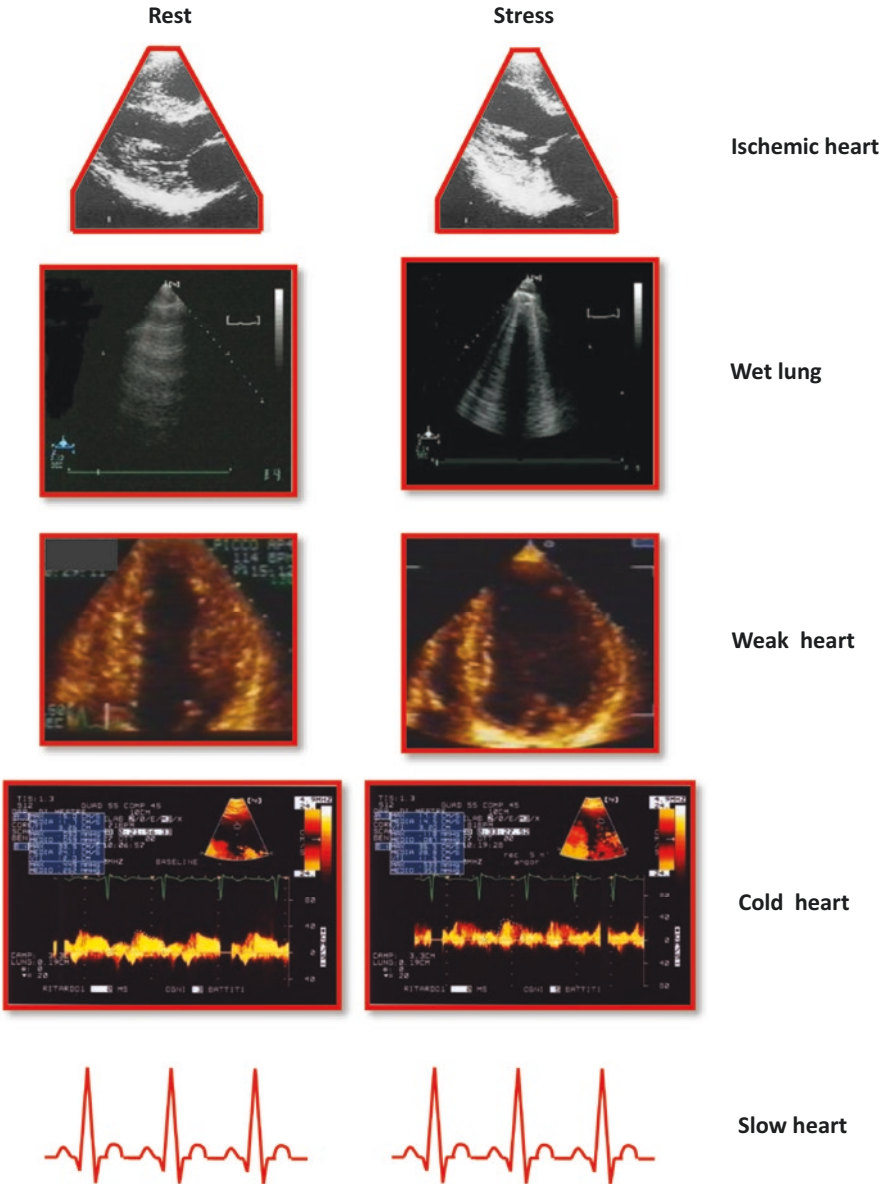

Fig. 11.5 Fully abnormal ABCDE-SE response. From top to bottom, the five different ABCDE steps of SE with a fully abnormal response from rest (left column) to stress (right column) are shown. The abnormal response is shown for an ischemic (step A), wet (step B), weak (step C), cold (step D), and slow (step E) heart. (Modified and adapted from Picano 2018 [20], http://creativecommons.org/licenses/by/4.0/)

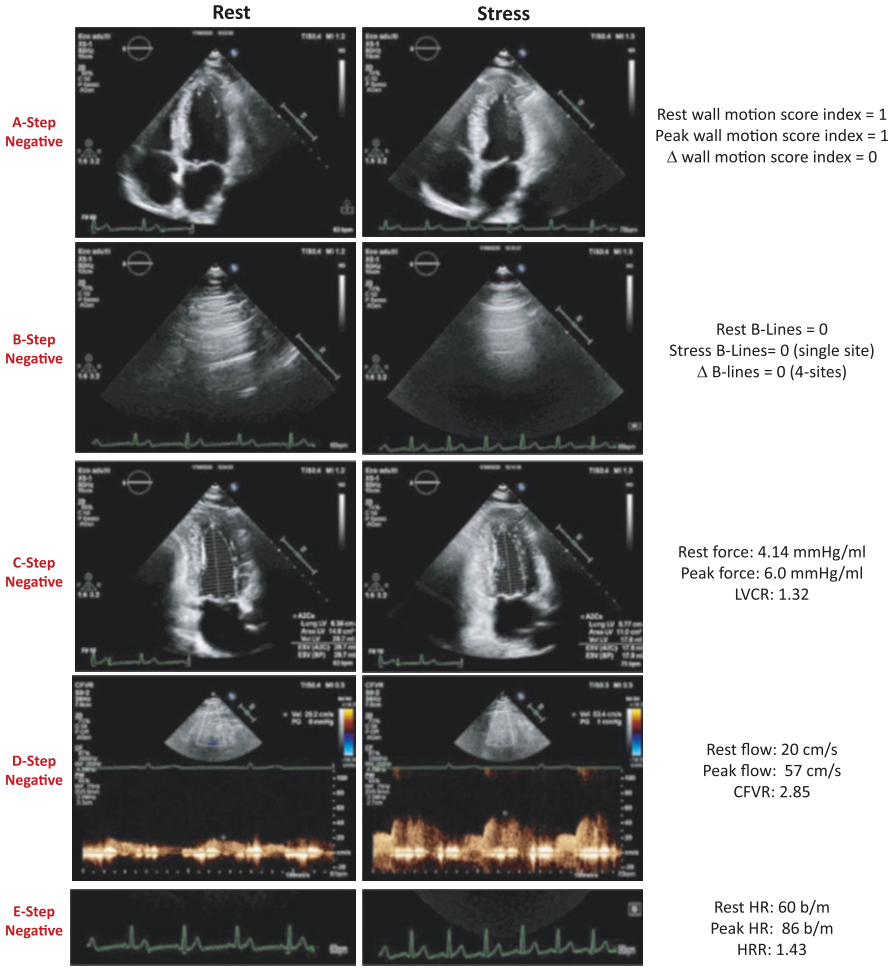

Fig. 11.6 Fully normal ABCDE-SE response. From top to bottom, the five different ABCDE steps of SE with a fully normal response from rest (left column) to stress (right column) are shown. The normal response is shown for a non-ischemic (step A), dry (step B), strong (step C), warm (step D), and fast (step E) heart with peak wall motion score index = 1, normal A-lines without B-lines, reduced left ventricular end-systolic volume during stress, normal coronary flow velocity reserve, and normal heart rate reserve (1.43 with dipyridamole, normal values ≥1.22)

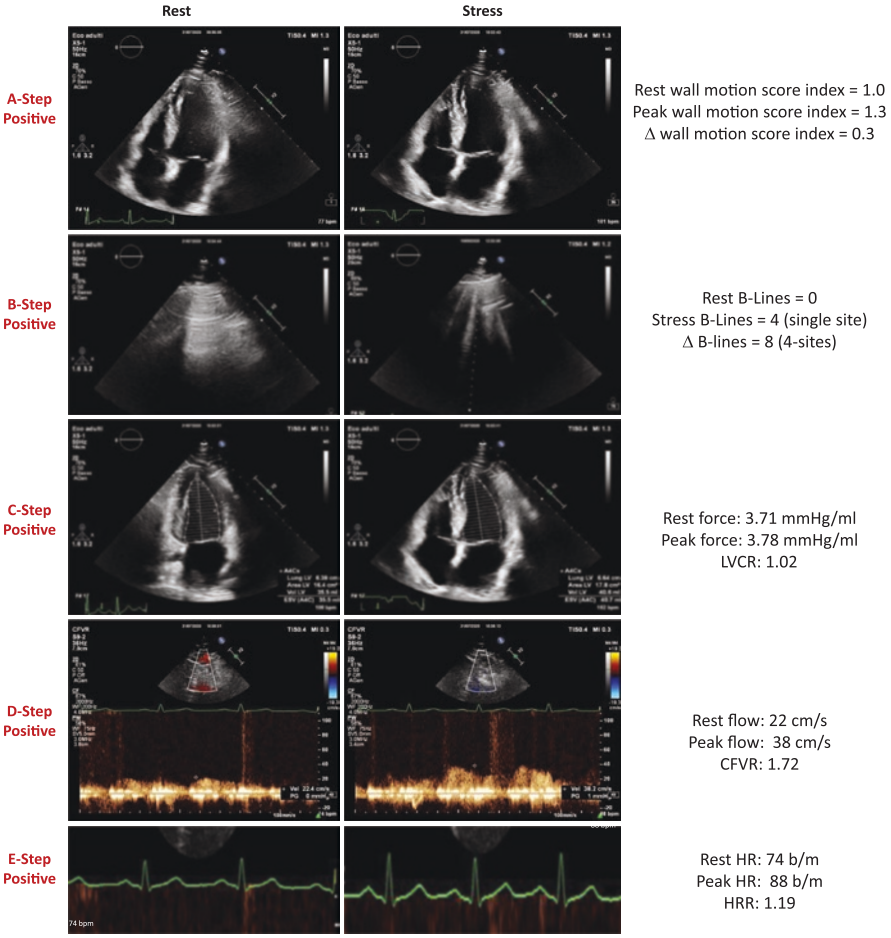

Fig. 11.7 Fully abnormal ABCDE-SE response. From top to bottom, the five different ABCDE steps of SE with a fully normal response from rest (left column) to stress (right column) are shown. The normal response is shown for an ischemic (step A), wet (step B), weak (step C), cold (step D), and slow (step E) heart with peak wall motion score index = 1.3, 4 B-lines in a single intercostal space, dilated left ventricular end-systolic volume during stress, reduced coronary flow velocity reserve = 1.72, and blunted heart rate reserve (1.19 with dipyridamole, normal values ≥1.22)

11.4 Coronary Anatomic and Functional Correlates

The presence, severity, and extent of CAD increase with increasing values of ABCDE score, lowest with a score of 0 (all parameters normal) and highest with a score of 5 (all parameters abnormal). The masking effect of therapy is highest for step A, but much less pronounced for other steps, which can be abnormal for levels of ischemia unable to induce detectable RWMA. Higher values of the ABCDE-SE score also correspond to a lower anaerobic threshold, higher New York Heart Association class, higher levels of cardiac natriuretic peptides, and more comorbidities, reinforcing the value of the score as an integrated index of the health of the patient [25, 26].

11.5 Outcome Data

With this methodologic and conceptual remodeling, the pathophysiologic model shifted from stenosis vulnerability to patient vulnerability. The global risk identifies the overall risk for death, but each parameter has its specific outcome events, which are better predicted coherently with pathophysiological premises. For instance, stress-induced RWMA will predict readmission for unstable angina and B-lines will predict readmissions for acute heart failure. Each step positivity will drive specific interventions, for instance, anti-ischemic therapy for inducible ischemia and diuretics for B-lines.

11.6 Tips and Tricks

Step B can be obtained at the end of stress after other measures have been completed. Other physiologic variables (such as myocardial ischemia, left ventricular function, or coronary flow) immediately come to normal within seconds, but lung water takes a few minutes to be reabsorbed and imaging can be performed in the first minute after the stress without loss of information. Step D can be obtained with myocardial contrast echocardiography instead of CFVR, but this takes time, training, expertise, and cost and the information is in the end comparable with simpler CFVR.

11.7 Recommendations: A Paradigm Shift

The ABCDE will eventually integrate the current view of coronary syndromes as a disease of epicardial coronary artery stenosis therapeutically centered on anatomy-driven revascularization. The approach based on coronary stenosis is appealingly simple, productive, and pervasive in mainstream cardiology, but not fully consistent with pathophysiological evidence and contradicted by milestone trials such as COURAGE, STICH, ORBITA, and ISCHEMIA showing that ischemia-driven or viability-driven myocardial revascularization does not prolong life or prevent major cardiac events [27–29]. The ABCDE perspective is more likely to capture the complexity of a patient's vulnerability and paves the way to personalized cardiology (Fig. 11.8) [7].

The Stress Echo 2030 Study is based on the new ABCDE protocol and aims to recruit in 5 years (2021–2025) ≥10,000 patients, allowing to build the platform of evidence required for changing the standard of practice (Fig. 11.9) [30]. ABCDE-SE is now the recommended standard of practice according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [31].

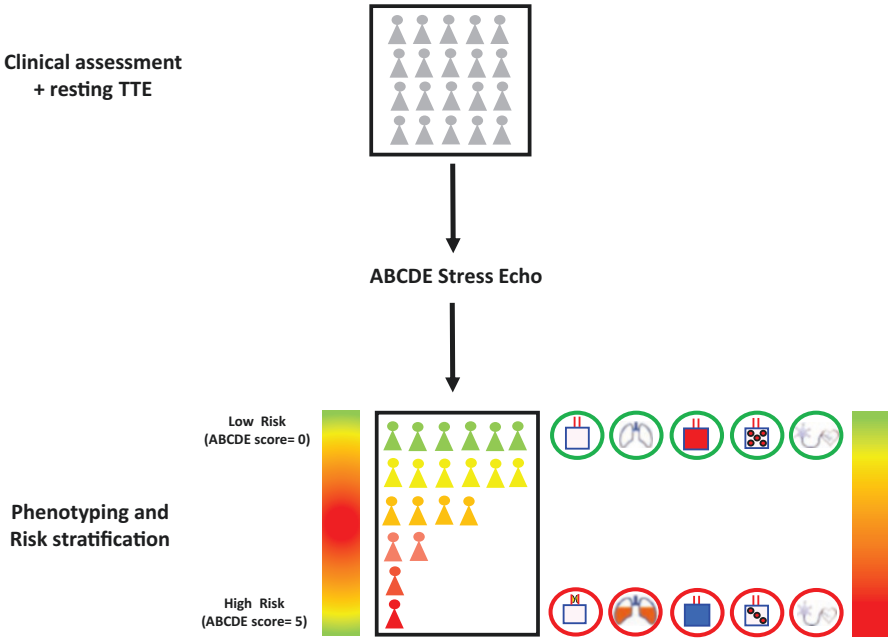

Fig. 11.8 From black-and-white to the color view of functional stress testing. A population of all-comers (*top panel*) is evaluated with the ABCDE-SE. The five targets of ABCDE-SE identify specific phenotypes (*central panel*): epicardial coronary artery stenosis (with step A); lung water (with step B); myocardial function (with step C); small vessels (with step D); and cardiac autonomic balance (with step E). After testing, the ABCDE score identifies different strata of risk, while the individual step response evaluates the specific phenotype, which can be targeted by tailored therapy (*bottom panel*). (Modified from Picano et al. [7])

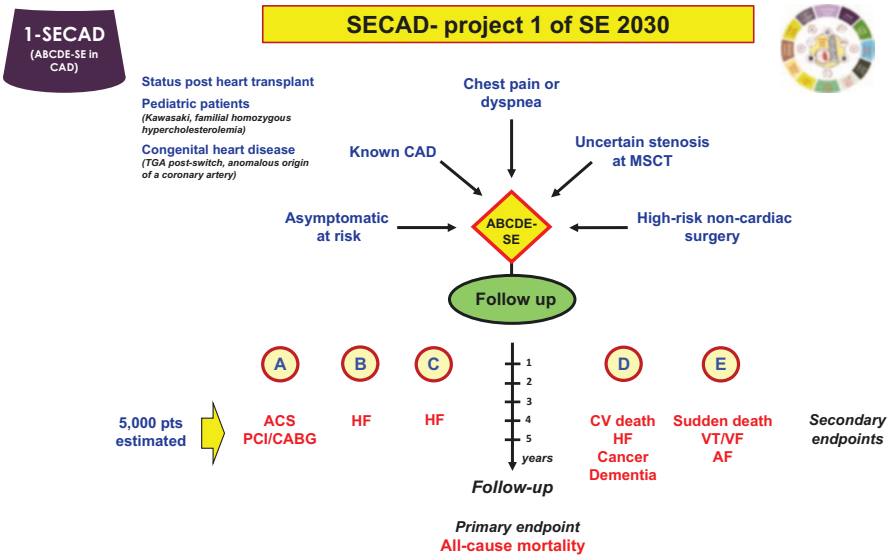

Fig. 11.9 Study protocol of Stress Echo 2030, subproject 1 (SECAD, stress echo in coronary artery disease). All patients will be tested with the ABCDE protocol, also adopted in the remaining projects on different patients' subsets, from heart failure to valvular heart disease. (Modified from Picano et al. [30])

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The ABCDE-FGLPR Protocol for Stress Echocardiography Beyond Coronary Artery Disease

12

Caroline Van De Heyning and Eugenio Picano

Keywords

Filling pressure · Left atrium · Gradients · Regurgitation · Pulmonary pressure · Right ventricular function

12.1 Beyond Coronary Artery Disease

Stress echocardiography (SE) based on the assessment of ABCDE protocol offers a comprehensive approach to studying patients beyond coronary artery disease [1]. Although the ABCDE protocol is an excellent tool to assess the functional correlates of ischemia, further steps can be useful in patients with ischemic equivalents like dyspnea. In these patients, the exclusion of ischemia is often the first aim, but adding several other steps can point to a different explanation for the symptoms. In a patient with exertional dyspnea and nonsignificant mitral regurgitation at rest, for instance, exercise echocardiography with the assessment of mitral regurgitant flow and pulmonary artery pressures can reveal dynamic mitral regurgitation with concomitant pulmonary hypertension (Fig. 12.1). Moreover, in several subsets of patients with known cardiac pathology, SE can provide additional information and improve risk stratification and clinical decision-making.

C. Van De Heyning (✉)
Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium
e-mail: caroline.vandeheyning@uza.be

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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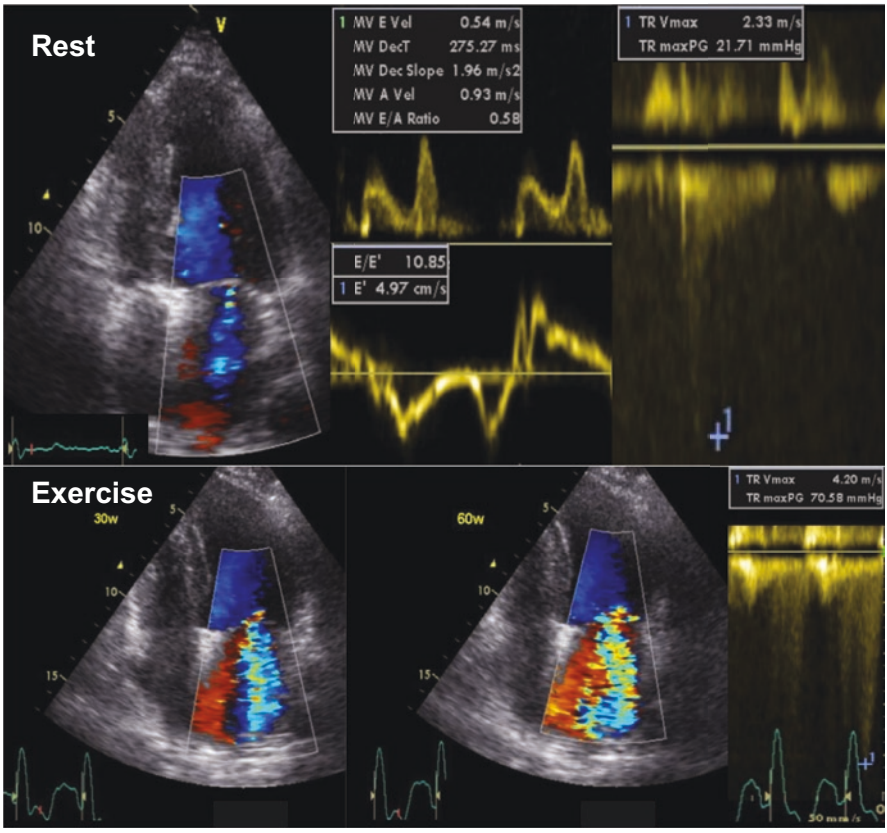

Fig. 12.1 A patient with exertional dyspnea despite recent revascularization, due to an exercise-related left bundle branch block with dynamic mitral regurgitation. At rest, echocardiography showed mild regurgitation, grade 1 diastolic dysfunction, and no signs of elevated pulmonary artery pressures. During exercise, the patient developed a left bundle branch block with severe mitral regurgitation and pulmonary hypertension. Exercise echocardiography can identify the underlying cause of exertional symptoms by revealing pathologic cardiac hemodynamics which are not apparent at rest

ABCDE is applied in all patients as the default protocol. The same vulnerabilities that affect the outcome in patients with ischemia are also important in conditions outside of coronary artery disease. Inducible regional wall motion abnormalities, pulmonary congestion, global left ventricular dysfunction, coronary microvascular disease, and cardiac autonomic dysfunction are now identified as possible mechanisms of initiation, progression, and complication of disease [2]. As an example, inducible wall motion abnormalities (step A) occur in hypertrophic cardiomyopathy patients with angiographically normal coronary arteries and negatively affect prognosis [3]. B-lines (step B) are present in valvular heart disease and establish a relationship between acute heart failure and dyspnea during stress in patients who may have multiple causes of cardiogenic and non-cardiogenic dyspnea

[4]. Impairment of the left ventricular contractile (step C) reserve plays an important role in the prediction of outcomes in patients with heart failure [5]. The reduction in coronary flow velocity reserve (step D) is an early diagnostic marker of acute rejection in transplanted hearts and precedes the development of clinically overt heart failure [6]. Reduced sympathetic reserve with reduction of heart rate variability (step E) is a powerful risk factor together with coronary microvascular dysfunction in hypertrophic cardiomyopathy [7]. However, in these patients, the common comprehensive platform is not enough. The clinical presentation is so diverse, the diagnostic questions are so heterogeneous, and the technical challenges are so disparate that new letters of the SE alphabet must be used to address the challenges of personalized medicine. The test must be tailored to the individual patient, and useful extra information can be selectively explored with other parameters of established or potential use in specific subsets of patients.

Following the intuitive alphabetic order, additional useful parameters beyond ABCDE are mitral regurgitant flow (step F), dynamic left ventricular or transvalvular obstructive gradient (step G), left atrial volume changes (step L), filling pressures and pulmonary hemodynamics (step P), and right ventricle function (step R). With this systematic approach, all patients referred to the SE laboratory can be adequately studied with tailored answers for each patient (Fig. 12.2).

Step F and step G are essential in valvular and congenital heart disease, hypertrophic cardiomyopathy, and athletes. SE has a definite role in the heart valve clinic and

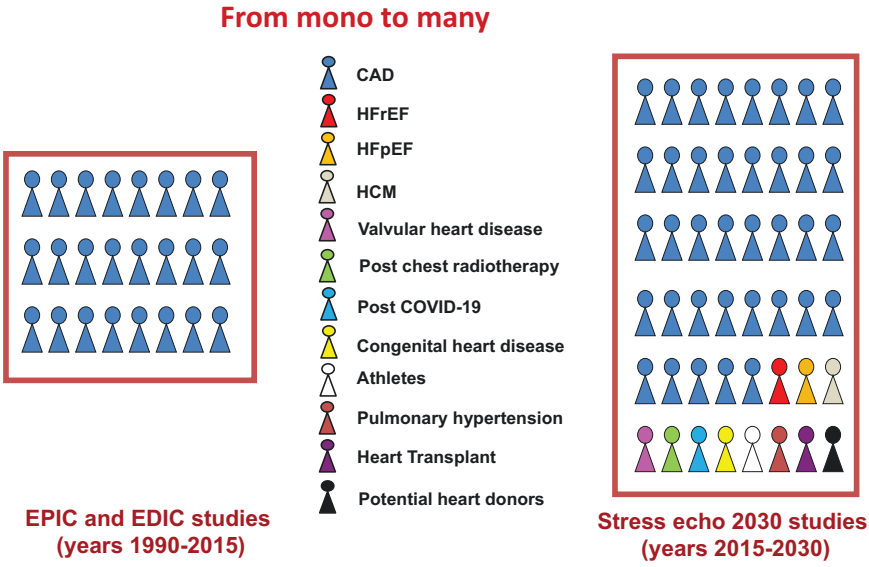

Fig. 12.2 Patient profile of SE yesterday and today. On the left, patients were recruited in large-scale studies in the years 1990–2015: one patient (with CAD), one technology (2D), and one sign (RWMA). On the right, patients were recruited in the years 2015–2023 in large-scale SE2020 and SE2030 studies: many different patients, all technologies, and multiple signs

is especially indicated when symptoms do not match the severity of valvular heart disease at rest, or in the asymptomatic patient with evidence of severe valvular disease by echocardiography at rest [8]. In hypertrophic cardiomyopathy, one patient out of 3 shows intraventricular obstruction at rest, and 1 out of 3 during stress, and this represents a specific indication of myosin inhibitors, beta-blockers, or surgical or percutaneous intervention if symptoms cannot be controlled with medication [9].

The left atrium (step L) is a highly dynamic chamber and plays an active part in the physiology of the entire cardiovascular system. The left atrial volume index can be easily measured during SE, with an excellent success rate and good reproducibility. Combined with peak atrial longitudinal strain, it provides a composite index of left atrial form and function during stress, potentially valuable in several conditions from heart failure to hypertrophic cardiomyopathy [10].

Step P (for pressures) allows an estimation of the pulmonary artery pressure from the tricuspid regurgitant jet velocity and the left ventricular filling pressure from E/e′. A possibility to overcome the present limitations in estimating the pulmonary artery systolic pressure is to assess the pulmonary acceleration time when the tricuspid regurgitant jet velocity is not obtainable. The pulmonary acceleration time is based on systolic antegrade pulmonary flow, and a shortening indicates increased pulmonary artery pressures [11]. It is feasible in almost all patients during stress. The issue remains of flow dependence of systolic pulmonary arterial pressures, but changes in pressures can be normalized by minutes of exercise or changes in cardiac output to obtain a flow-normalized index of the pulmonary vascular reserve [12]. Limitations of E/e′ can be minimized with the combination of step B for B-lines and assessment of preload reserve of the left atrium and left ventricle. This approach is feasible in all patients and provides an integrated assessment of lung water correlated to acute variations in wedge pressure and preload changes. These approaches have been developed in SE 2020 and are adopted in the SE 2030 study.

Step R (right ventricular function) is important in many conditions from heart failure to valvular heart disease and is especially relevant in pulmonary hypertension, in some forms of congenital heart disease such as repaired tetralogy of Fallot, and in valvular heart disease when right ventricular function and pulmonary hemodynamics determine prognosis and drive management [12].

12.2 How to Do the New Steps: FGLPR

In a comprehensive protocol, two-dimensional echocardiographic images must be acquired throughout the whole study with at least three apical views during each stage; when registered, they may give wall motion score index, left ventricular volumes, ventricular and atrial strain, left atrial volume with a left atrium-focused view, and right ventricular areas with right ventricular-focused views. The suggested general sequence of acquisition employs all methods (Table 12.1).

This is like the *menu à la carte* of a restaurant. It is impossible to eat everything every time, because there is little time to scan and too many things to see. Rather, the

Table 12.1 General protocol of ABCDE-FGLPR stress

	Rest	Intermediate load	Peak stress	Recovery <2 min
1. 2D (A4C, 2C, 3C, LAX, SA, RV)	v	v	v	v
2. LUS for B-lines	v			v
3. Color Doppler (MR, TR, LAD)	v	v	v	
4. CW Doppler (MR, TR, AS)	v	v	v	
5. PW Doppler (MV, LAD)	v	v	v	
6. TDI (e′ for E/e′, s′)	v	v	v	v
7. M-mode (TAPSE)	v		v	
8. ECG (heart rate)	v		v	
9. BP (SBP, DBP)	v		v	
10. Symptoms	v	v	v	v

Suggested Sequence of Acquisition

1. 2D LV views apical 4C, 2C, and 3C; parasternal long-axis (LAX) and short-axis (SA) basal-middle- and apical levels (step A, C, and L) and focused RV view (R)
2. Lung ultrasound (LUS) 4-site scan for B-lines (step B)
3. Color Doppler for mitral regurgitation (MR) (step F), tricuspid regurgitation (TR) (step P), and LAD localization (step D)
4. CW Doppler for MR (step F), aortic stenosis (AS) or LV gradient (step G) quantification, and TR velocity estimation (step P)
5. PW Doppler mitral valve inflow (E wave velocity) (step P) and LAD flow velocity (step D)
6. TDI for measuring e′ (step P) or right ventricular s′ (step R)
7. M-mode to measure tricuspid annular plane systolic excursion (TAPSE) (step R)
8. ECG (heart rate rest and peak) (step E)
9. Blood pressure by cuff sphygmomanometer (to assess the left ventricular force and hypertensive or hypotensive response during stress)
10. Symptoms (chest pain, dyspnea, palpitations, and syncope should always be correlated with SE findings)

best solution should be tailored for a given patient, and the scan sequence should be prioritized according to the specific clinical question. All parameters should be put in the context of clinical symptoms, electrocardiographic, and blood pressure response.

12.3 Tips and Tricks

Each step has a different methodology, severity criteria, and specific field of application. Nevertheless, a unified conceptual view of test results is possible and can further enrich the broader view gained with the ABCDE protocol.

Accuracy and precision are two measures of the observational error. Accuracy is how close is the observed value to its true value. The precision (the test–retest variability, how close the measurements are to each other on repeated attempts) is only fair for step F (even with the quantitative assessment).

The feasibility (how many times the test finds a target to be hit) is good for most parameters, but not for step P if only tricuspid regurgitant velocity is used. When the tricuspid regurgitation velocity cannot be sampled adequately, the pulmonary acceleration time can be used to evaluate the pulmonary pressures, as previously

Table 12.2 Fundamental features of steps beyond ABCDE during stress

	Accuracy	Repeatability	Feasibility	Simplicity
Step F	C	C	C	C
Step G	A	A	B	C
Step L	A	A	B	A
Step P	B	B	B	B
Step R	A	A	A	A

School grades: A = excellent, B = very good, C = fair, D = sufficient, E = insufficient

mentioned. Another way to improve sampling of the tricuspid regurgitation velocity signal is to enhance it by colloid contrast [13], but this requires the insertion of an intravenous line.

Some measurements (step L, step R) are very simple, others (step F, step P) are less simple, and training and expertise are required to obtain consistent results (Table 12.2).

Some parameters can look at the same functional aspect from a different angle. Diastolic function, for instance, is assessed with E/e′ but also with left atrial volume, left ventricular preload reserve, pulmonary pressures, and B-lines. In case of discordance, the simplest and most reproducible parameters tend to prevail.

Several vendors allow the creation of different templates for the cardiovascular ultrasound machine. The personalized template can be used for specific clinical scenarios or clinical trial study protocols. This may help to perform SE uniformly at the echo laboratory so that all necessary steps are obtained. It may also facilitate analysis afterward, not only to compare rest and stress images simultaneously for visual wall motion assessment but also to measure a certain parameter at different stages, which can be exported to a worksheet or a dedicated software application to generate an automatic echo report.

With this methodologic and conceptual remodeling, the pathophysiologic model shifted from stenosis vulnerability to patient vulnerability including all aspects of cardiac pathophysiology. They should be considered like apps in the last generation smartphone: They are all there and can be used based on daily needs and specific circumstances.

They are letters in the alphabet of SE. Some letters are more used and useful than others, for instance, the letter A, for many years the only one used in SE. Other letters are so easy to learn, for instance, step E, a window on cardiac autonomic balance, with 100% feasibility and 0% variability. Some other letters will come as we better focus their meaning and impact, for instance, step S for synchrony and strain. But the rationale is simple. With all these letters, you can write all words and address most diagnostic queries in many patients. With this refined armamentarium, SE will move in the era of personalized cardiology.

Table 12.3 Selective applications of SE beyond regional wall motion abnormality

Step G, gradient	Step G, LVOTG	Step F, MR grade	Step P, E/e'	Step P, PASP	Step R, TAPSE
LF-LG AS	HCM	Primary MR	HFpEF	HFpEF	Repaired ToF
MS		Secondary MR		MS, MR	
Aortic coarctation				Symptomatic patients with systemic sclerosis	
Subvalvular, valvular, supravalvular AS in CHD				Suspected PH in CTEPH	

CHD congenital heart disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *HFpEF* heart failure with preserved ejection fraction, *LF-LG AS* low-flow, low-gradient aortic stenosis, *LVOTG* left ventricular outflow tract gradient, *MR* mitral regurgitation, *MS* mitral stenosis, *PASP* pulmonary artery systolic pressure from tricuspid regurgitant velocity, *PH* pulmonary hypertension, *ToF* Tetralogy of Fallot

12.4 Recommendations and Guidelines

SE has already a place in the recommendations for specific applications beyond coronary artery disease [14], and many parameters have a potential role even in known or suspected coronary artery disease [15]. For instance, the assessment of a dynamic intraventricular pressure gradient can be useful to establish a noncoronary cause of ischemia in a patient with normal coronary arteries. The current level of acceptance of signs different from regional wall motion abnormality in recent guidelines is summarized in Table 12.3. The class of recommendation ranges from class 1 to class 2 b.

In summary, guidelines accept SE mainly with 6 markers: RWMA (in chronic coronary syndromes, heart transplant patients for rejection, Kawasaki disease, or coronary anomalies for ischemia detection post-switch operation), coronary flow velocity reserve (ischemia with normal coronary arteries), E/e′ (for diastolic SE in heart failure with preserved ejection fraction) [16], tricuspid regurgitant velocity jet (for diastolic SE, valvular heart disease and pulmonary hypertension) [16–20], transvalvular gradient assessment with simultaneous assessment of cardiac flow reserve and LV contractile reserve in low-flow, low-gradient AS with reduced ejection fraction [17, 18], valvular heart disease or aortic coarctation in congenital heart disease [20, 21], and LV outflow tract obstruction in hypertrophic cardiomyopathy [22, 23].

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Part II

Training and Technology

Strain and Real-Time Three-Dimensional Stress Echocardiography

13

Rosina Arbucci and Eugenio Picano

Keywords

Contractile reserve · Deformation imaging · Global longitudinal strain · Preload reserve · Real-time three-dimensional echocardiography

13.1 Toward Quantitative Stress Echocardiography

Stress echocardiography (SE) is an established and mainstream method for the diagnosis and risk stratification of patients with known or suspected coronary artery disease [1, 2]. While the overall accuracy of SE techniques is high, these methods are inherently limited by the subjective, eyeballing nature of image interpretation [3] and the learning curve [4] with relatively wide interinstitutional variability [5], unless conservative reading criteria are developed a priori through consensus [6]. In addition, the diagnosis is based on a visual assessment of systolic thickening and endocardial motion, estimating radial function, which is theoretically less sensitive to ischemia than longitudinal and circumferential function [7]. Electrical activation disturbances (such as left bundle branch block or right ventricular pacing),

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R. Arbucci (✉)
Cardiodiagnosticos, Investigaciones Medicas Center, Buenos Aires, Argentina

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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hemodynamic conditions (such as right ventricular overload), or extracardiac factors (such as cardiac surgery or constrictive physiology) may affect wall motion independently of ischemia [8]. Tachycardia and an increase in blood pressure may mimic ischemia, inducing a reduction of wall motion and thickening, more often global but sometimes regional [9]. Conversely, ventricular unloading (e.g., caused by mitral insufficiency) may mask ischemic wall motion abnormalities because of hyperkinesis and low wall stress [10]. The standard approach to subjective wall scoring is to evaluate contraction on a regional basis, without the ability to selectively assess subendocardial function, which is more sensitive to ischemia than the subepicardial layer [8]. Furthermore, the current application of SE is certainly full of useful clinical information, but the results cannot be easily reduced to an intuitive graphical display, understandable immediately and also by a non-imaging specialist. The development of an objective, quantitative method for wall motion analysis during stress testing would overcome these limitations, translating the inducible wall motion abnormality from an opinion into a number (Table 13.1).

This would improve accuracy, shorten the learning curve, and improve communication of SE results with referring clinicians, ultimately strengthening the current clinical and scientific role of the technique. In addition, the quantitative assessment of the time course of left ventricular (LV) contraction would allow a more comprehensive assessment of the complex physiology of LV function, which is incompletely described with a simple assessment of radial function through endocardial motion and thickening at a single end-diastolic and end-systolic time point during the cardiac cycle.

Strenuous efforts have been made in the last 30 years by bioengineers, industry, and researchers to target the quantitative assessment of LV function. Different waves of new ultrasound technologies have been proposed to overcome the limitations of conventional echocardiography [11]. Each approach can be broadly assigned to five technological generations of ultrasound imaging: M-mode, 2D, tissue Doppler, two-dimensional speckle tracking echocardiography (STE), and real-time three-dimensional echocardiography (3DE) (Table 13.2).

Each of the five approaches can be combined with artificial intelligence, which provides a robust approach for operator-independent assessment of regional wall motion abnormalities, LV ejection fraction (EF), and volumetric echocardiography of LV, right ventricle, left atrium, and right atrium. The two approaches that have gained clinical acceptance for the definition of LV global and regional function are STE and 3DE.

Table 13.1 Present reality and future promises in SE

	What we have	What we need
Regional function	Thickening, motion	Strain
Ventricular function	Radial	Longitudinal, circumferential
Segmental function	Transmural	Subendocardial
Graphical display	Informative	Intuitive
Operator-dependence	High	Low
Learning curve	Long	Short
Diagnostic gold standard	Expert opinion	Automatic number

Table 13.2 Five main approaches to quantification

	M-mode	2D	Tissue Doppler	STE	3DE
Signal	Motion	Thickening	Velocity	Deformation	Volume
Main function	Long.	Rad.	Long.	Long, Rad, Circum	Composite
First generation	MAPSE	Centerline	TDI	2D speckle	Offline 3D
Second generation	An. M-mode	Color kinesis	SRI	3D speckle	RT3D
Analysis time	Seconds	Minutes	Minutes	Minutes	Minutes

An anatomical, *Circum* circumferential function, *Long* longitudinal function, *Rad* radial function, *RT3D* real-time three-dimensional echocardiography, *MAPSE* mitral annular plane systolic excursion, *TDI* tissue Doppler imaging, *SRI* strain rate imaging

13.2 Anatomic Basis of Myocardial Contraction

The LV shape is a consequence of its fiber orientation, and there is a close relationship between myocardial fiber architecture and its function. The ventricular myocardium acts as a continuous helicoid muscle band, formed by basal and apical loops, with a lack of motion of the apex during the cardiac cycle, characterized by the downward movement of the entire base in early systole. It is the peculiar counter-woven double-helix arrangement of muscle fibers that allow the efficient transduction of the contractile unit of the cardiac myocyte into the pump function of the LV expressed by the EF. A sarcomere shortening by about 13% is associated with an LV shortening in length (longitudinal strain) and circumference (circumferential strain) by about 20%, with 40% systolic thickening (radial strain) leading to an EF of 60% [12, 13]. EF is the most widely used LV systolic function index in clinical practice; however, it only considers changes in ventricular volume, and it is highly dependent on preload and afterload, heart rate, ventricular geometry, and contraction synchrony. For these reasons, it is unable to detect early, mild systolic dysfunction. Since the beginning of the twenty-first century, STE allows the analysis of strain or myocardial deformation [14, 15]. This tool provides a quantitative regional analysis of LV function, confirming a correlation with functional anatomy [16]. According to Ballester, Ferreira, and Carreras, the different segments of the continuous myocardium basal and apical loop correlate with strain, analyzed by the 4-chamber view. In early systole, the base of the heart is pulled toward the apex for the contraction of the descending fibers, and in late systole, it is pulled away from the apex due to the contraction of the ascending fibers. Short axis views show a complex distribution of myocardial segments, with a predominant ascending segment (green) in the apex evidencing greater curvature radius or torque [17]. Torque is the rotational equivalent of linear force and represents the capability to produce a change in the rotational motion of the heart. In the middle region, the descending (yellow) and ascending (green) segments are balanced, while the base of the heart shows the continuity of the right (blue) and left (red) segments (Fig. 13.1) [17].

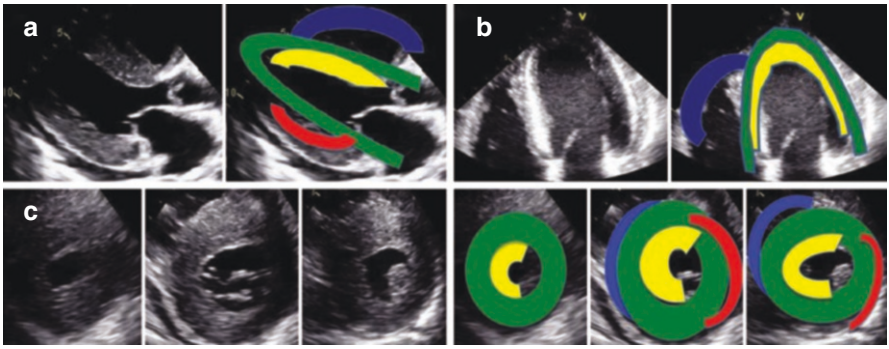

Fig. 13.1 (**a**) Long-axis parasternal view. The right basal segment makes up 100% of the right ventricular wall (blue). The left segment occupies a minimal area in the LV inferolateral portion (red). The ascending (in green) and descending (in yellow) fibers complement each other at the anteroseptal level. (**b**) Apical four-chamber view. The descending segment occupies the internal ventricular surface and is surrounded by the ascending segment. Part of the basal loop right segment is found in the basal third of the lateral wall (blue). (**c**) Short axis views show a complex distribution of myocardial segments, with a predominant ascending segment (green) in the apex evidencing a greater curvature radius or torque. In the middle region, the descending (yellow) and ascending (green) segments are balanced, while the base of the heart shows the continuity of the right (blue) and left (red) segments

13.3 Spatial and Temporal Heterogeneity of Left Ventricular Contraction

During systole, the LV myocardial fiber function undergoes a three-dimensional deformation, characterized by longitudinal strain (shortening in apical views), circumferential strain (shortening in the minor axis), and radial strain (thickening in the minor axis). Its accuracy has been validated with sonomicrometry and cardiac magnetic resonance [18–20]. The three dimensions of LV contraction show physiologic heterogeneity in time and space. Peak systolic longitudinal shortening is highest in apical segments (Fig. 13.2).

Radial thickening is higher in basal and midsegments and lower in apical segments (Fig. 13.3).

The cardiac contraction follows the direction of the myocardium, changing its orientation according to the arrangement of the fibers, predominantly oblique longitudinal in the endocardium and epicardium and circumferential at the level of the mesocardium. Shrinkage reveals a shortening from an initial dimension, so longitudinal and circumferential strain is negatively coded. Conversely, radial thickening reveals enlargement of an initial dimension that is positively coded. In addition, because of the oblique myofibrillar fiber arrangement, a progressive change of angulation is generated from the endocardium to the epicardium with a right-hand helical direction in the subendocardium and a left-hand helical orientation in the subepicardial layer. The anatomical arrangement originally described by Torrent Guasp and validated in anatomy-functional investigations by Trainini et al. [21, 22]

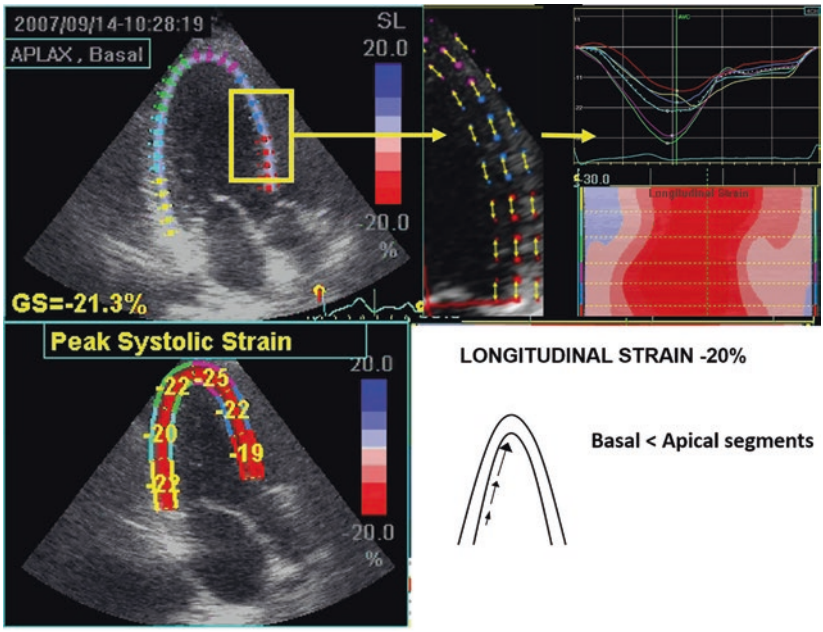

Fig. 13.2 Longitudinal strain is lower in basal and midsegments and higher in apical segments. Note that the y-axis scale shows negative resting values (–20%) for longitudinal strain. Courtesy of Rosina Arbucci, MD, and Jorge Lowenstein, MD, Buenos Aires, Argentina

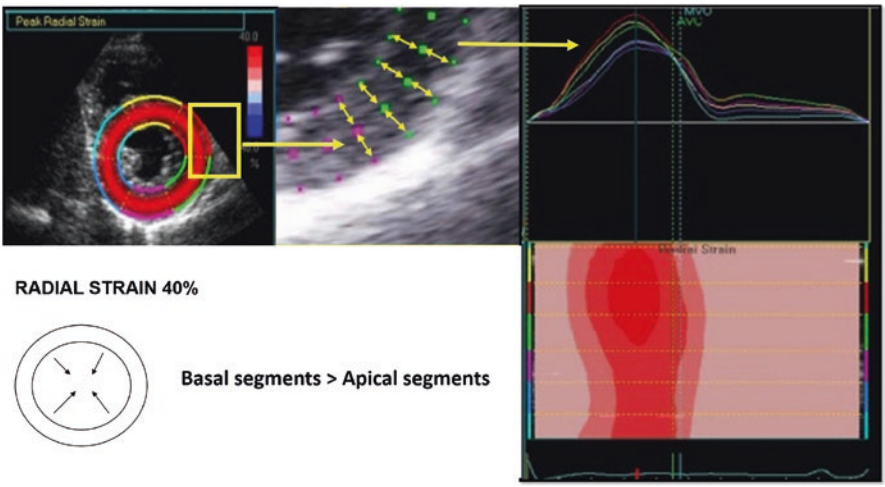

Fig. 13.3 Radial strain is higher in basal and midsegments and lower in apical segments. Courtesy of Rosina Arbucci, MD, and Jorge Lowenstein, MD, Buenos Aires, Argentina

is corroborated by STE findings [23–25]. The myocardial muscle mass is more important at the mid-basal level (basal and apical loop fibers), which justifies that the maximum deformation radial strain is produced at the basal and mid (44 ± 18%) vs. the apical (23 ± 16.5%) levels. The descending fibers adopt a progressively more oblique arrangement until they reach the apex. Longitudinal strain is greater at the ventricular apex (apical longitudinal strain –21.9% ± 2.4 vs. basal longitudinal strain –19.6% ± 2.4). However, this region is too thin and almost deprived of muscle, so some echocardiographic algorithms make a weighted mathematical average of the neighboring segments to express segment 17 deformations, while the deformation is less in the basal segments because, at this level, the wall stress is greater. The circumferential strain has a greater amplitude at the apical level (Fig. 13.4) facilitating apical rotation (–25.6% ± 6.6); at the basal level, the fibers are arranged more transversally so that deformation results are less important (–16.8 ± 3.5).

Because of the oblique myocardial fiber arrangement around the LV, an opposite rotation between the apex and the base of the heart is produced. Rotation is the result of the contraction of helical fibers. Both the intensity and direction are given by the balance of subendocardial and subepicardial fibers. Subendocardial fibers are responsible for longitudinal deformation, while medial and especially subepicardial fibers contribute mainly to rotation and torsion [18]. The subepicardial rotation radius is larger than that of the subendocardium; therefore, it provides a greater rotational force, and is expressed more significantly at the apical level [17, 26–28]. Viewed from the apex, the apical rotation is anticlockwise (positive), while the base rotation is clockwise (negative). The resulting motion is called twist, essential for LV ejection.

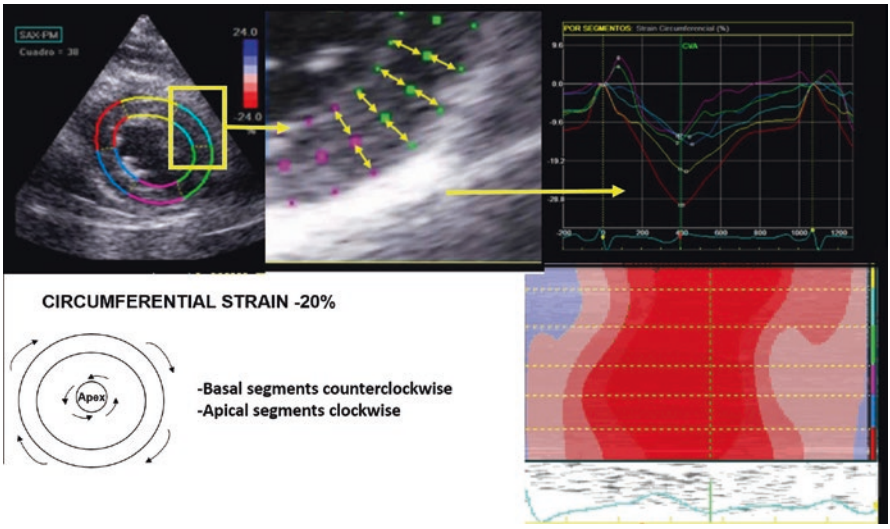

Fig. 13.4 Circumferential strain is higher at the apical level. Viewed from the apex, the apical rotation is counterclockwise (positive), while the base rotation is clockwise (negative). Courtesy of Rosina Arbucci, MD, and Jorge Lowenstein, MD, Buenos Aires, Argentina

Systolic ventricular contraction is caused by the combination of ventricular longitudinal shortening and torsion simultaneously [29–31]. This interaction contributes to myocardial thickening toward the ventricular centroid and the ensuing ejection of stroke volume. During diastole, the untwist motion occurs, which generates a suction force driving the early, rapid LV diastolic filling [32]. The complexity of this movement is further magnified by the physiological spatial and temporal heterogeneity observed in humans among different LV segments both in resting conditions [33–35] and during stress [36, 37]. The presence of stress-induced ischemia reduces (and may abolish), all three components of deformation—radial [38], longitudinal [39], and circumferential [40]—but not all of them simultaneously and symmetrically. Subendocardial fibers are mainly longitudinally oriented and are more susceptible to ischemia. During stress, circumferential and longitudinal strain abnormalities are altered earlier than the radial strain, but only radial strain contributes to regional systolic thickening at the basis of regional wall motion abnormality in SE [41].

This is also valid in early heart failure, where initially the reduced longitudinal function is compensated by supernormal circumferential function, yielding a falsely reassuring normal EF [42]. When the GLS decreases from 20% to 15%, EF decreases from 60% to 57%, but if global circumferential strain decreases from 20 to 15%, EF falls from 60% to 45%. EF is approximately two times more sensitive to an increase in circumferential than to an increase in longitudinal strain, and a decrease in longitudinal strain can be offset by a lesser increase in circumferential strain masking the initial dysfunction with a normal EF [42]. Due also to the greater precision and reproducibility compared to EF, GLS can help to reclassify baseline function for any level of impaired EF, especially in the normal LV. GLS results (expressed in absolute, positive values for simplicity) are classified as supranormal (>20%), normal (18–20%), borderline (16–18%), reduced (12–16%), severe (<12%), and very severe (<8%) [43].

13.4 Speckle Tracking Technique

STE is a grayscale-based technique that allows the assessment of myocardial deformation independently from the insonation angle [44]. Therefore, STE overcomes the two main limitations of tissue Doppler deformation imaging: the heavy dependence on insonation angle and the possibility of analyzing only longitudinal deformation. Myocardial deformation can be quantified as strain or strain rate. Strain is the difference between the length of a myocardial segment after contraction and its resting length, expressed as a percentage of myocardial deformation; strain rate is the rate at which this deformation takes place, expressed as 1/s. By convention, strain can be either positive, which indicates lengthening, or negative, which indicates shortening. Values for normal longitudinal and circumferential strain are therefore negative numbers, whereas those for radial strain are positive numbers.

Normally, both values are negative in systole when the myocardium shortens and positive in diastole when the myocardium lengthens. For its correct assessment,

high-quality images should be taken from the long-axis view, apical four-chamber view, and two-chamber view with the LV occupying most of the sector and without LV shortening. A frame rate between 40 and 90 frames/s is optimal for image acquisition [45]. ECG-gating is mandatory. Three cardiac cycles are sampled for each view. The timing of aortic valve closure is essential in the deformation study; therefore, it is recommended to start from the apical long-axis view, where aortic valve leaflets motion is displayed. The endocardial borders are manually traced in the end-systolic frame automatically generated by the software. Then, the software brings up a region of interest, including the entire myocardial thickness, which can be manually modified in width. Subsequently, myocardial speckles are automatically tracked frame by frame. If tracking is not adequate, the operator can adjust the region of interest. Once the tracking is approved, the LV myocardium is divided by the software into segments, and segmental and GLS, myocardial velocities, and strain curves are provided. The magnitude and homogeneity of longitudinal strain for each segment are intuitively displayed with a color map from red (normal, >16%) to pink (mildly abnormal, 6–15%) and blue (abnormal, ≤5%), with a normal subject showing a uniformly red pattern.

Peak GLS is a negative number since the myocardium shortens in systole and the systolic length is smaller than the diastolic length. This is a source of confusion since more negative numbers indicate increasing values of the function, differently from the EF which also assesses the LV function. For this reason, European and North American societies recommend the use of the absolute value of strain (%) concerning an increase or decrease in strain, but this reasonable suggestion is not universally followed, and negative values and positive (absolute) values coexist in the scientific literature and practice.

The whole process of GLS measurement needs to be repeated for the apical four- and two-chamber views to obtain strain values for all myocardial segments, and their average, the LV GLS. The most recent echo software has fully automated the process, based on artificial intelligence, allowing automatic recognition of the three apical views for analysis. Strain data can be displayed through a bull's eye plot, which intuitively shows segmental and GLS values [46].

Currently, STE can be performed either online at the patient's bedside, or offline on a workstation, and even with portable devices. The difficulty of establishing the normal values and the lower limit of normality has been one of the major problems for the uptake of GLS in guidelines. A recent meta-analysis establishes the normal value of GLS at 20.7%, with the cutoff value of abnormality <16%. Values among vendors are highest with TomTec, higher with GE compared to Toshiba and Philips, and lowest with Siemens [47]. With any given vendor, GLS increases during stress, on average 4 points in healthy subjects [48], and any increase <2 points is considered abnormal. Similar values of normality (–21.5 ± 3.2%) have been found for the right ventricular GLS [49].

Currently, through atrial strain, the intrinsic left atrial reservoir function can be assessed with peak amplitude longitudinal strain. Its values are expressed as positive because the atrial deformation is opposite to the ventricular one. The onset of the QRS complex is used as a reference point for the analysis of left atrial strain. Six

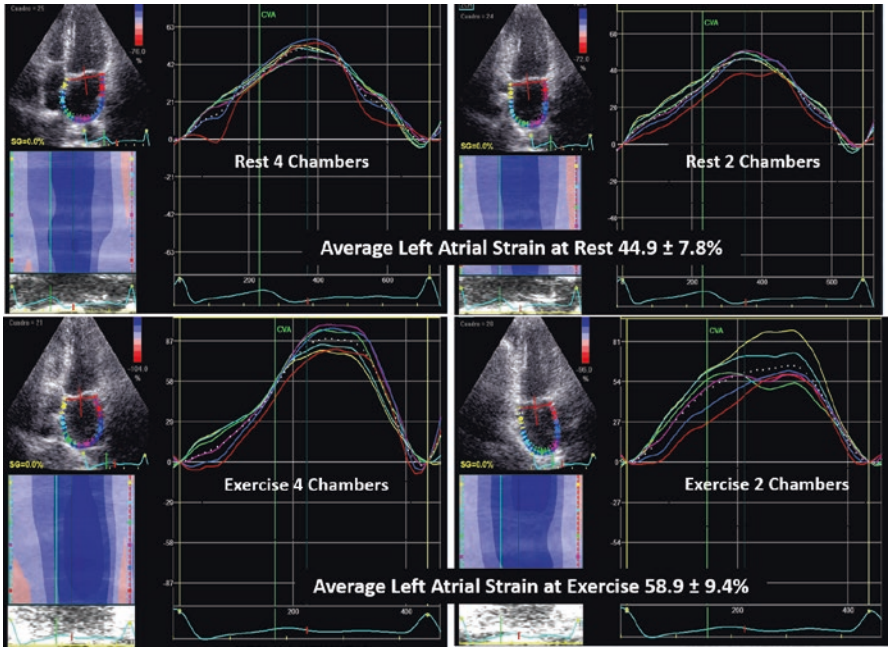

Fig. 13.5 Left atrial peak amplitude reservoir strain at rest (upper panel) and during exercise (lower panel), obtained from the average of 4-chamber and 2-chamber views. The normal response is the increase of left atrial reservoir strain from rest (44.9%) to exercise (58.9%)

segments per view are considered, and the strain (%) curves were analyzed in the atrial reservoir phase. A recent meta-analysis establishes the normal value of peak amplitude longitudinal strain at 40%, with the cutoff value of abnormality <30% [50]. It increases during stress (Fig. 13.5), on average 15% points in healthy subjects [51], and any increase <5% is considered abnormal [52]. The reservoir function mirrored by peak amplitude longitudinal strain increases during exercise to maintain optimal LV filling and decreases in hypertrophy and heart failure, correlating with increased left atrial pressure.

To calculate the LV twist, the ultrasound machine algorithm performs an algebraic sum (it adds the positive value of apical rotation to the negative one of basal rotation) [53]. The value in normal subjects is around +19 ± 9°, always with predominant apical rotation. The torsion corresponds to twist divided by end-diastolic apex–base distance.

The STE has been validated experimentally with excellent results, especially for the sensitivity and reproducibility of longitudinal strain [54]. The first clinical studies showed high feasibility and good accuracy especially of longitudinal strain, with good reproducibility but a lack of incremental diagnostic value over conventional eyeballing wall motion analysis [55]. Images allow to show the regional and global impairment, provide integrated and quantitative data on function and synchrony of contraction, and are ideally suited to transfer information with a polar map, immediately, to the clinical end user (Fig. 13.6).

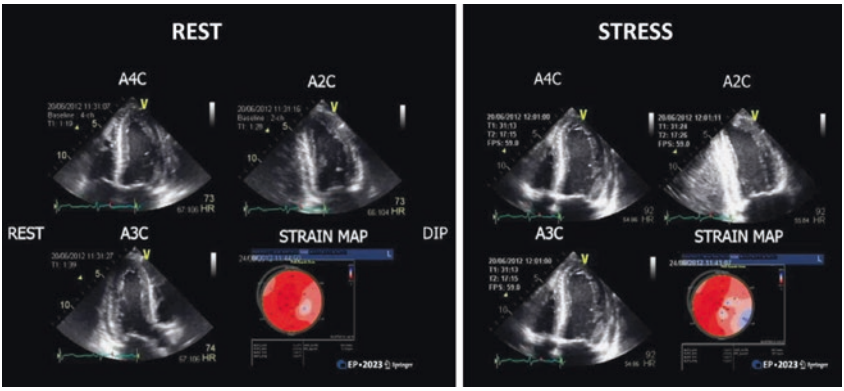

Fig. 13.6 Left panel, rest; right panels, stress. The standard two-dimensional display with end-systolic frames from apical four-chamber (left upper panel), two-chamber (right upper panel), and three-chamber view (left lower panel) are enriched and complemented, not replaced, by deformation imaging with a strain polar map (right lower panel). Both image formats concordantly show a mild hypokinesis of the anterolateral wall, proximal and distal segments, at rest, with frank akinesia during stress. See accompanying Video 13.1. Video images courtesy of Jorge Lowenstein, MD, Buenos Aires, Argentina

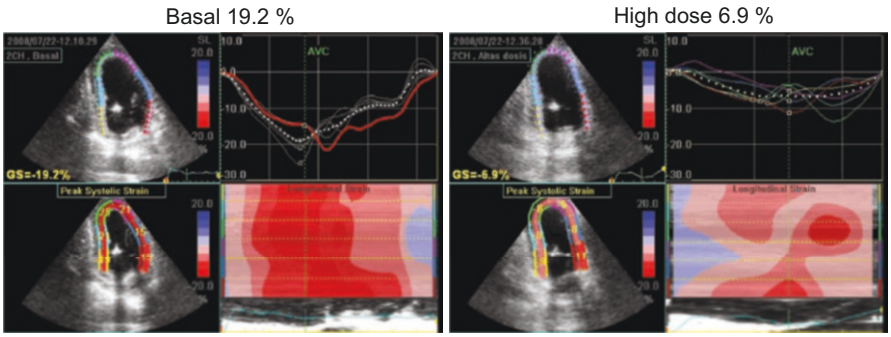

Fig. 13.7 Two-chamber 2D-STE image showing a normal apical strain at rest (left panel) showing a decrease in the strain at the maximum dose of pharmacological stress (right panel), both with their respective curves and M-mode parametric image. Quantitative assessment of regional strain at the time of aortic valve closure provides integrated information on contraction in each segment. Courtesy of Rosina Arbucci, MD, and Jorge Lowenstein, MD, Buenos Aires, Argentina

The standard, conventional two-dimensional display and the quantitative deformation imaging usually offer concordant results, with the geographical localization of ischemia corroborated in a synthetic and straightforward presentation by polar strain maps of severity and spatial localization of ischemia (Fig. 13.7).

Finally, deformation imaging can also provide evidence of ischemia missed by regional wall motion analysis in patients with angina, angiographically normal coronary arteries, and coronary microvascular angina documented with a reduced coronary flow velocity reserve [56]. Patients with a reduced coronary flow velocity

reserve also show a reduced reserve of GLS, with increased myocardial mechanical dispersion which may reflect a vulnerability to electrical dispersion and arrhythmic instability.

However, there are disadvantages and challenges (Table 13.3).

The afterload dependence of GLS by STE could be solved with the noninvasive assessment of myocardial work [57].

The current state-of-the-art diagnosis remains subjective by visual eyeballing, but it might be possible to corroborate the current naked-eye diagnosis with a quantitative assessment of regional and global myocardial deformation indices. The rationale behind strain SE is its quantitative nature, ability to differentiate tethering from surrounding segments, and earlier onset than regional wall motion abnormality during the ischemic cascade (leading to higher diagnostic sensitivity). At present, it cannot be used routinely in clinical practice with exercise due to limited feasibility (around 80%), noisy data in high heart rate states (>120 bpm), lack of standardization of parameters and software, and missing effectiveness studies [58, 59].

However, in selected patients with high image quality, STE might achieve also high sensitivity and specificity to recognize the ischemic response at high heart rates [60]. The analysis of the 2D longitudinal deformation is feasible in the immediate post-exercise, and the lack of increase or decrease in the 2D longitudinal deformation of the apical segments is consistent with the presence of visually detected ischemia. High heart rates are responsible for obtaining unreliable results in the basal and medial inferoposterolateral segments, so longitudinal 2D strain would only help analyze the territory of the left anterior descending artery.

The problem with the ultrasonic windows and the high heart rate is not an obstacle when SE is performed with dipyridamole, also ideally suited to be combined with simultaneous assessment of coronary flow velocity reserve [59]. As additional limitations, speckle-derived methods measure systolic strain, but not diastolic strain rates, which are evaluated by tissue Doppler techniques and may in theory be useful in detecting ischemia [59]. A major, limiting problem of STE is the difference in results among vendors, driven by the fact that STE is performed on data stored in a proprietary scan line (polar) format, which cannot be analyzed by other vendors' software, with the lack of vendor interchangeability. Today, GLS can be analyzed

Table 13.3 Quantitation by 2D speckle tracking in SE

	Advantages	Disadvantages
Imaging	Standard apical views	Very good image quality needed
Acquisition	Angle-independent	Low frame rate (40–90/s)
Analysis	Semi-automated	Manual adjustment of ROI
Display	Color-coded polar map	Cutoff values uncertain
Reproducibility	High for GLS	Low with high heart rates
Accuracy	High for peak longitudinal	Moderate for radial
Load dependence	Modest for preload	High for afterload

ROI region of interest, *GLS* global longitudinal strain

with vendor-independent systems based on artificial intelligence, which is easy to incorporate in echocardiographic data analysis.

Myocardial ischemia affects regional contraction, not only in space but also in time, increasing the mechanical dispersion of segmental contraction and delaying the timing of peak systolic thickening. Myocardial mechanical dispersion is measured as the standard deviation of time to peak longitudinal strain of each segment of the LV and is related to the risk of malignant arrhythmias in non-ischemic dilated cardiomyopathy and other conditions [60, 61]. In acute experimental ischemia, 20 s after a coronary occlusion a delay in contraction can be observed with a post-systolic thickening that appears before the myocardial wall stops contracting completely; therefore, during SE it is important to evaluate the time data of deformation events for the assessment of post-systolic deformation present in acute ischemia [62].

The value of resting regional post-systolic thickening by strain imaging is also mentioned in European 2019 guidelines as possibly helpful in patients with apparently normal LV function but clinical suspicion of chronic coronary syndromes [1]. However, the clinical value of regional strain and post-systolic strain during stress is still debated, and probably, this parameter works better, with higher reproducibility and diagnostic yield, with stresses with a mild increase in frequency such as vasodilators [63–65] compared to stresses increases substantially heart rate such as exercise or dobutamine, with less favorable signal-to-noise ratio [66–69]. The mechanical memory of recent ischemia is absent with regional strain [70] and presents with post-systolic thickening, which can be an earlier (first to appear) and more persistent (last to disappear) marker of ischemia [71]. The optimal threshold value for the detection of the disease remains indeterminate, and it would need automation to be applied according to the American Society of Echocardiography 2020 recommendations [71].

13.5 The Possible Role of Stress Speckle Tracking Echocardiography

Strain can complement coronary flow reserve, especially in the territory of the left anterior descending coronary artery [72]. Therefore, it might become an effective parameter for the assessment of ischemia, viability, contractile reserve, and subclinical dysfunction of the LV. In perspective, with technology standardization and automation, it could become an integral part of comprehensive SE, possibly step S (for strain) providing quantitative support to the assessment of regional wall motion of step A and the global systolic function of step C (Fig. 13.8).

There are several examples of clinically useful applications of STE providing quantitative support to the qualitative assessment of regional and global wall motion, beyond the main application of detection of ischemia. In segments with resting dysfunction, the inotropic challenge increases regional strain and GLS, and this

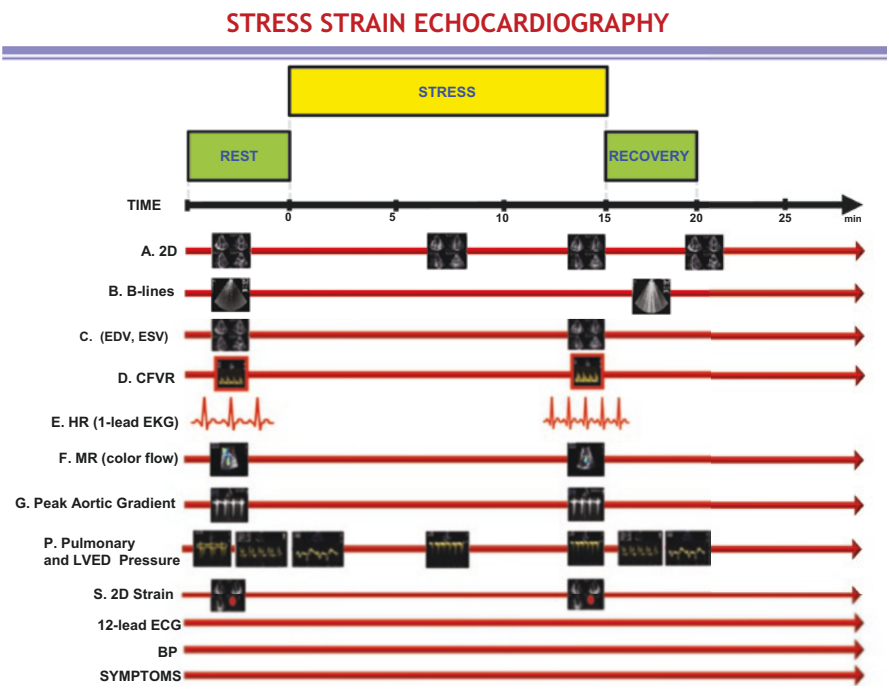

Fig. 13.8 Strain SE (step S) is an integral part of a comprehensive state-of-the-art protocol. Global and regional strain provide quantitative and operator-independent support to step A (regional wall motion analysis with regional apical strain); step C (global LV function with GLS); step L (with peak amplitude longitudinal strain of the reservoir function); and step R (right ventricular strain)

contractile reserve is associated with lower degrees of transmural necrosis or fibrosis and higher chances of contractile recovery of function following revascularization [72–79].

LV longitudinal systolic dysfunction is common among patients affected by heart failure with preserved ejection fraction [80–82]. A resting GLS value <16% is considered one of the minor criteria for diagnosis, according to 2019 European Society of Cardiology (ESC) guidelines, with class 2a recommendation [83]. During exercise, an abnormal GLS value may be an independent predictor of all-cause death and hospitalization for heart failure [84]. Probably, LV longitudinal systolic dysfunction may favor an insufficient increase in stroke volume and cardiac output during exercise, contributing to reduced functional capacity during exercise in these patients [85].

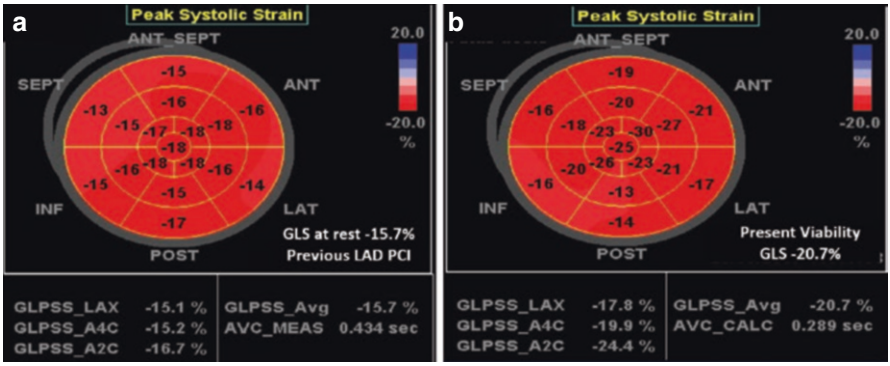

Fig. 13.9 (**a**) GLS at rest of a patient with previous revascularization (PCI) of the LAD. (**b**) GLS presence of viability after infusion of 20 mcg/kg of dobutamine. Courtesy of Rosina Arbucci, MD, and Jorge Lowenstein, MD, Buenos Aires, Argentina

GLS can detect contractile reserve, considered present with a difference of >2 absolute points between rest and stress (Fig. 13.9) [68, 70, 86].

A reduced contractile reserve with GLS during stress (exercise or dobutamine) is associated with worse outcomes in patients with severe aortic stenosis [87–90]. A blunted contractile reserve by GLS is also an early sign of cardiomyopathy in diabetics [91–93] and cardiac allograft vasculopathy in transplanted patients following heart transplantations [94]. The presence of contractile reserve by GLS during dobutamine or exercise predicts a favorable response to cardiac resynchronization therapy [95, 96].

There are still significant requirements and challenges to the application of STE during stress, as outlined in the American Society of Echocardiography 2020 recommendations [71]. The feasibility of STE should be specifically tested during different types of stress, with and without ultrasound-enhancing agents. There is a need for additional, specific training of sonographers and physicians, since the human interaction is substantial to optimize imaging for strain assessment, including depth and sector width selection, and the sonographer interaction is required, with knowledge of causes of poor tracking and manual adjustment of the regions of interest. The assessment of strain values should account for changes in loading conditions. Timing parameters such as post-systolic shortening or mechanical dispersion still need the identification of the optimal parameter for disease detection at rest and during stress and are likely to be stress-specific for differences in heart rate and contractile reserve response among different stresses. Adequate frame rates are needed to enable the tracking of high heart rates. There are significant inter-vendor variations in GLS and—with the same vendor—for different generations of software. Inter-vendor variability is even more pronounced with regional strain. During stress, GLS must increase in healthy subjects but sometimes decreases, possibly for the reduction in end-diastolic volume and inadequate frame rates generating an unfavorable

signal-to-noise ratio during tachycardia. Regional strain is in principle more attractive for the detection of a regional dysfunction induced by coronary artery disease, but—when the same vendor, with the same generation of software, is used—has uncertain reproducibility and accuracy, especially in the posterior circulation. In addition, STE is critically dependent on image quality and therefore is less feasible than visual analysis of regional wall motion. At present, STE has not shown incremental accuracy compared to visual assessment of regional wall motion abnormality [71].

13.6 Three-Dimensional Echocardiography

LV volumes and EF can be assessed with great accuracy using real-time 3DE, which has clear advantages over standard 2D echocardiography, both conceptually and practically. The technique is a major development in echocardiography over the last decade, having evolved from slow and labor-intense offline reconstruction to real-time volumetric imaging. The major advantage of this technique over more conventional 2D echocardiography is the improvement in the accuracy of the evaluation of cardiac chamber volumes, which is achieved by eliminating the need for geometric modeling and the errors caused by foreshortened views [97]. Another fundamental advantage of the 3DE format is the advantage of communicating with the patient, the other imaging specialists, and the cardiological community at large with the common language of all competing and complementary imaging techniques [97]. You do not need to be a radiologist to understand a 3D picture of the heart from cardiac magnetic resonance, but you need to be a dedicated echocardiographer to try to understand a tissue Doppler or strain rate imaging display. Eventually, the new technique will be faster to learn, easier to implement, and less operator-dependent in the interpretation, also based on a robust quantitative package of excursion, synchronicity, shape, and volumes.

Two types of imaging modes, full-volume and multiplane modes, can be used to acquire and analyze SE. Both modes have their particular benefits and limitations [97]. The multiplane mode is suitable for regional wall motion analysis, since the regional function can be represented as a function of time, and a series of plots is obtained representing the change in volume for each segment throughout the cycle. In the presence of ischemia, the minimum volume will be reached for each segment at different times and ischemic segments will have higher end-systolic regional volumes (Fig. 13.10).

A complete 3DE image acquisition can be obtained in a shorter time than with 2D echocardiography, and this is a valuable advantage, especially when imaging children and adults during stress [97]. Parametric polar map displays (of the 2D data) of the timing and extent of regional contraction have been developed to simplify the interpretation of results. The positive SE response is characterized by higher dyssynchrony, greater heterogeneity, and larger end-systolic volumes than the negative SE responses (Fig. 13.11) [98–103].

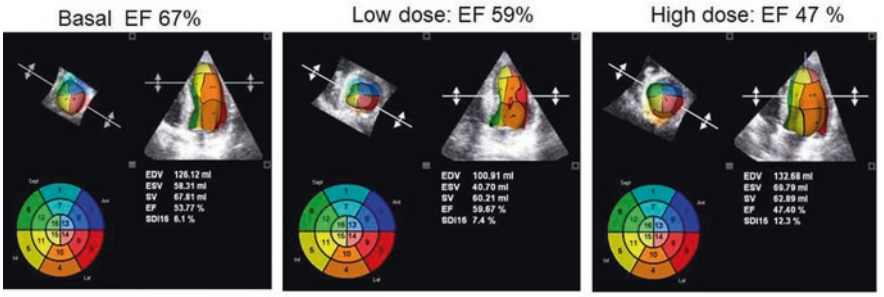

Fig. 13.10 A 3DE positive SE test. The positive test result is characterized by an area of reduced regional and global EF at peak stress (*right panel*) when compared to rest (*left panel*) and low dose (*middle panel*). A quantitative assessment of LV volumes and stroke volume is possible at each stage. Courtesy of Dr. Jorge Lowenstein, Buenos Aires, Argentina

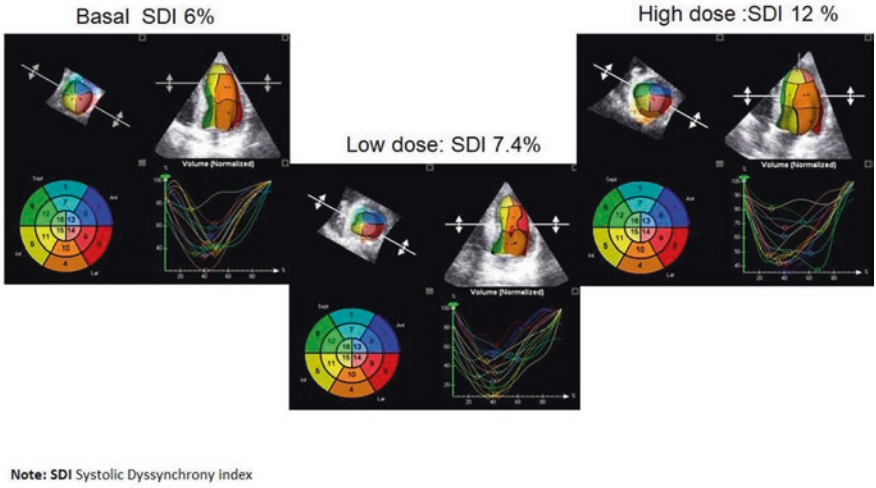

Fig. 13.11 A 3DE positive SE test with dyssynchrony assessment. The positive test result is characterized by an area of greater segmental dyssynchrony at peak stress (*right panel*) when compared to rest (*left panel*) and low dose (*middle panel*). During ischemia, the peak of contraction is reached by different segments at different time points. *SDI* systolic dyssynchrony index, higher values representing higher levels of dyssynchrony. Courtesy of Dr. Jorge Lowenstein, Buenos Aires, Argentina

A negative SE for regional wall motion can be integrated with 3D to have a better estimate of end-diastolic and end-systolic volume changes during stress, essential to estimate global function and preload reserve accurately (Fig. 13.12).

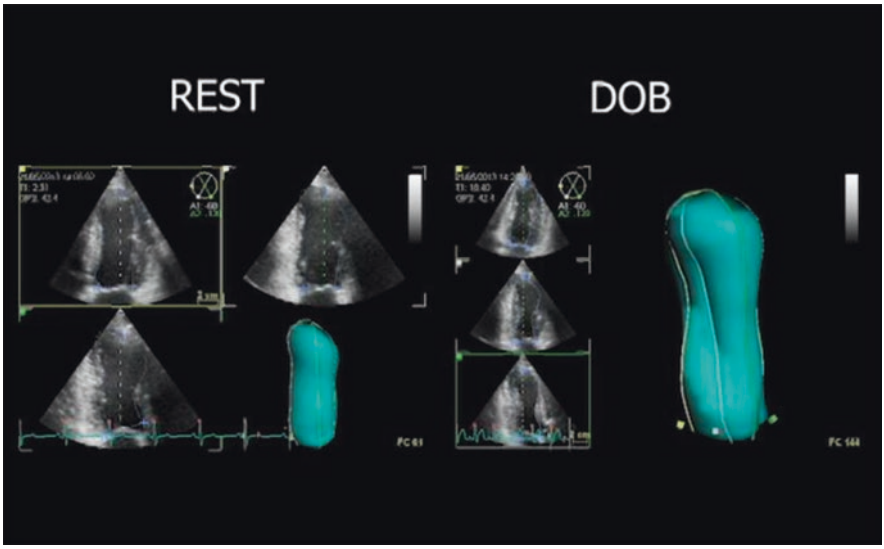

Fig. 13.12 A 3DE negative dobutamine stress test. The apical region is dyskinetic at rest (*left panel*), and the increase in global LV function is due to the enhanced function of regions already well-functioning at rest (*right panel*). A quantitative assessment of LV volumes and stroke volume is possible at each stage. See accompanying Video 13.2. Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil

Table 13.4 2D vs RT3D SE

	2D better	3D better
Apex imaging		No foreshortening
Temporal resolution	High frame rate (90/s)	
Analysis of volumes		No geometric assumptions
Technology	No extra cost and training	
Display		Intuitive, natural
RWMA	Excellent resolution	
LV volumetric changes		Excellent reproducibility

However, despite this exciting potential, the overall accuracy of 3DE SE is at present no better, and the feasibility is markedly lower than 2D echocardiography [98–103]. The 3DE version has a lower spatial resolution than 2D, and the resolution becomes worse when you need it more, at faster heart rates during stress (because of 3DE's frame rate of 40 frames per second, compared to 100 for 2D) (Table 13.4).

However, the 3DE evaluation of volumes (plus a standard assessment of heart rate and blood pressure) is ideally suited for a quantitative and accurate calculation of a set of parameters allowing a complete characterization of cardiovascular hemodynamics (including cardiac output and systemic vascular resistance), LV elastance

(an immaculate index of LV contractility, theoretically independent of afterload and preload changes heavily affecting the EF) [104], arterial elastance [105] (essential to characterize the distal impedance of the arterial system downstream of the aortic valve), ventricular–arterial coupling (a central determinant of net cardiovascular performance in normal and pathological conditions), and diastolic function (through the diastolic mean filling rate). All these parameters were previously labor-intensive and now become, at least in principle, available in the SE laboratory since all of them need an accurate estimation of LV volumes and stroke volume, both easily derived from 3DE (Table 13.5).

Table 13.5 Cardiovascular hemodynamics derived from real-time 3DE

Parameter	Raw 3DE data	Formula	Normal values (rest)	Normal values (stress)	Meaning
Cardiac index	SV (EDV-ESV)	SV × HR	2.5 L min^{-1} m^{-2}	× 2 (ex) × 2 (dob) × 1.5 (dip)	Cardiac pump function
Systemic vascular resistance	SV	80 × (MAP-5)/CO	900–1300 (dyne s) cm^{-5}	−30 (ex) −40 (dip)	Vascular resistance
Systemic arterial compliance	SV	SVi/PP	0.50 (mL × m^{-2} mmHg)	−30% (ex) +20% (dip)	Arterial compliance
Ventricular elastance	ESV	SBP/ESV	7 mmHg mL^{-1} m^{-2}	× 2 (ex) × 1.2 (dip) × 1.5 (pac)	LV contractility
Arterial elastance	SV	SBP/SV	4 mmHg mL^{-1} m^{-2}	× 1.5 (ex)	Integration of arterial resistance, compliance, and heart rate
				× 0.9 (dip) × 1.5 (pac)	
Ventriculoarterial coupling	SV and ESV	SV/ESV ventricular elastance/ arterial elastance	≥1.5	× 1.5 (ex)	Ventricular elastance/ arterial elastance
				× 1.3 (dip) × 1.0 (pac)	
Diastolic mean filling rate	SV	SV/diastolic time	100 ml $m^{-2}s^{-1}$	× 3 (ex) × 1.5 (dip)	Diastolic function

End-systolic pressure (ESP) = SBP × 0.90. 5 is an approximation of right atrial pressure. Diastolic time can be calculated from a phonocardiogram or 2D echocardiography; with a high heart rate, the diastolic time is progressively more reduced than the systolic time. *MAP* mean arterial pressure, *PP* pulse pressure (systolic arterial pressure—diastolic blood pressure), *CO* cardiac output, *DIP* dipyridamole, *DOB* dobutamine, *EX* exercise, *HR* heart rate, *PAC* pacing, *SBP* systolic blood pressure by a sphygmomanometer, *SV* stroke volume

It is expected that the technology will improve present critical areas of the technique, such as the need for transducers with higher frequencies, smaller footprints, full Doppler capabilities, and higher frame rates, especially important for SE applications. The incorporation of 3DE into standard 2D examination is made easier with the newer all-in-one probes, which allow switching from one mode to the other, both available in the same probe.

13.7 Pitfalls

What we need to ensure is that technology in medicine is tested scientifically, that it is applied with data relating to cost and benefit, and that it is driven by patient needs rather than market forces [106]. In the current economic and cultural milieu, the "seed" of efficacy obtained under ideal conditions should not be mistaken for the "fruit" of effectiveness: the value of the technique when deployed in the field [107] (Table 13.6).

Any emerging biomarker should, like a new drug, withstand a chain of validation before arriving at clinical impact [108]. With new technologies, like new drugs, large-scale experience should be gathered before accepting the catchy definition promoted by the marketing offices as proven. The additional merits of the new technique should be weighed against the established and more easily accessible methods, and the new technologies should be assessed against other competitive imaging tools. Only at that point will innovation in engineering be valid in physiological terms and will it give patients the promised diagnostic help, changing an attractive technological gadget into a medical advance. Some of these techniques already have a clear clinical role outside of SE application, but stress administration often stresses the technology, not only the patient. Maintenance of a critical attitude on the part of the clinical cardiologist and sonographer faced with the forest of new technologies proposed every year by the manufacturers is essential [109].

Table 13.6 New technologies between efficacy and effectiveness

	Efficacy	Effectiveness
Dictionary definition	Ideal conditions	Deployed in the field
Responsible physician	Research fellow in training	Busy cardiologist
Scientific interest	Present	Absent
Patient	Part of the method	The protagonist
Technology	Under validation	Validated
Results	Published	True, but unpublishable
Economic induction	Present	Absent

13.8 Clinical Guidelines

As expressed by the joint writing group of the American Society of Echocardiography and the European Association of Echocardiography in 2013, new technologies "*significantly contribute to the much-needed process of the transformation of echocardiography from a subjective art of image interpretation to a set of objective diagnostic tools*," but "*this methodology is not yet ready for routine clinical use*" [110]. In the last years, two technologies entered the clinical armamentarium of SE: 2D-STE and RT3D. The clinical value of resting GLS to assess LV systolic function is recognized by 2015 joint North American and European recommendations [111]. There is extensive evidence that GLS at rest may detect subtle abnormalities of regional and global myocardial function not otherwise detectable with EF or regional wall motion analysis. Resting GLS is superior to resting EF in predicting outcomes in patients with heart failure, acute myocardial infarction, valvular heart disease, and other conditions, especially with preserved EF [112]. ESC 2019 general cardiology guidelines on chronic ischemic syndromes recommend the echocardiographic assessment of resting GLS which provides incremental information to EF and may be considered (class of recommendation 2b) when EF is >35% [1]. Simultaneous assessment of regional deformation captured by the bull's eye polar map allows us to recognize the typical pattern of myocardial damage that supports the specific diagnosis, for instance, the apical-sparing pattern of cardiac amyloidosis. A relative change of resting GLS >15% from baseline values is a recommended criterion for the detection of cardiotoxicity in oncologic patients, and it should lead to the start of cardioprotective therapy or drug dose down-titration [113]. However, three significant problems must be solved before clinical acceptance of deformation imaging during stress: (1) across-vendors standardization of strain acquisition, analysis, and values to establish true reproducibility of parameters in real-world conditions under stress (when image quality degrades) [114]; (2) assessment of the incremental clinical value of advanced imaging parameters over conventional ones in prospective, multicenter, outcome-based studies; (3) impact of new parameters in decision making and cost-effectiveness. Also, RT3D has proven benefits in accuracy and reproducibility, but its methodology is still time-consuming and impedes optimal clinical workflow. Its impact on SE can be critically important, once automated quantification tools that could be used immediately as the images are acquired are developed, although the low temporal and spatial resolution remains a limiting problem during stress.

Therefore, quantitative methods during SE find little room in current clinical recommendations. Peak GLS is recommended to assess the LV contractile reserve, considered to be present when stress-to-rest variation is >2% during low-level exercise or low-dose dobutamine, when heart rate is still <100–110 bpm. This cutoff has been proposed for risk stratification in valvular heart disease and as a potential marker of response to cardiac resynchronization therapy in non-ischemic dilated cardiomyopathy [115]. However, this parameter should be handled with care, since a decrease in GLS from rest to stress can be observed in normal subjects, possibly due to the reduction in diastolic volume and change in blood pressure since loading

conditions may affect strain values, and most importantly for inadequate frame rates in the setting of tachycardia associated with stress, as emphasized by 2019 American Society of Echocardiography recommendations [71]. Quantification of SE remains a challenge with new technologies, but artificial intelligence is rapidly changing the scenario allowing the quantitative, operator-independent assessment of regional wall motion, LV volumes, GLS, and other parameters included in comprehensive SE.

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Contrast Stress Echocardiography

14

Nicola Gaibazzi and Eugenio Picano

Keywords

Coronary flow velocity · Left ventricular volumes · Regional wall motion · Very low mechanical index

14.1 Historical Background and Pathophysiological Basis

Ultrasound-enhancing agents (UEAs) are an important advance in the practice of echocardiography [1, 2]. Initial attempts to better delineate endocardial borders used agitated saline, indocyanine green dye, or radiologic contrast agents. The history of contrast echocardiography began in 1968 when an accidental injection of saline solution in the ascending aorta during an angiography examination caused the production of microbubbles that led to better ultrasound signals in the lumen of the aorta and cardiac chambers [3]. A major limitation was the large and variable size of the air bubbles, which could not transit the pulmonary circulation and opacify the left heart. The early 1990s saw the development of commercial agents with air- or gas-filled microbubbles, similar in size to red blood cells with a distribution similar to blood flow. Exciting reports described the potential of myocardial contrast

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N. Gaibazzi (✉)
Cardiology Department, Parma University Hospital, Parma, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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echocardiography (MCE) to assess myocardial perfusion in the diagnosis of coronary artery disease, microvascular integrity, myocardial viability, and coronary flow reserve. In the year 2000, three agents had been approved and at least 13 other agents were undergoing evaluation [4]. At that time, more than $ US 1 billion had been spent worldwide to develop these agents and bring them to market.

While contrast echocardiography has many important applications, the greatest benefits from this technique are expected from stress echocardiography (SE). The information provided by contrast during SE is potentially important and versatile: from improved border recognition to myocardial perfusion and from coronary flow velocity enhancement to potentiation of regurgitant tricuspid jet velocity to analyze pulmonary artery systolic pressure (Fig. 14.1).

The main clinically driven application of contrast is the left ventricular endocardial border delineation allowing the rescue of procedures that do not provide results of diagnostic quality, especially in patients with obesity and lung disease [5].

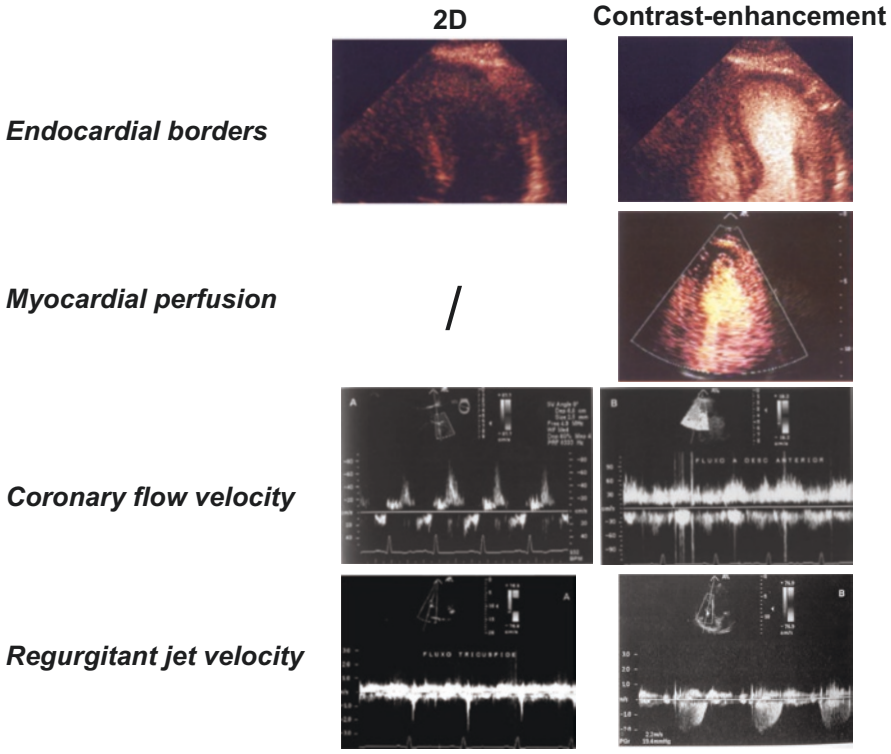

Fig. 14.1 Main potential clinical applications of contrast in the SE laboratory: improved endocardial border definition (*first row*), myocardial perfusion (*second row*), pulsed wave Doppler signal enhancement on the left anterior descending coronary artery (*third row*), and enhancement of continuous wave Doppler tricuspid regurgitant jet velocity for analyzing pulmonary artery systolic pressure (*last row*). For each panel, on the *left*, the 2D image is without contrast; on the *right*, the contrast enhancement image. Myocardial perfusion imaging is only possible with contrast. Courtesy of Dr. Ana Cristina Camarozano, Curitiba, Brazil

Stress MCE for myocardial perfusion imaging has a clear and strong rationale allowing to detect of flow-limiting coronary artery stenosis as a regional flow heterogeneity under hyperemic conditions, which is an earlier marker of ischemia than regional wall motion abnormality in the ischemic cascade and the only marker in myocardial ischemia due to coronary microvascular disease which typically occurs without regional wall motion abnormality during stress. During hyperemia, perfusion heterogeneity will occur with lower blood flow increase in the regions supplied by the stenotic artery, even in absence of myocardial ischemia (Fig. 14.2).

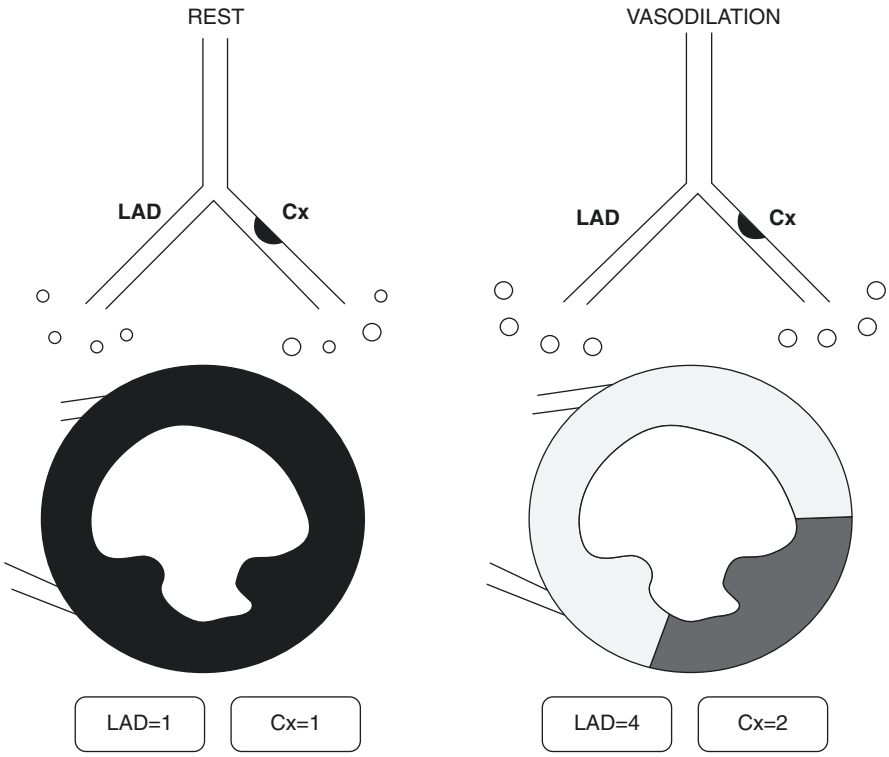

Fig. 14.2 Schematic illustration of the principle underlying myocardial perfusion imaging for the diagnosis of coronary artery disease. At rest, myocardial perfusion is homogeneous, with no differences between the territory of the normal coronary artery (*LAD* left anterior descending artery) and the diseased coronary artery territory (*Cx* left circumflex, with 80% stenosis). The resting flow image (obtained, for instance, with thallium-201 scintigraphy or contrast echocardiography) does not show any inter-region variation. However, the perfusion in the territory of the stenotic coronary artery is maintained at the price of partial exhaustion of coronary reserve, with partial dilatation of the arteriolar bed, represented by *larger circles* located downstream from the epicardial coronary arteries. The normal arteriolar tone is represented by *smaller circles* (normal arterioles with vasoconstriction). During vasodilation obtained with a metabolic stimulus, such as exercise, or with a pharmacological stimulus, such as dipyridamole, the arteriolar tone is lost, causing an increase in flow that will be greater in the normal coronary artery (which, at rest, has a preserved tone in the entire arteriolar district) than in the stenotic coronary artery (with lower coronary flow reserve). Perfusion imaging will see the stenosis mirrored in the myocardium as a region with relative under-concentration of flow tracer when compared with the normal contralateral region. The septal and anterior walls appear *brighter* (due to greater contrast concentration) when compared with the *darker* inferolateral wall (lower contrast concentration)

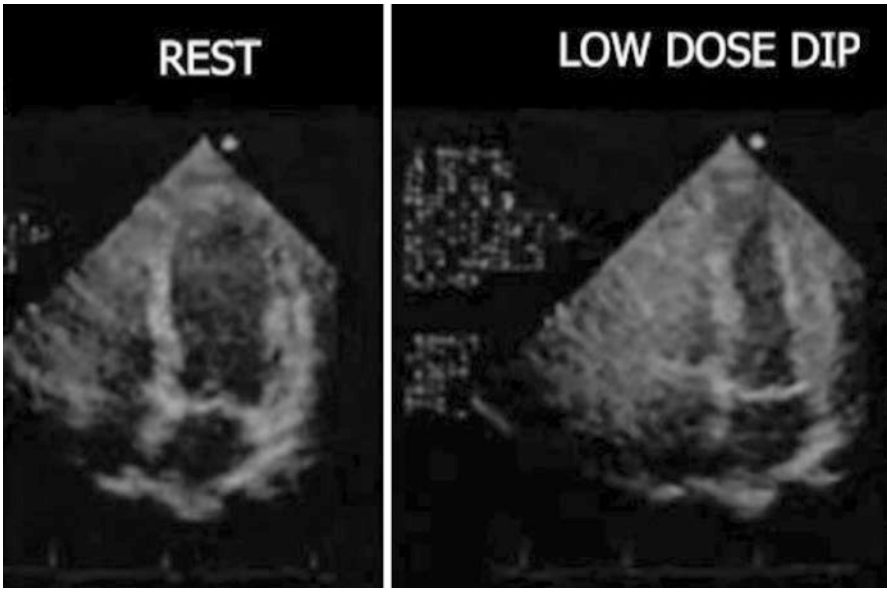

Fig. 14.3 Intracoronary contrast during dipyridamole test for viability. The appearance of four-chamber end-systolic frames, both at rest (mid) and stress phase (right), when using intracoronary contrast before and after intravenous dipyridamole in a patient with recent anterior myocardial infarction. The region with severe wall motion abnormality and perfusion defect at rest recover flow and function in the stunned, but viable, infarcted region. See accompanying Video 14.1. Video images (the year 1996) courtesy of Dr. Daniele Rovai, Pisa, Italy [6]

Initial applications required intracoronary contrast administration, with spectacular image enhancement, but obvious problems of feasibility and potential problems of safety. An example of intracoronary contrast during low-dose dipyridamole stress showing a functional recovery of the apical akinesia mirrored by an increase in contrast distribution to the same apical region is shown (Fig. 14.3) [6].

Clinical applications gained popularity through the advancement in contrast chemistry and ultrasound signal analysis. The microbubbles that constitute contrast agents are pure intravascular tracers and remain entirely within the vascular space with intravascular rheology similar to that of erythrocytes. The key technical advance was online signal processing of ultrasound signals from microbubbles, which made it possible to separate bubble signals (nonlinear) from myocardial tissue backscatter (linear), with no need for time-consuming offline processing. Despite the theoretical appeal and technological advances, MCE for myocardial perfusion imaging remained on the threshold of widespread clinical acceptance for at least 30 years, and it is still there, at the crossroads between success and failure. In the meantime, new exciting future diagnostic and therapeutic applications are underway, from imaging of neovascularization of vulnerable atherosclerotic plaque to molecular and cellular imaging of atherosclerotic plaque and activated platelets [7] and contrast-enhanced thrombolysis of acute coronary thrombosis with high mechanical index ultrasound [8].

Table 14.1 Commercially available contrast agents

	Sonovue (Lumason)	Optison	Luminity (Definity)
Gas	Sulfur hexafluoride	Perfluoropropane	Perfluoropropane
Shell content	Phospholipid	Albumin	Phospholipid
PEG component	Yes (excipient)	No	Yes (shell and excipient)
Manufacturer	Bracco Diagnostics	GE Healthcare	Lantheus Medical Img

GE General Electric, *PEG* polyethylene glycol

14.2 Contrast Agents

Contrast agents can be homemade or industrial. In hospital-generated custom-made agents consists of an agitated saline solution containing air bubbles. This "homemade" contrast is used for right heart opacification and for enhancement of continuous wave Doppler signal of tricuspid regurgitant jet velocity for analyzing pulmonary artery systolic pressure. If there is an insufficient quality of the signal of the tricuspid regurgitation envelope, the intravenous administration of agitated saline (or contrast) will permit measurement of the peak tricuspid regurgitation velocity [9]. The right heart contrast is impressive, but the air quickly dissolves into the blood. The smaller bubbles that are capable of crossing the lung capillary bed do not survive long enough for imaging the left heart because the air quickly dissipates into the blood. In commercial contrast agents, persistence is achieved using an impermeable shell or a higher-density encapsulated gas that is relatively insoluble in blood. Gas composition is one of the most important factors in maintaining microbubble size in circulation.

At present, three agents are licensed for left ventricular opacification and endocardial definition (Table 14.1): Sonovue (Bracco, Italy), Definity (called Luminity in Europe, Lantheus medical imaging, previously Bristol-Myers Squibb, New York, NY, USA), and Optison (General Electric, Fairfield, CT, USA) [10].

14.3 Contrast Administration

Contrast agents can be administered either via a bolus injection or continuous infusion. Bolus injections have the advantages of using lower contrast volumes and are simple to administer, with bolus injections of all agents (Sonovue 0.5 mL, Luminity 0.2 mL, and Optison 0.2 mL), followed by a slow 5 mL saline flush over 20 s. However, they often result in attenuation in the image plane for an initial transient period, and there is often only a short period, during the decay phase when the contrast agent concentration is appropriate for analysis of myocardial blood volume. Bolus administration is preferentially used for regional wall motion assessment, left ventricular cavity opacification, and Doppler signal enhancement.

Continuous infusion of contrast agents is more complex to administer and usually requires a larger volume of the agent. However, they need less operator

involvement during the stress study, and it is easier to adjust the infusion rate to optimize myocardial opacification without excessive attenuation. The infusion mode is preferentially used for myocardial perfusion imaging [10].

In SE, both the contrast agent and pharmacologic stress agent (e.g., dobutamine or dipyridamole) can be administered via a three-way tap through the same intravenous line.

14.4 Contrast Imaging Modalities

Microbubbles enhance echocardiographic images because they oscillate under acoustic pressure in a very peculiar way. Under low-energy pressure, they oscillate linearly, reflecting ultrasound at the fundamental frequency. Ultrasound with an intermediate energy level induces nonlinear oscillations of microbubbles (the dilation of the microbubble is typically more pronounced than the following compression), resulting in the generation of frequencies other than the fundamental frequency and harmonics (non-exact multiples of the fundamental frequency). Under high-intensity ultrasound (within the energy levels used for diagnostic imaging), microbubbles are destroyed. Although cardiac tissue also produces harmonic frequencies, their intensity is much lower than the microbubbles, cardiac tissue has only a linear behavior, and it does not produce non-exact multiples of the fundamental frequency. Therefore, imaging techniques that cause selective reception of harmonic frequencies or nonlinear signals (exclusive of microbubbles) will detect signals emanating from microbubbles rather than cardiac tissues. MCE imaging technology attempts to detect contrast microbubbles in the very small quantities with which they occur in the myocardium while suppressing the myocardial tissue signal [10]. The three main technical approaches are summarized in Table 14.2.

In the American Society of Echocardiography guidelines, the range of mechanical index typically used and currently recommended in clinical practice for real-time

Table 14.2 Contrast imaging methods

Methods	Synonymous	Output power (MI)	Bubble destruction	Left ventricular borders	Wall motion
Harmonic power Doppler	Angiopower	High (>0.5)	++	–	–
Grayscale harmonics Real-time contrast imaging	Power pulse inversion; ultra-harmonics Power modulation; power pulse inversion; contrast pulse sequencing	Low (0.2–0.5)	+/–	+	–
Real-time contrast imaging	Power modulation; power pulse inversion; contrast pulse sequencing	Very low (<0.2)	–	+	+

MI mechanical index

MCE and specifically for myocardial perfusion imaging is defined as "very low" and corresponds to <0.2; this very same mechanical index range is defined "low" in the European Association of Cardiovascular Imaging. The heart of the matter does not change, and a mechanical index <0.2 is recognized as a fit for real-time MCE for both myocardial perfusion imaging and endocardial border enhancement, while a slightly higher mechanical index (0.2–0.5) can still be used for real-time endocardial border enhancement, but it is unfit for myocardial perfusion imaging, due to partial but continuous destruction of a significant percentage of insonated microbubbles.

High-power ultrasound (mechanical index >0.5) is destructive and used to be coupled with complex single-image triggering protocols; it did not permit real-time imaging and simultaneous wall motion information, and today, it is only of historical interest. High-mechanical index fast repetitive impulses (flash) can still be used to destroy the microbubbles in the myocardium followed by observing the replenishment of microbubbles using very low real-time imaging. The rate of increase in intensity following bubble destruction with several high-energy pulses represents red blood cell velocity (β), and the product of signal intensity (myocardial blood volume) × β is proportional to myocardial blood flow. Dedicated software can automatically construct background-subtracted plots of peak myocardial contrast intensity, A, and the slope of the replenishment curve depicting mean microbubble velocity, β reserve. Myocardial blood flow can be derived. Myocardial blood flow reserve (i.e., stress myocardial blood flow/rest myocardial blood flow) can then be calculated from regions of interest in segments perfused by each of the three coronary arteries.

Real-time perfusion imaging has many potential advantages. The technique is relatively easy to use, many artifacts can be avoided, and wall motion information is obtainable alongside perfusion, making this technique particularly valuable during SE. Perfusion adds prognostic value to regional wall motion [11]. In the past decade, real-time very low (<0.2) mechanical index techniques have been available on nearly all ultrasound systems. The very low mechanical index imaging techniques (pulse inversion Doppler, power modulation, contrast pulse sequencing) are inherently tissue cancellation techniques that eliminate or reduce myocardial and valvular signals in the absence of contrast. During SE, we need a simultaneous assessment of wall motion, and therefore, a low or very low mechanical index is required. It is recommended to acquire flash-replenishment sequences (15 cardiac cycles) of the apical four-, two-, and three-chamber views with the flash delivered after the second cardiac cycle.

14.5 Clinical Applications 1: Enhancement of Left Ventricular Endocardial Borders

UEAs make wall motion assessment of the left ventricle more reproducible among different readers [12], slightly but significantly more accurate [13], and more feasible for almost the totality of patients [14], including the small but existing percentage of technically inadequate patients in whom SE was previously precluded (Fig. 14.4).

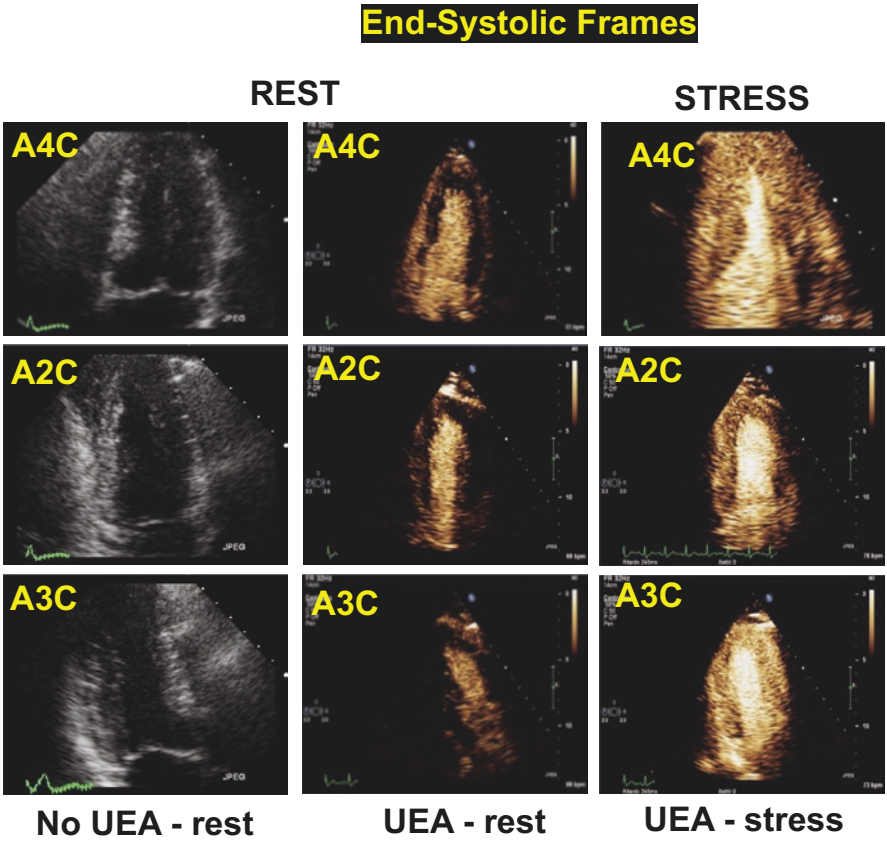

Fig. 14.4 Contrast for endocardium, volumes, and myocardial perfusion. The appearance of four-chamber, two-chamber, and three-chamber end-systolic frames, both at rest (mid) and stress phase (right), when using low mechanical index real-time imaging in conjunction with contrast. Courtesy of Dr. Nicola Gaibazzi, Parma, Italy

14.6 Clinical Applications 2: Quantitative Volumetric SE

The enhancement of left ventricular borders is also helpful for the quantitative assessment of left ventricular end-diastolic volume (an index of preload reserve), end-systolic volume (an index of contractile reserve), and ejection fraction. This assessment is easier, simpler, and faster with the good image quality provided by UEA compared to images without contrast [15].

14.7 Clinical Applications 3: Enhancement of Color Doppler Imaging of the Mid-Distal Left Anterior Descending Artery

UEAs are useful to enhance color Doppler imaging of the mid-distal left anterior descending [16, 17] or (probably less) posterior descending coronary artery [18], by so doing increasing the feasibility of coronary flow reserve measurement for non-experts or in very difficult patients (Fig. 14.5). The downside of color Doppler contrast enhancement is that the technical quality of pulsed wave Doppler tracing may degrade [19].

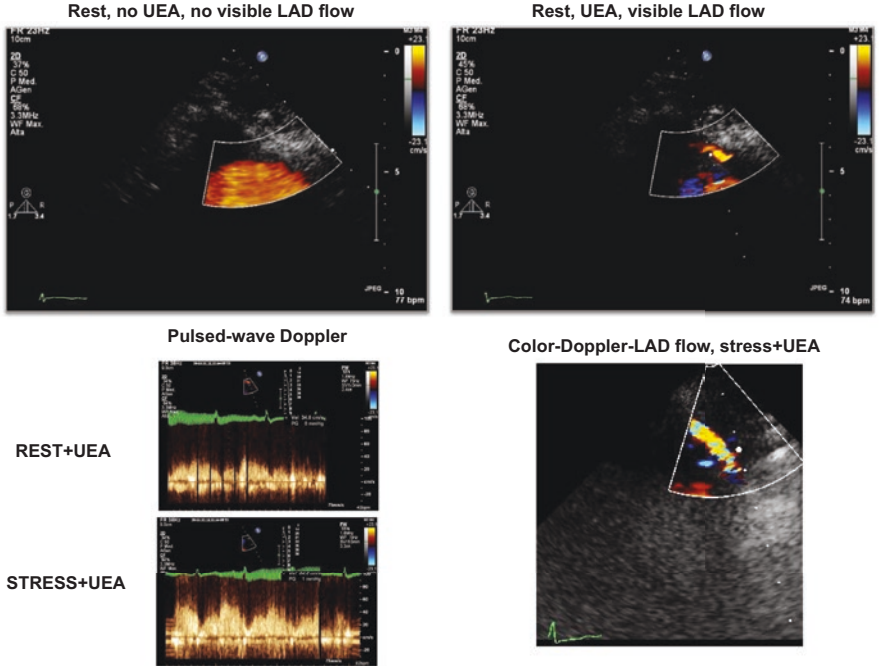

Fig. 14.5 Use of contrast for the enhancement of the left anterior descending color flow in technically difficult cases, in which the rest coronary flow is difficult to localize. Figure (lower part) also shows the downside of noisier pulsed wave Doppler tracings, although the quality is usually sufficient for the measurement of diastolic peak velocities. Courtesy of Dr. Nicola Gaibazzi, Parma, Italy

14.8 Clinical Applications 4: MCE for Myocardial Perfusion Imaging

MCE during stress allows the simultaneous evaluation of regional function and myocardial blood flow. For the detection of myocardial ischemia, a regional perfusion abnormality is more sensitive, although less specific, than regional wall motion abnormalities (Fig. 14.6, Video 14.6). Perfusion imaging provides incremental

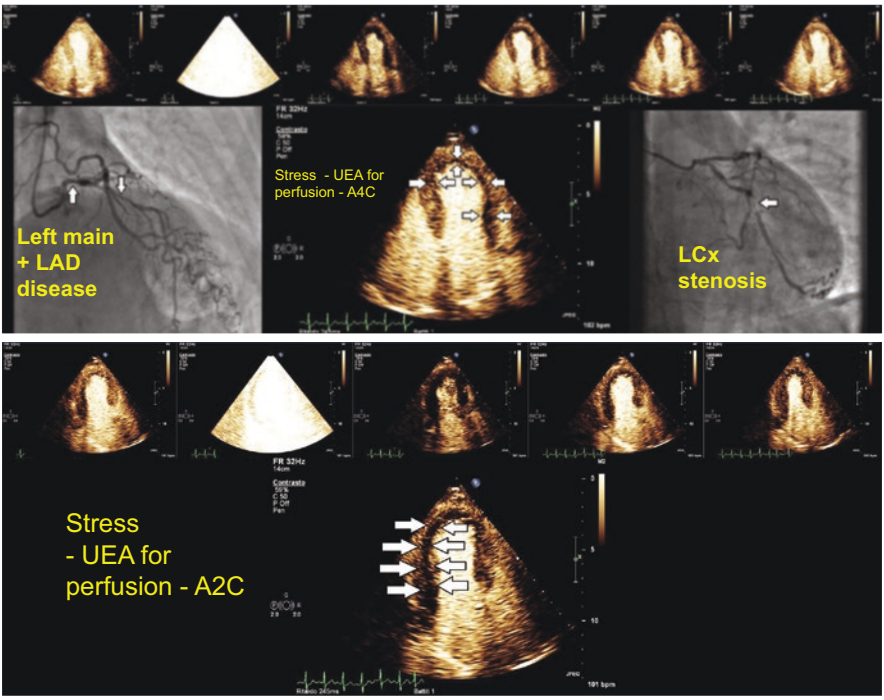

Fig. 14.6 Myocardial SE with vasodilator perfusion imaging. Stress phase in a patient who underwent contrast dipyridamole echocardiography (0.84 mg/kg/6 min). The upper part of the figure shows a four-chamber view contrast flash-replenishment sequence, from left to right which demonstrates black areas in the subendocardial region of the true apex, apical-septal, apical, mid, and basal lateral segments (arrows) up to 4 cycles after microbubbles destruction, representing perfusion defects. The lower part shows the three-chamber view (contrast flash-replenishment sequence from left to right), similarly demonstrating the perfusion defect (arrows), in this case almost transmural, in the inferolateral segments. Flash-replenishment sequences allow for assessing myocardial replenishment after microbubble-destructive impulses. The angiogram on the left side of the figure shows the left main disease (50–60% stenosis, arrow) and LAD disease (arrow), while the angiogram on the right shows the very severe stenosis of the left circumflex artery (arrow), which caused a more profound reduction in myocardial blood flow, with inferolateral transmural perfusion defect. Myocardial perfusion defects may underscore the presence of "balanced disease" in which regional differences in wall motion may often be absent or difficult to detect, at any severity of coronary artery disease (mild or severe); subendocardial stress perfusion defects in several territories are apparent in this case, due to epicardial/endocardial "vertical" steal phenomenon, although the horizontal would mostly go undetected. See accompanying Video 14.2. Courtesy of Dr. Nicola Gaibazzi, Parma, Italy

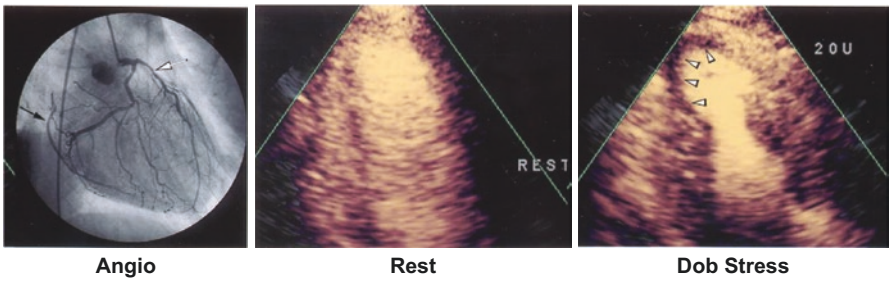

Fig. 14.7 Myocardial dobutamine SE with perfusion imaging. An example of an inducible inferior and apical myocardial perfusion defect (*arrowheads*) during dobutamine SE following a 0.3-ml bolus intravenous injection of Optison. These images were obtained in real-time at frame rates of more than 25 Hz and pulse inversion Doppler. The subsequent coronary angiogram (with left main injection) demonstrates that the right coronary artery fills from the left main injection because of a 100% right coronary stenosis. In addition, there is a long left anterior descending stenosis (*arrows*). Courtesy of Dr. Thomas Porter, Omaha, USA

prognostic value over regional wall motion alone, as shown in a 2021 meta-analysis based on 12 studies enrolling a total of 5953 patients [20].

During stress, a regional wall motion abnormality accompanied by a transient perfusion defect unequivocally localizes myocardial ischemia and an underlying significant coronary artery stenosis (Fig. 14.7).

The superior image quality of contrast pharmacological SE is also ideally suited for the combination of wall motion, perfusion, and quantitation with technologies such as color kinesis (Fig. 14.8), 3D, and all techniques in which the signal-to-noise ratio must be excellent for robust endocardial border recognition during stress.

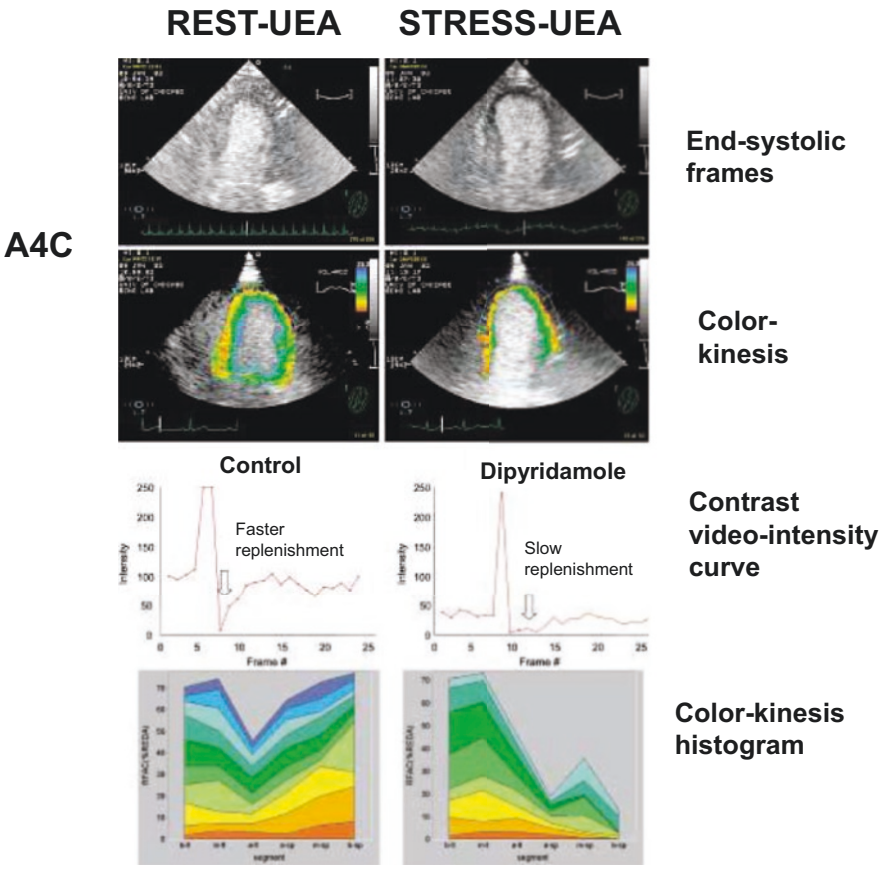

Fig. 14.8 Simultaneous quantitative assessment of myocardial perfusion and function during a dipyridamole stress test. *Top left*: The presence of uniform intramyocardial contrast enhancement and color kinesis (CK) bands of uniform thickness qualitatively indicates normal myocardial perfusion and function at rest, respectively. *Right*: Diminished intramyocardial contrast in the apex together with thinning of the CK color bands in the same segments qualitatively indicates a dipyridamole-induced apical perfusion defect and wall motion abnormality. *Bottom*: the video intensity curves and CK histograms were obtained from the above images. *Left:* Quantitative assessment of normal myocardial perfusion and function at rest. The video intensity curve demonstrates rapid intramyocardial contrast replenishment after a high-energy ultrasound impulse, while the CK histogram demonstrates normal RFAC in all myocardial segments. *Right:* Dipyridamole induced an apical myocardial perfusion defect with corresponding apical and septal hypokinesis. The segmental video intensity curve demonstrates a slow rate of intramyocardial contrast replenishment following high-energy ultrasound destruction, reflecting a perfusion abnormality. The CK histogram below quantifies the percentage reduction in RFAC in the apex and septum. RFAC, regional fractional area change; REDA, regional end-diastolic area. Courtesy of Dr. Roberto Lang, Chicago, USA

14.9 Pitfalls

Despite the extensive literature supporting its use, the diffusion of MCE in clinical practice remains disappointingly low, with only <10% of SE units utilizing the technique. There are technical, economic, and regulatory problems with this underutilization. There is a need for an intravenous line, and the establishment of adequate access is important for optimized contrast stress. Gain settings for the optimization of myocardial contrast may differ from those used for wall motion, and the ability to detect perfusion abnormalities may be reduced if the assessment of wall motion is—as it should be—the primary diagnostic endpoint. Imaging systems have now on board the microbubble signal detection scheme, but the user experience is important for the optimal adjustment of settings such as power, dynamic range, and acoustic focus. Very low mechanical index techniques are recommended for optimal left ventricular opacification and endocardial border resolution. It is recognized that MCE is sensitive in detecting resting myocardial perfusion defects. However, specificity can be detrimentally altered by attenuation artifacts mainly in basal segments and the left ventricular lateral wall. If that occurs, the addition of wall motion analysis may improve specificity, since resting myocardial perfusion defect should always be associated with myocardial segmental abnormality. Another possible artifact during MCE is the presence of swirling or reduced contrast in the apex of the left ventricle. The way to overcome these artifacts is to increase the contrast infusion rate or lower the mechanical index. We may also move the focus temporarily to the near field for better evaluation of the left ventricular apex.

A frequent problem is an excessive contrast in the left ventricular cavity, causing the inability to image adequately the basal segments for acoustic shadowing. For this reason, it is recommended that the initial bolus doses should be low with a stepwise increase when needed.

No contrast agent is currently approved by the Food and Drug Administration or European Medicine Agency for myocardial perfusion assessment, and use for this purpose remains "off-label." Perfusion imaging is ideally suited to be paired with vasodilator stress, still underutilized when compared to exercise or dobutamine, during which perfusion imaging is more difficult for tachycardia.

The recent diffusion of pulsed wave Doppler evaluation of coronary flow velocity reserve in the mid-distal left anterior descending coronary artery has further reduced the appeal of contrast for myocardial perfusion imaging, since coronary flow velocity reserve is much simpler, less expensive, and less risky, and rapidly accumulated in a few years more evidence [21] still lacking for contrast after 40 years of use and despite substantial industry support. As of January 2017, real-time myocardial perfusion imaging was used in <1%, and coronary flow velocity reserve in >50% of Italian SE laboratories [22].

14.10 Safety and Cost

The safety of contrast was challenged by the issuance of a black box safety warning by the US Food and Drug Administration in October 2007 [23], but a series of subsequent publications were reassuring on the safety record of contrast agents and there is now consensus that contrast agents have a high benefit-to-risk ratio when used appropriately. In 2008, the FDA downgraded the contraindications listed in the black box to warnings. In 2011, it removed the mandatory 30 min of monitoring after UEA administration in patients with pulmonary hypertension or unstable cardiopulmonary conditions. In late 2016 and early 2017, the FDA further removed the contraindication for the administration of Optison, Lumason/SonoVue, and Definity in patients with intracardiac shunts. The American Society of Echocardiography 2018 guideline recommends the routine use of contrast agents in evaluating patients with patent foramen ovale and small right-to-left shunts. As of August 2017, the only contraindication was intra-arterial injection and for SonoVue and Definity was known hypersensitivity to sulfur hexafluoride and perflutren, respectively. In summary, despite initial Food and Drug Administration contraindications to the contrary, there is substantial evidence to show that echocardiographic contrast agents are not only safe in critically ill patients but also that important diagnostic data can potentially be derived from these studies [24]. In 2021, the Food and Drug Administration released an alert on presumed Type I immediate hypersensitivity reactions to the polyethylene glycol (PEG) component of UEAs [25].

Ultrasound contrast, like all contrast agents, is not completely safe [26, 27]. The risks were overstated in the Food and Drug Administration's original 2007 warning; however, life-threatening reactions are rare but may occur in <1 in 10,000. The current Food and Drug Administration labeling warns that most serious reactions occur within 30 min of administration and suggest always having resuscitation equipment and trained personnel readily available—but this is the general rule in SE laboratory with or without contrast use. The frequency of side effects is very low (1 in 10,000) for very serious life-threatening anaphylaxis reactions, which can be due to CARPA (C′ activation-related pseudo-allergy reaction) or to PEG-related complement present in the excipient of Sonovue and Luminity (not in Optison). PEG is an excipient frequently used to stabilize medications, including COVID-19 microRNA vaccines and preparations for colonoscopy. Both mechanisms induce the excess release of histamine from activated mastocytes. The symptoms are those of an anaphylaxis reaction, with skin erythema, urticaria, dyspnea, and throat tightness, up to anaphylactic shock. Prompt recognition leads to treatment with intravenous antihistamines, steroids, and small doses of epinephrine if needed to treat hypotension and shock. Rarely, anaphylaxis can occur for C′-activation pseudo-allergy reaction with a mechanism independent of PEG and possibly with all three commercially available UEAs. Other symptoms such as headache, chest pain, and back pain are more frequent but less severe (Table 14.3). They have been attributed to microembolic phenomena due to the aggregation of microbubbles and rarely require specific treatment with analgesics.

The cost of contrast varies In Europe, around €50, and in the USA, around $100 per exam. It is reimbursed in some states in the USA, but not in others. It is not separately reimbursed in most countries, and this makes the SE laboratory (receiving a flat reimbursement of €150–400) less economical if contrast is added.

Table 14.3 Risks of ultrasound-enhancing agents

Incidence	Symptoms	Timing	Mechanism
1 in 10,000	Anaphylaxis	<30′	CARPA; PEG allergy
1 in 100	Headache, chest pain, back pain	Minutes	Microembolism

CARPA C′ activation-related pseudo-allergy reaction

14.11 Clinical Indications and Recommendations

The currently available UEAs are approved for left ventricle opacification and Doppler enhancement. The current recommendation for SE is mainly focused on contrast enhancement of endocardial contour for analysis of regional wall motion abnormalities and left ventricular volumes [25–27], although a possible application is also in the enhancement of pulsed wave Doppler signal for left anterior descending flow detection in 5% of patients without readable signal at rest (Table 14.4). Regarding the most attractive application of perfusion imaging, "*despite its tremendous proven potential, perfusion imaging with real-time MCE is NOT a Food and Drug Administration-approved technique*" [28]. Also, the European Medicine Agency did not approve the contrast for this specific application. As a result, in the USA and Europe, real-time MCE is seldom used. Its main domain of application would be improved diagnosis and risk stratification beyond regional wall motion abnormality in coronary artery disease (mainly with vasodilator stress) and detection of viability particularly in segments non-responders for wall motion improvement (mainly with dobutamine).

The key points of UEAs utilization in SE have been summarized by the American Society of Echocardiography recommendations as follows [28]:

1. UEAs should be utilized during SE whenever two or more contiguous segments cannot be visualized or a coronary artery territory cannot be completely visualized (class of recommendation 1; level of evidence B).
2. Use of very low-dose bolus injections (0.1 ml of Definity, 0.20–4 ml of Optison, and 0.5–1.0 ml of Lumason) followed by slow saline flushes is optimal for reducing cavity shadowing. Alternatively, Definity has been given as a 3–5% dilution in normal saline, and Optison has been infused as a 10% dilution (class of recommendation 1, level of evidence C).
3. Very low mechanical index pulse sequence schemes that detect nonlinear fundamental frequency responses at <0.2 mechanical index are recommended for optimal left ventricular opacification and reduced basal segment attenuation. Brief high mechanical index (>0.8) impulses (5–15 frames) can be used to clear the myocardium and improve endocardial border resolution (class of recommendation 2a, level of evidence B).

In the SE network 2030 study network, a pragmatic approach is used [29, 30]. Contrast is used in its easiest single bolus administration both at rest and during stress, after standard acquisition without contrast, and such enhancement duration is sufficient for regional wall motion, left ventricular cavity, and coronary flow velocity assessment (Fig. 14.9).

Table 14.4 Appropriate indications for MCE in SE

CoR	1	2a	LoE
Indication			
≥2 Contiguous segments unreadable at rest	v		A
≥2 Contiguous segments unreadable at rest after deep inspiration mimicking exercise		v	C
When LV volumetric data are needed irrespective of image quality		v	B
Real-time MCE in coronary artery disease for ischemia		v	B
Real-time MCE in coronary artery disease for viability		v	B
Administration			
Very low-dose bolus injection followed by slow saline flashes for endocardial border enhancement	v		C
Infusion with pump optimal for perfusion imaging		v	B
Imaging			
Low (<0.3) or very low (<0.2) mechanical index, fundamental nonlinear pulse sequence scheme		v	B

CoR class of recommendation, *LoE* level of evidence

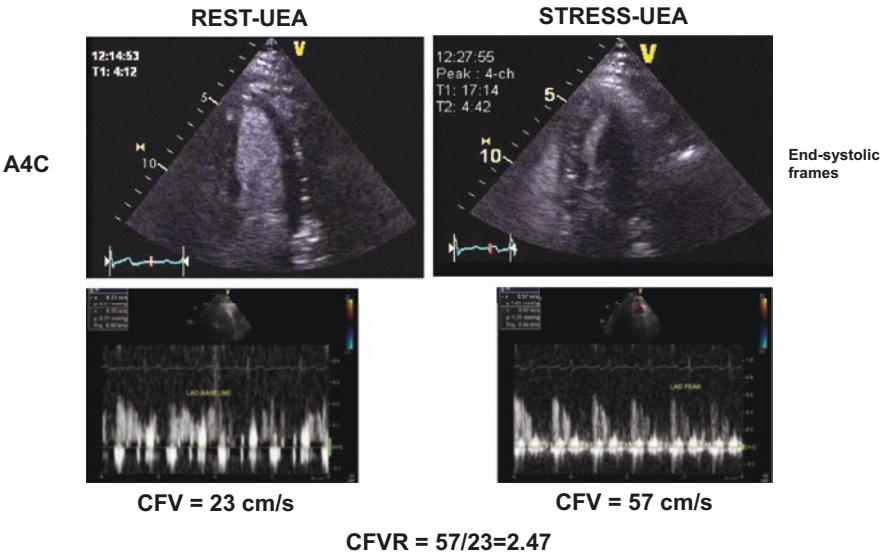

Fig. 14.9 Simultaneous assessment of coronary flow velocity reserve in the left anterior descending artery and contrast-enhanced assessment of myocardial function and left ventricular volumes during a dipyridamole stress test. The patient shows normal coronary flow velocity reserve (rest = 23 cm/s, stress = 57 cm/s, peak/rest = 57/23 = 2.47), normal regional function at baseline and during stress, reduction in end-systolic volume during stress, and normal heart rate reserve (rest = 64 beats/min; stress = 87 beats/min, peak/rest = 87/64 = 1.36, normal vale > 1.22). The corresponding Video 14.3. is shown. Courtesy of Dr. Dimitrios Soulis, Kosmoiatriki Medical Diagnostic Center, Athens, Greece

This approach has no need for specific vendor equipment since myocardial perfusion is not specifically evaluated, not to add another layer of complexity. All machines with a basic contrast preset can be used. According to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology, UEAs for regional wall motion left ventricular

opacification, and Doppler signal enhancement is a basic level familiar to every lab, while UEA for myocardial perfusion imaging is more complex, technically demanding, and less reproducible and may provide useful information, especially in laboratories without the expertise for coronary flow velocity reserve assessment with Doppler in the left anterior descending coronary artery [31].

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Artificial Intelligence and Robotic Stress Echocardiography

15

Arnas Karuzas and Eugenio Picano

Keywords

Click-free echo · Operator independence · Precision · Reproducibility · Workflow

15.1 The Need for Artificial Intelligence in Stress Echocardiography

Echocardiography remains the cornerstone of medical imaging in cardiology for its undisputed advantages of widespread diffusion, portability, versatility, safety, and radiation-free nature, with no need for iodine and gadolinium-based contrast agents. Still, echocardiography faces limitations because of its operator dependence, which results in greater subjectivity of interpretation. In addition, in recent years, the tremendous versatility of the technique has resulted in a huge increase in the information that can be extracted from ultrasound imaging, which can be difficult for cardiologists to handle and interpret. They now receive information on anatomy, function, flow, cardiac structure, coronary supply, and lung appearances, with different techniques such as M-mode, two-dimensional, three-dimensional echocardiography, color, continuous wave, pulsed wave, and tissue Doppler, contrast, lung

A. Karuzas (✉)
Lithuanian University of Health Sciences, Institute of Cardiology, Kaunas, Lithuania

Ligence, UAB, Vilnius, Lithuania
e-mail: a.karuzas@ligence.io

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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ultrasound, and deformation (strain) imaging. Artificial intelligence (AI) and hybrid imaging approaches may provide a solution to simplify the handling of this wealth of this imaging information with four main aims [1]: (1) to make objective what is currently done by the "naked eye" (for instance, regional wall motion analysis) or by "hand measurements" (for instance, ejection fraction from left ventricular end-diastolic and end-systolic volumes); (2) to detect what is undetectable by "natural" intelligence (for instance, myocardial fibrosis with conventional gray level analysis of two-dimensional image texture); (3) to combine information coming from different imaging sources (for instance, stress echo and computed tomography in hybrid imaging combining coronary anatomic data obtained with noninvasive coronary angiography with functional information with stress echo); and (4) to mine big data with techniques such as network analysis to identify interconnected variables and thereby optimize risk stratification for individual patients (Fig. 15.1).

AI is an umbrella term that has expanded in use to encompass different approaches, which have evolved as the methodology has developed: **Machine learning** describes the ability of machines to learn for themselves using datasets with minimal supervision; **deep learning** is a type of machine learning that makes decisions based on networks of decision nodes that mimic the human brain neural network; and **convolutional neural networks** are a specific type of deep learning neural network that have multiple interconnected layers of nodes [2] that have proved particularly effective for learning about image structure. For instance, a convolutional neural network can be developed to recognize an image by dividing the image into separate features, which are then considered by the different layers of the network, from deepest to more superficial. The lowest layer might recognize simple features such as edges. The next layer would recognize combinations of simple features such as edges and circles or gray levels. Each level provides increasing levels of complexity and definition allowing some conclusion about the likely nature

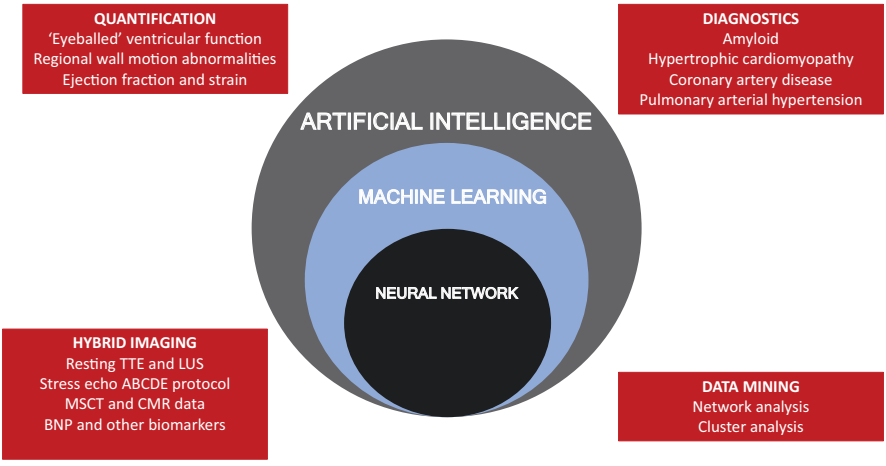

Fig. 15.1 Artificial intelligence for echocardiography. The diagram to illustrate the potential applications of AI to large-scale echocardiography datasets and clinical practice

Table 15.1 From conventional to artificial intelligence stress echo

	Standard	AI
Training	Long	Absent
Acquisition	Operator-dependent	Operator-independent
Analysis	Minutes	One-click
Interpretation	Subjective	Objective
Integration	Difficult	Easy
Expertise needed	High level	Basic

of the image. The features of the top layer are then typically used in a multinomial logistic regression model to generate a classification of the image based on a probabilistic output. Once a process, or "algorithm," has been developed using AI to process images, whether simply to recognize the image, or make quantifiable conclusions from the image, the next critical step is to test the "algorithm" to ensure it continues to accurately make predictions when faced with new data [3]. The transition from conventional to AI echocardiography has the potential to make the technique simpler to learn and use, removing barriers of subjectivity and experience (Table 15.1).

15.2 From Eyeballing to Quantification

Some of the first applications of AI within echocardiography have been to make operator-independent what is currently done "by hands" and "by eyes." The basic informatics infrastructure for data acquisition, data transfer, and analysis is either built-in in the echo machine or based on a dedicated external software (Fig. 15.2).

Recognition of a correct echocardiographic view [4, 5] or calculation of left ventricular ejection fraction has now been effectively performed with AI [6, 7]. Heart chambers areas and volumes can be measured and synchronized in the display making the examination less tedious and more informative (Fig. 15.3).

AI-based approaches can even overcome technical challenges such as the identification of borders in poor-quality images, which limit other automated approaches. "*A computer that has never seen an image before can now take an echocardiogram, look at 2 views and, without any user input or need to contour the ventricle, estimate what it thinks is the ejection fraction with astonishing precision*" [8]. Traditionally, ejection fraction interpretation at the point of care has been conducted through the visual estimation, but variation in clinician experience across point-of-care settings has raised concerns about accuracy. AI software that uses advanced pattern recognition algorithms to imitate the way the human eye identifies borders and motion should remove this variability between operators. It also introduces an automatic assessment of image quality with a quantitative threshold that automatically discards images of low quality with low reliability of measurements. AI applies the universal GIGO principle (garbage in, garbage out) and tells the cardiologist or sonographer when "garbage" is too much, the image is too noisy, to be seriously analyzed. However, image denoising is also possible with AI and can be usefully

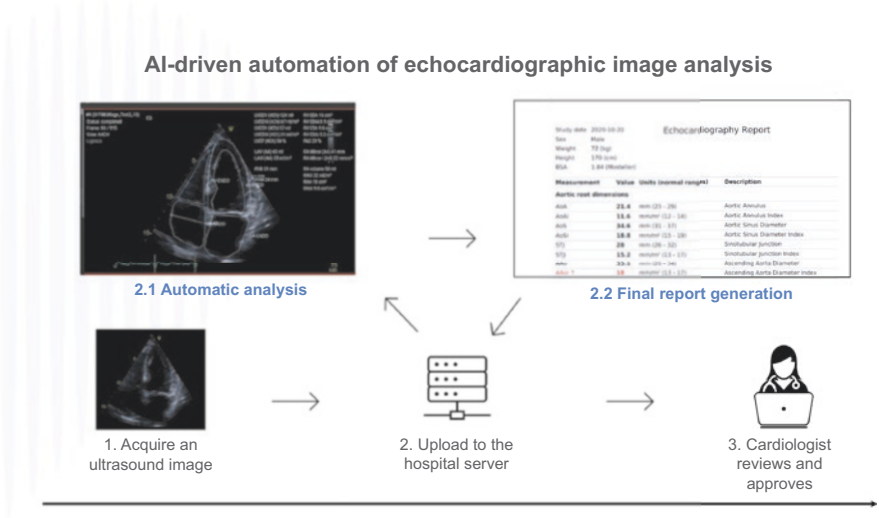

Fig. 15.2 Informatic architecture of AI-based echocardiography

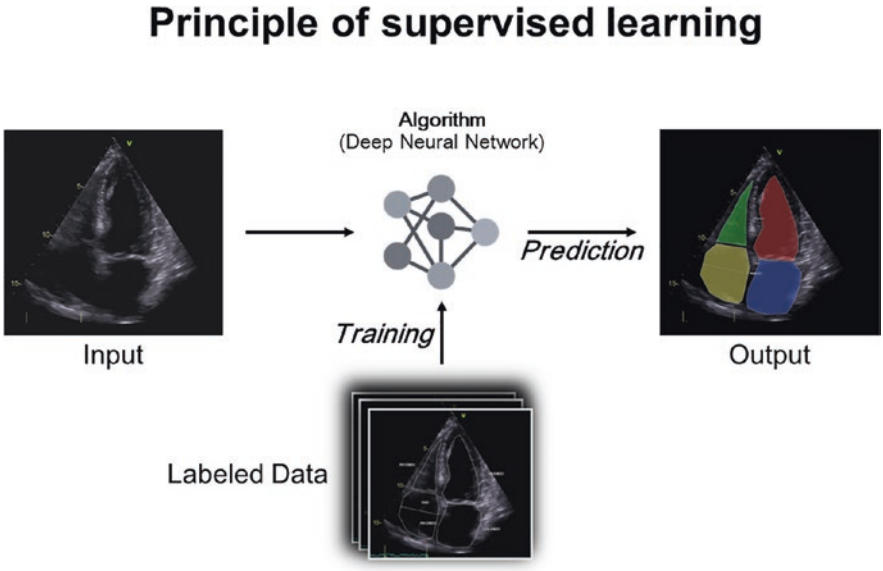

Fig. 15.3 AI-based four-chamber volumetric stress echo. On the left, 2D images are read and analyzed by an experienced operator to obtain left ventricular, right ventricular, left atrial, and right atrial volumes. On the right, the same images analyzed by an AI algorithm based on convolutional neural networks (Ligence Heart) provide the same information in a shorter time with an operator-independent approach. The results are very similar, especially regarding intra-patient (rest to stress) changes that are the most relevant for stress echo analysis

applied to rescue unreadable images or to minimize the use of ultrasound-enhancing agents.

Another example of AI replacing or corroborating naked eye diagnosis is regional wall motion abnormalities at rest and during stress. A deep learning approach has the same accuracy as experienced readers in identifying regional wall motion abnormalities and has now been applied both in resting conditions [9] and during stress [10].

As AI-based approaches are further developed, traditionally complex, time-consuming, and technically demanding measurements performed by eye or hand should start to be undertaken in automated and highly reproducible ways. These approaches should be able to encompass assessment of right ventricular size and function [11], automatic quantification of mitral regurgitation [12], measurements of mitral valve [13], aortic root [14], or left ventricular filling pressures [15].

15.3 Exposing Information Missed by the Eye

AI methods may also allow the extraction of information missed by the "eye." For years, video densitometric features of the 2D image have been used to identify myocardial fibrosis as increased gray levels and reduced cyclic variation from systole to diastole [16, 17]. This approach has never been implemented clinically due to sources of error such as nonlinearity between displayed signal and received signal, the possibility of artifacts, and anisotropy of myocardial walls showing different reflectivity features in different projections. Now, a cardiac ultrasonic fingerprinting approach has shown the potential to identify myocardial fibrosis, consistent with findings from the gold standard of delayed gadolinium enhancement. This method combines information on gray levels, global longitudinal strain, left ventricular volumes, and clinical risk factors [18].

A similar approach can be applied to the detection of complex carotid plaque morphology. Ultrasound has the clear potential to identify a lipid core separated from fibrotic and calcified plaque components. Therefore, the texture and morphological features of a complex, rupture-prone plaque may be identifiable with image processing and generate greater insights about clinical plaque stability that can be achieved just by relying on plaque geometry and stenosis [19, 20]. By undertaking this analysis with machine learning, the approach should allow the identification of vulnerable plaques in a solid, operator-independent manner [21] that might further expand the potential of comprehensive risk stratification based on the integration of resting carotid scan and stress echo.

15.4 Hybrid Imaging

Echocardiography is generally used as a stand-alone technique, independently of other imaging techniques. A different approach is hybrid imaging, a multimodal approach using information derived from different techniques, usually

complementary (e.g., anatomical and functional) rather than overlapping (anatomical and anatomical) [22]. Hybridization implies the simultaneous interpretation of obtained scans for critical online decision making (for instance, in echocardiography-fluoroscopy fusion) but may also imply a simultaneous interpretation of different sets of images obtained independently and combined offline for purposes of interpretation, for instance, to match an anatomic disease (most typically a coronary atherosclerotic plaque) with a functional defect (usually a stress-induced perfusion defect or a regional wall motion abnormality). However, no application in cardiology has reached the clinical acceptance of hybrid imaging with PET-CT in oncology. The main application of real-time fusion imaging in echocardiography is the combination with fluoroscopy in percutaneous structural heart interventions to increase procedural success [22].

Another less mature field of application of fusion imaging is coronary artery disease. The combination of coronary computed tomography angiography and strain maps of deformation imaging obtained with 2D or 3D echocardiography can show a match or mismatch between anatomic coronary stenosis and longitudinal strain maps, allowing direct visualization of each coronary artery and myocardial longitudinal strain in its territory [23]. This approach can be derived from deformation maps at rest or—more conveniently—with strain maps during stress, and hybrid fusion software is available allowing anatomical matching between 3D strain stress datasets superimposed on 3D coronary computed tomography datasets. These packages allow a spectacular comprehensive anatomic and functional representation of coronary anatomy and regional stress myocardial function at the same time [24]. The fusion and matching can be done offline and independently with multimodality imaging [24]. Multimodality imaging is a surrogate for hybrid imaging and may work well in selected circumstances.

15.5 Data Handling: Network Analysis

Increasingly, it is being realized that regional wall motion analysis on its own is insufficient for accurate diagnosis and risk stratification of a patient with suspected or known coronary artery disease and/or heart failure. However, a rational approach that can combine the enormous amount of information available on individual patients to provide optimal risk prediction has been lacking. Network analysis is ideally suited to mine big data and could be used to identify key variables and optimize risk stratification. For instance, in coronary artery disease, multiple clusters of information can be collected during stress echo that may be of benefit for diagnosis [25]. A simple machine learning approach exposes clinically important information overlooked by conventional prognostic analysis. As an example, a dataset of close to 7000 patients followed-up for a mean of 5 years shows that regional wall motion abnormalities (step A) and coronary flow velocity reserve <2.0 (step D) have independent value in predicting survival, but machine learning analysis shows—in the very same data set—information important for the clinician, that mortality increases linearly for increasing

positive values of wall motion score index (indicating more extensive and/or severe inducible ischemia). In addition, the association between coronary flow velocity reserve and mortality is steep and starts to rise for values below 3.0, well within the range of normality [25].

15.6 Robotic Stress Echocardiography

Stress echocardiography has its major weakness in the operator dependence in the acquisition of images and interpretation of data. The situation is rapidly changing with the advent of robotic and AI-assisted echocardiography.

There are several reasons for the progressive inclusion of robotic (hands-off) stress echo in daily practice (Table 15.2).

Robotic medicine has been applied to all fields of medicine and surgery, including interventional cardiology and electrophysiology. It is more than reasonable to guess that the technology behind these advanced applications is more sophisticated than the one needed for the remote control of an ultrasound probe. First and foremost, since echocardiography is dependent on operator skills in image acquisition and analysis, it would be especially appealing to have a robotic image acquisition and an AI-assisted image analysis, removing the human factor from echocardiography. The robot will echo you now [26]. Second, work-related musculoskeletal pain of cardiac sonographers is endemic in the echo laboratory and affects up to 90% of sonographers after 10 years of work [27]. It occurs more frequently in the neck, shoulder, lower back, and hand, and often leads to work restrictions and considering changing employment. The shift from hands-on to hands-off imaging is the best approach to radically solve this problem that costs discomfort and pain and reduces the quality of work in the echocardiography laboratory.

Third, there are radiation exposure risks in patients injected for nuclear medicine procedures, and these innocent bystander risks are significant for sonographers involved in the catheterization laboratory in invasive procedures or the echo laboratory with patients recently injected for perfusion imaging [28]. During a 20-minute examination, the sonographer radiation exposure during transthoracic echocardiography performed on the same day after a myocardial perfusion imaging is equivalent to 20–100 chest X-rays, and yearly cumulative exposures are far from being negligible in high-volume laboratories and may total 250- to 500 chest X-rays, which warrants radiation protection measures [29]. Exposures are higher for sonographers working in the stress testing laboratory when imaging times are longer [30].

Table 15.2 From hands-on to robotic echocardiography

	Standard scan	Robotic scan
Human factor	Operator dependence	Remote scan
Orthopedic strain	Operator discomfort	Hands-off
Radiation exposure	Irradiated patient	The operator at a distance
Contagion risk	Face to face	Face-off

Fourth and perhaps most important, the need for robotic stress echo has increased in the COVID-19 era, since less contact and shorter face-to-face imaging time between patient and sonographer means less risk of contagion and improved safety for COVID-19 and any other infection [31].

The same results of minimizing imaging time and discomfort to the doctor can be achieved with probe holders, which, however, do not allow remote manipulation of the probe usually necessary during ultrasound imaging.

The new era should produce a new emphasis on robotic image acquisitions, controlled by sonographers removed from the patient, or eventually by automated algorithms based on image recognition. Such devices are already available, but further advances will enhance safety and effectiveness. In the short run of a decade, automation with AI and robotics will force 30% of the present workforce to find new jobs and 60% of present-day activities could be taken over by automation [32].

15.7 Recommendations and Vision

AI echocardiography will close the gap between experts and beginners potentially allowing unsupervised diagnosis [33–35]. For individual echocardiography laboratories, increased precision and reproducibility derived from AI means volumes of activity will no longer be necessary to guarantee the accuracy of measures [36]. Professional societies expressed concerns that echocardiographic examinations could become so automated that sonographers become obsolete, but the workflow and quality of laboratories have already improved with AI [37]. The echocardiographic analysis is loaded with manual work (250 clicks per exam), and sonographers are at risk for work-related musculoskeletal disorders, much less likely when imaging time is reduced with AI-assisted image acquisition and offline analysis time is minimized with AI-assisted measurements.

With AI echocardiography and AI stress echo possibly combined with robotic image acquisition, we are witnessing a new exciting era that will rapidly change the daily life of our laboratories, allowing integration, quantification, and operator independence, from the initial step of image acquisition to the intermediate step of image analysis to final step of data integration and interpretation. This is the ultimate step that will establish echocardiography as the definitive, quantitative, unsupervised, and objective imaging test. The industry is eager to sell and the market is eager to buy AI software, but in the real world it is not always easy to find the right product for the right user with a specific need. The buyer's guide developed in 2020 by the United Kingdom National Health System is useful and timely [38]. The checklist for AI in health and care also applies to cardiac imaging products. Among the key questions to be addressed, some are especially relevant to cardiac imaging: "*What problem are you trying to solve, and is AI the right solution? Does this product meet regulatory standards? Does this product perform in line with the manufacturer's claims? Will this product work in practice? Can you secure the support you need from staff and service users? Can you build and maintain a*

culture of ethical responsibility around this project? What data protection protocols do you need to safeguard the privacy and comply with the law? Can you manage and maintain this product after you adopt it? Is your procurement process fair, transparent, and competitive? Can you ensure a commercially and legally robust contractual outcome for your organization, and the health and care sector?" As always, the answer is the responsibility of the final end user, not in the brochures of marketing experts or in the statements of opinion leaders who invested their time and talent in the field.

Echocardiography generates an immense amount of digital data that can be combined with traditional risk factors, clinical presentation, other imaging techniques, and laboratory biomarkers. Making sense of this landslide of data is a challenge even for the best cardiologist, but AI provides a potential key for interpretation and data mining hibernating in a DICOM file or an electronic health record. The methods could uncover complex clinical relationships that redefine disease and previously unseen clinically relevant information hidden within ultrasound images [39]. The trend for use of data mining will allow the extraction of data currently buried in the image and make them readily available for clinical use (Fig. 15.4). According to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of

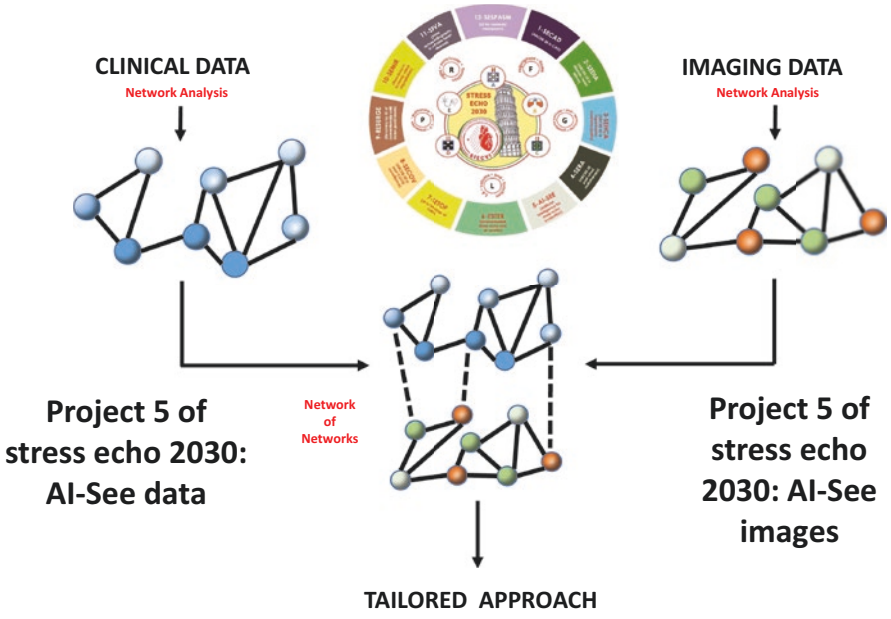

Fig. 15.4 The roadmap of AI-based stress echocardiography in the stress echo 2030 study. AI will be applied to images (project AI—see images) to make the diagnosis operator-independent (left side) and to data (project AI—see data) to detect outcome information previously buried in data storage systems. From the combination of data and image analysis, individual phenotypes can be identified that become actionable therapeutic targets. Adapted from Picano [39]

Cardiology, "*stress echo is ideally positioned to have the greatest benefit from AI in image data acquisition, analysis, and interpretation. Stress echo empowered with AI can integrate multi-mode data, guide sonographers during acquisition, provide objective quantifications, measurements, and diagnoses, improve SE workflow in clinics, and lower healthcare costs*" [40].

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Technology and Training Requirements in Stress Echocardiography

16

Bogdan A. Popescu, Monica Roşca, and Eugenio Picano

Keywords

Competence · Reproducibility · Subjectivity · Wall motion · Training

16.1 Introduction

Stress echocardiography (SE) is relatively simple and widely available [1]. However, skills in interpretation cannot be acquired in a few days or weeks. With a handheld echocardiographic machine and an inexpensive drug or an ergometer, any sonographer can become a stress echocardiographer [2]. Ordering patterns might be distorted by financial incentives because the test can be performed in a physician's office. In the absence of a strict system of credentialing and quality control, any lab may experience a backlash of distrust regarding the technique [2]. Interpretation of SE requires extensive experience in echocardiography and should be performed only by physicians with specific training in the technique [3, 4].

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B. A. Popescu (✉) · M. Roşca
Cardiology Department, Emergency Institute for Cardiovascular Diseases 'Prof. Dr. C. C. Iliescu', University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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16.2 General Test Protocol

The patient lies in a decubitus position, the position required to achieve an optimal echocardiographic view. Electrocardiographic leads are placed at the standard limb and precordial sites, slightly displacing (upward and downward) any leads that may interfere with the chosen acoustic window. A 12-lead electrocardiogram is recorded in resting conditions and at each minute throughout the examination. An electrocardiographic lead is also continuously displayed on the echocardiography monitor to provide the operator with a reference for ST-segment, arrhythmias, and heart rate changes (Fig. 16.1).

Cuff blood pressure is measured in resting conditions and at each minute thereafter with an automatic device. Echocardiographic monitoring is usually performed from the apical (both four- and two-chamber views) and parasternal (both long- and short-axis) approaches. In some cases, the sub-xiphoidal view is employed. Images are recorded in resting condition from all views. The echocardiogram is continuously monitored and intermittently recorded. In the presence of obvious or suspected regional wall motion abnormalities, a complete echocardiography examination is performed and recorded from all approaches employed to allow optimal documentation of the presence and extent of myocardial ischemia. The same projections are obtained and recorded in the recovery phase, after cessation of the stress (exercise or pacing) or administration of the antidote (aminophylline for dipyridamole, beta-blockers for dobutamine). The regional wall motion can be evaluated through a triple comparison: stress versus resting state; stress versus recovery phase; and at peak stress, with the neighboring normally contracting segments. A clear standardization of the procedures allows the workflow to be optimized, thus improving the overall quality of diagnostic performance in the SE laboratory. The nurse explains the procedure and the aims of testing to the patient, marks the acoustic approaches, and in the case of pharmacological stresses, prepares the doses of drugs, including the antidote. A 12-lead electrocardiogram is recorded, and blood pressure is measured. After placement of the intravenous line (in the case of

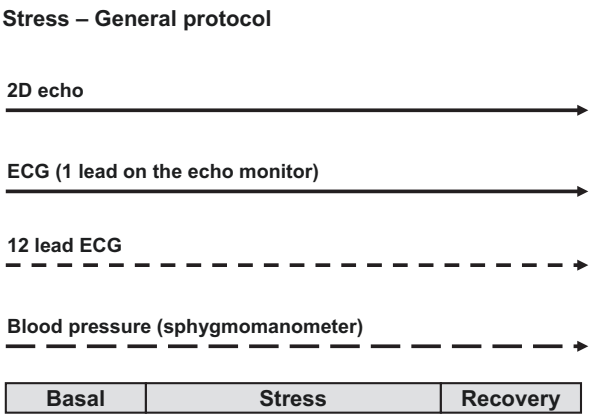

Fig. 16.1 General protocol of SE test

Table 16.1 Diagnostic endpoints of SE testing

Maximal dose/workload
Target heart rate
Obvious echocardiographic positivity
Severe chest pain
Obvious ECG changes (>2 mm ST-segment shift)

Table 16.2 Submaximal nondiagnostic endpoints of SE testing

Limiting symptoms
Limiting asymptomatic side effects:
Hypertension: SBP > 220 mmHg; DBP > 120 mmHg
Hypotension (relative or absolute): >30 mmHg drop in blood pressure
Supraventricular arrhythmias: supraventricular tachycardia, atrial fibrillation
Ventricular arrhythmias: ventricular tachycardia, frequent and polymorphic premature ventricular beats

SBP systolic arterial pressure, *DBP* diastolic arterial pressure

pharmacological stress or contrast administration), the sonographer records the resting echocardiogram and the stress begins. Throughout the study, the nurse keeps a written protocol of the study (clinical events, drugs injected, electrocardiographic and echocardiographic changes noted by the physician), infuses drugs or varies the workload, measures blood pressure, and evaluates the 12-lead electrocardiogram each minute. A well-trained nurse with sonographer skills is essential to increasing the workflow and expanding the imaging service in a SE lab [5]. Diagnostic endpoints of SE testing are reported in Table 16.1.

Nondiagnostic endpoints of SE testing are reported in Table 16.2.

16.3 Imaging Equipment and Techniques

Digital acquisition of images has evolved from the days of stand-alone computers that digitized analog video signals, to the current era in which ultrasound systems have a direct digital output. By digitizing two-dimensional echocardiographic images, it is possible to put a single cardiac cycle into a continuous loop so that the cycle can be viewed whenever necessary for an indefinite time. This technique offers valuable advantages. Even in an exercising individual who is breathing rapidly and deeply, one can still see a technically good cardiac cycle between inspirations; therefore, it reduces the respiratory artifact. Another advantage of using the computer to record the two-dimensional echocardiogram digitally is that it is possible to place the resting and stress cardiac cycles side-by-side in a split-screen or quad-screen format (Fig. 16.2).

This reduces the time and difficulty of analyzing the examination and may also simplify the recognition of subtle changes in wall motion. Although there is no evidence that it improves diagnostic accuracy when compared with videotape reading [6, 7], digital acquisition certainly makes storage, retrieval, analysis, and communication of SE data faster and easier.

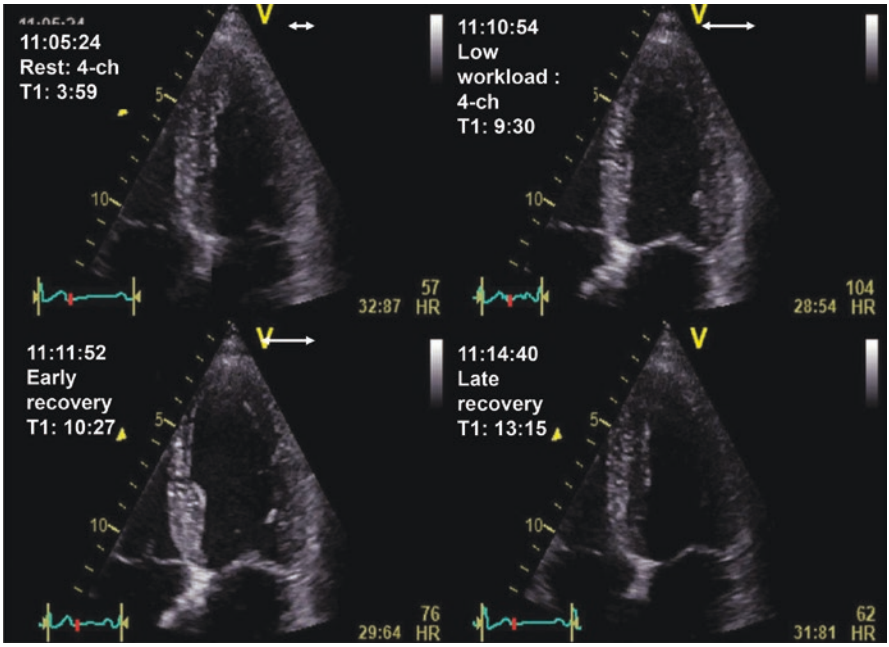

Fig. 16.2 A 58-year-old man with multiple cardiovascular risk factors (ex-smoker, hypertension grade 1, dyslipidemia—LDL cholesterol 170 mg/dL, overweight—body mass index 28 kg/m^2), complaining of rare episodes of typical angina was admitted to deciding on the need for revascularization of a known 60% stenosis of the proximal left anterior descending coronary artery. He was referred for exercise echocardiography to assess the hemodynamic significance and clinical consequences of this stenosis. The patient exercised only 50 W, 4 min, to a maximum heart rate of 85 beats per minute (52%). At peak exercise, the patient was symptomatic with severe dyspnea, but no angina. The blood pressure increased from 140/80 mmHg at rest to 175/85 mmHg at peak exercise. Extended akinesia (apex, medial segments of the anterior wall, anterolateral wall, and interventricular septum) occurred at a low level of exercise and persisted 4 min into the recovery phase. A significant increase in left ventricular systolic diameter at the mid-apical segments in end-systolic frames during low-workload exercise and the early recovery phase can be observed. One can note the lack of contractile reserve and a significant decrease in left ventricular ejection fraction during exercise. The test was positive for ischemia in the territory of the left anterior descending artery and revealed an increased risk for cardiovascular events. After the test, the patient underwent successful revascularization with stent implantation at the level of the left anterior descending coronary artery stenosis, followed by symptom relief. This case illustrates the role of SE in the assessment of hemodynamic significance and clinical consequences of known coronary stenosis, estimated as borderline severity by visual assessment at coronary angiography. See accompanying Video 16.1. (Video images courtesy of Prof. Bogdan A. Popescu and Dr. Monica Roşca, Bucarest, Romania. The video is available under the chapter's "Supplementary Material" on Springer Link)

Tissue harmonic imaging improves image quality over conventional imaging. This is obtained mainly through the elimination of ultrasound artifacts (namely the side-lobe, near-field, and reverberation artifacts) with a consequent increase in lateral resolution and signal-to-noise ratio. The increased image quality is mirrored in better visualization of the left ventricular endocardium and epicardium, and this has a favorable impact on the evaluation of both global and regional left ventricular function at rest.

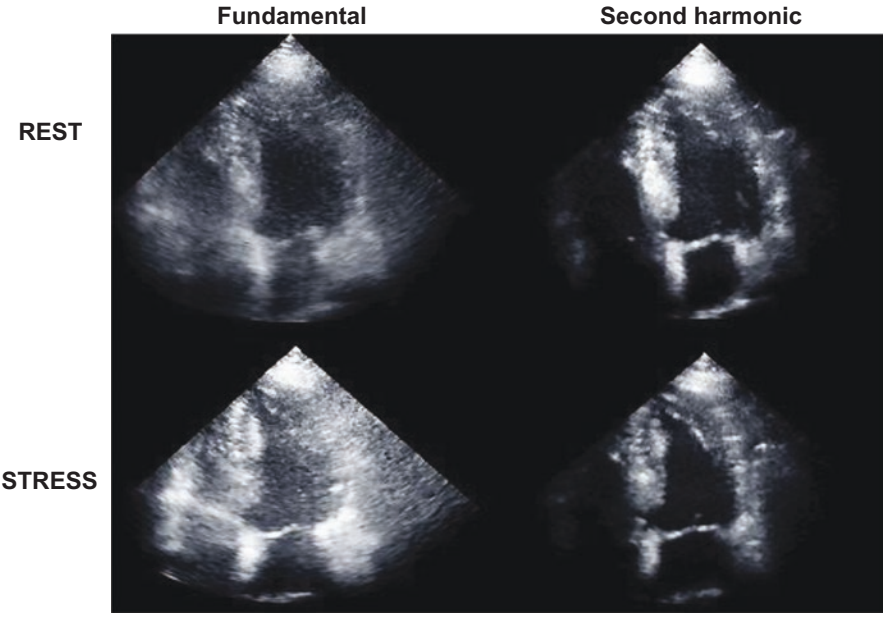

Fig. 16.3 Fundamental (*left*) and tissue harmonic imaging (*right*) of rest (*upper panels*) and stress (*lower panels*) end-systolic still frames of an apical four-chamber view. Basal and apical segments of the lateral wall are more sharply delineated with tissue harmonic imaging mode. (From Rodriguez et al. [8])

In the setting of SE, tissue harmonic imaging reduces the number of uninterpretable segments, deflates observer variability, and increases diagnostic accuracy [8, 9]. The increase in interpretable myocardium is particularly valuable for the apical, lateral, and anterior wall segments (Fig. 16.3) imaged in the apical views at higher heart rates. Tissue harmonic imaging should be used for SE imaging [3, 4].

When used in conjunction with harmonic imaging, ultrasound-enhancing agents increase the number of interpretable left ventricular wall segments, improve the reproducibility of planimetric area measurement of the left ventricle needed for volumetric SE, and reduce the need for additional noninvasive tests due to equivocal noncontrast stress examination [10]. Previous concerns regarding the safety of contrast agents have been addressed by recent data supporting the excellent safety profile of contrast agents, which should be used when two or more segments are not well-visualized [11].

16.4 Training Requirements

For the proper and safe performance of SE, accreditation of both the individual performing the study and the laboratory where the study is performed should be mandatory. Establishing clear standards for the requirements of personnel training,

staffing level, and equipment available in a SE laboratory is an important measure with the ultimate goal of safeguarding patients undergoing SE.

It is not reasonable to begin using SE without thorough training in transthoracic echocardiography (level 2, American Society of Echocardiography). The basic skills required for imaging the heart under resting conditions are not substantially different from those required for imaging the same heart from the same projections during stress. Furthermore, the echocardiographic signs of ischemia are the same as those during myocardial infarction. In both cases, the assessment is based on a comparison between the "suspected" zone and the neighboring normal regions; in induced ischemia, however, the operator can use the suspected region as its control, considering both resting conditions and the recovery phase. The use of stress is associated with the possibility of life-threatening complications, both ischemia-related and ischemia-independent. Therefore, as happens with a simple exercise test, the cardiologist-sonographer (and the attendant nurse) should be certified in Basic and Advanced Life Support, as also required by the American Heart Association guidelines for stress testing [12].

The diagnostic accuracy of an experienced echocardiographer who is an absolute beginner in SE is more or less equivalent to that achieved by tossing a coin (Fig. 16.4). However, 100 SE studies are sufficient to build the individual learning curve and reach the plateau of diagnostic accuracy [13]. With Doppler, it is wise to assess one's learning curve in cases where a recent catheterization provides a standard against which the presence and severity of regurgitation and gradients can be estimated; instead, with SE, it is wise to test one's initial performance in patients who have recently undergone coronary angiography, and possibly with other imaging techniques using the same stress.

After 15–30 days of exposure to a high-volume SE laboratory, the physician should begin to accumulate his or her own experience with a stepwise approach, starting from more innocuous and simple stresses such as low-level supine exercise echocardiography and moving up to more technically demanding ones.

The interpretation of SE is necessarily qualitative and subjective. The cardiologist-echocardiographer performing the test evaluates the study online. Rarely is a "blind"

Fig. 16.4 Histograms showing the diagnostic accuracy of the five beginners (*black bars*) and five experts (*white bars*) who reviewed two sets of 50 videotapes before and after a 6-month training period (100 SE studies with a supervisor); $*p < 0.001$. (From Picano et al. [13])

reading by two independent observers made for diagnostic or clinical purposes. Quantitative analysis of regional wall motion is never performed for purely diagnostic reasons; quantitative methods are time-consuming, require extra equipment and images of better quality than those interpretable with a qualitative assessment, and they certainly do not clarify uncertain readings; they simply measure and make the obvious "certain" without reducing the number of questionable studies. Diagnostic accuracy is not increased by quantitative methods, since the human eye naturally integrates space and time, and its discriminatory power is very difficult to equal and virtually impossible to surpass. However, it is also true that different individuals have different eyes, and the degree of interinstitutional variability tested on identical images can be substantial, even among laboratories of unquestionable reputation [14]. Diagnostic accuracy is not only a function of experience; for a given diagnostic accuracy, every observer has his/her sensitivity-specificity curve: there are "over-readers" (high sensitivity, low specificity) and "under-readers" (low sensitivity; high specificity), depending on whether images are aggressively or conservatively interpreted as abnormal. Many studies yield unquestionably negative or positive findings; still, there is a "gray zone" of interpretable tests in which the visualization of some regions can be suboptimal and the cardiologist's level of experience in interpreting the test is critical for a correct reading.

Interobserver variability is certainly a common problem in medicine. In cardiology, variability can be substantial with almost all diagnostic methods, including resting electrocardiography [15], exercise electrocardiography [16], perfusion scintigraphy [17], and coronary angiography [18]. For myocardial perfusion imaging, the interobserver agreement for a majority of observers was found to be 75% for an abnormal and 68% for a normal interpretation [19]. In only 65% of coronary angiograms, all four experienced invasive cardiologists (from the same institution) agreed on the significance of stenosis [18]. However, a perception of the diffuse nature of the problem does not reduce interobserver variability in SE. There are several ways to minimize this variability, representing the key factor that may ultimately determine the real impact of SE in modern cardiology. Again, experience with nuclear medicine has taught us that agreement can be doubled by moving from an interpretation without standardization to an interpretation with standardization of display and quantification [19]. Similarly, many precautions that may minimize variability, provide not only higher accuracy but also better reproducibility.

These parameters are related to the physician interpreting the study, the technology used, the stress employed, and the patient under study (Table 16.3).

Variability will be substantially reduced if one agrees in advance not to consider minor degrees of hypokinesia, since mild hypokinesia is a normal variant under most stresses and there is a wide overlap between normal and diseased populations [20, 21]. Also, the inclusion of isolated abnormality of basal inferior or basal inferoseptal segments among positivity criteria will inflate variability. The inclusion of patients with resting images of borderline quality, or the use of stresses degrading image quality, will also dilate variability, which is closely linked to the quality of the images. The single most important factor deflating

Table 16.3 SE and the human factor

	Increases variability	Reduces variability
Physician-related		
1. Previous training in SE	No	Yes
2. Exposure to joint reading	No	Yes
3. Development of "a priori" reading criteria	No	Yes
4. Positivity for basal inferior septum hypokinesis	Yes	No
5. Positivity for "lack of hyperkinesis"	Yes	No
6. Positivity for "severe hypokinesis"	No	Yes
Technology-related		
7. Cine loop display	No	Yes
8. Native tissue harmonic	No	Yes
Stress-related		
9. Use of stressor polluting image quality	Yes	No
Patient-related		
10. Resting images of borderline quality	Yes	No

variability is dedicated training in a large-volume SE laboratory with exposure to joint reading [22] and "a priori" development of standardized [23] and conservative [24] reading criteria.

16.5 Pitfalls

Regardless of the number of SE studies performed and the intensity of training, some readers still do not reach a satisfactory degree of accuracy and can be considered "nonresponders" to SE, which can be done by many but not all sonographers [24]. This is true with all activities involving the development of cognitive skills. The five most frequent mistakes in SE training can be summarized as follows:

1. *Self-made SE:* It is far better to perform and/or review 100 SE studies with an expert supervisor than 1000 SE studies done all by oneself without a diagnostic reference standard.
2. *Starting one's learning curve at the university level:* Post-treadmill exercise is the most familiar stress for the cardiologist and the patient but by far the most technically demanding. The best way to improve image quality, diagnostic accuracy, and interobserver reproducibility is to use semi-supine exercise as physical stress and a vasodilator as pharmacological stress.
3. *Underestimating ischemic risk:* The technicalities of pharmacological SE can be surprisingly simple, but one has to know how to treat ischemia and its unforeseeable and potentially catastrophic complications. A SE laboratory run by technicians and sonographers without an attending experienced cardiologist can be a real danger to the patient. For instance, the early stop of pharmacological stress for an obvious regional dysfunction developed after a low dose of a drug (dipyridamole or dobutamine) can make the difference between uneventful and

catastrophic stress. Not all patients were created equal during stress, and a fixed, inflexible approach with maximal dose administration in all can be dangerous.

4. *Skills in resting echocardiography are not enough:* Pediatric, transesophageal, transthoracic, and vascular echocardiography speak a different ultrasound idiom than SE. SE requires dedicated training, or the experience will be disappointing and results inconsistent.
5. *Technology without cardiology:* It is better to have the best eyes with a suboptimal technology than the worst eyes with the best technology. Usually, there is an economic interest in selling technology, not in improving culture. Unfortunately, to date, no method for quantitative analysis has increased the clinical impact of SE [25], although artificial intelligence is a game-changer and is rapidly establishing an operator-independent assessment for regional wall motion and volumetric SE. SE—and especially pharmacological SE—requires tight integration of echocardiographic knowledge and cardiological experience. If this happens, clinical rewards will be outstanding, and SE is now an integral part of the core curriculum of the clinical cardiologist according to the European Society of Cardiology.

16.6 Clinical Guidelines

The checklist for starting and keeping alive a SE activity is reported in Table 16.4 (training requirements recommended by the American Society of Echocardiography) [26–28].

Cultural requirements suggested by the Task Force of the American College of Cardiology/American Heart Association are shown in Table 16.5.

Staff and organization/equipment requirements as proposed by the European Association of Cardiovascular Imaging are reported in Table 16.6.

As an additional requirement, the American Society of Echocardiography recommends for cardiac sonographers a dedicated training course in radiation safety, since echocardiography (and more frequently SE) is often performed in radiation-emitting ("hot") patients injected with radionuclides for myocardial perfusion studies [29]. This leads to a significant exposure (up to 0.5 milliSievert, around 25 chest X-rays) per exam to the sonographer [30], with the potential for significant cumulative risk in case of protracted exposure, especially worrying in women, young people, during pregnancy [31], and in individuals who may require additional time for the scan, such as novice sonographers including students and fellows.

The increased demand for SE activity posed by guideline recommendations [32, 33], growing concern about radiation exposure and the cost of alternative imaging techniques [31], and the expansion of indications and applications of SE well beyond coronary artery disease [34] can only be met with optimization of training, cardiology staff, and resources, ideally within the framework of a continuous structured quality improvement project, with a tailored teaching and training program, creation of a uniform procedural protocol, and implementation of regular internal audits [35–37]. High volumes of activity are necessary, but not sufficient, to grant diagnostic accuracy with the reading of regional wall motion abnormalities [38].

Table 16.4 Summary of recommendations of the American Society of Echocardiography for training in SE

	Fellows in training	Post fellowship training	Maintenance of skills
Qualifications for training	• Level 2 training + ability to interpret resting wall motion	• Level 2 training or equivalent	Not applicable
		• Current active practice of echocardiography	
Conditions for training	• Laboratory performing 40 SE studies per month	• Laboratory performing 40 SE studies per month	Not applicable
	• Supervisor with level 3 training and experience with more than 200 SE studies	• Supervisor with level 3 training and experience with more than 200 SE studies	
Number of cases recommended	• Participation in the performance of at least 50 exercise and/or pharmacologic SE studies	• Participation in the performance of at least 50 exercise and/or pharmacologic SE studies	Interpretation of 15 SE studies per month
	• Interpretation of at least 100 SE studies with supervision as above	• Interpretation of at least 100 SE studies with supervision as above	

Modified from Rodgers et al. [26]

Table 16.5 Additive skills necessary to perform, interpret, and report pharmacological SE according to the Task Force of the American College of Cardiology/American Heart Association

1. Knowledge of the advantages and disadvantages of the different agents
2. Knowledge of the pharmacokinetics and the physiological response to the different agents
3. Knowledge of the contraindications of the different agents
4. Knowledge of the side effects and complications of the different agents and how to manage them
5. Competence in cardiopulmonary resuscitation
6. Knowledge of the endpoints of pharmacological stress and indications for terminating the test

Modified from Ryan et al. [27]

The competence levels and the training requirements for SE proposed in 2020 by the European Association of Cardiovascular Imaging [39] are summarized in Table 16.7.

The levels of independence in performing and interpreting diagnostic techniques, including echocardiography have been recently redefined by the European Society of Cardiology as "Entrustable Professional Activities" (EPA) levels (five levels). American Society of Echocardiography, on the other hand, recognizes three levels of competence, while the European Association of Cardiovascular Imaging recommends two levels of expertise for training in echocardiography: basic and advanced (Table 16.8).

Table 16.6 Summary of the European Association of Cardiovascular Imaging criteria for rating SE laboratories

Basic standard	Advanced standard
Staff	
Designated Head of SE	Head maintains CME for SE
Performing a minimum of 100 studies/year per laboratory	More than 300 studies/year per laboratory
Studies are performed by at least two people, one of whom is a clinician. At least one must have Advanced Life Support or equivalent	
Head has substantial experience with TTE and SE	
Organization/equipment	
List of indications, provision of information to the patient, and written informed consent	A machine capable of changing mechanical index and having a full digital SE package
ECG and blood pressure monitoring capabilities	Audit of results against angiography or other independent standards
Established appropriate protocols	Advanced software dedicated to contrast imaging
Machine with second-harmonic imaging and Tissue Doppler Imaging software	Capacity for both pharmacological and exercise stress
Resuscitation facilities are readily available and record of complications	Additional quantification packages should be available
Lockable drug cupboard	Standard operating procedures should be available
Contrast agent for LV opacification available	A history of training junior doctors
Provisions for continuing educational activities	

Modified from Popescu et al. [28]. *CME* continuing medical education, *LV* left ventricle, *TTE* transthoracic echocardiography

Table 16.7 Levels of competence and recommended procedures for SE

Level	Basic	Advanced	Maintenance
SE exams	50	100	100
Contrast SE	25	50	50
Contrast perfusion	50	100	100

Table 16.8 Competence levels

ESC EPA levels	ASE levels	EACVI levels
1. Observe	Level I	Basic
2. Direct Supervision	Level II	
3. Indirect Supervision		
4. Distance Supervision	Level III	Advanced
5. No Supervision		

The basic level corresponds to the European Society of Cardiology Core Curriculum requirements for general training for cardiologists. The advanced training level is appropriate for cardiologists with a subspecialty in echocardiography and a special interest in SE. The maintenance level is the minimum number of examinations independently performed per year to maintain competence [39]. As

already stated in the 2014 recommendations [28], the 2020 update reaffirms that "*if a study is performed by a sonographer-technician, a physician with expertise in both echocardiography and resuscitation should always be attending in case a life-threatening complication occurs*" [39]. This is probably the most important and mandatory recommendation to enhance the safety of SE activity.

Acquisition and maintenance of competence can be more demanding for SE applications beyond coronary artery disease since there are multiple targets, different approaches, and a variety of different parameters. The minimal procedural volume for level III echo competencies identified by the American Society of Echocardiography is 200 SE studies per year, of which 25 with noncoronary indications [40].

For physicians who use contrast agents in SE studies, a minimum of 50 examinations under the supervision of a level III reader trained in contrast imaging, in a high-volume laboratory, and ideally with angiographic verification of the results are recommended. For perfusion studies, 100 supervised examinations in a high-volume center are recommended. Level III competency in contrast echocardiography requires extensive experience in resting and stress contrast echocardiography, as well as awareness of different imaging protocols, pitfalls, artifacts, and certain machine settings to improve image quality [39, 41].

Although not part of every echocardiographic study, deformation imaging plays an increasing role in modern cardiology. Global longitudinal strain by speckle tracking echocardiography is the most robust deformation parameter, detecting alterations in global, and regional myocardial function. Proper training under expert supervision can improve the concordance and precision of global longitudinal strain measurements. Other applications of deformation imaging (e.g., right ventricular and left atrial function) are less well standardized and more seldom applied in daily practice. Independent performance of the spectrum of these techniques requires level III training under the supervision of an expert in a laboratory in which these procedures are performed daily [39, 42].

For the new steps of the ABCDE protocol, training is virtually zero for imaging-independent heart rate measured automatically from one-lead electrocardiogram present in the echo monitor and minimal for B-lines [43]. Left ventricular volumes can be measured automatically, in a highly reproducible and operator-independent way, with artificial intelligence and this will further decrease the training burden for volumetric SE [44]. A significant hurdle remains for coronary flow imaging in the left anterior descending artery require broadband frequency or high-frequency cardiac transducers, optimal vendor-specific settings, and a learning curve of about 100 cases, with the need for contrast to visualize flow in <5% of cases [45]. Imaging of coronary flow is more technically demanding in the right coronary and left circumflex than in the left anterior descending artery, in obese than in lean patients, in women than in men, in high heart rate conditions above 80 beats per minute, with exercise compared to pharmacological stress, and with dobutamine compared to vasodilators.

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Part III

The Stresses: How, When, and Why

Exercise Echocardiography

17

Luc A. Piérard and Eugenio Picano

Keywords

Exercise · Ischemia · Semi-supine bike · Viability · Treadmill · Valvular heart disease

17.1 Historical Background

For the diagnosis of organic coronary artery disease, exercise remains the fundamental stress test and the first which was combined with stress echocardiography (SE). In the early 1970s, M-mode echocardiography of the left ventricle was used in normal subjects [1] and patients with coronary artery disease [2]. Subsequently, two-dimensional echocardiography was employed to document ischemic regional wall motion abnormality during exercise [3]. The technique was at that time so challenging, that many laboratories used pharmacological stress even in patients who were able to exercise. Exercise echocardiography was only really applied as a clinical tool in the early 1990s [4] and it is now increasingly used for the diagnosis of

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L. A. Piérard (✉)
Medicine, University of Liège, Walloon Region, Belgium
e-mail: lpierard@chu.ulg.ac.be; lpierard@uliege.be

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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coronary artery disease, the functional assessment of intermediate stenosis, and risk stratification. A series of successive improvements led to a progressively widespread acceptance: digital echocardiographic techniques, allowing capture and synchronized display of the same view at different stages [5], improved endocardial border detection by harmonic imaging [6], and ultrasound-enhancing agents [7]. In the United States, the Bruce protocol with the treadmill is used by 70% of centers [8], and therefore, most SE laboratories use the post-treadmill approach with imaging at rest and as soon as possible during the recovery period. Peak treadmill imaging is however feasible, in expert hands, and improves the diagnostic accuracy of postexercise imaging [9]. In Europe, bicycle exercise is frequently used, and several centers have implemented their SE laboratory with a dedicated bed or table allowing bicycle exercise in a semi-supine position and real-time continuous imaging throughout the exercise [10]. The diffusion of semi-supine exercise imaging—much more user-friendly for the sonographer than the treadmill test—made image acquisition easier and interpretation faster. Semi-supine exercise gained its well-deserved role in the SE laboratory for coronary artery disease diagnosis and, with growing frequency outside coronary artery disease, in the assessment of pulmonary hypertension, valve disease, cardiomyopathy, and heart failure [11].

17.2 Pathophysiology

Exercise protocols are variable and include treadmill tests as well as upright and supine bicycle ergometry. All these forms of stress increase myocardial oxygen consumption and induce ischemia in the presence of a fixed reduction in coronary flow reserve [12]. The mechanism of exercise-induced ischemia can be easily fitted into the familiar concept framework of ischemia as a supply-demand mismatch, deriving from an increase in oxygen requirements in the presence of a fixed reduction in coronary flow reserve (Fig. 17.1).

During exercise, heart rate increases two- to threefold, contractility three- to fourfold, and systolic blood pressure by 50%. Exercise is a strong chronotropic, inotropic, and hemodynamic stress and, therefore, a powerful inducer of ischemia, when exercise level is maximal in a patient with underlying coronary artery disease (Fig. 17.2).

Coronary blood flow increases three- to fourfold in normal subjects, but the reduction in diastolic time (much greater than the shortening in systolic time) limits mostly the perfusion in the subendocardial layer—whose perfusion is mainly diastolic, whereas the perfusion in the subepicardial layer is also systolic [13]. In the presence of a reduction in coronary flow reserve, the regional myocardial oxygen demand and supply mismatch determines myocardial ischemia and regional dysfunction, with reduced regional wall motion and impaired regional thickening. When exercise is terminated, myocardial oxygen demand gradually declines, although the time course of resolution of the wall motion abnormality is quite variable [14]. Some induced abnormalities may persist for several minutes, permitting their detection on postexercise imaging. However, wall motion and thickening usually recover very rapidly, and postexercise imaging can easily miss wall motion

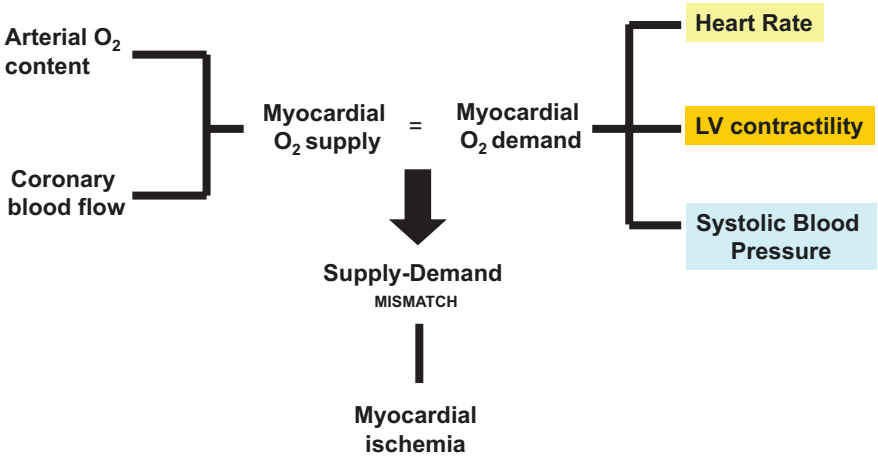

Fig. 17.1 The hemodynamic mechanism of myocardial ischemia. Myocardial ischemia develops when there is a mismatch between myocardial oxygen supply and demand. The main determinants of myocardial oxygen demand are heart rate, systolic blood pressure, and the contractile state of the myocardium. (From Picano [12])

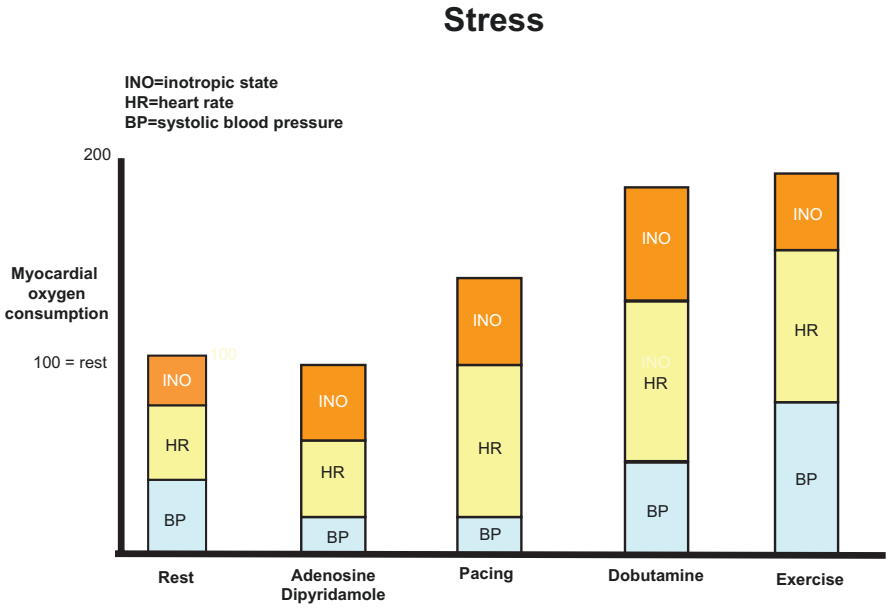

Fig. 17.2 Determinants of the increase in myocardial oxygen consumption during stress. Exercise determines a more pronounced increase in myocardial oxygen consumption compared to pacing or dobutamine. The increase is mild with vasodilators which however achieve the same ischemic strength through a different mechanism of inappropriate coronary arteriolar vasodilation. (From Picano [12])

Table 17.1 Exercise versus pharmacological stress

Parameter	Exercise	Pharmacological
Intravenous line required	No	Yes
Diagnostic utility of blood pressure response	Yes	No
Use in deconditioned patients	No	Yes
Use in physically limited patients	No	Yes
Level of echocardiography imaging difficulty	Higher	Lower
Safety profile	High	Moderate
Clinical role in valvular disease	Yes	Limited
Clinical role in pulmonary hypertension	Yes	No
Fatigue and dyspnea evaluation	Yes	No

abnormalities. Regional and global functions, although linked, may behave differently during stress. For example, if a small wall motion abnormality develops because of limited ischemia, the remainder of the left ventricle may become hyperdynamic, and the ejection fraction can increase despite the presence of an ischemic wall motion abnormality. In such a case, a regional abnormality will be present in the absence of global dysfunction. Alternatively, severe exercise-induced hypertension in the absence of coronary artery disease may lead to an abnormal ejection fraction response without an associated regional wall motion abnormality. There are distinct advantages and disadvantages to exercise versus pharmacological stress (Table 17.1).

The most important advantages of exercise are that it is familiar to both patient and doctor; it adds echocardiographic information on top of well-established and validated electrocardiographic and hemodynamic information, and it is the safest stress procedure. The disadvantages are the limited ability to perform physical exercise in many individuals, who are either generally deconditioned or physically impeded by neurologic or orthopedic limitations. In addition, SE during physical exercise is more technically demanding than pharmacologic stress because of its greater difficulty and tighter time pressure [15].

17.3 Exercise Techniques

As a rule, any patient capable of physical exercise should be tested with an exercise modality, as this preserves the integrity of the electrocardiogram response and provides valuable information regarding functional status. Performing echocardiography at the time of physical stress also allows links to be drawn among symptoms, cardiovascular workload, and wall motion abnormalities. Exercise echocardiography can be performed using either a treadmill or bicycle protocol, with modest differences in hemodynamic response (Table 17.2).

The treadmill is performed with the patient upright. Bicycle exercise echocardiography is done with the patient either upright or recumbent (Fig. 17.3).

Treadmill exercise is usually performed following a standardized Bruce protocol (Table 17.3).

Table 17.2 Exercise methods

Parameter	Treadmill	Upright bicycle	Supine bicycle
Ease of study for patients	Moderate	High	High
Difficulty for sonographer	High	Moderate	Low
Stage of onset of ischemia	No	Yes	Yes
Peak rate pressure product	High	High	High
Systolic blood pressure	Lower	Higher	Higher
Heart rate	Higher	Lower	Lower
Induction of spasm	Higher	Lower	Lower
EDV normal response	Increase	Increase	Increase
ESV normal response	Decrease	Decrease	Decrease
PCWP	Increase	Increase	Larger increase
Preferred modality in	USA	Europe	SE lab

EDV end-diastolic volume, *ESV* end-systolic volume, *PCWP* pulmonary capillary wedge pressure

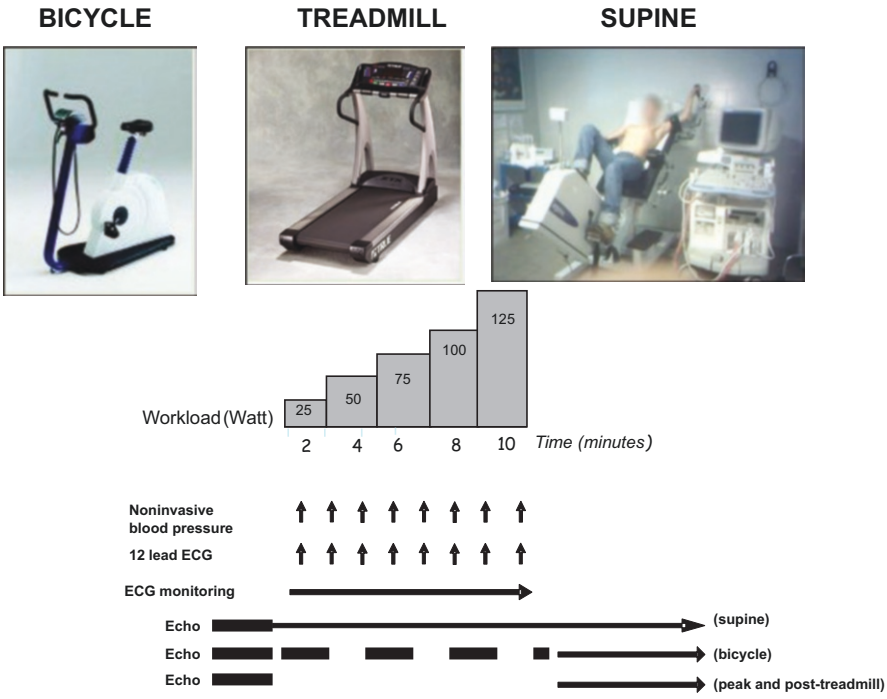

Fig. 17.3 Protocols of exercise SE: upright bicycle (*left*); treadmill (*middle*); semi-supine bicycle (*right*). Postexercise imaging is usually performed with a treadmill only, but peak treadmill imaging is also possible; at peak and postexercise upright; and during, at peak, and after exercise with semi-supine

Table 17.3 Bruce protocol for treadmill exercise

Stage	Grade (%)	Speed (%)	Time (min)	METS[a]
1	10	1.7	3	5
2	12	2.5	6	7
3	14	3.4	9	10
4	16	4.2	12	13
5	18	5.0	15	15
6	20	5.5	18	18
7	22	6.0	21	20

[a] *METS* metabolic equivalents, One MET = 3.5 mL O_2/kg/min

Table 17.4 Commonly used supine bicycle exercise protocol

Stage	Watts	Time (min)	METS
1	25	2	2.4
2	50	4	3.7
3	75	6	4.9
4	100	8	6.1
5	125	10	7.3
6	150	12	8.6
7	175	14	9.8
8	200	16	11.0
9	225	18	12.2
10	250	20	13.5

When treadmill exercise is performed, scanning during exercise is difficult, and therefore most protocols rely on postexercise imaging. It is imperative to complete postexercise imaging as soon as possible. To accomplish this, the patient is moved immediately from the treadmill to an imaging table and placed in the left lateral decubitus position so that imaging may be completed within 1–2 min. This technique assumes that regional wall motion abnormalities will persist long enough to be detected in the recovery phase. When abnormalities recover rapidly, false-negative results occur. The advantages of treadmill exercise echocardiography are the widespread availability of the treadmill system and the wealth of clinical experience that has accumulated with this form of stress testing. Information on exercise capacity, heart rate response, rhythm, and blood pressure changes are analyzed and, together with wall motion analysis, become part of the final interpretation.

With bike exercise, the patient pedals against an increasing workload at a constant cadence (usually 60 rpm). The workload is escalated in a stepwise fashion while imaging is performed (Table 17.4). Successful bicycle stress testing requires the patient's cooperation (to maintain the correct cadence) and coordination (to perform the pedaling action).

The most important advantage of bicycle exercise is the possibility to obtain images during the various levels of exercise (rather than relying on postexercise imaging). With the patient in the supine position, it is relatively easy to record images from multiple views during graded exercise. With the development of

ergometers that permit leftward tilting of the patient, the ease of image acquisition has been further improved. In the upright posture, imaging is generally limited to either apical or subcostal views. By leaning the patient forward over the handlebars and extending the arms, apical images can be obtained in most cases. To record subcostal views, a more lordotic position is necessary and care must be taken to avoid foreshortening of the apex. When considering the various forms of exercise, it is important to appreciate fundamental differences. For most patients, both duration of exercise and maximum achieved heart rate are slightly lower in the supine position [16, 17], due primarily to the development of leg fatigue at an earlier stage of exercise. The limitation is overcome in part by the occurrence of ischemia at a lower workload with supine exercise. The earlier development of ischemia is the result of both a higher end-diastolic volume and higher mean arterial blood pressure for a given level of stress in the supine position [18]. Semi-recumbent exercise increases pulmonary capillary wedge pressure more than upright exercise [19]. These differences contribute to higher wall stress and an associated increase in myocardial oxygen demand compared with an upright bicycle. Coronary spasms are provoked more frequently during treadmill tests than during bicycle exercise [20].

The typical abnormal response pattern for regional wall motion abnormality is shown in Fig. 17.4.

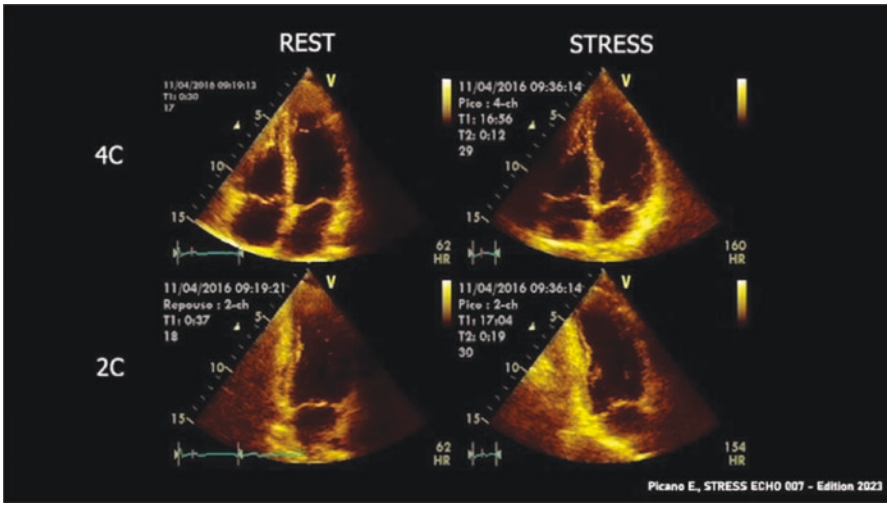

Fig. 17.4 End-systolic frames from apical four-chamber view (A4C, upper panels) and apical two-chamber view (A2C, lower panels) showing normal wall thickening at rest (left panels) and akinesia involving the lateral and apical walls, and mid-inferior and inferior apical segments, at peak treadmill test (right panel). See accompanying Video 17.1. (Video images courtesy of Jesus Peteiro, MD, Valencia, Spain. The video is available under the chapter's "Supplementary Material" on Springer Link)

17.4 Safety and Feasibility

The safety of exercise stress is witnessed by decades of experience with electrocardiography testing and stress imaging. In exercise echocardiography registries collecting over 85,000 studies, exercise echocardiography was the safest SE test [21–23]. Death occurs on average in 1 in 10,000 tests. Major life-threatening effects (including myocardial infarction, ventricular fibrillation, sustained ventricular tachycardia, and stroke) were reported in about 1 in 1000 patients with exercise in the international SE registry—twofold less than with dipyridamole echocardiography, and threefold less than with dobutamine echocardiography (Fig. 17.5).

Nevertheless, complications occur also during exercise, and it is important to be ready, with all the necessary drugs and equipment at hand in the laboratory. An example of a complication is shown in Fig. 17.6, with a cardiac tamponade for cardiac rupture, treated with echo-guided pericardiocentesis and cardiac surgery [24].

The feasibility of obtaining interpretable studies of good quality—relatively unchanged versus baseline images—is sufficient with post-treadmill, good for upright, and almost excellent with semi-supine testing which should be the test of choice for exercise SE. From the perspective of the SE laboratory, there is evidence that semi-supine exercise is easier, more feasible, and more informative than the other forms of exercise stress. It is also undisputed that semi-supine exercise is more technically demanding than dobutamine and much more technically demanding than vasodilator stress.

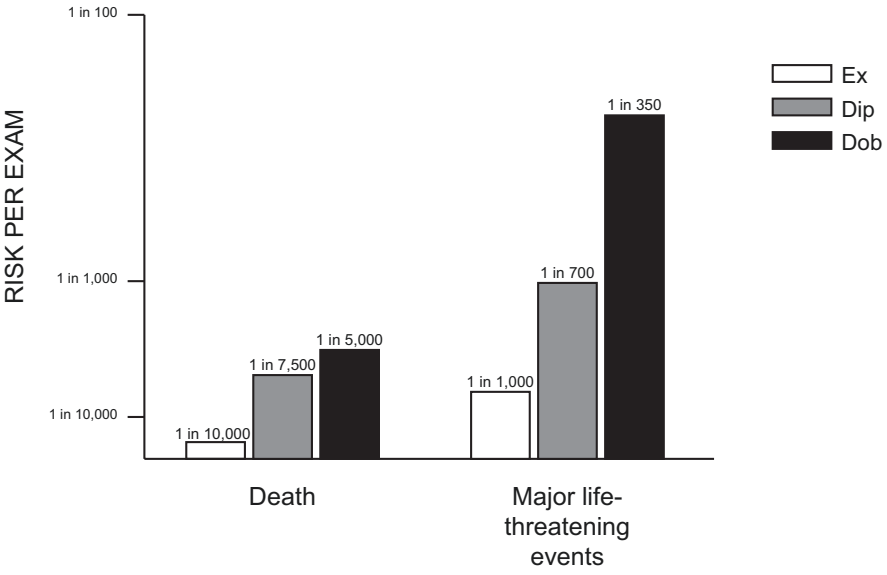

Fig. 17.5 Safety of SE: highest for exercise, intermediate for dipyridamole, lowest for dobutamine stress. (Original data from [21–23], summarized in [11])

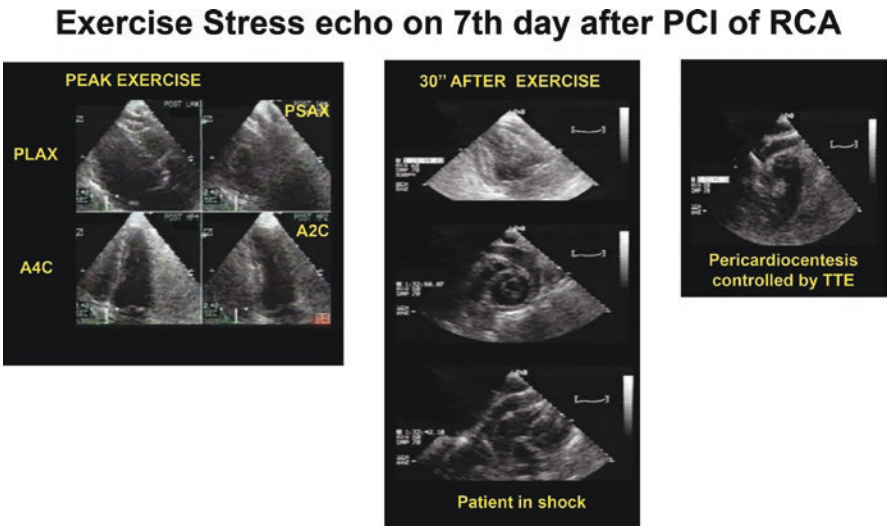

Fig. 17.6 Exercise SE in a patient with recent inferior myocardial infarction. The patient shows a pericardial effusion and syncope 30 s after the cessation of exercise. Echo-guided pericardiocentesis was performed. The patient was submitted to surgery at another Hospital with success. The patient died 12 years later of cancer. The availability of resuscitation know-how and facilities made all the difference [24], see accompanying Video 17.2. (Video images courtesy of Dr. Carlos Cotrim, from Lisbon, Portugal)

17.5 Diagnostic Results for Detection of Coronary Artery Disease and Myocardial Viability

For the detection of angiographically significant coronary artery disease repeatedly assessed in a series of continuously updated meta-analyses [25–29], the overall sensitivity and specificity of exercise echocardiography have been reported to be 83% and 85%, respectively, according to the most updated meta-analysis of 55 studies with 3714 patients [29]. The diagnostic sensitivity is lowered in populations studied on beta-blockers, masking the ischemic effect of exercise, and these drugs should be discontinued to optimize the sensitivity of exercise echocardiography.

The specificity of exercise echocardiography is like dobutamine echocardiography, lower than dipyridamole echocardiography, and higher for all forms of SE compared to stress single-photon emission computed tomography [29]. The diagnostic accuracy is like other forms of stress imaging (dobutamine or dipyridamole SE or stress scintigraphy). Although the available information is only limited, exercise echocardiography can also be useful for detecting myocardial viability. Endogenous catecholamines produced during a low-level exercise test can also serve as a myocardial stressor to elicit contractile reserve in viable myocardium, with an accuracy comparable to low-dose dobutamine echocardiography [30]. A maximum exercise test can also identify a biphasic response suggesting the presence of viable myocardium in jeopardy [31].

17.6 Prognostic Value

The presence, location, extent, and severity of exercise-induced wall motion abnormalities have a proven prognostic impact, as shown by over 20 studies on 5000 patients—ranging from patients with normal or abnormal baseline function [32–34] to women [35, 36] to patients evaluated early after an acute myocardial infarction [37, 38], after a coronary angioplasty [39], or in hypertensive subjects [40]. The prognostic value of exercise SE is high, comparable to other forms of pharmacological (dobutamine or dipyridamole) SE and stress scintigraphy [41].

Among patients who have a normal exercise echocardiogram, the prognosis is favorable, and the coronary event rate is quite low. An abnormal SE, defined as a new or worsening wall motion abnormality, substantially increases the likelihood of a coronary event during the follow-up period. This finding, coupled with the presence or absence of resting left ventricular dysfunction and the exercise capacity of the patient provides a great deal of prognostic information on the individual patient. The prognostic value is incremental over clinical and electrocardiographic variables [41].

Other markers, beyond regional wall motion, can further stratify the prognosis during exercise echocardiography. In patients with a positive test result, the prognosis is more malignant, and in patients with a negative test result, the prognosis is less benign, with exercise-induced left ventricular cavity dilation or severe mitral regurgitation. Their greatest clinical value is outside coronary artery disease, in patients with heart failure [42] or valvular heart disease [43, 44]. Patients with negative SE by regional wall motion criteria can still have an abnormal response if global indices of the cardiac reserve are used, beyond the load-dependent ejection fraction. These indices can be a force (systolic blood pressure/end-systolic volume), stroke index, or cardiac power (a measure of cardiac performance that incorporates both pressure and flow components) reserve [45–48]. With each of these indices, patients with negative exercise SE can show a heterogeneous risk, higher when the global left ventricular cardiac or contractile reserve is reduced. This is plausible since regional wall motion abnormalities mostly sense subendocardial ischemia. A more limited sub-endocardial impairment, or scar, necrosis, and subepicardial involvement may affect intramyocardial and intracavitary pressure development and volume reduction without affecting regional wall motion [49, 50]. The sub-endocardial layer mainly generates systolic thickening and intracavitary pressure, and the subepicardial layer mainly generates lower volumes for any given pressure with an acute antiremodeling effect during stress. Indices of global reserve such as ejection fraction, global longitudinal strain, force, cardiac power, or stroke index can be more sensitive than regional wall motion abnormalities in detecting a global disease of the left ventricle, and therefore their information is prognostically independent, and incremental over regional wall motion abnormalities both in and beyond coronary artery disease.

17.7 Exercise Echocardiography Outside Coronary Artery Disease

The baseline transthoracic echocardiogram performed at the time of SE permits recognition of many causes of cardiac symptoms in addition to ischemic heart disease, including dilated cardiomyopathy or hypertrophic cardiomyopathy, pulmonary hypertension, and valvular heart disease. As with coronary artery disease, also in these diseases, the application of exercise stress under controlled conditions can unmask structural defects which—although occult in the resting or static state—may occur under real-life loading conditions, and lead to dysfunction detected by echocardiography.

Nowadays, in the SE laboratory, we can assess a variety of parameters beyond left ventricular function: valvular gradients and regurgitant flows; left and right heart hemodynamics including pulmonary artery systolic pressure, ventricular volumes, and extravascular lung water. From a practical viewpoint, it is not feasible to do everything for all patients since there is little time during stress and there are so many things to see. Therefore, the variables of potential diagnostic interest should be strategically tailored and prioritized to the individual patient based on the perceived incremental value of each. Exercise is the test of choice for most applications [51].

17.8 Pitfalls

There are contraindications to exercise echocardiography, such as the classical contraindications to exercise stress, including unstable hemodynamic conditions or severe, uncontrolled hypertension. Additional relative contraindications to exercise stress are the inability to exercise adequately, and—specifically for exercise echocardiography—a difficult resting echocardiogram. These conditions are not infrequent, especially in an elderly population, since out of five patients referred for testing, one is unable to exercise, one is capable to exercise sub-maximally, and one has an interpretable but challenging echocardiogram, which makes pharmacological SE a more practical option. Difficult echocardiograms can often be salvaged by ultrasound-enhancing agents for border enhancement of unreadable left ventricular segments at baseline and during stress. For risk stratification purposes, the negative predictive value of a negative exercise echo is lowered in presence of a submaximal exercise [52]. Even with maximal exercise, the negative predictive value is suboptimal in contemporary patient populations often studied under antiischemic therapy [53], and it can be enhanced by adding the evaluation of several other prognostic vulnerabilities of the patient beyond ischemia. The exercise test is suitable for the comprehensive ABCDE SE protocol, allowing the assessment of inducible ischemia (step A), pulmonary congestion (step B), contractile reserve (step C), Doppler-based coronary flow velocity reserve (step D), and heart rate reserve (step E) in one test, each step showing independent and incremental prognostic value [54]. The feasibility of step D is good with semi-supine exercise, but lower than with

pharmacological stress, and some centers prefer to adopt the standard exercise approach (with ABC and E steps) and to add the assessment of coronary flow velocity reserve with an intravenous adenosine test at the end of the recovery phase of exercise with a two-stress approach [55].

Outside coronary artery disease, the versatility of exercise SE is limited in assessing *E*/*e′* as a proxy of left ventricular end-diastolic pressure and tricuspid regurgitant jet velocity to estimate pulmonary artery systolic pressure. *E*/*e′* signal is often lost for wave fusion during tachycardia and should be measured before (at intermediate stages) or after (in the recovery phase) the fusion of E and A waves. The success rate of adequate imaging of tricuspid regurgitant jet velocity is reduced at a high workload. However, B-lines are related to pulmonary capillary wedge pressure and systolic pulmonary artery pressure variations during stress [56]. B-lines can be detected by lung ultrasound and their technical success rate is high at baseline and peak stress in patients with chronic coronary syndromes [57, 58], but also heart failure with preserved ejection fraction [59], valvular heart disease [59–61], hypertrophic cardiomyopathy [62], secondary ischemic mitral regurgitation [63]. Stress B-lines show a marked prognostic value, independent and incremental over conventional parameters such as regional wall motion abnormality or peak ejection fraction and therefore they can usefully complement standard transthoracic echocardiography for the assessment of pulmonary congestion during exercise SE.

17.9 Clinical Guidelines

Exercise is the only physiologic stressor. In patients with chest pain or dyspnea as the presenting symptom, exercise-echo is appropriate as a first-line test, since it combines the advantages of nonimaging exercise testing (exercise tolerance, symptoms, arrhythmias, blood pressure, and heart rate response) with the benefits of cardiac functional testing (ischemia, viability, integration with cardiac function and valvular function) [64]. If a patient can exercise, this is the preferred stress modality [64–66] (Table 17.5). The warranty period after a normal, maximal test is 1 year [66].

A unique advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and tremendously versatile evaluation of valve function, pulmonary hemodynamics, diastolic and systolic function, right ventricle, and intraventricular gradients (Table 17.6). In all these patients, the physiologic nature of exercise stress and the versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the SE laboratory [67].

Left ventricular contractile reserve and pulmonary pressure are important in almost all conditions, while some parameters are more specific for certain conditions, such as *E*/*e′* in heart failure with preserved ejection fraction or intraventricular gradients in hypertrophic cardiomyopathy. For applications outside coronary artery disease, the key point is that "*a variety of parameters may be assessed: ventricular function, valvular gradients, regurgitant flows, left and right heart hemodynamics including pulmonary artery systolic pressure, and ventricular volumes. As it is not*

Table 17.5 Applications of exercise SE in known or suspected coronary artery disease

Indication	CoR	LoE	Source
Assessment of symptoms, arrhythmias, blood pressure, heart rate	1	C	ESC 2019
Symptomatic patients to exclude coronary artery disease	1	B	ESC 2019
CTA has shown CAD of uncertain functional significance	1	B	ESC 2019
If a pt can exercise, this is the preferred stress modality	1	A	ASE 2020
Intermediate-to-high pretest probability (preserved or reduced EF)	1	A	ASE 2020
Resting ECG abnormality, LBBB, women	1	B	ASE 2020
Dyspnea as the presenting symptom	1	B	ASE 2020
New symptoms after CABG or PCI	2a	B	ASE 2020
Asymptomatic with diabetes, PVD, coronary calcium score >400	2b	B	ASE 2020
Intermediate-risk pts with acute chest pain and no known CAD	1	B	ACC 2021
Intermediate-risk pts with known CAD and new/worsening symptoms	2a	B	ACC 2021

ACC American College of Cardiology/American Heart Association [66], *ASE* American Society of Echocardiography [65], *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *COR* class of recommendation, *CTA* computed tomography angiography, *ESC* European Society of Cardiology [64], *LBBB* left bundle branch block, *LOE* level of evidence, *PCI* percutaneous coronary intervention, *PVD* peripheral vascular disease, *pt* patient

Table 17.6 Applications of exercise SE beyond coronary artery disease

Heart failure with a depressed ejection fraction	LV function, MR, TRV, TAPSE, B-lines
Heart failure with a preserved ejection fraction	*E*/*e′*, MR, LVOTG, TRV, GLS, B-lines
Valvular heart disease	LV function, MR, Valve gradients, B-lines
Congenital heart disease	TRV, TAPSE, LV function, B-lines
Hypertrophic cardiomyopathy	LV function, LVOTG, MR, B-lines
Athletes and extreme physiology	LVOTG, MR, TRV, TAPSE, B-lines
Pulmonary hypertension	TRV, TAPSE, B-lines

From Lancellotti et al. [67]
GLS global longitudinal strain, *LV* left ventricle, *LVOTG* left ventricular outflow tract gradient, *MR* mitral regurgitation, *TAPSE* tricuspid annulus systolic anterior excursion, *TRV* tricuspid regurgitant velocity jet

feasible to assess all possible parameters during stress, the variables of potential diagnostic interest should be prioritized for the individual patient based on the perceived importance of each. Physiology determines the choice of stress and the key echocardiographic variables of interest. Exercise is the test of choice for most applications. Bicycle ergometer stress testing is optimal for obtaining Doppler data during exercise, but patient endurance is generally less than with treadmill exercise unless the patient has trained cycling muscles." [67]. The prospective, large-scale, international validation of the protocol ABCDE as the new standard for exercise SE in chronic coronary syndromes and beyond coronary artery disease is currently in progress in the SE 2030 study, which aims to recruit in 5 years (2021–2025) ≥10,000 patients, allowing to build the platform of evidence required for changing the standard of practice [68].

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Dobutamine Stress Echocardiography

18

Ana Cristina Camarozano and Eugenio Picano

Keywords

Beta-receptors · Heart rate · Myocardial contractility · Safety · Viability

18.1 Historical Background

Dobutamine infusion is suitable pharmacological stress to induce regional wall motion abnormalities in presence of critical coronary artery stenosis, as shown by experimental studies at the beginning of the clinical applications of pharmacological stress echo (SE) in 1987 [1]. All major general cardiology guidelines recommend exercise SE over pharmacological SE since exercise provides a simultaneous physiologic assessment of functional capacity and symptom onset. However, many patients are unable to exercise on a treadmill or a bicycle due to rheumatologic, orthopedic, pulmonary, or neurological problems. For these patients, pharmacologic stress should be pursued [2].

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A. C. Camarozano (✉)
Medicine Department, Hospital de Clinicas UFPR, Federal University of Paraná, Curitiba, Brazil

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Dobutamine stress echocardiogram (DSE), like exercise and dipyridamole echo, has found its primary application in ischemic heart disease. Dobutamine is the prototype of pharmacological adrenergic and inotropic stress. It was initially proposed for the diagnosis of coronary artery disease in combination with perfusion imaging [3] and later with two-dimensional echocardiography by the Liège group of Luc Pierard [4]. Performing SE with a pharmacologic agent like dobutamine allows simulation of heart rate and increases myocardial oxygen demands like exercise echocardiography. Other sympathomimetic agents have been proposed for SE, including isoproterenol [5] and epinephrine [6], but these drugs often bring more pronounced side effects. The evolution of dobutamine stress paralleled that of other pharmacological stresses. With echocardiography, it began at relatively "low" doses (20 μg/kg/min), which gave low sensitivity values; later, more aggressive doses were adopted (up to 40 μg/kg/min), and finally it was coadministered with atropine [7], which overcame the limitation of moderate sensitivity to minor forms of coronary artery disease. Low-dose dobutamine is also used as a test of myocardial viability. It was the first [8] and still the most common way to assess myocardial viability using the contractile reserve.

In addition, DSE can help in the evaluation of valvular heart disease by helping to assess the effects of mitral and aortic stenosis, as well as in differentiating true-severe valvular aortic stenosis from pseudostenosis that may occur in the setting of left ventricular systolic dysfunction [9].

DSE can be performed with state-of-the-art ABCDE (Asynergy, B-lines, Contractile reserve, Doppler flow reserve, and Heart rate reserve) protocol validated in SE2020 Multicenter Study [10], with a slightly lower success rate than vasodilator stress for step D of coronary flow velocity reserve.

18.2 Pharmacology and Pathophysiology

The drugs that affect adrenergic transmission, also called catecholamines, can be endogenous (produced by the body itself) such as noradrenaline, adrenaline, and dopamine, or synthetic (produced in the laboratory) such as dobutamine. These drugs act on adrenergic receptors that are divided into alpha (1 and 2) and beta (1 and 2) [11, 12] (Table 18.1).

Dobutamine acts on adrenergic receptors, and acetylcholine (blocked by atropine) on muscarinic receptors, with a variety of different effects on myocardial cells (Fig. 18.1).

Table 18.1 Pharmacodynamics of dobutamine

	Receptor populations		
	α_1	β_1	β_2
Myocardium	Increased inotropy	Increased chronotropy Increased inotropy	–
Vasculature	Vasoconstriction	–	Vasodilation

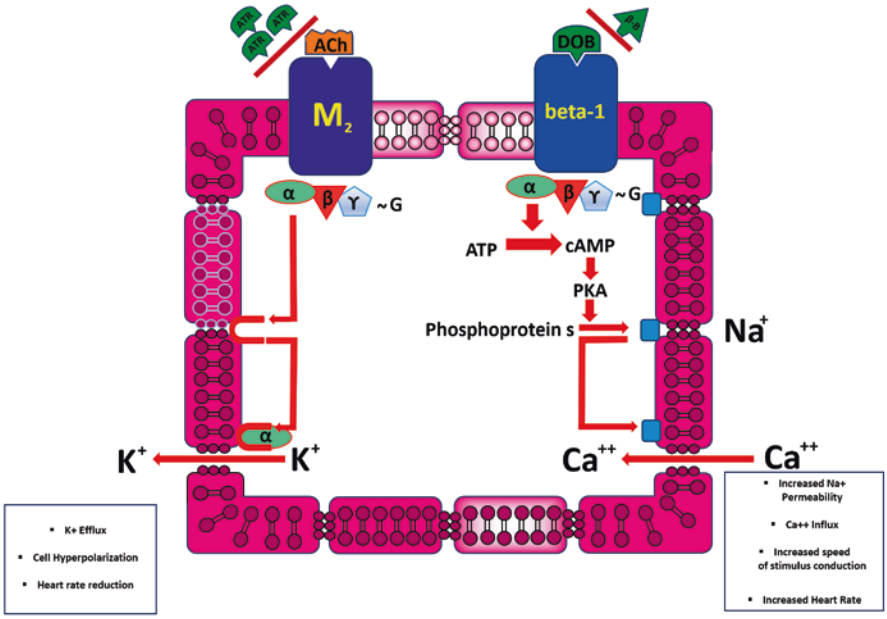

Fig. 18.1 The main cardiovascular receptor targets and physiologic effects of dobutamine, beta-blockers, atropine, and acetylcholine in the cardiac cell

Dobutamine is a synthetic catecholamine resulting from the modification of the chemical structure of isoproterenol. It acts directly and mainly on beta-1 adrenergic receptors of the myocardium, producing an increase in heart rate, enhancement of atrioventricular conduction, and increased contractility with relatively weak beta-2 and alpha-1 activity [11] (Fig. 18.2).

Its mechanism consists, through beta-1 action, of primarily increasing the force of contraction and secondarily the heart rate and blood pressure, having as a final product the increase in cardiac output and the increase in myocardial oxygen consumption (Fig. 18.3). Heart rate increases twofold, and myocardial contractility increases two- to threefold at the peak versus baseline [12].

The dobutamine dose usually employed for SE testing causes a two- to threefold increase in coronary blood flow [13]. The extent of the increase in myocardial oxygen demand is similar to exercise, and in this sense, it has been called an "exercise-simulating agent," but in many ways, it differs from exercise. During exercise, stroke volume increases also through a Frank-Starling mechanism with an increase in end-diastolic volume at intermediate stages of stress, while the end-diastolic volume decreases with dobutamine with more marked hyperkinesis [14]. Dobutamine is different from exercise stress also for other important aspects since the response to antiischemic therapy does not parallel the response to exercise [15]. For applications beyond coronary artery disease, the pattern of changes in pulmonary

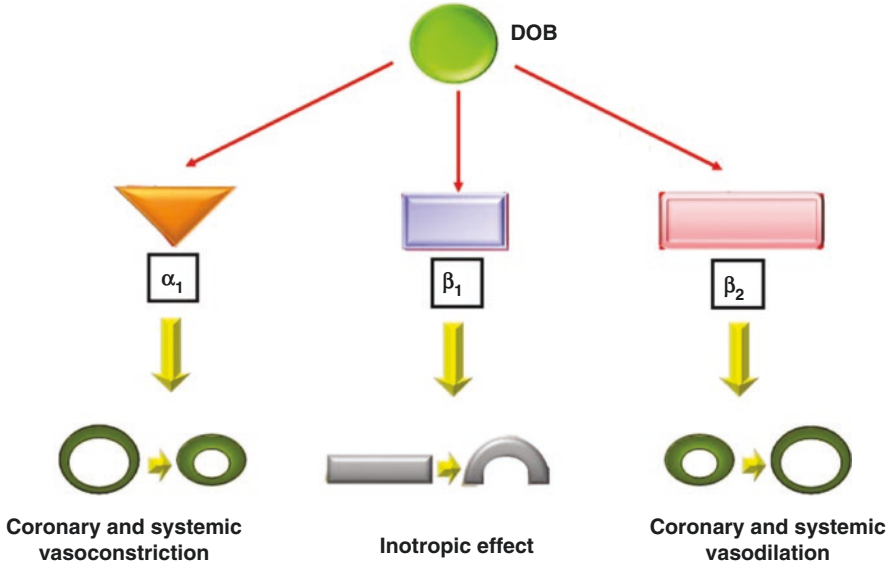

Fig. 18.2 The main cardiovascular physiologic effects of dobutamine

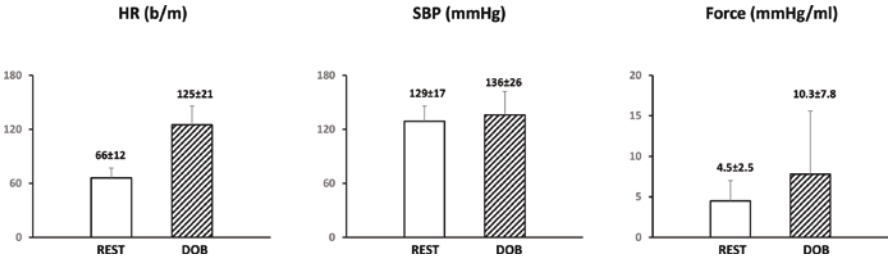

Fig. 18.3 Major determinants of myocardial oxygen consumption in resting conditions (*left*) and during peak dobutamine stress (*right*). The relative contributions of heart rate, systolic blood pressure, and force (an index of the inotropic state) are represented. During dobutamine, there is a marked increase in heart rate and inotropic state. The increase in systolic pressure is milder in populations under beta-blockers. (Redrawn and modified from Ciampi et al. [12])

hemodynamics, venous return, mitral regurgitation, and intraventricular obstruction induction is completely different from exercise and limits the applications of dobutamine stress beyond coronary artery disease.

Alpha-adrenergic activity can mediate systemic vasoconstriction, an increase in blood pressure, and increased coronary constriction up to coronary vasospasm, especially when the alpha-mediated vasoconstriction is enhanced by chronic or acute beta-blockade. Stimulation of beta-2 receptors on coronary arterioles may induce coronary arteriolar vasodilation. However, endothelial dysfunction and enhanced alpha-adrenergic tone contribute to the loss of dobutamine-induced vasodilation in coronary atherosclerosis [16]. The effect of normally increased coronary

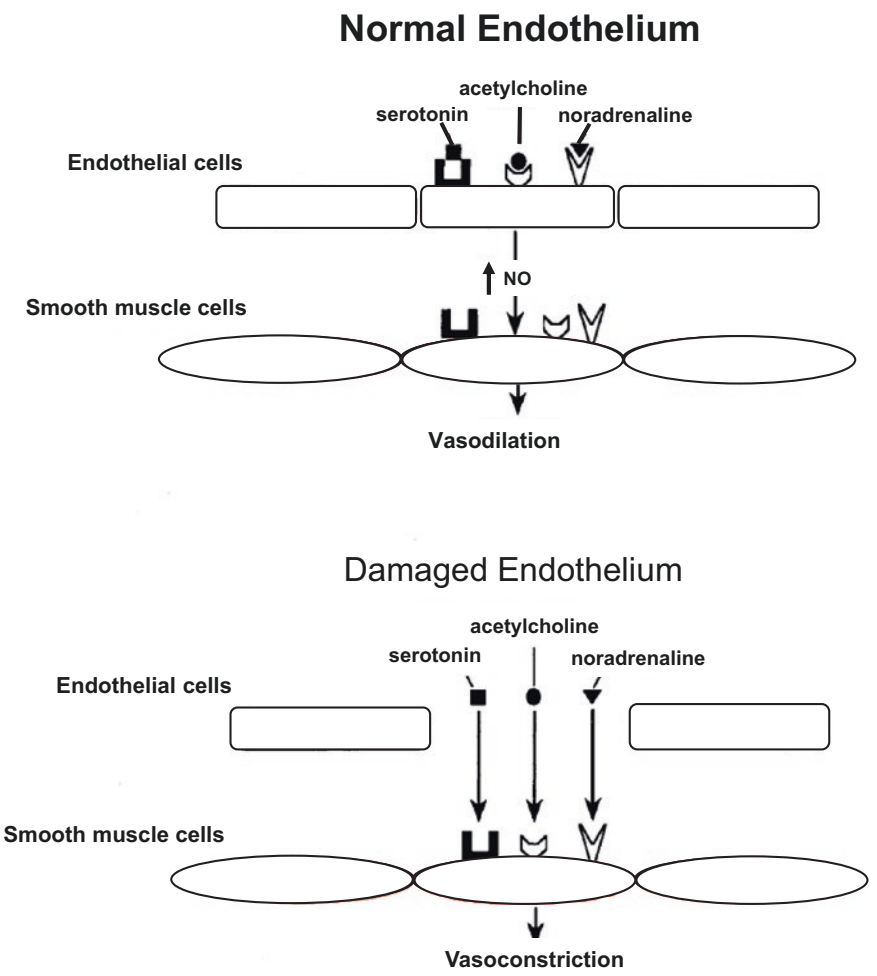

Fig. 18.4 *Top*: endothelial and smooth muscle cells in coronary vessels in the presence of intact endothelium. Mediators such as serotonin, acetylcholine, noradrenaline or exogenous dobutamine acting on noradrenaline receptors stimulate the corresponding receptors present on the endothelial surface, which induce smooth muscle cell relaxation and vasodilation via nitric oxide release. *Bottom*: when the endothelium is damaged, the same mediators act directly on the corresponding receptors present on the smooth muscle membrane, causing vasoconstriction

flow in normal vessels can become paradoxical coronary vasoconstriction in coronary vessels with abnormal, damaged endothelium (Fig. 18.4).

Dobutamine is an adrenergic agonist traditionally used in the intensive care unit for the treatment of decompensated heart failure. The onset of action of dobutamine is 1–2 min and the plasma half-life is approximately 2 min. Dobutamine is metabolized hepatically and in peripheral tissues, but there is no set dose reduction for those patients with hepatic or renal dysfunction. The short half-life of dobutamine

allows rapid resolution of its effects once the intravenous infusion is discontinued. However, the alpha-mediated coronary constrictive and platelet-aggregating effects are not reversed and may be potentiated by a beta-blocker. These undesired effects peak at 30–45 min after the end of dobutamine infusion, and therefore the patient must remain in the waiting room for at least half an hour after the test, even if the result was negative.

Dobutamine provokes ischemia mainly through the inotropic and chronotropic response to stimulation of myocardial beta-1 receptors determining temporarily an increase in myocardial oxygen demand.

Other mechanisms are the flow maldistribution mediated by beta-2 receptors of coronary arterioles and coronary vasospasm mediated by alpha-adrenoreceptors present on smooth muscle cells of epicardial arteries [16] (Fig. 18.5).

Tests inducing vasospasm (ergonovine infusion and hyperventilation) explore the functional component. Tests trying to unmask coronary stenosis (exercise, dipyridamole, adenosine, dobutamine, pacing) mostly explore the coronary reserve due to fixed, organic stenosis (Fig. 18.6). Some of these stressors (such as exercise or dobutamine) may also induce variations in coronary tone which can be superimposed on the organic factors, thus blurring the correlation between coronary anatomy and test positivity.

On top of dobutamine, atropine is usually given in refracted doses up to a cumulative dose of 1 mg, sometimes 2 mg. Atropine is a naturally occurring antimuscarinic drug consisting of an alkaloid of the belladonna plants. During the time of the Roman Empire, the plant was frequently used to produce poison. This prompted Linnaeus to name the shrub *Atropa belladonna*, after Atrops, the eldest of the Three Fates, who cuts the thread of life. The name belladonna (i.e., "beautiful woman") derives from the alleged use of this preparation by Italian women to dilate their

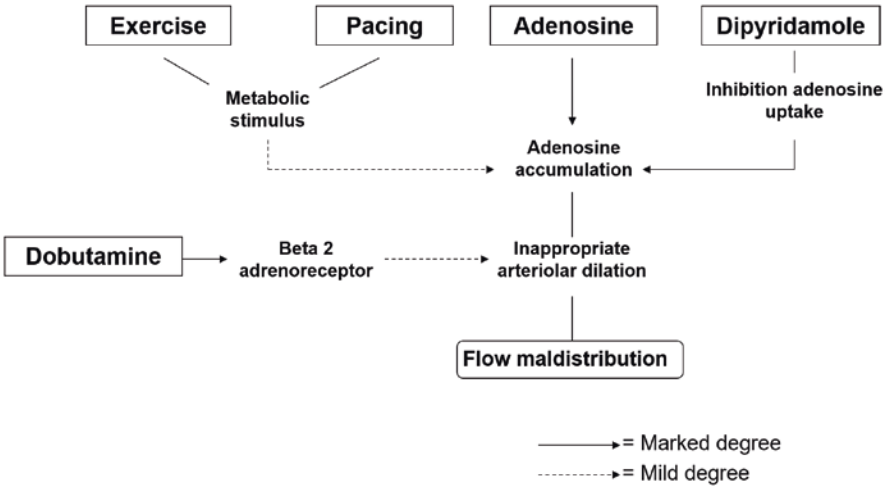

Fig. 18.5 The biochemical pathways leading to inappropriate arteriolar vasodilation under different stresses

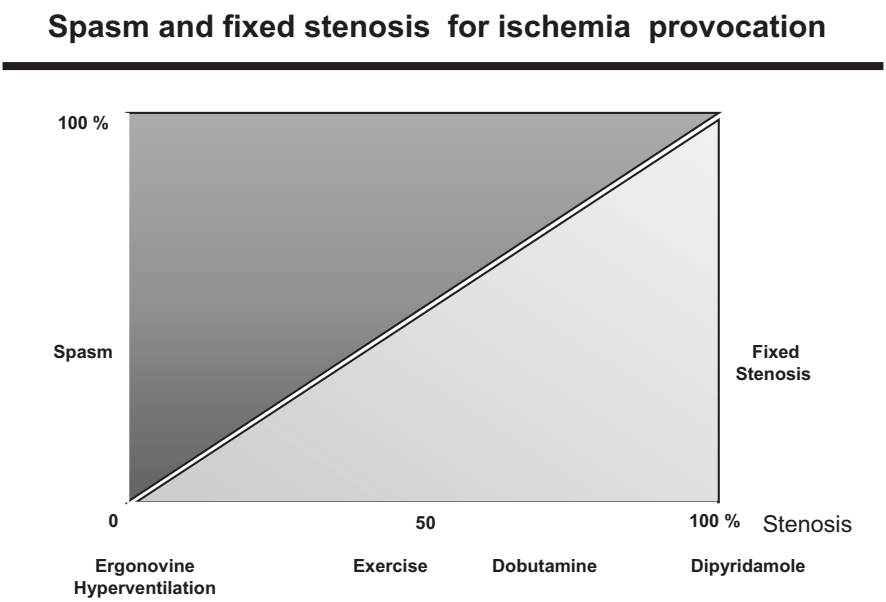

Fig. 18.6 Conceptual allocation of the tests employed in combination with echocardiography to induce ischemia via coronary vasospasm (*left*), coronary stenosis (*right*), or both mechanisms

pupils [17]. Atropine is the prototype of antimuscarinic drugs, which inhibit the actions of acetylcholine on anatomical effectors innervated by postganglionic cholinergic nerves. The main effect of atropine on the heart is to induce tachycardia by blocking vagal effects on the M2 receptors in the sinoatrial nodal pacemaker. Atropine also enhances atrioventricular conduction. Atropine-induced mydriasis may occasionally raise intraocular pressure in patients with glaucoma, which is, therefore, a contraindication to atropine administration. Atropine also decreases the normal amplitude of bladder contraction, and severe prostatic disease is thus another contraindication to atropine administration. Not surprisingly, however, the risk of resistant ischemia increases with atropine, along with nonischemic side effects. Nonischemic side effects described after DSE with atropine coadministration include atropine intoxication, consisting of restlessness, irritability, disorientation, hallucinations, or delirium, usually disappearing spontaneously over a few hours.

18.3 Methodology, Protocol, and Performance of DSE

A graded dobutamine infusion is given typically at a starting dose of 5 μg/kg/min. The goal of the dobutamine infusion is to achieve a heart rate of 85% of the maximal predicted heart rate for the patient's age. Accordingly, the dobutamine dose is increased every 3–5 min (usually 3 min) to doses of 10, 20, 30, and finally to 40 μg/kg/min.

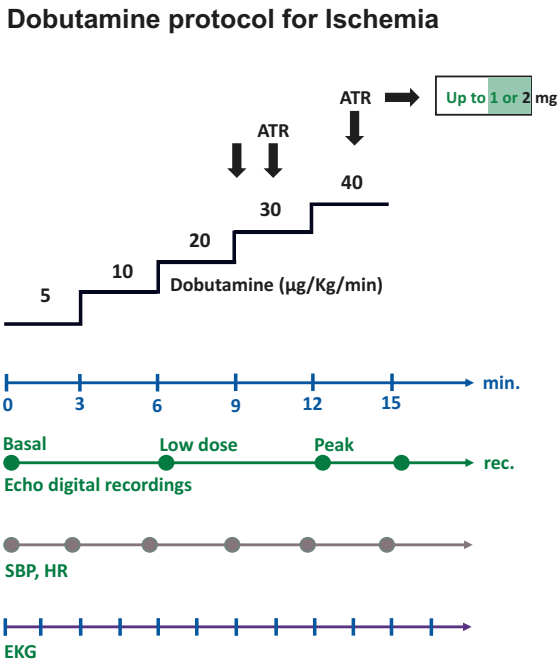

Fig. 18.7 The standard dobutamine-atropine protocol for detection of coronary artery disease and induction of ischemia

Figure 18.7 shows the most used protocol in patients with known or suspected coronary artery disease. It has been endorsed as the state-of-the-art protocol by both the European [18] and American [19] recommendations. Lower doses are associated with insufficient sensitivity, while higher doses are associated with a high rate of side effects [20].

In the standard protocol, the addition of atropine demonstrated great value at the end of this protocol, but if administered early in the test is faster, with a decrease in the number of inconclusive tests with a similar rate of adverse effects [21–23].

In DSE, the images can be obtained in the parasternal (or apical) long axis, parasternal short axis (mid ventricle), and apical four- and two-chamber views. During a DSE, images of the left ventricle from each projection are obtained during rest, low-dose dobutamine, peak-dose dobutamine, and poststress (at the same plane and the same depth). When the heart rate is lower than 100 beats or close to baseline levels, the acquisition of images corresponding to the recovery phase is suitable. In addition, metoprolol or short-acting esmolol can be used to antagonize the effects of dobutamine. Esmolol is administered 500 µg/kg IV followed by 250 µg/kg every 5 min until symptoms are relieved, or to a maximum of 1000 µg/kg. Another possibility is to administer metoprolol 5 mg intravenous push over 2 min and repeat every 5 min up to a total of three doses.

For viability assessment, the protocol is a little different by searching for the "biphasic response" where a myocardial territory with resting severe hypokinesia or akinesia augments its contraction at a low dose but later becomes hypokinetic or

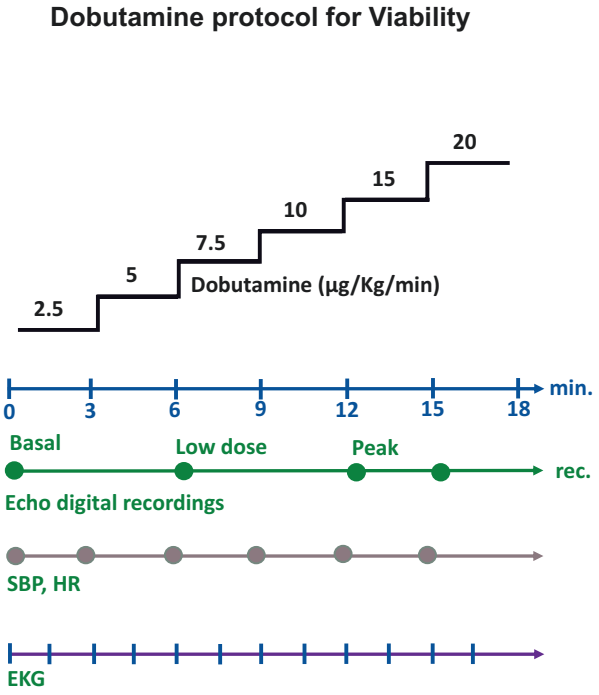

Fig. 18.8 The dobutamine protocol for myocardial viability analysis

akinetic at higher dobutamine doses. Steps of 5 min can be used starting from 5 up to 20 μg [20]. The worsening phase of the biphasic response usually occurs with doses ≥20 μg/kg/min (Fig. 18.8) [20]. If the aim is viability and ischemia assessment, after 20 μg/kg/min without myocardial ischemia demonstrated, the protocols can continue with the ischemia protocol up to 40 μg/kg/min plus atropine [20].

As DSE depends on reaching the endpoint of 85% of the maximum heart rate for the age when the dobutamine-atropine protocol manages to reach this endpoint, the test becomes diagnostic and can be stopped. With beta-blockers, a fast and significant increase in blood pressure can occur.

DSE is also influenced by therapy with calcium channel blockers and nitrates, although to a lesser extent than with beta-blockers [19]. Because of this, the beta-blocker therapy needs to be suspended at least 24 h before the exam, and ideally 3–4 days before the test, if the sensitivity of the test is the main diagnostic goal. This is not always feasible, practical, or safe in real-life conditions.

DSE response is affected by antiischemic drugs such as beta-blockers, calcium channel blockers, and nitrates in a matter different from exercise, and beta-blockers cause a rightward shift in the dose-response curve to dobutamine which cannot help to predict the response of exercise to the same drugs [7, 15].

For application beyond coronary artery disease, no atropine is recommended. In patients who are receiving beta-blocker therapy in the ischemia investigation, high doses (up to 40 μg/kg/min), with atropine, are often required [20]. For the specific application in patients with low-dose, low-gradient aortic stenosis and reduced ejection fraction, a lower dose (until 20 μg/kg/min) is recommended for safety reasons [20].

Patients need to be fasting for 4 h before the test. In all cases, the patients need to sign the informed consent. The endpoints of the DSE protocol include achievement of the target heart rate (at least 85% of maximum predicted heart rate for age, 220-age), detection of moderate wall motion abnormalities in at least two segments, symptomatic or sustained arrhythmias, hypotension, or severe hypertension (systolic pressure ≥220–240 mmHg or diastolic pressure ≥120 mmHg), or if a patient develops intolerable symptoms.

18.4 Myocardial Response and Testing Interpretation

The responses resulting from DSE may be: normal (contractile improvement with dobutamine), ischemic (contractile worsening during stress echocardiogram), viable sustained (a segment with resting akinesia or marked hypokinesia showing a gradual functional improvement with a low and high dose of dobutamine), viable biphasic (improvement at a low dose and worsening at the high dose of dobutamine), and fibrosis or scarring (akinesia or dyskinesia with no improvement in regional function during DSE) [20] (Fig. 18.9). Resting akinesia that becomes dyskinesia during stress should not be considered true active ischemia. It reflects a purely passive mechanical phenomenon, due to increased intraventricular pressure developed by normally contracting walls.

The normal response pattern is a marked increase in regional and global left ventricular function with a marked increase in heart rate and reduction of left ventricular end-systolic volume during stress. The entity of contractile and chronotropic response is comparable to exercise (Fig. 18.10).

The abnormal response pattern is a regional wall motion abnormality, often with preserved global left ventricular function (Fig. 18.11).

The typical SE report should comment both on global left ventricular function and regional function [19, 20]. Ischemia at DSE is based on decreased wall thickening in two or more contiguous segments (Fig. 18.12).

Contrast enhancement should be considered to augment endocardial definition when two or more left ventricle segments cannot be visualized in apical view at rest. This occurs in approximately 10% of stress echocardiograms [19, 20].

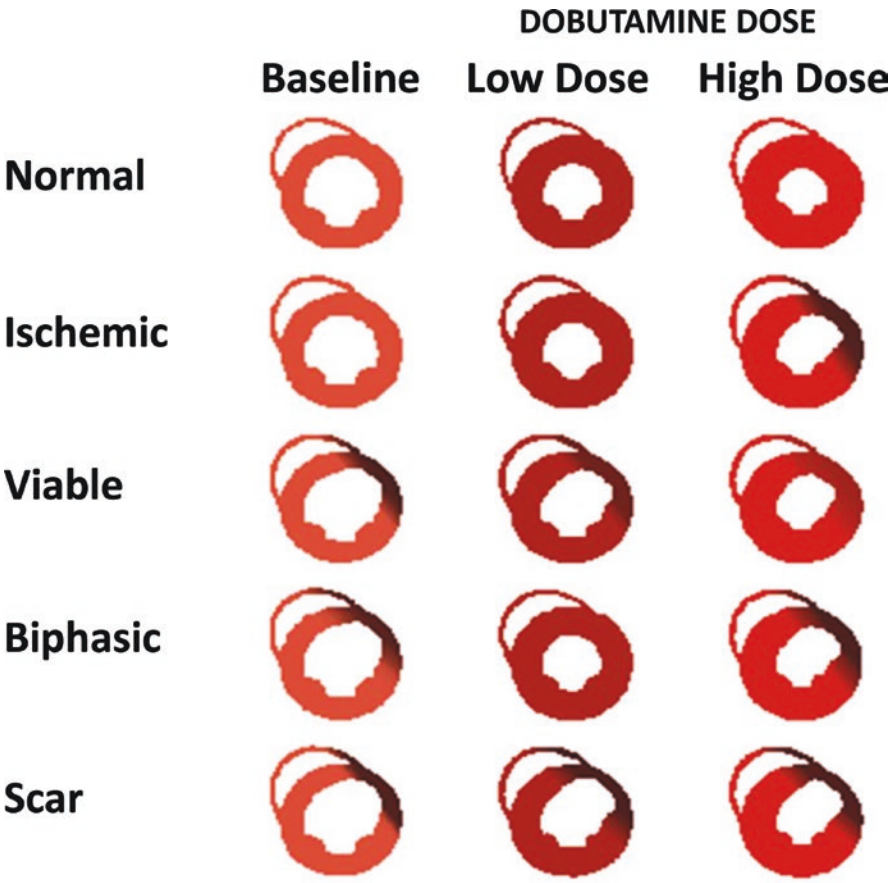

Fig. 18.9 Myocardial responses induced by dobutamine stress echocardiogram

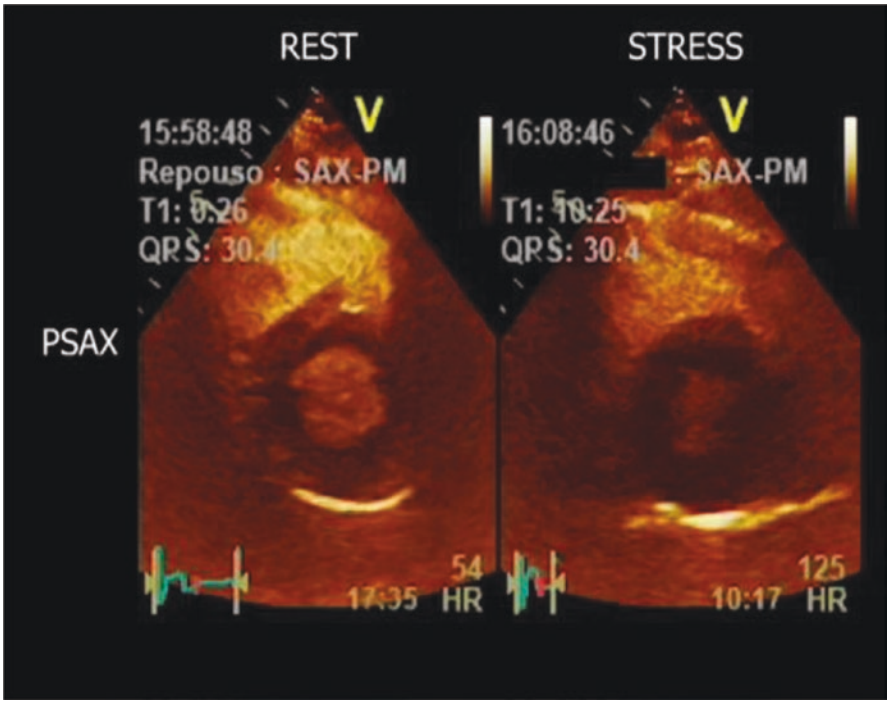

Fig. 18.10 Parasternal short-axis view at the mid-ventricular level showing a normal DSE response, with regional and global hyperkinesis and reduction of left ventricular end-systolic volume during stress, with the normal increase in heart rate. See accompanying Video 18.1 with more projections: apical four-chamber, apical two-chamber, parasternal long-axis, and short-axis. (Video images courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

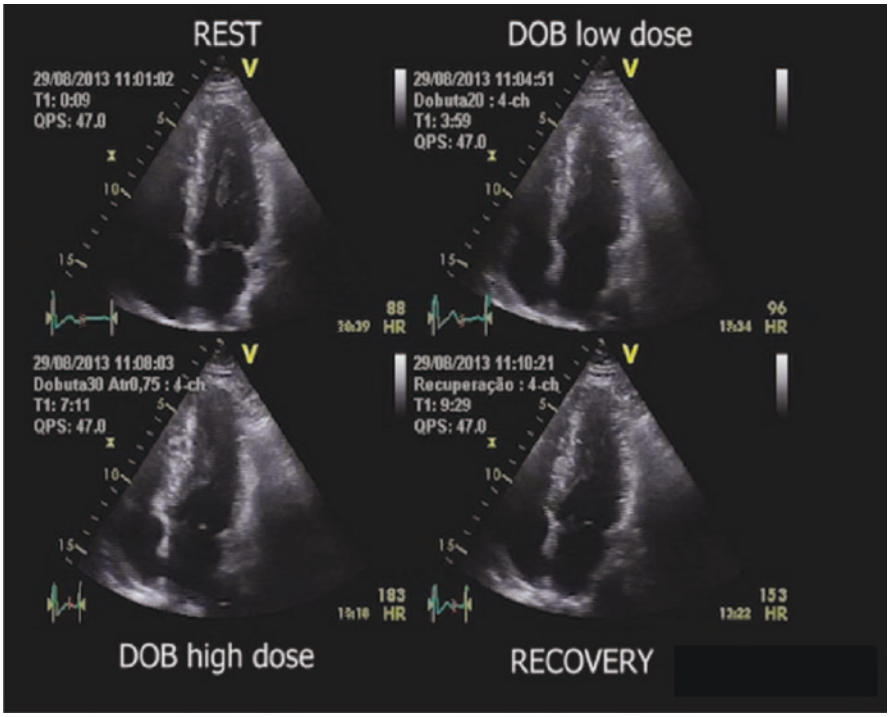

Fig. 18.11 Apical four-chamber view showing a normal regional and global wall motion at rest (left upper panel) with a normal hyperkinetic response after the intermediate dose (right upper panel), and abnormal apical akinesia at peak stress (left lower panel). There is full recovery after discontinuation of dobutamine infusion and beta-blocker administration (right lower panel). See corresponding Video 18.2. (By courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

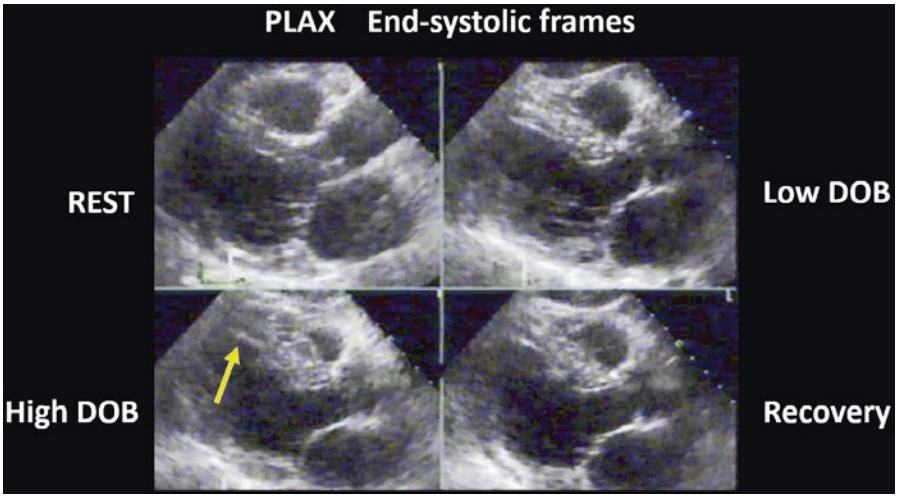

Fig. 18.12 Parasternal long-axis view showing an abnormal regional wall motion in the inferolateral wall at rest (left upper panel), with akinesia in the anterior septal wall at peak stress (left lower panel). See the corresponding Video 18.3, with the parasternal long- and short-axis view, apical four-chamber, and two-chamber views. (By courtesy of Dr. Ana Cristina Camarozano, Curitiba, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

18.5 Feasibility and Safety

Centers that perform a high volume of DSE procedures have the highest diagnostic yield and the lowest rate of complications [20]. Minor but limiting side effects preclude the achievement of maximal pharmacological stress in about 10% of patients [19, 20]. These side effects are complex ventricular tachyarrhythmias (frequent, polymorphic, premature ventricular beats, couplets, triplets, nonsustained ventricular tachycardia); nausea and/or headache; hypotension (>30 mmHg drop in blood pressure) and/or bradycardia; supraventricular tachyarrhythmias; and hypertension. Limiting side effects are more often asymptomatic with dobutamine, and more often symptomatic with dipyridamole [19]. Side effects usually disappear upon interruption of drug infusion, due to the short half-life. When symptoms or ischemia persist, intravenous beta-blockers are given, unless coronary vasospasm is suspected.

Both the patient and the physician should be aware of the rate of major complications that may occur during dobutamine stress. As concordantly shown by single-center experiences [24–30] and multicenter registries [31–34], major side effects occur in 1 of 300–350 cases (Table 18.2).

Tachyarrhythmias are the most frequent complication occurring during DSE. In some cases, they are associated with an ischemic regional wall motion abnormality. The mechanism of their onset can be attributed to the direct adrenergic

Table 18.2 Life-threatening complications in early single-center large experience (>1000 patients), and multicenter registries for DSE

Author, year	Patients	Complications(s)
Single institution experience		
Mertes et al., 1993 [24]	1118	None
Poldermans et al., 1994 [25]	1000	1 AMI, 4 VT, 1 prolonged ischemia
Zahn et al., 1996 [26]	1000	2 VF, 1 seizure
Seknus et al., 1997 [27]	3011	5 VT, 1 AMI, 1 prolonged ischemia, 1 hypotension
Bremer et al., 1998 [28]	1035	1 VF, 1 VT
Mathias et al., 1999 [29]	4033	1 VF 8 VT, 1 MI; 5 atropine intoxication
Kane, 2008 [30]	6755	6 major complications (0.09%)
Multicenter registry		
Picano et al. (EDIC), 1994 [31]	2949	2 VF, 2 VT, 2 AMI,
Pezzano (RITED), 1994 [32]	3041	2 VF, 1 asystole
Beckmann, 1999 [33]	9354	324 (2 VF)
Varga, 2006 [34]	35,103	63 (5 deaths)

AMI acute myocardial infarction, *VT* ventricular tachyarrhythmia, *VF* ventricular fibrillation, *MI* myocardial infarction

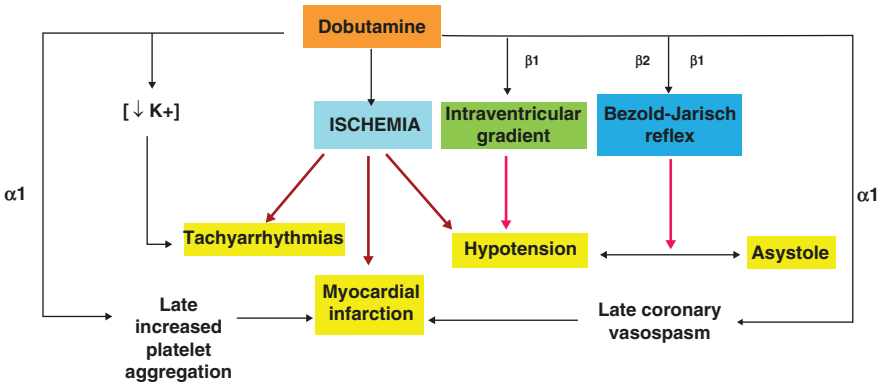

Fig. 18.13 The main myocardial, coronary, and hemodynamic effects of dobutamine. Complications may occur through ischemia-dependent and ischemia-independent pathways

arrhythmogenic effect of dobutamine, through myocardial β-receptor stimulation, which is particularly evident in patients with ischemic heart disease. However, in some cases, they are independent of ischemia and can also develop at low dobutamine doses. Dobutamine infusion can also lower the blood potassium level, thereby contributing to the genesis of ventricular ectopy through a depolarizing effect on the cell membrane [35, 36].

Side effects and complications can occur via ischemia-dependent and ischemia-independent pathways (Fig. 18.13). Ventricular and atrial tachyarrhythmias are more frequent when baseline (pretest) levels of potassium are low. The occurrence of atrial fibrillation during dobutamine stress is about 1%, especially in elderly patients (4% in those >80 years and those with a previous history of paroxysmal

atrial fibrillation) [37]. Significant hypotension is another adverse reaction during DSE. In some cases, this finding has been attributed to dynamic intraventricular obstruction provoked by the inotropic action of dobutamine [38], especially in hypertrophic hearts. Beta-blockers can reverse this situation. A vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation (Bezold–Jarisch reflex) due to excessive inotropic stimulation may be an alternative mechanism for hypotension [39].

In very rare situations, dobutamine can induce increased delayed coronary occlusion through coronary vasospasm and platelet aggregation, possibly provoking prolonged myocardial ischemia, and acute myocardial infarction on the anatomic substrate of a vulnerable, possibly noncritical, plaque unable to induce ischemia during the stress [40]. In these cases, the patient is admitted to the intensive care unit.

Due to anticholinergic properties, the atropine may cause urinary retention, increased intraocular pressure, delirium (in high doses), dry mouth, weakness, and constipation [41].

However, in the universe of exams with appropriate indications that are performed with dobutamine, the benefits largely outweigh the risks, the number of major complications are acceptable, and often occur when the exam is performed under unfavorable conditions (such as in the first days after myocardial infarction, patient with the arrhythmogenic substrate or little experience of the examiner who does not identify ischemia initially).

In the general context, DSE is a safe and well-tolerated method, even when applied to the elderly, patients with left ventricular dysfunction, or more aggressive protocols.

18.6 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiography-assessed coronary artery disease has been consistently reported to be high, with sensitivity and specificity of 81% and 84%, respectively, in a meta-analysis of 102 studies with over 7900 patients [42]. The diagnostic accuracy is similar to other forms of stress testing, such as exercise echocardiography, high-dose dipyridamole echocardiography, or stress scintigraphy [43]. In particular, the diagnostic accuracy, sensitivity, and specificity are identical to dipyridamole SE when state-of-the-art protocols are used for both stresses [44–48] as shown by meta-analyses including five studies on 435 patients (Fig. 18.14) [49].

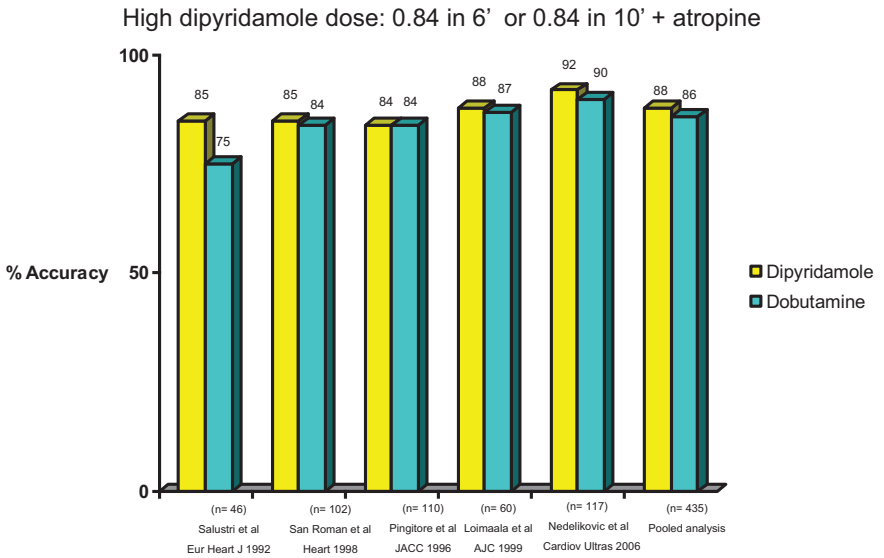

Fig. 18.14 The diagnostic accuracy of dobutamine echocardiography versus dipyridamole echocardiography for the detection of angiographically assessed coronary artery disease. (Redrawn from the meta-analysis of Picano et al. [49])

18.7 Dobutamine as a Test of Coronary Vasospasm by Serendipity

Coronary vasospasm can be elicited by dobutamine stress through stimulation of alpha-1 adrenergic receptors [50, 51]. This effect can occur during dobutamine infusion or when beta-blockers are administered at the end of testing since beta-blockers remove possible beta-2 receptors coronary vasodilation and leave vasoconstrictive alpha tone unopposed. Although dobutamine testing is targeted at the diagnosis of coronary artery disease, the unmasking of a coronary vasospastic mechanism by serendipity is not infrequent and should be recognized for its important clinical implications.

Coronary vasospasm may contribute to increasing the sensitivity of dobutamine (when the increase of coronary tone is superimposed on significant coronary artery stenosis) and is also a frequent cause of false positivity, due to true ischemia induced by coronary vasospasm. Dobutamine-induced coronary vasospasm can go unrecognized and progress to myocardial infarction when treated with beta-blockers. It is also possible that true ischemia is induced by coronary vasospasm with a direct action on small coronary vessels, with patent epicardial coronary arteries and a reversible Takotsubo-like effect with regional (most frequently apical) wall motion abnormality in absence of epicardial artery stenosis [52–54]. In this case, the likely cause is a severe diffuse coronary vasospasm in vessels too small to be imaged by coronary angiography.

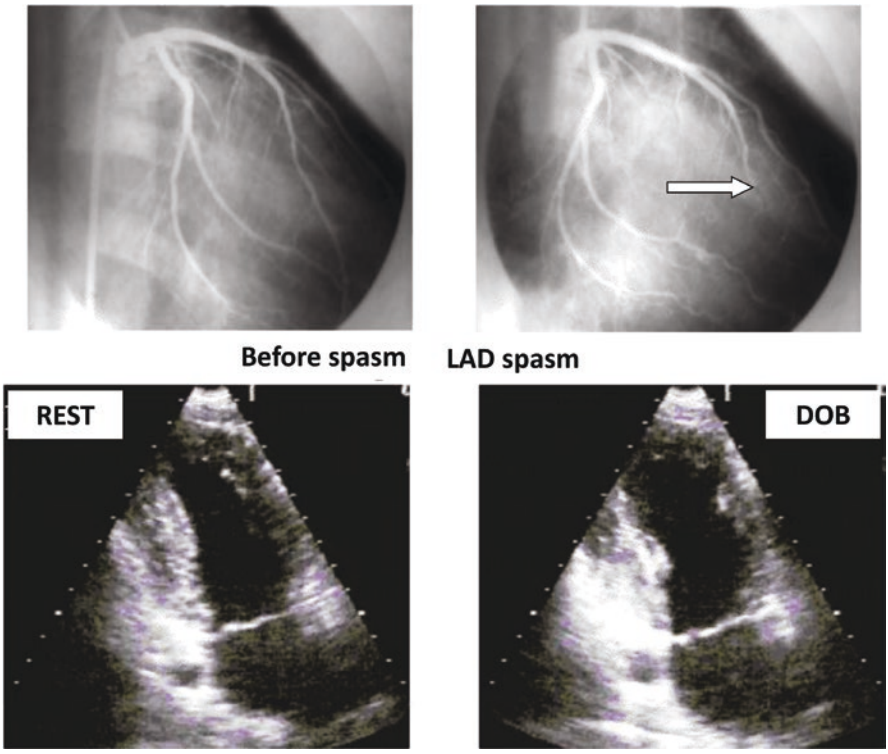

Fig. 18.15 Normal coronary angiogram (left upper panel) and spontaneous spasm of the left anterior descending coronary artery (indicated by arrow) during coronary angiography (right upper panel). In the lower panels, end-systolic frames from the apical two-chamber view showing normal thickening at rest (left lower panel) and akinesia of the anterior wall and inferior-apical segments during peak dobutamine dose. (Modified from Varga et al. [50])

Three positivity patterns are highly suggestive of coronary vasospasm. Coronary vasospasm can be elicited by dobutamine stress through stimulation of alpha-1-adrenergic receptors [55–66]. Consequently, DSE becomes positive during dobutamine for coronary vasospasm (Fig. 18.15).

This effect can occur during dobutamine infusion or when beta-blockers are administered at the end of testing since beta-blockers remove possible beta-2 receptors-mediated coronary vasodilation and leave vasoconstrictor alpha tone unopposed (Fig. 18.16).

Another possible vasospastic pattern is that a mildly positive test becomes markedly positive, with more extensive and severe ischemia after metoprolol administration (Fig. 18.17).

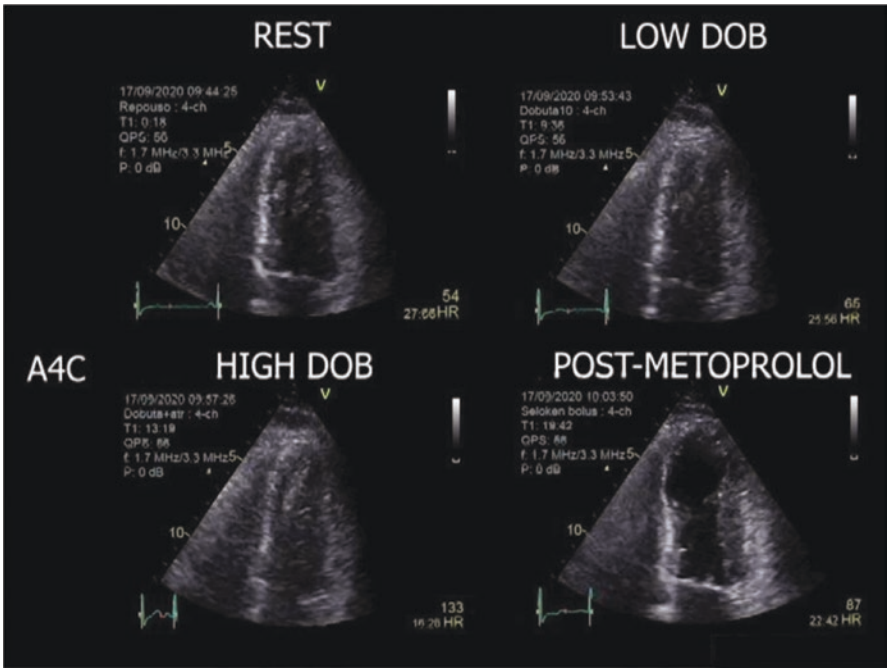

Fig. 18.16 Apical four-chamber view showing end-systolic frames with normal wall thickening at rest (left upper panel), intermediate dose (right upper panel), and peak dose (left lower panel), with reduced thickening of the mid-septal, septoapical, apical, and middle lateral segments after metoprolol, in presence of left ventricular end-systolic cavity dilation. Apical four-chamber view (A4C) is shown at end-systole. See corresponding Video 18.4, inclusive of apical four-chamber, two-chamber, and three-chamber views. (By courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

In each of the three conditions, coronary artery stenosis can be either absent or present but is not responsible for the induction of ischemia. The dominant mechanism of epicardial artery vasospasm should be recognized to be effectively treated. Patient with ischemia is usually given beta-blockers. But if the cause of the worsening effect of beta-blockade is recognized, further beta-blockers should be put on hold, and i.v. nitrates should be given. If the vasospastic origin is not recognized, catastrophes may occur.

The recognition of coronary vasospasm is not a pathophysiological curiosity but has very practical implications. In all these cases, the vasospastic origin must also be incorporated into decision-making since chronic therapy with beta-blockers is contraindicated. In coronary vasospastic disorders superimposed on organic coronary stenosis, coronary revascularization gives unsatisfactory results.

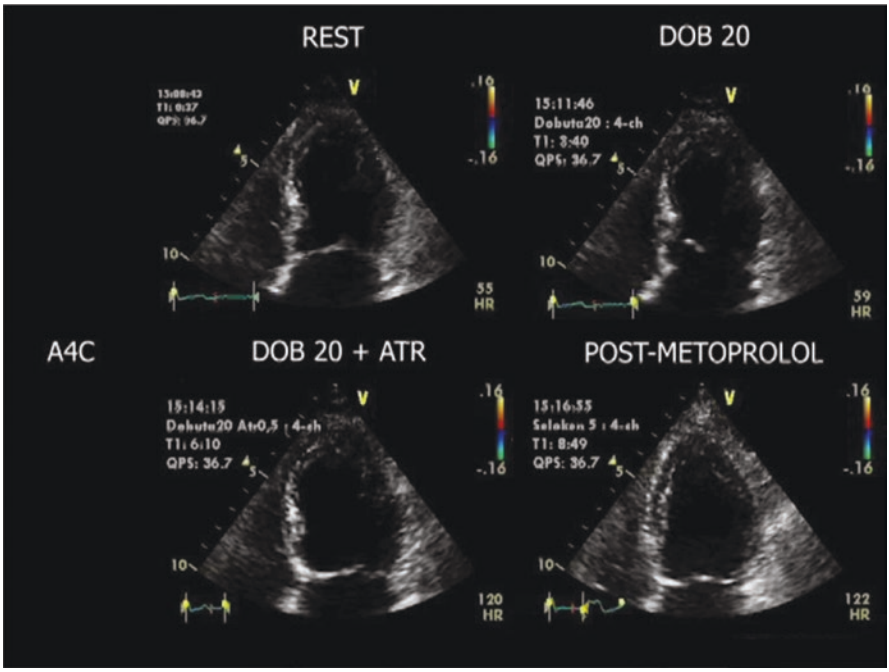

Fig. 18.17 End-systolic frames showing normal wall motion at rest in the apical four-chamber view (left upper panel). DSE is positive in the lateral and latero-apical segments during the dobutamine administration (right upper panel) and more positive after atropine (left lower panel) and beta-blocker (right lower panel) administration. See the corresponding Video 18.5. (By courtesy of Dr. Dimitrios Soulis, Athens, Greece. The video is available under the chapter's "Supplementary Material" on Springer Link)

18.8 Identification of Myocardial Viability

"Hibernating" myocardium refers to viable but under-perfused myocardial tissue that regains functionality after revascularization. Stunned myocardium is a normally perfused myocardium with a depressed function that regains functionality over time. Hibernating or stunned myocardium is viable and must be separated from necrotic myocardium, with a scar and irreversible damage, that will not improve and will not respond to any revascularization, electrical or medical therapy. At low-dose, dobutamine recognizes myocardial viability through the regional contractile reserve with high specificity and good sensitivity, with excellent diagnostic [55] and prognostic values. A contractile reserve is associated with a mild degree of myocardial damage and can predict functional recovery with higher specificity than other diagnostic markers of myocardial viability, such as thallium uptake by SPECT or fluorodeoxyglucose uptake by PET or myocardial scar at the delayed enhancement with cardiac magnetic resonance (Fig. 18.18).

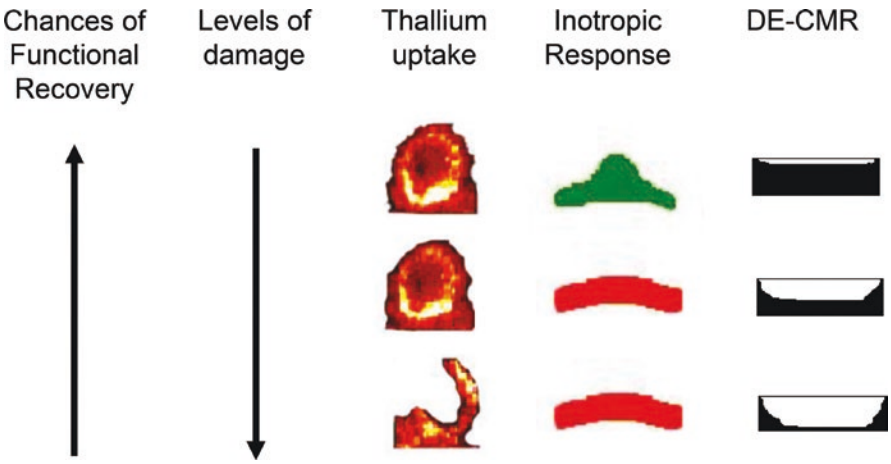

Fig. 18.18 The viability cascade. Higher cellular damage corresponds to a progressive loss of cellular function. Mild damage is associated with preserved inotropic response. Severe damage is expressed by loss of contractile response. *DE-CMR* delayed enhancement with cardiac magnetic resonance

There are three possible response patterns with dobutamine testing for myocardial viability.

In the viable response, an akinetic segment shows inotropic reserve and improves to hypokinesis or normokinesis. In the fixed response, an akinetic segment remains unchanged during stress and this response is indicative of a scar. In the biphasic response, an akinetic segment improves at the intermediate dose and worsens at the high dose. This response is indicative of viability and ischemia.

In patients with severe resting left ventricular dysfunction, a large amount of myocardial viability identified by low-dose DSE is associated with better survival in very different clinical settings, both in the presence and absence of underlying coronary artery disease. The better outcome associated with a contractile reserve with dobutamine has been observed in revascularized patients studied after chronic myocardial infarction (a model of hibernating myocardium) [56], medically treated patients studied early after acute myocardial infarction (a model of stunned myocardium) [57], with nonischemic dilated cardiomyopathy [58], and in patients treated with cardiac resynchronization therapy [59].

When compared to optimal medical therapy, viability is not related to better outcomes following either coronary artery bypass surgery or percutaneous coronary intervention, as shown by the large-scale, multicenter, randomized Surgical Treatment of Ischaemic Heart Failure (STICH) and REVIVED-BCIS2 trials [60, 61] . However, in patients with reduced resting ejection fraction, a significant (≥5 segments) left ventricular contractile reserve assessed with dobutamine stress identifies patients more likely to improve resting EF and to develop a favorable LV remodeling with end-systolic volume reduction at follow-up, with a lower rate of cardiovascular events.

18.9 Prognostic Value

In a meta-analysis of 36 studies including over 100,000 patients, a normal baseline and stress echocardiogram gives an annual risk for death of <1%, the same as for a normal stress myocardial perfusion scan [62]. The prognostic value of DSE is excellent and comparable to dipyridamole echocardiography in various patients' subsets, from chronic coronary syndromes [63, 64] to preoperative evaluation of patients before major vascular surgery [65, 66] and dilated cardiomyopathy [67].

However, as happened with all functional tests based on regional wall motion abnormalities or perfusion defects, the predictive value of a negative DSE declined in the last decades, probably due to the policy to study patients under antiischemic and plaque-stabilizing therapy and the proliferation of referral of patients with atypical symptoms [62]. Therefore, DSE was remodeled to capture the multiple prognostic vulnerabilities of the patient beyond coronary stenoses, such as the diastolic, contractile, coronary microcirculatory, and cardiac autonomic reserve [68]. The prognostic value of dobutamine is expanded with a comprehensive approach integrating regional wall motion abnormalities, B-lines, global left ventricular contractile reserve, coronary flow velocity reserve in the left anterior descending coronary artery, and heart rate reserve, each step adding a new variable with independent and incremental value over the others [10]. There is great potential to incorporate this protocol into routine practice.

18.10 Pitfalls and Specific Considerations

The limitations of DSE are related to feasibility, safety, technical difficulty of echocardiographic interpretation, sub-optimal possibility to combine coronary flow reserve and wall motion information, and inability to predict physiologic therapy-induced changes in exercise stress results. Minor but limiting side effects occur in 5–10% of tests, and submaximal results with nontarget heart rate have limited diagnostic, and prognostic, power [69].

The echocardiographic image degradation during stress is less than with exercise, but significant, since high heart rate and hypercontractility make the wall motion interpretation more challenging, and coronary flow velocity assessment less easy and feasible than with vasodilators [10, 70]. New technologies such as strain deformation imaging [71], real-time three-dimensional echocardiography [72], and artificial intelligence for regional wall motion assessment can be combined with DSE [73], but the reliability may be challenged by the high heart rate and image quality degradation.

Patients with a history of complex atrial arrhythmias (paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia) or complex ventricular arrhythmias (such as non-sustained ventricular tachycardia) or with moderate to severe

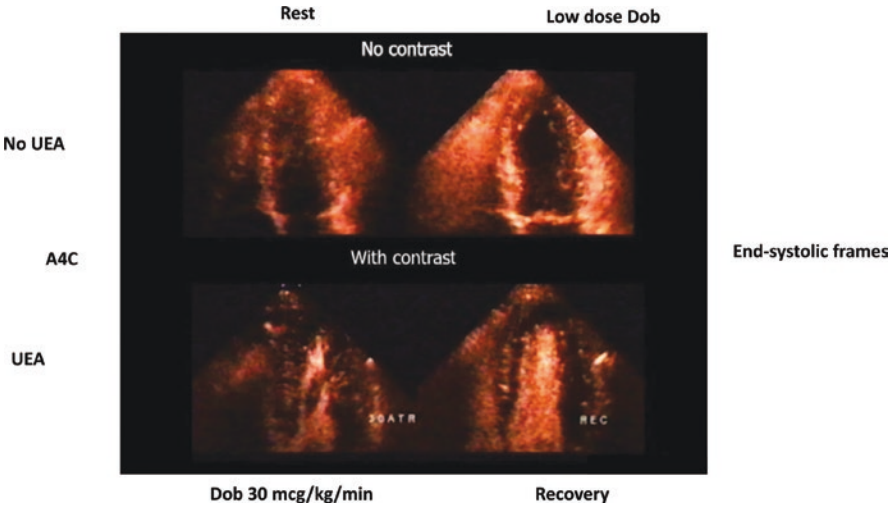

Fig. 18.19 Apical four-chamber at rest (left upper panel) and after low dose (right upper panel) without contrast, and at peak dose (left lower panel) and the recovery phase (right lower panel) following ultrasound-enhancing agents, with the improvement of image quality and endocardial border delineation in a negative test without wall motion abnormalities. See the corresponding Video 18.6. (By courtesy of Dr. Ana Cristina Camarozano, Curitiba, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

hypertension should probably not undergo dobutamine stress testing and be referred for safer vasodilator stress [19, 20].

The use of ultrasound-enhancing agents to analyze the endocardial border is able to improve the accuracy and reading reproducibility for regional wall motion and left ventricular volume measurements if two or more segments are not well visualized in the apical view (Fig. 18.19) [19, 20].

The proliferating anecdotal reports of catastrophes during DSE also contribute to assessing the safety of the test. Cardiac rupture [74–79], papillary muscle rupture [80], ventricular fibrillation [81–83] which may occur also 15 min after a negative test, refractory coronary vasospasm [84, 85], myocardial infarction [86, 87], cardiac asystole [88, 89], and acute Takotsubo syndrome [90] have all been described during dobutamine testing.

Ventricular arrhythmias can occur during dobutamine stress, and more frequently with the induction of myocardial ischemia. An example of torsade de point is shown in Fig. 18.20.

Ventricular fibrillation can occur also with low ("viability") doses, in patients with severe left ventricular dysfunction, when the search viability is indicated, and sometimes even low doses elicit an ischemic response. An example of ventricular fibrillation is shown in Fig. 18.21.

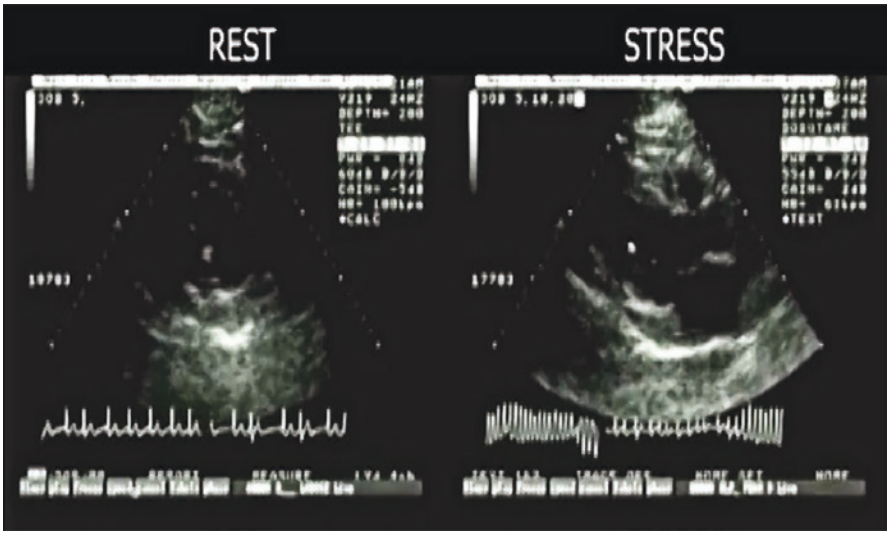

Fig. 18.20 Parasternal short axis (left, resting conditions) and long-axis (right, dobutamine 20 μg/kg/min) views of a patient with frequent ventricular ectopic beats suddenly evolving in torsade de point simultaneously with the development of septal akinesis. See the corresponding Video 18.7. (By courtesy of Dr. Rafael Payà, Valencia, Spain. The video is available under the chapter's "Supplementary Material" on Springer Link)

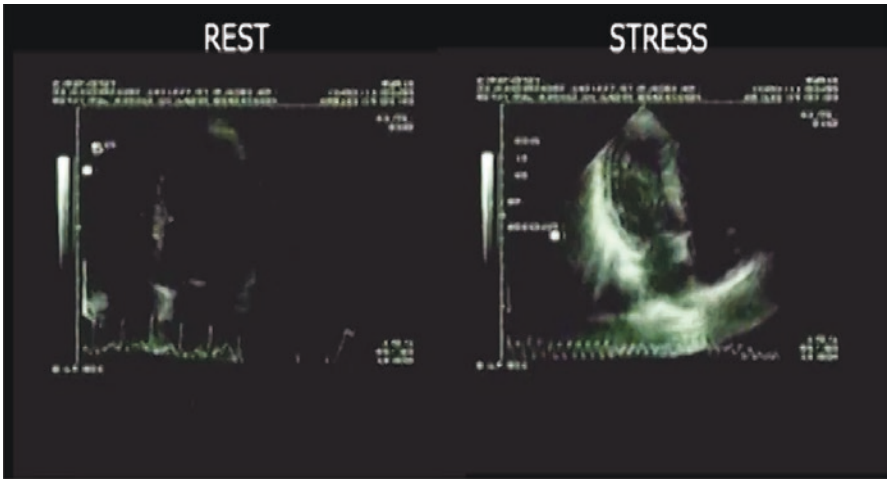

Fig. 18.21 Apical views at rest (left) and during stress (right, dobutamine 10 μg/kg/min) of a patient with global left ventricular dysfunction and tested for myocardial viability with low-dose dobutamine. The frame on the right captures the ventricular fibrillation in presence of left ventricular cavity dilation, spontaneous contrast in the left ventricular cavity, and comet-like B-lines departing from the pericardial line. See the corresponding Video 18.8. (By courtesy of Professor Albert Varga. Szeged, Hungary. The video is available under the chapter's "Supplementary Material" on Springer Link)

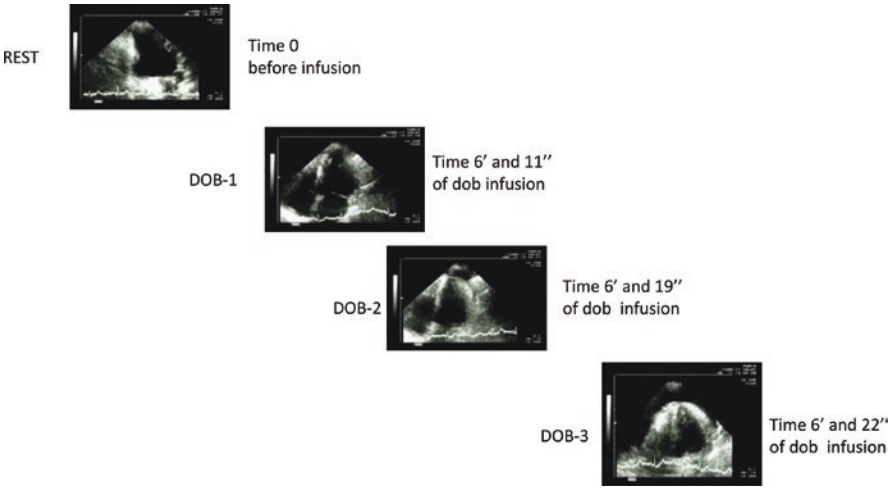

Fig. 18.22 Apical view at rest (left) and during stress (right, dobutamine 30 μg/kg/min) in a patient with recent (7 days) inferior myocardial infarction with wall thinning and dyskinesia of the inferobasal segment at rest. The frame on the right captures the rapidly developing pericardial effusion for cardiac wall rupture or fissuration. See the corresponding Video 18.9. (By courtesy of Dr. Barbara Reisenhofer, Pontedera, Italy. The video is available under the chapter's "Supplementary Material" on Springer Link)

The catastrophic event of cardiac rupture has been reported with dobutamine early after an acute myocardial infarction with thinned aneurysmatic inferobasal wall. An example of cardiac rupture is shown in Fig. 18.22.

Every stress test carries a risk, and probably dobutamine stress test is less safe than other forms of physical or pharmacological stresses, such as exercise, dipyridamole, or adenosine [91]. A tenfold rise in high-sensitivity troponin T suggestive of subclinical myocardial injury occurs in 13% of patients after negative high-dose dobutamine, especially when atropine is administered in elderly patients, and in 0% of patients after high-dose dipyridamole [92].

It is necessary to perform dobutamine stress, even at low doses, with a cardiologist attending and with personnel and facilities always ready for resuscitation. This is true for all forms of SE in all patients, and especially true for dobutamine stress even at low doses and particularly in patients with reduced global left ventricular function. A regional wall thinning in resting conditions increases the risk of rupture during testing. In all cases, recommended protocols should be followed, and careful monitoring by the physician with immediate access to resuscitation facilities is warranted. Finally, both the patient and the physician should be fully aware of the rate of complications during dobutamine infusion [93].

18.11 Contraindications

The contraindications of the exam help must be considered to minimize adverse effects [19]. In addition to usual contraindications to all forms of stress testing for clinical or hemodynamic instability, specific contraindications to dobutamine are severe arterial hypertension (>180 mmHg systolic blood pressure or 110 mmHg diastolic blood pressure), uncontrolled tachycardia (heart rate >110 bpm), and hypertrophic cardiomyopathy or significant left ventricular outflow obstruction (resting peak late gradient ≥30 mmHg).

Specific contraindications to atropine coadministration are known glaucoma and severe prostatic disease.

Caution is warranted in patients with recent inferior wall myocardial infarction, especially with wall thinning and resting dyskinesia, and in large aortic aneurysms at risk of rupture. Patients with severe left ventricular dysfunction should be studied with doses not exceeding 20 μg/kg/min. In patients with uncontrolled arterial hypertension, a history of atrial fibrillation, or significant ventricular arrhythmias, a safer vasodilator test may be considered. Formal contraindications to stress testing, dobutamine, and specifically atropine coadministration are listed in Table 18.3.

Table 18.3 Dobutamine and atropine main contraindications, and diagnostic criteria

	Contraindication to dobutamine	Contraindication to atropine	Premature termination	Diagnostic end point
Unstable coronary syndromes	x (all stresses)			
Uncontrolled cardiac arrhythmias	x (all stresses)			
Allergy/hypersensitivity to Dobutamine	x			
HR >110 b/m	x			
SBP >180 mmHg	x			
LVOTG >30 mmHg	x			
Untreated acute narrow-angle glaucoma		x		
Untreated severe urinary retention		x		
SBP <90 mmHg			v	
SBP >240 mmHg			v	
AV block ≥2			v	
PSVT, AF, VT			v	
Intolerable symptoms			v	
New RWMA (any dose)				v
HR >85% max predicted HR (any dose)				v
Maximal doses				v

AF atrial fibrillation, *HR* heart rate, *LVOTG* left ventricular outflow tract obstruction, *SBP* systolic blood pressure, *RWMA* regional wall motion abnormality, *VT* ventricular tachycardia, *PSVT* paroxysmal supraventricular tachycardia, *AV* atrioventricular

18.12 Guidelines and Recommendations

DSE based on the analysis of wall motion and thickening is recommended (class 1, must be considered) in general cardiology guidelines as an alternative to exercise for myocardial ischemia and prognosis of patients with chest pain or dyspnea [94, 95], or before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (<4 METs). It is also recommended as the test of choice for myocardial viability assessment in patients with severe or moderate left ventricular dysfunction [20]. Beyond coronary artery disease, DSE is recommended ("may be useful," class 2a) by the International Society of Heart and Lung Transplantation Guidelines for the detection of cardiac allograft vasculopathy in heart transplant recipients, since following denervation heart rate response is often inadequate with exercise [96, 97]. DSE is recommended by the American College of Cardiology/American Heart Association 2020 and European Society of Cardiology 2021 general cardiology guidelines in valvular heart disease in patients with suspected low-flow, low-gradient severe aortic stenosis with reduced ejection fraction for differentiating true-severe from pseudo-severe aortic stenosis, and in patients with mitral stenosis or valve prostheses with a mismatch between symptoms and resting echo findings who cannot exercise [98, 99]. Specialty recommendations also suggest its use in nonischemic dilated cardiomyopathy to assess the contractile reserve, a marker of response to medical therapy, and—in patients with indication based on clinical and electrocardiographic criteria—to cardiac resynchronization therapy [21]. The use of dobutamine is discouraged in hypertrophic cardiomyopathy due to the nonphysiological mechanism of induction of gradients, and nonpredictive of exercise-induced gradients (Table 18.4) [100].

Table 18.4 The most common DSE indications

	Appropriate	Uncertain	Inappropriate
Diagnosis of CAD in a patient unable to exercise	√		
Diagnosis of viability in ejection fraction <35%	√		
High-risk noncardiac surgery in an intermediate-risk patient	√		
Low-flow, low-gradient aortic stenosis for gradients and flow reserve	√		
Before cardiac resynchronization therapy for contractile reserve	√		
Dilated cardiomyopathy for contractile reserve	√		
Need to evaluate antianginal therapy efficacy		√	
Intermediate-risk noncardiac surgery in an intermediate-risk patient		√	
Evaluation of dynamic gradient in hypertrophic cardiomyopathy			√
Severe hypertension, malignant ectopy, inferior wall aneurysm early after AMI			√
Low-risk noncardiac surgery in low-risk patient			√

AMI acute myocardial infarction, *CAD* coronary artery disease

With the last-generation comprehensive SE protocol, DSE can be performed with simultaneous assessment also of B-lines, contractile reserve, coronary flow reserve, and heart rate reserve to capture the many vulnerabilities of the patient beyond coronary artery stenosis. The large-scale validation of ABCDE DSE is ongoing in the prospective, international, multicenter SE 2030 study [101].

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Dipyridamole Stress Echocardiography

19

Jorge Lowenstein and Eugenio Picano

Keywords

Adenosine · Coronary flow velocity reserve · Horizontal steal · Strain · Vertical steal

19.1 Background

Dipyridamole was the first pharmacological stress agent used for the diagnosis of coronary artery disease, with a pioneering indication proposed in Germany by Martin Tauchert for the identification of ischemia during stress electrocardiography [1] and later in the United States by Gould as hyperemic stress perfusion imaging [2]. Its main cardiac imaging applications stem from two fundamental properties, which are the two imaging sides of the same pathophysiological coin of coronary arteriolar vasodilation: the hyperemic effect and the ischemic effect [3]. The

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J. Lowenstein (✉)
Cardiodiagnosticos: Investigaciones Medicas Center, Buenos Aires, Argentina

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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hyperemic effect is the conceptual basis for myocardial perfusion imaging, usually with radionuclide scintigraphy. The ischemic effect is the requisite for functional imaging, usually with two-dimensional echocardiography during stress echocardiography (SE), but also performed with magnetic resonance simultaneously with perfusion imaging [4, 5].

Hyperemic and ischemic stress require endogenous adenosine accumulation as the common biochemical pathway (Table 19.1).

The predominance of the hyperemic over the ischemic manifestation will depend on the dose of dipyridamole (determining the amount and speed of endogenous adenosine accumulation) and on the underlying coronary anatomy. With relatively low intravenous dipyridamole doses, with absent to moderate coronary artery disease, the hyperemic effect will prevail. With relatively high doses, in the presence of moderate-to-severe coronary artery disease, the ischemic effect will dominate. With echocardiography imaging that requires ischemia as a mandatory endpoint, testing began with relatively low doses (0.56 mg kg^{-1} over 4 min), which gave low sensitivity values [6]. After 1 year, higher doses were adopted (up to 0.84 mg kg^{-1} over 10 min) [7]. Finally, it was coadministered with atropine [8]) or—more simply—with a high dose but a shorter infusion time (the accelerated protocol) [9], which overcame the limitation of limited sensitivity to minor forms of coronary artery disease, especially in patients receiving antianginal therapy (Fig. 19.1).

The two lines of functional (wall motion) and hyperemic (coronary flow reserve) imaging are destined to converge conceptually and clinically with the diffusion of new-generation imaging technologies such as coronary flow velocity imaging [10], which allows simultaneous assessment of flow and function at the same high, fast infusion protocol, which was recommended as state of the art by the European Association of Echocardiography since 2008 [11].

Table 19.1 The split personality of dipyridamole stress

Parameter	Hyperemic imaging	Ischemic imaging
Endpoint	Flow heterogeneity	Wall motion abnormality
Ischemia required	No	Yes
Dominant technique	Radionuclide scintigraphy	2D echocardiography
Dose–effect response	Flat over 0.56 mg/kg	Steep up to 0.84 mg/kg
Optimal dose	0.56 mg/kg in 4′	0.84 mg/kg in 6′ or 4′

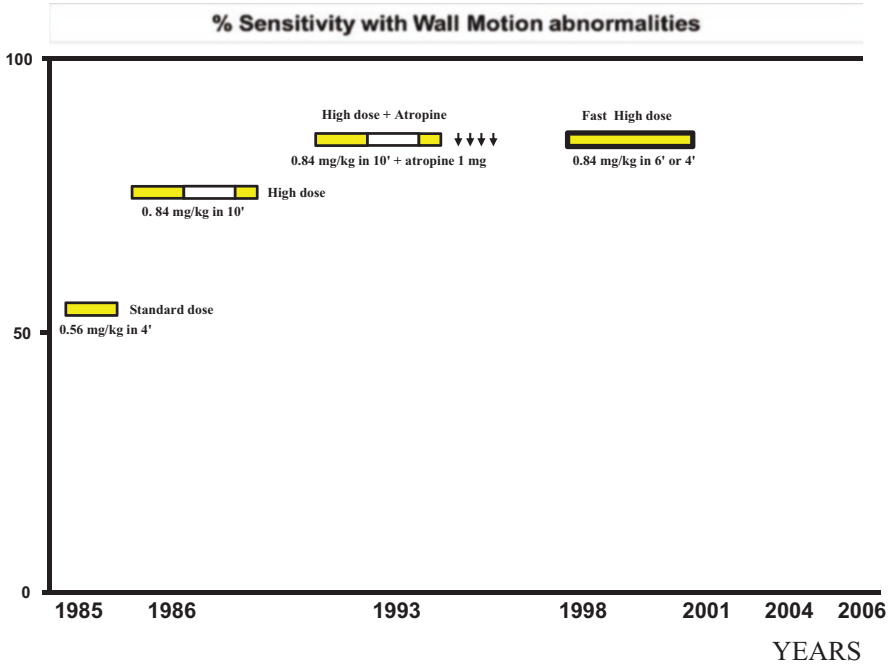


Fig. 19.1 Evolving dipyridamole SE protocols over the years. The most sensitive and accurate protocols proposed over the last 15 years are the high dose (0.84 mg kg^{-1} in 10 min) with atropine up to 1 mg (recommended by the American Society of Echocardiography guidelines in 1998 and 2007) or the fast (or accelerated) high dose (0.84 mg kg^{-1} in 4 or 6 min). The latter is currently recommended as the state-of-the-art protocol since 2008 and is usually preferred since the imaging time is shorter and no multiple drug administration is needed

19.2 Pharmacology

Adenosine is an endogenous nucleoside playing an essential role in the regulation of vasomotion in the coronary artery system, mainly by activating its A2A receptors. Endogenous adenosine is released by myocardial, endothelial, and immune cells during hypoxia, ischemia, or inflammation, each condition being present in coronary artery disease [12]. Dipyridamole is a vasodilator test that reduces myocardial oxygen supply through flow maldistribution (steal) phenomena by stimulating A2A adenosine receptors present on the endothelial and smooth muscle cells of coronary arterioles. Acting indirectly, dipyridamole increases endogenous adenosine levels by reduction of cellular reuptake and metabolism. It acts as a prodrug, increasing the interstitial levels of adenosine by the combined effect of inhibition of cellular uptake of adenosine and inhibition of its breakdown by adenosine deaminase.

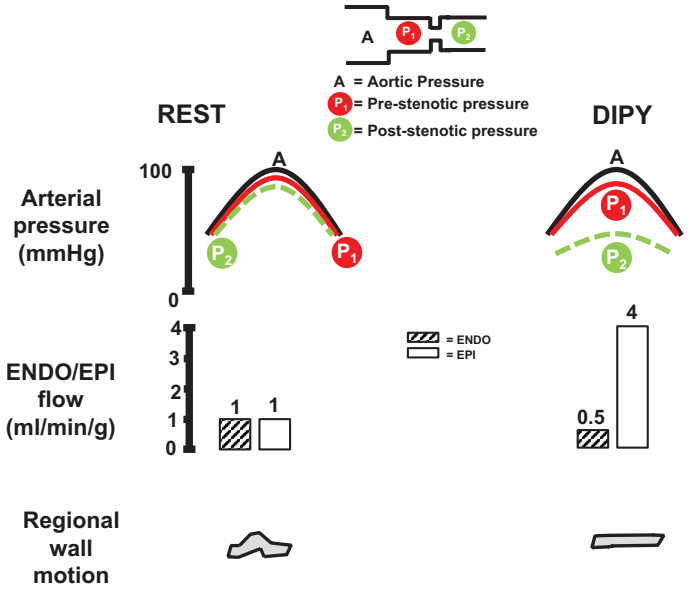
With a high dose, the peak effect occurs some minutes after the end of infusion and the half-time is 40 min, which suggests that the antidote aminophylline that blocks adenosine receptors should be routinely given at the end of the stress, even in negative cases. The dipyridamole dose usually employed for SE testing (0.84 mg kg^{-1}) causes a three- to fourfold increase in coronary blood flow in normal over resting values [12]. It is necessary to take into account that the patients we receive in our laboratories are usually elderly, hypertensive, with dyslipidemia, and with some degree of endothelial dysfunction. Thus, we define the magical number ≥ 2.0 as an adequate response, and if this twofold diastolic flow velocity is not reached, it indicates significant obstruction of the epicardial artery and/or microvascular disease. We measure velocity, not flow, and the increase in coronary flow is 30 to 40% higher than the increase in flow velocity when also the dilation of the coronary artery lumen induced by the drug is considered.

19.3 Pathophysiology

There is a strong experimental basis for the use of high-dose dipyridamole as ischemic stress for the induction of wall motion abnormalities. A vasodilator can induce vertical steal phenomena in single-vessel coronary disease and horizontal steal phenomena in multivessel disease or occluded coronary artery. The conditions required for a steal are a coronary vasodilator acting primarily on coronary arterioles, and the presence of critical coronary artery stenosis directly perfusing the ischemic area or supplying collateral flow to the ischemic region [13].

In "vertical steal," the subepicardial layer "steals" blood from the subendocardial layers [14]. The mechanism underlying vertical steal is a fall in post-stenotic pressure secondary to the increase in flow across the stenosis [15]. Regional thickening is closely related to subendocardial rather than a transmural flow, and this explains the regional wall motion abnormality despite regionally increased transmural flow. When high doses are used in experimental models of single-vessel disease, the sensitivity of dipyridamole echocardiography is high and similar to dobutamine echocardiography [16–18]. The significant reduction of the endocardial/epicardial flow ratio measured by microspheres was associated with the development of hypokinesis in these same regions (Fig. 19.2).

In presence of chronic coronary occlusion with coronary collateral circulation, the dipyridamole-induced vasodilation of the supply vessel (usually with stenosis) decreases the pressure at the point of origin of the collateral vessels. Such a reduction in collateral perfusion pressure decreases collateral blood flow to the myocardium dependent upon the occluded artery. "Horizontal steal" requires the presence of collateral circulation between two vascular beds; the victim of the steal is the myocardium fed by the more stenotic vessel.



(Adapted from Rowe Circulation 1970; Fung et al, Circulation 1987; Picano E, Circulation 1992)

Fig. 19.2 The hemodynamic basis of vertical steal. In resting conditions, even in presence of significant coronary artery stenosis, the post-stenotic coronary pressure is similar to aortic and pre-stenotic pressure. In conditions of maximal arteriolar dilation and flow increase induced by high-dose dipyridamole, the trans-stenotic pressure drops, and the distal, post-stenotic perfusion pressure falls below the lower limit of the coronary autoregulatory curve. The subendocardial flow starts to fall, despite the increase in transmural flow for a disproportionate increase in subepicardial flow. The regional wall motion is tightly linked to subendocardial flow, and regional wall thickening decreases. (Adapted and modified from Fung et al. [16])

After vasodilation, the flow in the collateral circulation is reduced relative to resting conditions, since the arteriolar bed of the donor's vessel "competes" with the arteriolar bed of the receiving vessel [19–22], whose vasodilatory reserve was already exhausted in resting conditions.

Therefore, the paradox of a potent coronary vasodilator which is also a potent inducer of ischemia, comparable to exercise or dobutamine, or pacing, is only apparent. Myocardial ischemia can be induced by an increase in myocardial oxygen demand, but also by coronary malignant arteriolar vasodilation inducing flow maldistribution and steal phenomena (Fig. 19.3).

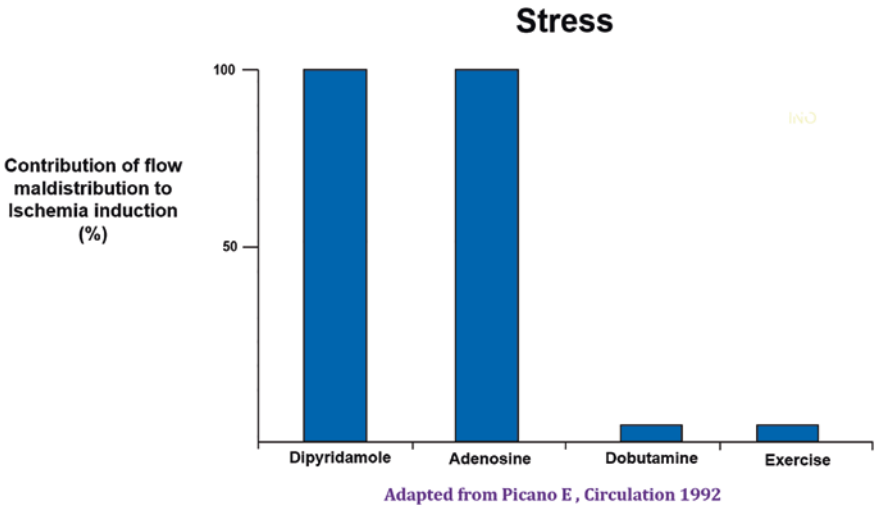


Fig. 19.3 The relative contributions of flow maldistribution (steal phenomena) with different stresses. The dominant mechanism of ischemia is flow maldistribution with vasodilators, although there is also a mild increase in heart rate and myocardial contractility. (Redrawn and modified from Picano E [3])

The flow increase is also considered to be important for the inotropic response of viable stunned or hibernating myocardium [23–27]. The increased flow improves the fiber condition through the Gregg phenomenon with changes in vascular distension that affect sarcomere length and thereby influence contractile function (micro-Starling effect) [24], although flow-independent beneficial effects of endogenous adenosine have been described [25].

The three effects—viability, hyperemia, and ischemia—are elicited with different, increasing doses observed, one after the other, during single stress with dose titration (Fig. 19.4).

Dipyridamole and dobutamine (or exercise) act on different cells and different receptors, with potentially synergic mechanisms. Their combination can be exploited to optimize diagnostic efficiency for the detection of myocardial viability with combined low doses of dipyridamole and dobutamine [28] and myocardial ischemia with combined high-dose testing [29], or high-dose dipyridamole followed by exercise [30, 31].

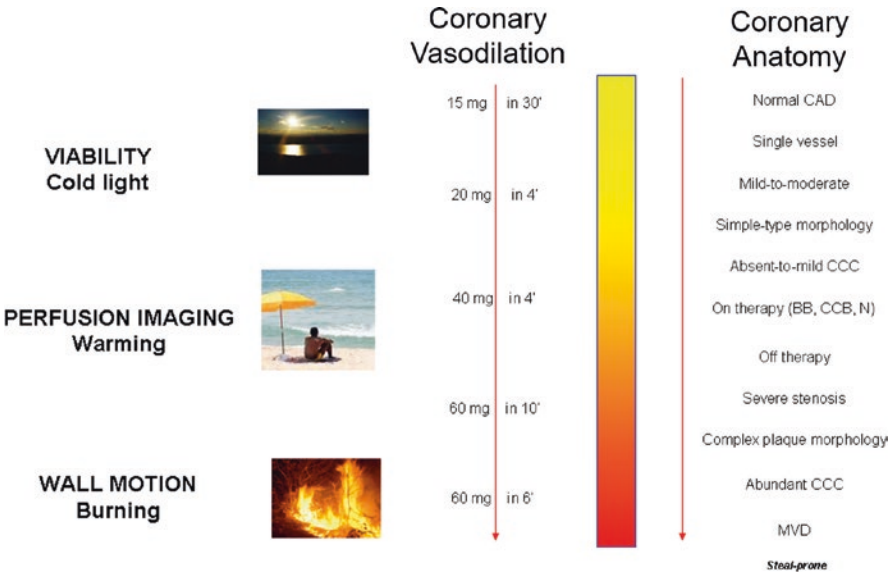


Fig. 19.4 The pathophysiological effects of dipyridamole at different dose windows and as a function of the underlying coronary anatomy in the individual patient. The ischemic effects dominate at the higher doses; the cardioprotective effect at very low doses; and the hyperemic effect at intermediate doses. The exposure of the vulnerable myocardium to the sunlight of coronary blood flow leads to three separate or sometimes overlapping effects: the "cold light" of the viability effect, the "warming" of regular-dose hyperemia, and the "burning" with high-dose ischemia [27]. (Modified from Picano [27])

19.4 Methodology and Response Patterns

The standard or regular dipyridamole protocol consists of an intravenous infusion of 0.84 mg kg^{-1} over 6 min, as currently suggested by the 2008 recommendations of the European Association of Echocardiography [11] or in 4 min as used in many laboratories. Aminophylline (240 mg IV over 3 min at a rate of 70 mg per minute) should be available for immediate use in case an adverse dipyridamole-related event occurs and is routinely infused at the end of the test, regardless of the result.

Whenever suitable technology and dedicated expertise are available, it is recommended to perform dual-imaging vasodilator SE with combined wall motion and coronary flow reserve assessment with pulsed Doppler velocity imaging on the left anterior descending coronary artery [11, 32] (Fig. 19.5) as a part of the comprehensive ABCDE protocol. It is now possible to corroborate the current

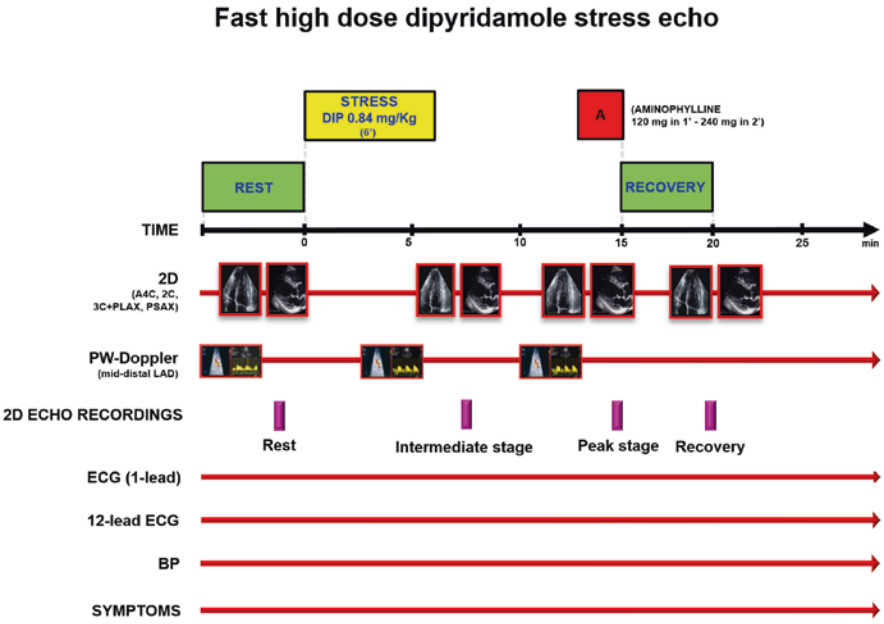


Fig. 19.5 The state-of-the-art protocol of high-dose, fast dipyridamole echocardiography test with dual imaging (wall motion and coronary flow reserve on the left anterior descending coronary artery). Blood pressure monitoring is also useful to calculate the left ventricular contractile reserve with force. Electrocardiographic monitoring is also useful to assess heart rate reserve. The baseline evaluation has a variable duration and it can last more than 5 min if it is the first-time assessment of a resting, complete examination. On top of the maximal dipyridamole dose, either atropine (1 mg) or handgrip can be added to maximize the diagnostic sensitivity

naked eye evaluation with numbers as are provided with coronary flow velocity reserve and quantitative assessment of regional and global myocardial deformation indices [33].

All caffeine-containing foods (coffee, tea, chocolate, bananas, and cola drinks) should be avoided for 12 h before testing, and all theophylline-containing drugs should be discontinued for at least 24 h. Some antiplatelet drugs such as dipyridamole and the novel oral antiplatelet agent ticagrelor should be withdrawn for at least 48 h.

The typical abnormal response pattern for regional wall motion abnormality is shown in Fig. 19.6.

The typical abnormal response pattern for regional wall motion abnormality in a region remote from the scar at rest is shown in Fig. 19.7.

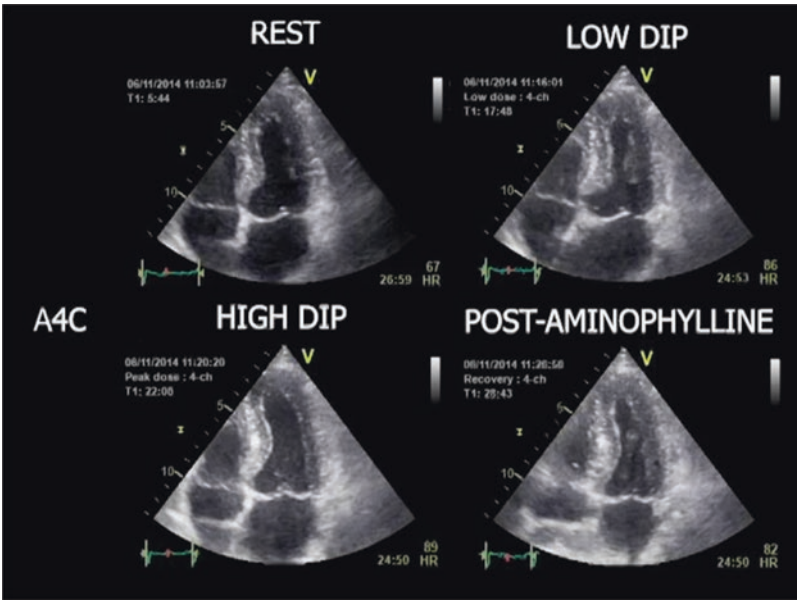


Fig. 19.6 End-systolic frames from apical 4-chamber view (A4C) showing normal wall thickening at rest (left upper panel), increased wall thickening at a low dose (right upper panel), abolished wall thickening involving the lateral and apical walls at the high dose of dipyridamole stress (right lower panel), with full recovery after aminophylline administration (right lower panel). (See accompanying Video 19.1 Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil). The video is available under the chapter's "Supplementary Material" on Springer Link

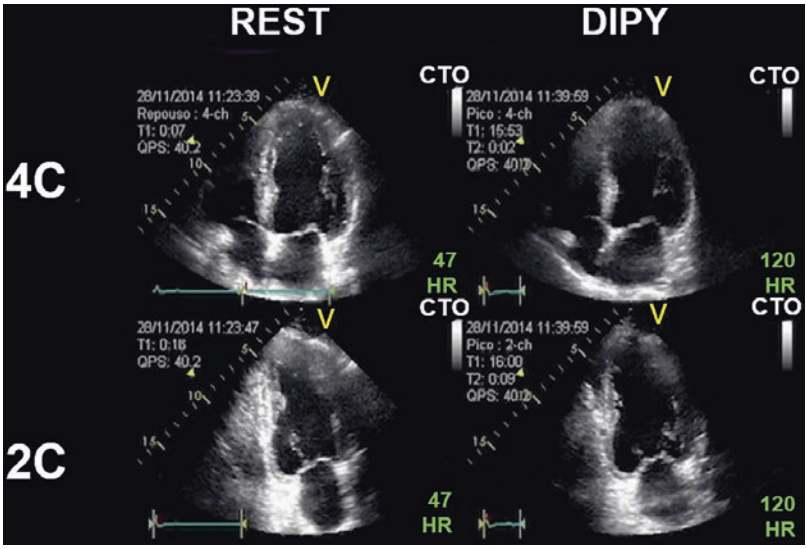


Fig. 19.7 End-systolic frames from apical 4-chamber view (A4C, upper panels) and apical 2-chamber view (A2C, lower panels) showing resting akinesia involving the inferior wall (left panels) and a lateral and anterior wall akinesis at the high dose of dipyridamole stress (right panels). (See accompanying Video 19.2 Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil). The video is available under the chapter's "Supplementary Material" on Springer Link

19.5 Feasibility and Safety

Minor but limiting side effects preclude the achievement of maximal pharmacological stress in less than 5% of patients [34]. In order of frequency, they are hypotension and/or bradycardia, headache, dizziness, and/or nausea. Roughly two-thirds of patients studied with the high-dose dipyridamole protocol experience minor side effects such as flushing and headache, which reflect the systemic vasodilatory effect of the drug. These side effects usually disappear following the administration of aminophylline at the end of testing. On rare occasions, dipyridamole-induced ischemia becomes resistant to aminophylline [35] In these cases, the administration of nitrates is necessary to reverse ischemia. Aminophylline is routinely given at the end of testing, also in negative cases, but it may trigger coronary vasospasm in about one-third of patients with variant angina: transient ST-segment elevation is the usual pattern, and nitrates (not further aminophylline or beta-blockers!) should be given immediately to relieve spasm [36].

Major life-threatening complications—i.e., myocardial infarction, third-degree atrioventricular block, cardiac asystole, sustained ventricular tachycardia, or pulmonary edema—occur in about 1 in 1000 cases, as shown by series encompassing over 35,000 patients with high-dose SE techniques [37]. The test induces major complications three times less frequently than dobutamine [38] (Table 19.2). The clinical data are also corroborated by clinical chemistry findings, showing subclinical myocardial injury reflected by high levels, greater than three-fold the baseline, of high sensitivity troponin T at 180 min after negative testing in 54% of patients with high-dose dobutamine, 24% with exercise, and 5% with dipyridamole [39].

From a technical viewpoint, the quality of echocardiographic images is unchanged during dipyridamole stress. This allows to have all the projections in the same patient and makes dipyridamole ideally suited for a quantitative assessment with strain or 3-dimensional techniques. Dipyridamole is fit for simultaneous wall motion analysis, coronary flow reserve, and 2D strain [40] (see Chap. 13).

Table 19.2 Safety profile of pharmacologic SE

	Dobutamine	Dipyridamole
% submaximal tests	10%	5%
Side effects	1/300 exams	1/1000
VT, VF	++	+
High-grade AV block	+	++
Death	1/5000	1/10,000

AV atrioventricular, *VT* ventricular tachycardia, *VF* ventricular fibrillation

19.6 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiographically assessed coronary artery disease has been consistently shown to be high, with sensitivity and specificity of 72% and 95%, respectively, in a meta-analysis of 58 studies (all generations of protocols included) [41]. When state-of-the-art protocols are used for both stresses [42–46], the sensitivity, specificity, and accuracy of fast (or atropine-potentiated) high-dose dipyridamole evaluated with regional wall motion abnormality as the only diagnostic endpoint are identical to dobutamine SE, as shown by a meta-analysis including five studies with 435 patients [47]. Dipyridamole is subjectively better tolerated by the patient than adenosine and equally well tolerated than dobutamine [48, 49]. The sensitivity is lower than dobutamine only when low doses, or high doses in 10′ and without atropine coadministration, are used [48]. With the high dose, the sensitivity is similar to the treadmill or high-dose dobutamine [49, 50], or even higher in the presence of well-developed coronary collateral circulation or severe coronary stenosis of the complex-type, more vulnerable to steal phenomena [21, 51].

The sensitivity increases, with a loss of specificity, when the coronary flow velocity is added to regional wall motion abnormalities for the detection of left anterior descending coronary artery disease [52, 53]. However, a single territory assessment cannot be satisfactory for diagnostic purposes, and the most important application of coronary flow velocity is to identify the coronary microvascular disease and coronary flow reserve, which has an outstanding prognostic value within and beyond coronary artery disease [54].

19.7 Myocardial Viability

Very low dose (0.28 mg kg^{-1}) in 4 min dipyridamole recognizes myocardial viability with high specificity (higher than dobutamine) [23], good sensitivity (lower than dobutamine) [24], and excellent prognostic value (comparable to dobutamine) [55].

19.8 Ischemia with Nonobstructive Coronary Arteries

Patients who present angina, ischemia, or even myocardial infarction may show, quite often, mild or no coronary artery disease on coronary angiography. This condition, called INOCA or ischemia and no obstructive coronary artery disease, is caused by microvascular dysfunction or vasospastic disorders. Coronary

microvascular dysfunction is usually accompanied by a normal regional and global function by two-dimensional echocardiography during stress [56]. The easy way to test non-invasively microvascular dysfunction is to measure transthoracic coronary flow velocity reserve with dipyridamole in the left anterior descending artery. A reduced coronary flow velocity reserve can be accompanied by a reduction in global longitudinal strain, while a normal coronary flow velocity reserve is usually matched by a normal strain increase and normal chronotropic reserve [57].

19.9 Prognostic Value

The prognostic value of dipyridamole SE based on wall motion abnormalities has been extensively proven, confirmed, and reconfirmed in different subsets of patients with chronic coronary artery disease [58–61], recent myocardial infarction [62–68], or major non-cardiac vascular surgery [69–74]. The prognostic value has been extensively demonstrated in special patient subsets, including hypertensives [75, 76], elderly patients [77], women [78], patients with left bundle branch block [79], with right bundle branch block and/or left anterior hemiblock [80], outpatients [81], patients with the single-vessel disease [82], and in a chest pain unit [83–85].

Ongoing ischemic therapy at the time of testing not only lowers the diagnostic sensitivity in a way somewhat symmetrical to the effects of exercise testing [86] but also heavily modulates the prognostic value of pharmacological SE. In the presence of concomitant anti-ischemic therapy, a positive test is more prognostically malignant, and a negative test is less prognostically benign [87]. The prognostic value of dipyridamole SE has also been evaluated in direct head-to-head comparisons with other forms of stress testing, and it was shown to be similar to dobutamine echocardiography [88–91]. This similar value has been confirmed by an updated meta-analysis [92]. The dipyridamole-induced contractile reserve has the same prognostic value as the dobutamine-induced recovery of function in patients with non-ischemic dilated cardiomyopathy [93].

19.10 The Added Value of ABCDE Protocol

The prognostic information supplied by vasodilator SE based on wall motion imaging has been recently expanded with the systematic use of dual imaging with combined wall motion and coronary flow reserve assessment [94]. The combination of conventional wall motion analysis with 2-dimensional echocardiography and coronary flow reserve with pulsed Doppler flowmetry of the mid-distal left anterior descending coronary artery has been shown to provide an independent and incremental power of prognostication in patients with known or suspected coronary artery disease [95, 96], normal coronary arteries [97], diabetes [98, 99], hypertension [100], left bundle branch block [101], idiopathic dilated cardiomyopathy [102], or hypertrophic cardiomyopathy [103, 104].

Similar data have been obtained with an assessment of perfusion reserve by myocardial contrast echocardiography in patients with coronary artery disease [105] and with dilated cardiomyopathy [106]. Recently, the comprehensive ABCDE protocol has been adopted to optimize the risk stratification potential of the test, addressing different vulnerabilities of the patient beyond epicardial artery stenosis or coronary microcirculatory disease, from diastolic reserve and B lines [107], left ventricular contractile reserve and reduction in end-systolic volume [108], cardiac sympathetic reserve and increase in heart rate [109], and subendocardial function with regional apical longitudinal strain in patients with preserved regional wall motion during dipyridamole SE [110]. Each of these variables has independent and incremental value in predicting outcomes since they assess separate and complementary aspects of cardiac vulnerability well beyond the hemodynamic impact of ischemia-producing coronary artery stenosis.

19.11 Indications and Contraindications

Fast, high-dose dipyridamole SE is an appropriate choice for pharmacological SE used for the detection of coronary artery disease, especially in patients with an inability to exercise or contraindications to exercise, or with resting images of borderline quality, making exercise echocardiography challenging. Dipyridamole is technically easier than exercise or dobutamine since the image quality is less degraded by tachycardia, hyperventilation, and hypercontractility. In the words of the Belgrade group, "*from the technical viewpoint, dipyridamole is the elementary school, dobutamine the secondary school, and exercise the university*" [101]. Dipyridamole is equally accurate, technically easier [102], and safer than dobutamine SE: as clearly stated by the 2008 recommendations of the European Association of Echocardiography, "*exercise is safer than pharmacological stress. Among pharmacological stresses, dipyridamole is safer than dobutamine*" [15]. It is subjectively better tolerated by patients than adenosine [103]. Dipyridamole SE is also appropriate in intermediate-risk patients undergoing elective high-risk non-cardiac surgery. Appropriateness is uncertain in intermediate-risk patients undergoing intermediate-risk non-cardiac surgery. For the identification of myocardial viability in patients in whom low-dose dobutamine is unsafe or not tolerated, low-dose dipyridamole can be an effective alternative, although the appropriateness of the specific indication is restricted by limited experience.

Patients with second- or third-degree atrioventricular block or with sick sinus syndrome should not receive dipyridamole (unless they have a functioning pacemaker). Also, patients with bronchial asthma or a tendency to bronchospasm are not indicated for dipyridamole testing (Table 19.3). Although according to the literature it is not a frequent complication, it is better to avoid dipyridamole SE in patients presenting severe bilateral carotid disease with unknown Willis polygon circulation, due to the theoretical possibility of producing circulatory steal and the potential risk of brain ischemia. Patients using dipyridamole (and possibly the novel oral antiplatelet agent ticagrelor) chronically should not undergo dipyridamole testing for at least 24 h after withdrawal of therapy (ideally 48 h) because

Table 19.3 Contraindications to dipyridamole SE

	Absolute	Relative
Active bronchospasm	√	
≥ Second-degree AV block	√	
SBP < 90 mmHg	√	
Methylxanthine use		√
Remote history of reactive airway disease		√
Chronic dipyridamole or ticagrelor therapy, recent (<12 h) coffee, tea, and chocolate ingestion		√

AV atrioventricular, *SBP* systolic blood pressure

Table 19.4 Pharmacological test for detection of coronary stenosis

	Vasodilator	Dobutamine
Receptor target	A2A adenosine	α-1; β-1; β-2 adrenergic
Hemodynamics	Reduces supply	Increases demand
Physiological targets	Coronary arterioles	Myocardium, SNA node
Cellular target	Smooth muscle cells	Myocytes
Antidote	Aminophylline	β-Blockers
Stress	Dipyridamole (adenosine)	Dobutamine
Contraindications	Asthma, bradyarrhythmias	Tachyarrhythmias, high BP

BP blood pressure, *SNA* the sinoatrial node

their blood levels of adenosine could be unpredictably high. Withdrawal of long-term theophylline or caffeine for at least 24 h is also required to have adenosine receptors free.

The main differences between dipyridamole and dobutamine SE are reported in Table 19.4. Inotropic and vasodilator stresses should both be used in a SE laboratory, for several reasons. Each test has different limitations and specific advantages: a versatile use of both makes it possible to tailor the stress to the individual patient. Whatever type of stress is the laboratory's first choice, in the case of submaximal results due to limiting side effects, the second choice should be used, to avoid the inaccuracies of non-diagnostic submaximal testing.

19.12 Pitfalls

Despite many advantages in terms of high accuracy, excellent safety profile, and robust evidence base supporting its prognostic value in several patients' subsets, dipyridamole is still relatively underused among pharmacological stresses in the United States and the United Kingdom. This may be due to a lack of commercial availability or high drug cost in some countries and established cultural imprinting in mainstream cardiologic knowledge that vasodilators produce little if any, myocardial ischemia and are more suitable for perfusion imaging—although with adequately high, state-of-the-art protocols there is no sensitivity difference versus exercise or dobutamine.

There are some advantages to dipyridamole SE and suggest using it as the drug of choice (Table 19.5) in patients in whom safety is essential (in case of hypertension, ventricular arrhythmias, atrial fibrillation), in those with associated cardiac pathology (complete left bundle branch block, left ventricular hypertrophy), and in patients with a dynamic sub-valvular obstruction or known vasospasm. Due to unchanged image quality and a mild increase in heart rate at peak stress, dipyridamole is also suitable to assess coronary flow reserve in various territories, quantify regional and global 2D strain, or be associated with myocardial contrast [104–107]. It is useful in laboratories with lower infrastructure and it is the ideal stress agent for those who are initiating the technique of SE.

The strengths and weaknesses of dipyridamole compared to dobutamine can be seen in Table 19.6.

The use of ultrasound-enhancing agents to analyze the endocardial border can improve the accuracy and reading reproducibility for regional wall motion and left ventricular volume measurements if two or more segments are not well visualized in the apical view (see Chap. 14).

Although dipyridamole is safe and probably safer than the dobutamine test, complications may occur. The intravenous infusion of aminophylline promptly resolves the complication, even ventricular tachyarrhythmias associated with inducible

Table 19.5 Drug of choice as a pharmacological stress agent

Dipyridamole	Dobutamine
When safety is essential in patients with hypertension, atrial fibrillation (moderate or high ventricular response), ventricular arrhythmias Patients with sub-valvular dynamic obstructions	Patients on beta-blockers that cannot be interrupted Left ventricular dysfunction (EF < 35%)
Patients with coronary spasm	Patients with decompensated severe chronic obstructive pulmonary disease, asthma, or bronchospasm
When it is necessary to evaluate coronary flow reserve	Patients receiving aminophylline or derivatives
When myocardial contrast is used	Patients with low-flow, low-gradient aortic stenosis

EF ejection fraction

Table 19.6 Relative strengths of the two pharmacological stress agents most used in clinical practice

Dipyridamole	Dobutamine
Fast study	More physiological study
Low drug costs in many countries	More used in USA and UK
Requires less technology	Larger experience
Greater feasibility	Excellent tolerance
Lower complication rate	Recognize insufficient test response
Excellent specificity	Viability studies
Better suited for CFVR and strain	Useful for LF, LG AS with reduced EF

CFVR coronary flow velocity reserve, *EF* ejection fraction, *LF LG AS* low-flow low-gradient aortic stenosis

ischemia, despite the primary arrhythmogenic effect of aminophylline, obscured in this case by the anti-ischemic action. As always with SE, the cardiologist should be present and the resuscitation facilities readily available. The SE laboratory should have the possibility of using all the stress modalities, as there is a scope for each stress agent according to the pathology, and the indications and contraindications of each specific patient.

19.13 Clinical Guidelines

Dipyridamole SE is the pharmacological test of choice for the assessment of inducible ischemia in patients unable to exercise [11, 108], especially when exercise is contraindicated or yielded submaximal, non-diagnostic results. In this application, it can be used as an option comparable to dobutamine, which is preferred in the USA [109]. Vasodilator SE is the test of choice for the evaluation of coronary flow reserve, which is increasingly recognized as a major prognostic determinant in chronic coronary syndromes and beyond coronary artery disease [110]. In the 2021 guidelines of the American College of Cardiology/American Heart Association for the diagnosis of chest pain, CFVR received a class 2b recommendation ("*may be useful*") in patients with ischemia and normal coronary arteries, and its role is acknowledged also in patients with known or suspected coronary artery disease for refining risk stratification [111]. The vasodilator test is especially suitable for the comprehensive ABCDE SE protocol, allowing the assessment of inducible ischemia (step A), pulmonary congestion (step B), contractile reserve (step C), Doppler-based coronary flow velocity reserve (step D), and heart rate reserve (step E) in one test, each step showing independent and incremental prognostic value [112, 113].

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Adenosine, Regadenoson Stress Echocardiography

20

Alla Boshchenko, Olga Zhuravleva, Alexander Vrublevsky, and Eugenio Picano

Keywords

Adenosine receptors · Hyperemia · Ischemia · Coronary flow reserve · Vasodilation

20.1 Background

Intravenous infusion of adenosine or an intracoronary bolus of adenosine induces maximal flow (hyperemia). Adenosine is a gold standard for invasive assessment of fractional flow reserve as a lesion-specific index of the functional significance of epicardial coronary stenosis. Under physiological conditions, the epicardial coronary artery has laminar flow and no or low gradient pressure from the proximal to the distal part. Coronary stenosis induces in-site flow acceleration and can decrease pressure distal to lesions at rest, limiting hyperemia flow acceleration and provoking an additional decrease of post-stenotic pressure during stress. Fractional flow reserve is a pressure gradient between the pressure distal to (i.e., guidewire pressure) and proximal to (i.e., the aortic pressure) stenotic lesions at maximal hyperemia and identified as normal at the level > 0.80 [1].

In addition, intravenous adenosine is a gold standard also for the invasive assessment of the microvascular coronary function, predominantly, but not exclusively, endothelium-independent vasodilation of coronary small vessels with a contribution

A. Boshchenko (✉) · O. Zhuravleva · A. Vrublevsky
Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russia

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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of endothelium-dependent vasodilation mostly evident in large epicardial vessels [2]. Under normal physiological conditions, myocardial perfusion is autoregulated by pre-arterioles in the epicardium and arterioles within the myocardium, so microvascular tone contributes to the majority of coronary resistance. Pathological microvascular conditions, including perivascular fibrosis (hypertension, [3] coronary artery disease [4], myocardial hypertrophy, diabetes mellitus, cardiac transplantation, etc.), can provoke microvascular angina by increasing microvascular tone at rest and/or limiting vasodilatation in stress. Small caliber vessels (≤300 μm in diameter) are not directly visualized during invasive coronary angiography; however, the index of microcirculatory resistance can be quantified using pressure and temperature-sensitive coronary guidewires during maximal hyperemia with adenosine [5]. It provides a direct assessment of microvascular function, independent of coronary stenosis severity, and could be helpful in the assessment of pathological microvascular changes and prognosis.

Therefore, the use of vasodilators to induce stress seems justified in non-invasive functional tests such as radionuclide scintigraphy [6], positron emission tomography [7], cardiac magnetic resonance [8], and stress echocardiography (SE). Early, radionuclide scintigraphy and positron emission tomography with vasodilators have been the modalities for the traditional assessment of myocardial perfusion imaging; SE and cardiac magnetic resonance with vasodilators have been the modalities traditionally utilized for wall motion imaging and detected regional wall motion abnormality as the main diagnostic criterion to indicate the presence of ischemia [3]. Now, contrast cardiac magnetic resonance and SE with or without contrast agent are used for combined real-time assessment of wall motion abnormalities, contractile ventricular reserve, and myocardial perfusion/coronary flow reserve imaging [2, 9]. To optimize the ischemic effect, higher doses than those needed for perfusion imaging are needed, and for this reason, the protocols employed in the SE lab must adopt higher and faster doses of vasodilator compared to perfusion imaging, which is, in theory, ischemia-free.

Vasodilator SE testing is a procedure in which patients are exposed to an intravenous infusion of vasodilator while symptoms, hemodynamic parameters, electrocardiogram, and imaging are simultaneously monitored [10].

Adenosine and dipyridamole have been the mainstays of vasodilator stress agents for almost 3 decades [11]. Various pharmacologic vasodilators are currently available, including older adenosine, dipyridamole, and most recently appeared regadenoson, binadenoson, and apadenoson (Table 20.1). These agents have a common

Table 20.1 Three generations of adenosinergic stress

	Prototype	First clinical application	Mediator	Stimulated receptors	Half-life
First generation	Dipyridamole	1980	Endogenous adenosine	A1, A2A, A2B, A3	Hours
Second generation	Adenosine	1990	Exogenous adenosine	A1, A2A, A2B, A3	Seconds
Third generation	Regadenoson	2000	Selective adenosine agonist	A2A (A1)	Minutes

mechanism, mediated through activation (non-selective or selective) of adenosine A2A receptors with resultant coronary vasodilation [12]. Regadenoson is a third-generation prototype acting as selective A2A adenosine agonist receptors.

20.2 Pharmacology and Pathophysiology

Adenosine is a nucleoside, i.e., a purine-based adenine bound to sugar ribose [13] acting through its specific purine (adenosine) receptors located on the outer surface of the cell membrane. In physiological conditions, adenosine is produced inside the cell and is diffused, driven by the concentration gradient, to extracellular space to activate its receptors (Fig. 20.1).

Approximately 90% of adenosine in the heart and vessels is created by the S-adenosyl homocysteine hydrolase pathway [11]. At physiological concentrations, this adenosine inside the cell is predominantly salvaged, i.e., metabolized to adenosine 5-monophosphate and further, by the enzyme adenosine kinase. When adenosine binds with the phosphate, it becomes a nucleotide, i.e., adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate. Therefore, the second and fast pathway of adenosine generation is the degradation (dephosphorylation) of those nucleotides with a help of the enzyme adenylate cyclase (5′-nucleotidase). Under normal conditions, this pathway contributes only up to 10% of the endogenous adenosine in the heart.

At higher concentrations in the cell, adenosine is degraded in a short time by the enzyme of adenosine deaminase to inosine, which is biologically inactive. It is the end stage of adenosine degradation in myocytes, but in the endothelial cells, adenosine is broken down from inosine to hypoxanthine and uric acid [11].

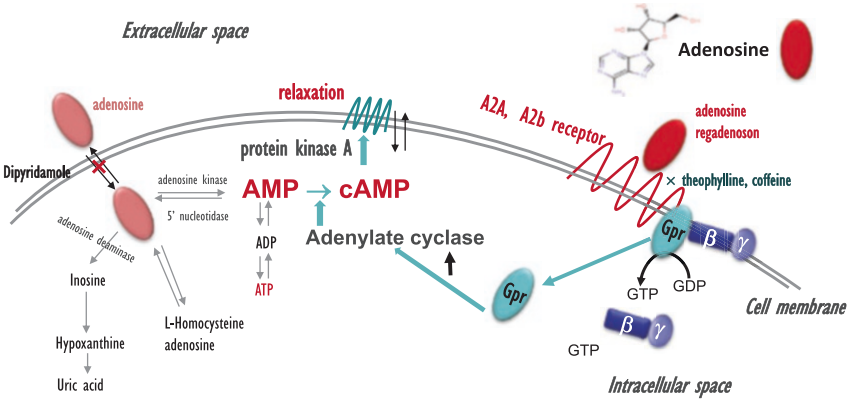


Fig. 20.1 The cellular actions and receptor distribution of adenosine and newer selective A2A receptor agonists

Extracellular adenosine returns to the cell by reuptake through the cell membrane by facilitated diffusion. Probably the chemistry signal that induces endogenous adenosine synthesis is the oxygen supply/demand ratio via the variation of the potential of phosphorylation. In fact, in case of insufficient oxygen supply, there is a reduction in the potential of phosphorylation and the consequent increment of free adenosine monophosphate in the cytoplasm that is available as a substrate of 5′-nucleotidase [14]. The increment of 5′-nucleotidase determines an increased production of adenosine (Fig. 20.1).

20.2.1 Adenosine Receptors

Adenosine receptors can be divided into two major subtypes: (1) A1 and A3 receptors, which inhibit adenylate cyclase (2) A2 receptors stimulated enzyme adenylate cyclase (Fig. 20.1). The A1 receptors predominate in the myocardium, whereas the A2 receptors are found in the coronary arteries (endothelial and smooth muscle cells).

All vasodilators exert the vasodilation effects by binding to A2A receptors; these receptors are stimulatory guanine nucleotide-binding proteins (G proteins), which activates adenylate cyclase, thereby increasing cyclic adenosine monophosphate, leading to the phosphorylation of protein kinase A and the production of membrane hyperpolarization (Fig. 20.1). Therefore, the activation of A2A receptors dilates the coronary arteries, causing hyperemia and increased coronary blood flow. Activation of A2A receptors in presence of critical coronary stenosis plays a key role in inappropriate vasodilation and subendocardial ischemia for vertical and horizontal steal phenomena and regional wall motion abnormality.

The human adenosine A2A receptor gene has been localized on chromosome 22q, and several genetic polymorphisms have been identified [15] as potentially responsible, at least partly, for the heterogeneity in response to coronary flow during stress imaging [16] (Fig. 20.1).

The main physiological effects of exogenous adenosine as significant factors for SE, classified according to the involvement of A1, A2, or A3 receptors [17] are presented in Table 20.2.

Table 20.2 Adenosine receptors: a view from the imaging laboratory

Receptor	Effect	Desired diagnostic endpoint
A1	Atrioventricular block Bradycardia Preconditioning	
A2A[a]		Coronary vasodilation, sympathetic surge
A2B[a]	Bronchoconstriction due to mast cell degranulation	
A3	Anti-inflammatory effects (peripheral blood mononuclear cells)	

[a]The additional effect of stimulation: A2B and A2A = peripheral vasodilation, A1 = renal vasoconstriction

20.2.2 The Pharmacological Goal for Vasodilator for SE

Exogenous adenosine usually has a nucleotide prototype (adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate) and is a precursor of adenosine, degrades in-site quickly to adenosine with non-selective acting to A1, A2 and A3 receptors (Fig. 20.1).

Dipyridamole blocks adenosine reuptake with a resultant increase of adenosine in extracellular space and greater non-selective activity on the adenosine receptor site (Fig. 20.1). When patients receiving adenosine (140 μg kg^{-1} per min) for controlled hypotension were pretreated with clinical doses of dipyridamole (to reduce the dose requirements of adenosine), the arterial plasma concentration was shown to be 2.5 μM, a level ten times the normal level [18].

Third-generation stress adenosinergic agents, such as regadenoson, binadenoson, and apadenoson, may be further enhanced by, i.e., they are short-acting selective A2A agonists [19] (Fig. 20.1). The affinity of regadenoson for human adenosine A2A receptors exceeds that for adenosine A1 receptors by more than nine-fold, and its affinity for A2B and A3 receptors is minimal. In April 2008, Regadenoson (generic name code: CVT-3146, Lexiscan, Astellas Pharma US, Inc. Deerfield, IL) was the first selective A2A agonist approved by the US Food and Drug Administration for use as a vasodilator in conjunction with radionuclide myocardial perfusion imaging. Its counterpart, Rapiscan (Rapidscan Pharma Solutions EU Ltd., London, UK), was authorized by the European Commission with the same indication in 2010. Now, up to 83% of all perfusion stresses are performed with selective A2A agonists [20].

Theophylline as an adenosine antidote and other methylxanthines (such as caffeine) block adenosine receptors in a dose-dependent manner [6].

20.2.3 Pharmacologic Comparison of Vasodilator Agents (Adenosine, Dipyridamole, and Regadenoson)

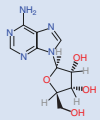
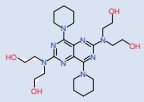
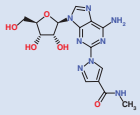
Pharmacologic differences between the three vasodilator stress agents are outlined in Table 20.3.

Regadenoson has, in theory, attractive features close to the "ideal" agent for its rapid onset of action, adequate duration of effect allowing image acquisition, and fewer side effects. The reason for that is its selective stimulation of A2A receptors specifically responsible for coronary vasodilation, avoiding undesirable effects of A1, A2B, and A3 receptors stimulation (such as dyspnea, headache, and flushing). The incidence of these side effects is not substantially reduced when compared to adenosine, although their severity is decreased [21].

20.2.4 Hemodynamic Effect Adenosine

The main hemodynamic effects of exogenous adenosine are caused by non-selective stimulation of adenosine receptors. They are listed in Table 20.4.

Table 20.3 Pharmacologic properties between the three vasodilator stress agents

	Adenosine	Dipyridamole	Regadenoson
Trade name	Adenoscan/ Adenocard	Persantine	Lexiscan (in USA) Rapiscan (in Europe)
Company	Astellas Pharma US, Inc. Deerfield, IL	Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT	Astellas Pharma US, Inc. Deerfield, IL/Rapidscan Pharma Solutions EU Ltd., London, UK
Indications	Pharmacologic stress in MPI Treating PSVT	Pharmacologic stress in MPI	Pharmacologic stress in MPI Orally to treat thrombotic states
Molecular formula	Endogenous vasodilator of purine derivatives $C_{10}H_{13}N_5O_4$ 	Pyrimidine derivative $C_{24}H_{40}N_8O_4$ 	Purine derivative $C_{15}H_{18}N_8O_5$ 
Mechanism of action	Non-selective A2A receptor activation	Blocks adenosine reuptake	Selective A2A receptor activation
Administration	Intravenous infusion	Intravenous infusion	Intravenous bolus
Half-life	<10 s	30–60 min	Triphasic(2–4 min, 30 min, 120 min)
Time to peak	30 s	7–15 min	1–4 min
Excretion	Cellular intake	Glucuronide conjugates an unchanged drug in feces	57% of drug unchanged in urine

MPI myocardial perfusion imaging, *PSVT* paroxysmal supraventricular tachycardia

Table 20.4 Cardiovascular effects of exogenous adenosine administered intravenously in humans

• Vagal inhibition (low doses), increase in heart rate
• Inhibition of the sinus node and atrioventricular conduction in high doses, bradycardia, atrioventricular block
• Sympathetic stimulation
• Vasodilatation in all arteriolar beds, except renal preglomerular arterioles (vasoconstriction)
• Decrease in reperfusion injury
• Hyperventilation (explained by interaction with carotid chemoreceptors)

The many cardiovascular effects substantiating the proposed potential clinical uses of adenosine are listed in Table 20.5.

Table 20.5 Potential clinical uses of adenosine

• Paroxysmal supraventricular tachycardia
• Exercise-induced ventricular tachycardia
• Controlled hypotension during intracranial vascular surgeries
• Afterload reduction in congestive heart failure
• Antiplatelet aggregation (cardiopulmonary bypass, hemodialysis)
• Reduction of reperfusion injury
• Diagnosis and prognosis of coronary artery disease

The most important diagnostic application of adenosine infusion is a cardiac stress imaging. The intravenous infusion of adenosine induces a slight increase in the heart rate and cardiac output, and a slight decrease in systemic pressure. The mild tachycardia occurs in spite of the direct, negative chronotropic and dromotropic effects of adenosine due to stimulation of A1 myocardial receptors; it is a consequence of adrenergic activation, occurring either through direct stimulation of sympathetic excitatory arterial chemoreceptors [22] or indirectly, through systemic vasodilation. In normal subjects, the coronary blood flow increases from four to five times the baseline flow following adenosine—an increase comparable to the one caused by high-dose dipyridamole and substantially higher than that induced by exercise or dobutamine, during which coronary blood flow increases about three times the baseline value [23]. The maximal coronary dilatory effect is reached within 2 min of adenosine administration and wears off rapidly within 2–5 min after the infusion is stopped [24]. Intravenous adenosine triphosphate in dose >140 $\mu g\ kg^{-1}$ per min has the same effect on coronary flow as intravenous and intracoronary adenosine diphosphate, but adenosine triphosphate has longer half-life (>20 s) and duration of effects [24, 25]. Adenosine can induce elevation in pulmonary capillary wedge pressure and/or left ventricular end-diastolic pressure only in presence of myocardial ischemia or diastolic dysfunction with normal coronary arteries [26]. The newer selective A2A receptor agonist, regadenoson, was shown to need lesser molecules to achieve 50% of the maximum vasodilator effect (5.9 nM of adenosine vs. 6.4 nM of regadenoson), and to be >100 times more potent than adenosine in increasing the coronary blood flow [27]. In the absence of coronary stenoses, regadenoson induces a two- to threefold increase in coronary blood flow and increased wall thickening.

The decrease in mean arterial blood pressure was similar between regadenoson and adenosine (13 mmHg and 18 mmHg, respectively). However, the increase in heart rate was higher with regadenoson than adenosine. The A2A-mediated sinus tachycardia was related to the direct sympathetic excitation and less due to baroreceptor reflex mediation [28].

The power and time course of the coronary vasodilator effect of adenosine and other newer synthetic adenosine receptor agonists are shown in Table 20.3 [19].

20.3 Methodology

Adenosine infusion enables combined assessment of global contractile ventricular function, wall motion analysis, and coronary flow reserve/myocardial perfusion imaging and is used more often in European (as adenosine monophosphate or adenosine diphosphate) and Asian countries (as adenosine triphosphate) [29].

For SE, the adenosine dose can be started at 100 μg kg^{-1} per min and gradually increased to a target of 140–210 μg/kg^{-1} per min for 6 min [4] (Fig. 20.2). However, adenosine vasodilator effect is dose-dependent, and only dose 140 μg kg^{-1} and upper can be enough to induce near maximal Doppler-flow hyperemia [24, 25, 30]. A dose of 140 μg kg^{-1} and upper provides the same vasodilation for adenosine and adenosine triphosphate [24, 25]. The dose of 100 μg kg^{-1} per min 2′ is used for the assessment of myocardial viability; the dose of 140 μg kg^{-1} per min in 6′ is routinely recommended for myocardial ischemia. Increasing the dose up to 160 and 210 μg kg^{-1} per min could be advised in case of a negative test at the step of 140 μg kg^{-1} per min and is needed only in 16–18% of cases [24, 30, 31]. When side effects are intolerable, down-titration of the dose is also possible. Earlier, heart rate change of >10% was used as a non-invasive marker of flow hyperemia, but a poor correlation between non-invasive markers of hyperemia, such as a change in heart rate, blood pressure, and rate-pressure product, and coronary hyperemia during invasive control was found in large studies [30].

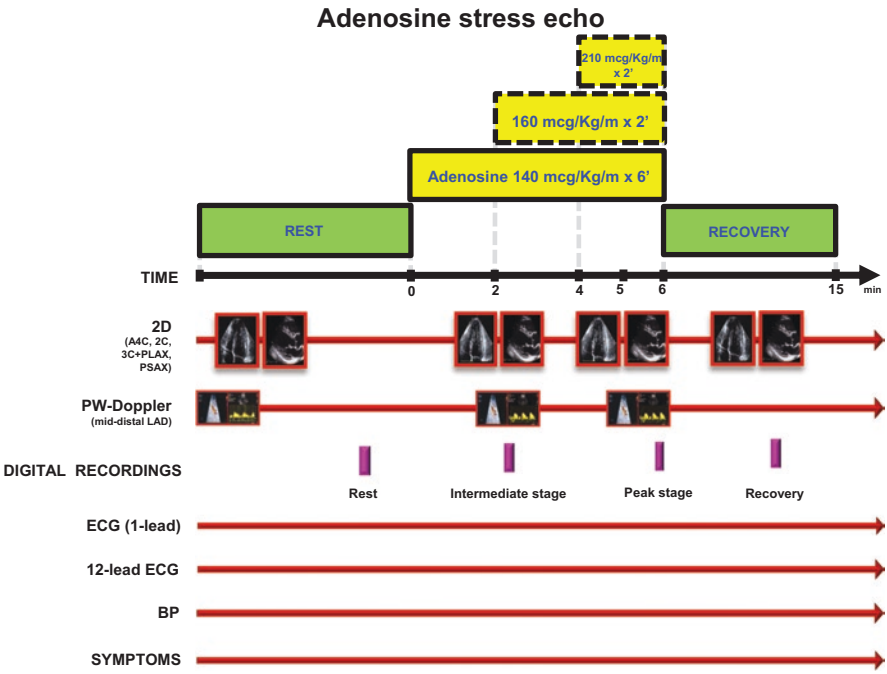


Fig. 20.2 Protocol of adenosine SE

As with dipyridamole, test sensitivity can be potentiated using a handgrip [32] or atropine, which can be added to adenosine infusion [31, 33].

Protocol with the dose 140 μg kg^{-1} per min in 2′ could be used for patients with chest pain and negative exercise stress test or with non-obstructive coronary artery disease. The main goal of this test is the assessment of coronary flow reserve for the appearance of microvascular disease and risk stratification.

Some authors suggest infusing adenosine for no more than 90 s, taking into account that the maximal hyperemic effect is already reached at 30–60 s [34, 35]. The short adenosine infusion seems to be more effective, safer, and better tolerated than the standard dosage, but it has a disadvantage that there is not enough time to perform a complete assessment of left ventricular wall motion. Although not routinely advised, adenosine injection of 2.5 mg bolus produces an increment in coronary flow reserve similar to that obtained a by 3-min venous infusion [32]; however, intense hyperpnea can be a result which is uncomfortable to the patient and can interfere with the technical acquisition of adequate echocardiographic images.

Similar to dobutamine, administration of adenosine requires an infusion pump, whereas dipyridamole may be injected with a handheld syringe. Regadenoson is currently administered as a bolus of 0.4 mg in a 5 mL solution (without weight-based dose adjustment) injected over 10 s followed by a 5 mL saline flush to ensure appropriate drug delivery. The optimum time for image acquisition for perfusion imaging is 2–10 min after drug infusion. Regadenoson enables combined assessment of myocardial perfusion imaging and wall motion analysis and is used most often in the United States and UK. The addition of atropine may be used to potentiate the stress [36–40].

20.4 Tolerability and Safety

Side effects are not infrequent and may become a limiting factor in a significant number of patients—up to 20% [41]. The most frequent limiting side effects for adenosine-mediated vasodilator stressors include shortness of breath, flushing, headache, arterial hypotension, intolerable chest pain (sometimes unrelated to underlying ischemia, possibly induced for direct stimulation of myocardial A1 adenosine receptors), and high-degree atrioventricular block. Atrioventricular block of I-II degree appears in 2% of tests, arterial hypotension below 90 mmHg—3%, severe bronchospasm—0,1% [29, 42]. Minor side effects such as feeling of heat, flushing, headache, nausea, and other appear in 80–84% [42]. Hemodynamically significant decrease in systolic blood pressure (>20 mmHg) is more likely in patients with severe aortic stenosis [43]. Adenosine triphosphate is better tolerated and causes fewer side effects than adenosine diphosphate [31]. Exogenous adenosine has an even more pronounced negative chronotropic and dromotropic effect than endogenous adenosine [19], making the appearance of advanced atrioventricular blocks more frequent with adenosine than with dipyridamole and adenosine triphosphate for equivalent doses. Most reactions with adenosine resolve within 1–5 min. On very rare occasions, an infusion of aminophylline is required. The quality of side effects is similar to ones experienced by the same patients during dipyridamole

stress, but these effects are quantitatively more pronounced during adenosine stress [43–46]. However, in contrast to dipyridamole, side effects from adenosine and regadenoson rapidly dissipate, and very rarely cause significant complications; this is due to the very short half-life of adenosine and regadenoson. The merits and limitations of adenosine and regadenoson in comparison with the prototype vasodilator dipyridamole are shown in Table 20.6. The incidence of major life-threatening complications (such as myocardial infarction, ventricular tachycardia, and shock) for adenosine has been shown but to be very low, with only one nonfatal myocardial infarction in approximately 10,000 cases (see Table 20.6). As happens with dipyridamole—Coronary vasospasm may occur rarely during or after adenosine stress, which may lead to serious adverse outcomes if unrecognized [47, 48].

Despite the theoretical benefit of increased safety and tolerability, especially in asthmatic patients [21], selective A2A agonist regadenoson has shown similar side effects compared to adenosine; most reactions resolve within 30 min. However, the severity of symptoms is less and the tolerance score greater after regadenoson stress when compared to adenosine [19]. Judging by the post-marketing experience, the most common side effects reported for regadenoson include the following: headache (26%), chest tightness (13%), nausea (6%), abdominal pain (5%); atrioventricular block, syncope, and seizure were reported in <1% of patients [20]. Furthermore, there was an increase in the incidence of seizures noted in the post-marketing experience. Importantly, regadenoson is given as a single rapid bolus, whereas both adenosine and dipyridamole are infused over minutes. This is of important implications in terms of physician and patient time.

Data shown from two major trials (The Adenoscan Versus Regadenoson Comparative Evaluations for Myocardial Perfusion Imaging [ADVANCE-MPI and ADVANCE-MPI 2] trials [49] demonstrated the non-inferiority of regadenoson as compared to adenosine for the overall symptoms including flushing, chest pain, and dyspnea. In November 2013, the US Food and Drug Administration

Table 20.6 Major side effects of pharmacological stress protocols

Stress protocol	Dipyridamole 0.56 mg kg^{-1}	Dipyridamole 0.84 mg kg^{-1}	Adenosine 140 μg kg^{-1} per min	Regadenoson 400 μg/5 mL bolus	Dobutamine 40 μg kg^{-1} per min ± atropine
Reference	Lette et al. [44]	Picano et al. [45]	Cerqueira et al. [41]	Iskandrian et al. [19]	Picano et al. [46]
No. of patients	73,806 (9066 with 0.75 or 0.84 mg kg^{-1})	10,451	9256	784	2949
Major side effects	0.04%	0.07%	<0.10%	<0.10%	0.4%
Fatal MI[a]	0.01%	0.01%	0%	0%	0%
Nonfatal MI[a]	0.017%	0.02%	0.01%	0%	0.07%
VT/VF	0.008%	0.01%	0%	0%	0.05%

MI myocardial infarction, *VT* sustained ventricular tachycardia, *VF* ventricular fibrillation
[a]In November 2013, some cases of MI were reported with regadenoson and adenosine

Table 20.7 Adenosine versus dipyridamole and regadenoson for vasodilator SE

	Dipyridamole	Adenosine	Regadenoson
Half-life	Hours	Seconds	Minutes
Aminophylline	Always	Rarely	Sometimes
Echo difficulty	Mild	Moderate	Mild
Limiting side effects	5%	10–20%	5%
Patient tolerance	Excellent	Good	Excellent
Prognostic value	Extensive	Proven	In progress

Communication warned health safety professionals of the very rare but serious risks of heart attack and death with regadenoson. Regadenoson can provoke myocardial ischemia up to myocardial infarction and—rather unexpectedly due to its relatively weak effect on A1 receptors—advanced atrioventricular blocks up to cardiac asystole. In principle, the application of the echo-controlled stress should increase safety, due to the possibility to detect ischemia in real-time and stop the test with the administration of aminophylline as soon as the diagnostic end point has been reached.

In summary, on the basis of the large experience gained in nuclear cardiology with myocardial perfusion imaging [41, 44–46], adenosine and regadenoson are probably the least well tolerated subjectively, but at the same time possibly the safest among pharmacological stressors (see Table 20.7).

20.5 Indications, Contraindications, and Influencing Factors

The main indications for adenosine/regadenoson stress test are the detection of macrovessel/microvessel coronary artery disease with phenotypes of myocardial ischemia, myocardial viability, myocardial dysfunction, and microvascular dysfunction.

The safety record and short half-life make adenosine especially indicated in patients with severe aortic stenosis [50, 51], asymptomatic post-operative children who have undergone arterial switch operation for transposition of great arteries [52], or elderly patients [53], who may be especially vulnerable to complications during dipyridamole or dobutamine stress. Possibly, emerging applications of regadenoson across varying clinical populations included regadenoson use in patients with the moderate and severe chronic obstructive pulmonary disease [37, 54], who have an indication to stress imaging and may want to avoid adenosine-induced bronchoconstriction and respiratory compromise, although in these patients the use of the bronchodilator dobutamine might be more reasonable.

The list of contraindications of adenosine and regadenoson is identical to that for dipyridamole. Absolute contraindications are severe hypotension and severe airway obstruction. Since 2013, changes to the vasodilator labels and updated recommendations for avoiding the use of these agents in patients with signs or symptoms of unstable angina or cardiovascular instability were implemented [55].

Like dipyridamole, antianginal drugs and caffeine-contained products lower adenosine SE sensitivity, whereas concomitant therapy with oral dipyridamole potentiates the cardiovascular effects of adenosine. So, methylxanthines (i.e., caffeine, theobromine, theophylline) and drugs with theophylline-elevating properties (beta blockers, cimetidine, erythromycin, etc.) should be removed 24 h before the stress test.

20.6 The Main Stress Markers of Coronary Artery Disease and Their Diagnostic Accuracy

Conventional vasodilator SE is based on functional imaging, to detect regional wall motion abnormality as a diagnostic criterion to indicate the presence of ischemia [3].

Ultrasound contrast enhancement improves endocardial border definition for regional wall motion abnormality assessment, but also uniquely enables myocardial perfusion imaging [5, 56]. Ultrasound contrast enhancement also allows improved Doppler coronary flow velocity imaging [57], which is currently recommended in combination with wall motion assessment during vasodilator SE [58]. With adequate dosing, adenosine SE has the potential to assess wall motion, left ventricle contractile reserve, B-lines, heart rate reserve, and coronary flow reserve (or myocardial perfusion) simultaneously in one sitting, with a single stress agent [59–61].

The full range of sensitivities of adenosine SE based on wall motion abnormality for detection of coronary artery disease has been reported, depending on the nature of the population studied [32, 62–66]. Higher values come from expert centers evaluating patients with previous myocardial infarction and multivessel disease (Table 20.8), and the lowest values in individuals without previous myocardial infarction and with single-vessel disease (50%) [69].

On the basis of a published meta-analysis of 11 studies, adenosine SE, based on wall motion abnormalities, showed the same sensitivity (79%), specificity (91.5%),

Table 20.8 Diagnostic accuracy of adenosine echocardiography with regional wall motion abnormalities

Authors	Reference	Year	Patients	Dose	Sensitivity (%)	Specificity (%)
Zoghbi et al.	[3]	1991	73	100–140	85	92
Edlund et al.	[62]	1991	54	60–200	89	Na
Martin et al.	[63]	1992	37	140	76	60
Marwick et al.	[65]	1993	97	180	86	71
Amanullah et al.	[67]	1993	40	140	74	100
Heinle et al.	[68]	1993	42	140	56	NA
Case et al.	[64]	1994	26	140	96	100
Takeishi et al.	[66]	1994	61	140	51	Na
Tawa et al.	[32]	1995	67	180	64	91
Djordievic et al.	[4]	1996	58	200	92	88
Anthopoulos et al.	[53]	1996	120	140	66	90

and accuracy as exercise echocardiography, dipyridamole echocardiography, and dobutamine echocardiography, with superior specificity when compared to SPECT stress imaging [68].

Increasing the dose of the vasodilator stress and/or the combination with a handgrip [32] can improve the diagnostic sensitivity without significant loss in specificity [4]. Coronary flow velocity reserve added to wall motion analysis can affect positively the sensitivity and negative predictive value of vasodilator SE [70, 71].

Adenosine can be used to assess the heart rate reserve as a marker of the sympathetic reserve, due to the sympatho-adrenergic stimulation of carotid chemoreceptors. The heart rate reserve is impaired in patients with angina and normal coronary arteries, especially in women [72].

Myocardial perfusion echocardiography with ultrasound contrast enhancement during vasodilator stress (analyzed visually and quantitatively) was shown to enhance the diagnostic performance over wall motion analysis alone for the detection of coronary artery disease [73–81]. Perfusion defects, quantitative myocardial flow, myocardial flow reserve, and prolongation of flow time after contrast flash are suggested as perspective markers of ischemia.

Some initial data show that adenosine infusion may elicit an inotropic response in viable myocardium with resting dysfunction [82], thereby representing an alternative to dobutamine for the recognition of viability through pharmacological stimulation.

A few studies have suggested benefits of the full or short 2-min protocol [68] with adenosine for analysis of coronary flow reserve in patients with suspected microvascular disease, with 94%-concordant results when compared to invasive hyperemic microvascular resistance [83]. Moreover, vasodilator myocardial perfusion imaging/coronary flow reserve is a unique non-invasive non-radiation tool for this diagnostic reason [1].

Data shown from two major trials (The Adenoscan Versus Regadenoson Comparative Evaluations for Myocardial Perfusion Imaging [ADVANCE-MPI and ADVANCE-MPI 2] trials [49] demonstrated the non-inferiority of regadenoson as compared to adenosine for detection of ischemia. Recently, a few studies have shown lower sensitivity (50%) and negative predictive value regadenoson SE as a bedside test to detect coronary artery stenosis and myocardial ischemia [84]. What is good for perfusion (which does not require myocardial ischemia) is not necessarily good for ischemia imaging. The ischemic effect is dissociated from the perfusion (vasodilatory) effect, and the coronary arteriolar vasodilation must be fast and sustained to achieve detectable ischemia with regional wall motion abnormality. With adenosine and dipyridamole, excellent sensitivity was achieved with a higher dose than with the dose of perfusion imaging. The adenosine echo dose is up to 200, compared to 0.56 μg/kg/min of the perfusion dose. Dipyridamole echo dose is 0.86 mg/kg (in 4 or 6 min), compared to the perfusion dose of 0.56 mg/kg over 4 min. For ischemia imaging vasodilators must be given at higher doses and/or faster rates compared to perfusion imaging.

20.7 Prognostic Value of Adenosine SE

Data on the prognostic value of adenosine SE findings are limited to date, but consistent with the larger evidence collected with perfusion imaging with nuclear and cardiovascular magnetic resonance techniques [85, 86]. A prognostic role of myocardial perfusion during SE has been demonstrated in studies with different pharmacologic stressors [87, 88]. The isolated reduction in heart rate reserve or coronary flow reserve derived from non-contrast or real-time myocardial perfusion contrast echocardiography during adenosine stress in patients with known or suspected coronary artery disease adds independent and incremental prognostic information over clinical and resting echocardiography variables in predicting events [89, 90]. In asymptomatic type-2 diabetics, a reduced coronary flow reserve was associated with poor glycemic control and a higher risk of subsequent events [91].

A positive viability response with wall motion recovery in segments with resting dysfunction identified a lower-risk subset in patients with acute myocardial infarction who underwent primary coronary angioplasty after an acute myocardial infarction [92].

20.8 Practical Aspects: Cost and Availability

The choice of one vasodilator stressor over the other depends on patient characteristics, drug cost, and the physician's preference. Cost plays a major role in that regard. In some countries, an additional limitation of adenosine is its exorbitant cost: in the United States, adenosine costs $ 179, dipyridamole $ 95, and dobutamine $ 1 per exam. In one study [93], the mean cost of the vasodilator stress agent was $154 ± 127 with adenosine and $10 ± 2 with dipyridamole ($p < 0.001$). When the cost of adverse effects and monitoring were included, the total cost rose to $160 ± 27 and $19 ± 3 with adenosine and dipyridamole, respectively ($p < 0.001$). In Europe, adenosine costs € 100, dipyridamole € 3, and dobutamine € 9. However, it is also possible to have an adenosine triphosphate or generic formulation of adenosine from the hospital pharmacy at a low cost of around € 1–2 [31, 58].

Regadenoson is more expensive than other drugs. However, regadenoson appears to have many of the attributes of an ideal pharmacologic stress agent and the less complex administration of regadenoson (fixed bolus dose) [19] will simplify the workflow and result in potential milder adverse effects which in turn lead to increased patient satisfaction and efficacy of the tests, all resulting in improved cost-effectiveness.

In one study [63], it was found that among adenosine, dipyridamole, and dobutamine, adenosine was the test most disliked by the patients. But the vasodilator stress test is the test most liked by doctors (especially beginners) for simplicity, body stability of the patient under stress, and low frequency of serious adverse events.

20.9 Clinical Guidelines

Adenosine or regadenoson SE based on the analysis of wall motion and thickening can be used as an alternative to dipyridamole for myocardial ischemia, myocardial viability, and prognosis of patients with chest pain or dyspnea. Doses required for wall motion imaging are higher than those needed for perfusion imaging since ischemia in vulnerable subjects is more frequent with stronger and faster vasodilation [94, 95].

Additional myocardial perfusion imaging with real-time myocardial contrast echocardiography or coronary flow imaging of the left anterior descending coronary artery can be used to improve the detection of coronary artery disease [54, 95]. Vasodilator stress is the test of choice for the assessment of coronary flow velocity reserve [96], although this assessment is also possible with dobutamine, pacing, and semi-supine exercise [97].

With the last-generation comprehensive SE protocol, adenosine SE can be performed with simultaneous assessment also of B-lines, left ventricular contractile reserve, and heart rate reserve to capture the many vulnerabilities of the patient beyond coronary artery stenosis [61]. Vasodilator perfusion imaging with dipyridamole, adenosine, or regadenoson is ideally suitable for ABCDE comprehensive SE. Adenosine (or another vasodilator test) with transthoracic Doppler echocardiography is recommended for the assessment of coronary flow velocity reserve in the mid-distal left anterior descending coronary artery with the class of recommendation 2b ("may be considered") in patients with angiographically normal coronary arteries and suspected microvascular disease in the 2019 guidelines of the European Society of Cardiology [1] and the 2021 guidelines of American College of Cardiology/American Heart Association [98].

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Pacing Stress Echocardiography

21

Edyta Płońska-Gościniak and Eugenio Picano

Keywords

Coronary flow reserve · Heart rate · Force-frequency · Permanent pacemaker

21.1 Historical Background

High-rate pacing is a valid stress test in conjunction with stress echocardiography (SE); it is independent of physical exercise and does not require drug administration. It started from an invasive (intravenous) right atrial pacing modality, combined with an ionizing imaging technique such as radionuclide ventriculography [1], moving to a semi-invasive modality combined with two-dimensional (2D) echocardiography, using a transnasal [2] or transoral [3] catheter for transesophageal left atrial pacing, and finally evolving to a noninvasive modality with external programming in patients with a permanent pacemaker for right atrial or ventricular pacing [4]. The appeal of the method has increased over the last 20 years in parallel with the exponential increase of implantation of permanent pacemakers related to the increase of the elderly population and the expanding indications for pacing. According to a 2017 report by the European Heart Rhythm Association, a total of 547,586 pacemakers, 105,730 implantable cardioverter-defibrillators, and 87,654 cardiac

E. Płońska-Gościniak (✉)
Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
e-mail: edytaplonska@life.pl

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Fig. 21.1 SE laboratory. Pacing SE with an external programmer in a patient with a permanent pacemaker. (Image courtesy of Prof. Edyta Plonska, Szczecin, Poland)

resynchronization therapy devices were implanted in the European area in 2016 [5]. People with cardiac implantable electronic devices often need stress testing and their therapeutic device can be the best diagnostic device for SE (Fig. 21.1). However, permanent pacemakers have programmed development of atrioventricular block at high heart rates so one may be required to liaise with the pacemaker technician.

21.2 Pathophysiology

The pathophysiological rationale of pacing stress is obvious, with the stress determined by a controlled increase in heart rate, which is a major determinant of myocardial oxygen demand, and thereby tachycardia may exceed a fixed coronary flow reserve in the presence of hemodynamically significant coronary artery disease. In healthy subjects, cardiac volumes decrease [6, 7], and blood pressure does not change significantly during pacing, whereas contractility increases only minimally, possibly due to the Bowditch-Treppe or staircase phenomenon [8], i.e., the increase in contractility due to the increase in heart rate [9] (Table 21.1).

Heart rate is a major factor influencing transmural blood flow distribution and regional function because when coronary vasodilation is maximal, there is

Table 21.1 Hemodynamic and volumetric changes during pacing stress

	Pacing-normal	Pacing-ischemic
End-diastolic volume	Decrease	Decrease
End-systolic volume	Decrease	Unchanged—increased
Systolic blood pressure	No change	No change
Ejection fraction	Mild increase	No increase—decrease

an inverse relationship between the heart rate level and subendocardial perfusion. The drop in the subendocardial-to-subepicardial flow ratio associated with rapid atrial pacing in the presence of tight coronary stenosis is critical to the development of regional dysfunction, because regional percent systolic thickening is linearly and tightly related to subendocardial, but not to transmural flow [10]. In experimental dog models, pacing stress shows good sensitivity, only marginally lower than high-dose dobutamine or dipyridamole stress, for the detection of significant coronary stenoses by SE [11]. In patients with permanent right ventricular pacing, perfusion defects can often be found in the inferior and apical walls, which are probably the earliest activated sites under right ventricular apical pacing [12]. The regional coronary flow reserve can be impaired in the dominant coronary artery perfusing these regions, whereas it is usually normal in the left anterior descending coronary artery. This abnormality is at least partially responsible for the low specificity of stress myocardial scintigraphy [13]. In patients with permanent pacemakers, chronic right ventricular pacing also induces asymmetric thickness of the left ventricular wall [14]. Asynchronous electric activation of the left ventricle decreases mechanical load in early vs. late activated regions of the ventricular wall. Accordingly, chronic right ventricular pacing induces redistribution of left ventricular mass, with thinning of early vs. late activated myocardium. Septal motion during right ventricular pacing can vary according to the site of stimulation and heart rate [15]. Pre-ejection septal beaking is observed—similarly to what can be found in other patients with relatively delayed left ventricular activation, caused by left bundle branch block or type B Wolff–Parkinson–White syndrome (Fig. 21.2).

The pre-ejection period septal beaking is not due to early activation and unopposed contraction of the interventricular septum, but rather it occurs in response to an altered transseptal pressure gradient. When pacing causes the right ventricle to be activated before the left, right ventricular pressure begins to increase in systole before left ventricular pressure, altering the normal left-to-right transseptal pressure gradient [16]. Coincident with the early unopposed increase in right ventricular pressure, the septum abruptly moves posteriorly toward the left ventricle. With the subsequent onset of left ventricular contraction, left ventricular pressure increases, the normal transseptal pressure gradient is restored, and the septum returns in the anterior direction toward its end-diastolic position. In the ejection phase, a ventricular-paced left ventricle can show a normal posterior motion and thickening (more frequent with pacing from the right ventricular apex) or a flat or paradoxical (anterior) motion (more frequent with pacing from right ventricular outflow or right

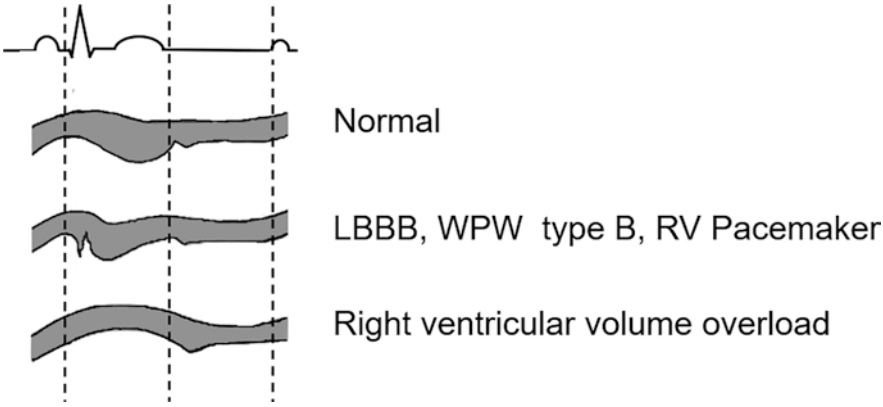


Fig. 21.2 Different types of non-ischemic septal wall motion changes. Abnormal (paradoxical) septal motion can be found in a variety of conditions, including (*from top to bottom*) abnormal electrical activation (left bundle branch block, Wolff-Parkinson-White type B, paced right ventricular rhythm), right ventricular volume overload. (Adapted and modified from De Castro and Pandian, [15])

ventricular inflow). The interpretation can be easier in the first case than in the second case, especially considering that in 30% of patients, a normal or flat motion can become paradoxical at high pacing rates of over 120 per min [17].

21.3 Methodology

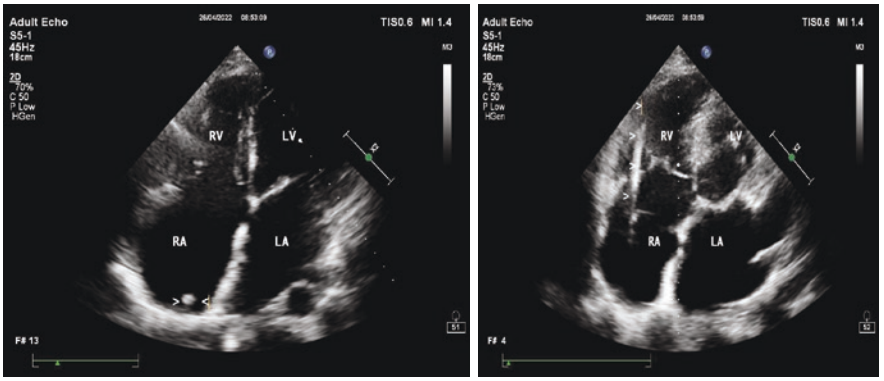
The main features of different pacing techniques are summarized in Table 21.2. Pacing can be atrial or ventricular. The paced chamber is the left atrium in transesophageal pacing and the right atrium or the right ventricle in permanent pacemaker stimulation.

All have good diagnostic results. However, intravenous atrial pacing [1] requires catheterization, which nullifies its utilization in the echocardiography laboratory. Utilization of the transesophageal approach as a stress test for ischemia has become possible thanks to recent improvements in this technique, enabling effective atrial capture at a relatively low threshold, which has reduced patient discomfort [2], and transoral stimulation with 10-French catheters [3]. The results reported have been good, but semi-invasiveness substantially limits the applicability of this approach. In a more clinically plausible approach, the presence of a permanent pacemaker can be exploited to conduct a pacing stress test in a noninvasive way by programming the pacemaker to increase frequencies [4]. The paced chamber is the right atrium in atrial stimulation and the right ventricle in ventricular stimulation mode (Fig. 21.3).

Table 21.2 Pacing mode and contractile pattern in pacing SE

	Paced chamber	Non-invasiveness	Septal movement	The simplicity of echocardiographic reading
Permanent PM atrial mode	Right atrium	++	Normal	++
Permanent PM ventricular mode	Right ventricle	++	Paradoxical (60%)	±
Permanent PM biventricular	Right and left ventricle	++	Normal	++
Transesophageal	Left atrium	±	Normal	++
Transvenous	Right atrium	–	Normal	++

++ excellent, + good, – poor



Pacemaker electrode in the RA Pacemaker electrode in the RV

Fig. 21.3 Transthoracic two-dimensional echocardiography. Right atrial (AAI) *(left)* and right ventricular (VVI) pacing mode *(right)*. Arrows: electrodes in the right atrium (RA) on the left, or right ventricle (RV) on the right panel. (Image courtesy of Prof. Edyta Plonska, Szczecin, Poland)

The diffusion of biventricular pacing also expands the domain of application of pacing SE, since this pacing mode induces a physiological contraction of the septum, making echocardiography interpretation easier. The interpretation must consider that regional wall motion in the septum is differently affected by the pacing mode (Fig. 21.4).

In the atrial and biventricular stimulation mode, the normal, physiological electrical activation sequence is preserved; therefore, the septal wall motion is normal and there are no special interpretation problems. Roughly one out of three patients with permanent pacemakers are studied in the right ventricular pacing mode. In approximately 30% of right ventricular-paced patients, the septal wall motion is normal, but in the majority of them, an anterior systolic interventricular septal motion (paradoxical motion) is present at baseline. In this case, it is necessary to focus on wall thickening rather than an endocardial excursion, and on non-septal regions of the left anterior descending territory to identify left anterior descending

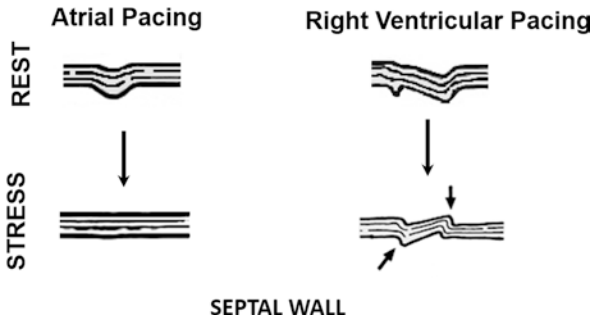


Fig. 21.4 Different types of baseline septal motion and stress-induced ischemia according to the pacing mode. Left panel, atrial stimulation mode; right panel, right ventricular stimulation mode

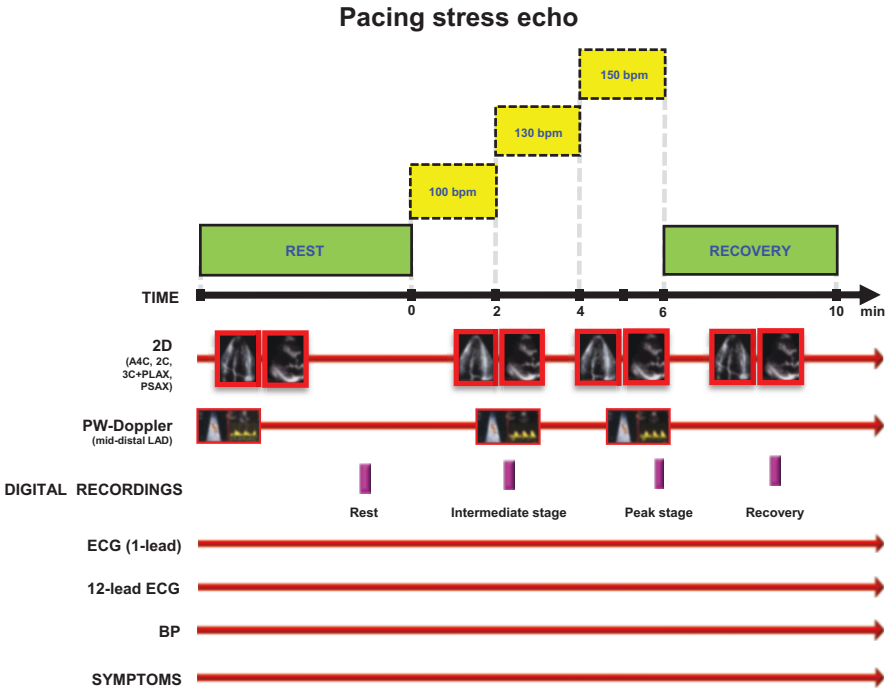


Fig. 21.5 Protocol of pacing SE: standard (*left*) or accelerated (*right*)

stenosis, but this interpretation will always be a challenge, especially at high heart rates. Now, to avoid apical right ventricular pacing, ventricular lead is rather implanted in the mid-septal position or close to the right ventricular outflow tract.

With external programming of the pacemaker, the pacing is started at 110 bpm and increased every 2 min by 10–20 bpm until 85% of the target heart rate (220 minus years of age for men; 200 minus years of age for women) is achieved (Fig. 21.5) or until other standard endpoints are reached.

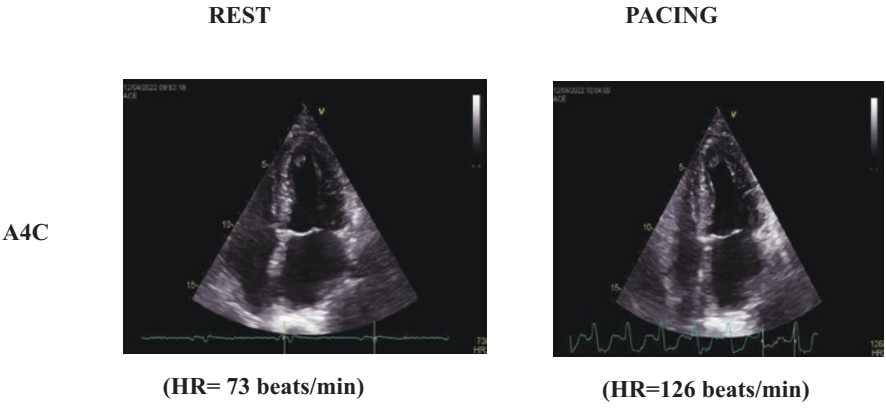


Fig. 21.6 Transthoracic two-dimensional echocardiography: evaluation of left ventricular myocardial function in end-systole at rest (left) and peak pacing (right) during two-step rapid pacing at the rate of 126 bpm and 85% of maximal age-predicted heart rate. At peak pacing, there is increased thickness of all walls, with a smaller end-systolic cavity of the left ventricle. (Image courtesy of prof. Edyta Plonska, Szczecin, Poland)

The same protocol can also be followed in an accelerated fashion, with faster steps (20–30 s each) up to the target heart rate. Left ventricular segmental contractility can be also assessed during two-step rapid pacing at the rate of 100 bpm and then at 85% of the maximal age-predicted heart rate (Fig. 21.6).

In patients with a dual-chamber pacemaker, the stress test is started with atrial pacing. The examination is performed with the patient supine or in the left lateral decubitus position. 2D echocardiographic images are obtained before pacing and throughout the stress test; the last recording being obtained after 3 min pacing at the highest rate reached (usually 150 bpm) or the target heart rate. Blood pressure and the electrocardiogram are monitored throughout the examination. Left ventricular wall motion abnormalities are evaluated at rest, during pacing, and immediately after pacing interruption.

21.4 Clinical Results and Comparison with Other SE Tests

Good diagnostic results have been obtained with noninvasive pacing SE, with good sensitivity and specificity [18–21]. As with other SE tests, the positivity can be effectively titrated in the time and space domain [4], and more severe degrees of underlying coronary artery disease are associated with a lower heart rate, necessary to induce ischemia and with more extensive wall motion abnormality.

Pacing-induced ischemia is also helpful in risk stratification of the patient with known or suspected coronary artery disease [22–25].

Noninvasive pacemaker SE has several advantages in comparison to conventional diagnostic techniques. The relative merits and limitations of noninvasive pacemaker SE vs. pharmacological SE are reported in Table 21.3.

Table 21.3 Pacing vs. pharmacologic SE

	Pacemaker	Pharmacological
Patient tolerability	Very high	High
Stress imaging time	5–10 min	10–20 min
Safety	Very high	High
Intravenous line	Usually not required	Required
Clinical experience	Initial	Extensive
Applicability	Patients with permanent pacemaker	All patients

The ability to instantly lower the rate and terminate stress results in high test safety. Pacemaker SE is rapid and can be conducted at the bedside and is therefore well tolerated by the patient and user-friendly for the physician. In contrast to physical stress, it does not require the patient's capability to exercise; contrary to pharmacological stress, it does not require an intravenous line and the additional cost (and risk) of drug administration. The SE imaging during pacing represents high quality. Imaging time is also shorter because the median time of pacing is less than 10 min with the accelerated protocol, which compares favorably with the approximately 10 min of imaging time for dipyridamole and about 20 min for dobutamine–atropine. In patients with a permanent pacemaker, 2D echocardiography during pacing is a useful tool in the detection of coronary artery disease and is equally effective in men and women [21]. It is less time-consuming (10 vs. 20 min), more feasible (99% vs. 90%), and associated with fewer major side effects (0% vs. 2%) compared to dobutamine testing [26].

Atrial pacing is also an efficient diastolic stress test, with only minimal changes in loading conditions and contractility and an increase in stiffness and end-diastolic pressure due to the reduction of diastolic time interval [27–29].

Pacing SE may be a useful tool for optimal programming of rate-adaptation parameters in heart failure patients with preserved ejection fraction, permanent atrial fibrillation, and permanent cardiac pacing in VVIR mode in case of exercise intolerance after conventional programming [30].

21.5 Pitfalls

Myocardial oxygen consumption as high as that reached with exercise is not obtained by atrial pacing because cardiac volumes decrease and blood pressure does not change significantly, such that in some patients with mild coronary artery disease, wall motion abnormalities may not develop. At a high rate, there are fewer video frames during the ejection period and less time to appreciate a regional wall motion abnormality. Only one-half of patients can be stressed in an atrial stimulation or biventricular mode that preserves the physiological sequence of contraction of the left ventricle. In patients with ventricular stimulation of long duration, specificity can perhaps be lowered, since long-term right ventricular pacing is associated with apical wall motion abnormalities at rest [31]. The external programming of the permanent pacemaker is simple and fast, but it requires technology (external

programmer) and expertise not readily available in the echocardiography laboratory—also requiring minimum cooperation and coordination with the pacemaker laboratory—which is usually, but not always and anywhere, easy to obtain. Perfusion changes are of limited diagnostic value during pacing stress since they are present especially in the septal and apical regions independently of underlying coronary stenoses for the associated non-ischemic wall motion abnormalities [32]. The use of heart rate reserve as step E of the comprehensive ABCDE protocol cannot be used since the increase in heart rate which is an index of the cardiac sympathetic reserve is obtained with electrical stimulation and not by an exercise or pharmacologically mediated rise in sympathetic tone.

21.6 Clinical Indications

Because of its safety and repeatability, noninvasive pacing SE can be the first-line stress test in patients with permanent pacemakers [33], especially if the stimulation can be performed in the most physiological and less technically challenging atrial or biventricular mode. In the recent surveys from the United Kingdom, Poland, and Italy, pacing SE was performed in a large number (40–60%) of SE laboratories and was applied in around 2–5% of patients referred for testing [26, 34–36]. It is suited for a comprehensive SE protocol with excellent feasibility for simultaneous assessment of regional wall motion, volumetric echocardiography, and coronary flow velocity reserve [37]. According to the latest American Society of Echocardiography 2020 recommendations, pacing stress modalities enable imaging during both early and late stages of stress, which may enhance test sensitivity [38].

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Ergonovine Stress Echocardiography for the Diagnosis of Vasospastic Angina

22

Jae-Kwan Song and Eugenio Picano

Keywords

Nocturnal angina · Rest angina · Stenosis · Sudden death · Vasospasm

22.1 Coronary Vasospasm of Large and Small Vessels

Coronary artery spasm has been considered one of the major mechanisms causing *dynamic* stenosis of epicardial coronary arteries, which can evoke acute myocardial ischemia. Vasospastic angina caused by coronary artery spasm has a wide clinical spectrum. One of its typical clinical manifestations is variant angina. Coronary vasospasm has also been documented to contribute to the development of unstable angina or acute myocardial infarction. Coronary vasospasm may also involve coronary small vessels showing increased microvascular constrictor activity [1]. Classically, coronary artery spasm is diagnosed by an invasive provocative procedure during diagnostic coronary angiography. Since various noninvasive diagnostic

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J.-K. Song (✉)
Asan Medical Center Heart Institute, University of Ulsan College of Medicine, Seoul, Republic of Korea
e-mail: jksong@amc.seoul.kr

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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tests for fixed atherosclerotic stenosis of epicardial coronary arteries such as exercise ECG, stress echocardiography (SE), and nuclear tests are being used in routine daily practice, it would be useful to establish a reliable, noninvasive, and safe diagnostic method to document coronary artery spasm in the management of patients with vasospastic angina.

The rare episodic nature of coronary artery spasms makes it extremely difficult to document spontaneous coronary vasospasm in clinical practice. The most effective stress tests used are ergonovine [2], acetylcholine [3], and systemic alkalosis by hyperventilation [4]. Of these, spasm provocation testing using ergonovine is considered the gold standard for the diagnosis of coronary artery spasm because of its high sensitivity and specificity. Acetylcholine seems to have comparable diagnostic validity for intracoronary administration, but its short half-life for the abundant pseudocholinesterase in human plasma makes intravenous injection inadequate for spasm provocation.

22.2 Basic Considerations

Ergonovine maleate is an important oxytocin alkaloid and a member of the ergobasine group, an amine alcohol derivative of lysergic acid. This drug can induce coronary vasoconstriction in patients who have undergone heart transplantation, which suggests that it does not act via the central nervous system. This drug is believed to stimulate α-adrenergic and 5-hydroxytryptamine (serotonin) receptors [5]. After intravenous injection, the half-life of the distribution phase is between 1.8 and 3 min, and the half-life of the disappearance phase is between 32 and 116 min [6]. This rapid mode of action explains why coronary spasm most often occurs between 2 and 4 min after the injection. The use of ergonovine in incremental doses starting with an intravenous injection of 0.05–0.1 mg followed by small increments of 0.1–0.15 mg at 5-min intervals up to a maximum cumulative dosage of 0.35 or 0.4 mg is generally recommended [1]. This general guideline is based on the finding that the cumulative doses (0.1 + 0.2 + 0.3 + 0.4 mg) at 5-min intervals have the same effects as a single dose of 0.4 mg [1]. The provocative test with ergonovine performed in the cardiac catheterization laboratory has a high sensitivity (98%) and specificity (98.7%) [7].

22.3 Protocol

For a diagnosis of vasospastic angina, the possibility of significant fixed atherosclerotic stenosis of major epicardial coronary arteries is usually ruled out using both functional (SE, exercise test, or myocardial perfusion scan) and anatomical tests (computed tomography or invasive coronary angiography). All cardioactive drugs (β-receptor blocker, calcium channel blocker, and nitrates) should be discontinued

for at least five half-lives; however, nitroglycerin should be administered sublingually as necessary. Resting hypertension is usually controlled using angiotensin-converting enzyme inhibitors; uncontrolled hypertension is a contraindication of this test.

It should be remembered that some drugs, especially long-action calcium channel blockers, may have persistent effects on coronary vasomotor tone as long as 2–3 weeks after discontinuation [8, 9].

Figure 22.1 shows the classic protocol of ergonovine echocardiography. A bolus injection of ergonovine (50 μg) is administered intravenously at 5-min intervals until a positive response is obtained or a total dose of 0.35 mg is reached. The 12-lead ECG is recorded after each ergonovine injection and left ventricular wall motion is monitored continuously. Positive criteria for the test include the appearance of transient ST-segment elevation or depression greater than 0.1 mV at 0.08 s after the J point (ECG criteria) or reversible wall motion abnormality by two-dimensional echocardiography (echocardiographic criteria). The criteria for terminating the test are as follows: positive response defined as ECG or echocardiographic criteria, total cumulative dose of 0.35 mg ergonovine, or development of significant arrhythmia or changes in vital signs (systolic blood pressure > 200 mmHg or < 90 mmHg). An intravenous bolus injection of nitroglycerin is administered as soon as an abnormal response is detected; sublingual nifedipine (10 mg) is also recommended to counter the possible delayed effects of ergonovine. These drugs can be administered as needed. The protocol can be modified just to decrease the test time (Fig. 22.1), with bolus doses of 50,100,100, and 100 μg every 5 min up to a cumulative dose of 350 μg.

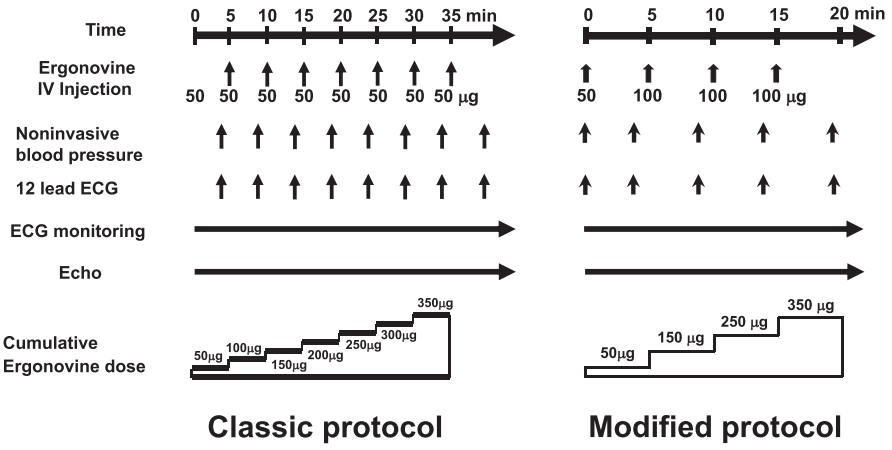

Fig. 22.1 Classic (*left*) and modified (*right*) protocols for ergonovine echocardiography

22.4 Noninvasive Diagnosis of Coronary Artery Spasm: Clinical Data

Bedside ergonovine echocardiography has been reported to be accurate for the diagnosis of coronary vasospasm and to monitor therapy efficacy [8–15]. The left anterior descending coronary artery vasospasm involves the anterior septum, apex, and anterior wall (Fig. 22.2).

The sensitivity of echocardiographic criteria (detection of reversible regional wall motion abnormalities) is higher than 90%, which is far greater than that of ECG criteria (ST-segment displacement, 40–50%). Characteristic ST-segment elevation during ergonovine testing occurred in about one-third of patients with variant angina [16]; the lower sensitivity with ECG criteria can be partially explained by an earlier development of regional wall asynergy during myocardial ischemia in the so-called pre-electrocardiographic phase rather than a true false-negative finding [10–13]. The earlier detection of ischemia with higher sensitivity is very important from the safety point of view, as the vicious cycle of the ischemic cascade can be terminated earlier, and the risk associated with prolonged ischemia reduced. A pooled analysis of over 20,000 patients published by 5 different groups (from South Korea, Italy, Spain, and Serbia) with ergonovine echocardiography shows an overall incidence of major side effects from 0.6 to 1.9%, comparable to dobutamine—the most used pharmacological stress [16–20]. No cases of acute myocardial infarction or death were reported. Side effects such as atrioventricular block or ventricular tachycardia are usually associated with ischemia, and reversed by intravenous or sublingual nitrates, and nifedipine administration. In 40% of cases, major side effects are ischemia-independent and consist of atrial fibrillation, atrioventricular block, and marked sinus bradycardia. Although intracoronary nitroglycerin could

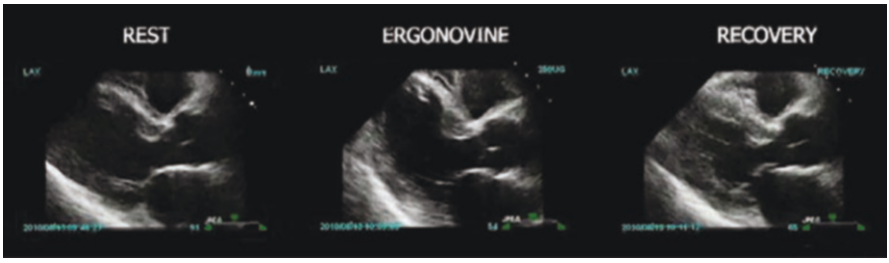

Fig. 22.2 Representative example of ergonovine SE. Left ventricular wall motion at end-systole recorded in the parasternal long-axis view was demonstrated in quad screen format at rest (left panel), peak stress (250 μg of ergonovine), and recovery (right panel). (From [9], with permission). The corresponding video 22.1 is shown. (Courtesy of Dr. Jae-Kwan Song. The video is available under the chapter's "Supplementary Material" on Springer Link)

not be used to reverse coronary vasospasm in this protocol, there were no serious complications such as the development of myocardial infarction or fatal arrhythmia during the test [8, 9].

Unlike other stress tests for fixed atherosclerotic stenosis of the coronary artery, this test shows high sensitivity even in patients with single-vessel spasm [16]; the transmural nature of supply ischemia due to coronary artery spasm may explain this difference.

As this test also showed extremely high specificity (>90%) for the diagnosis of coronary artery spasm before coronary angiography, invasive coronary angiography and spasm provocation testing can be avoided for the diagnosis of vasospastic angina [16, 18].

22.5 Special Safety Considerations

Issues regarding the safety of spasm provocation testing are summarized in Table 22.1.

Ergonovine echocardiography testing, undertaken either in the catheterization laboratory or at the bedside, is a risky and challenging procedure, demanding a high degree of skill on the part of the operator [8]. Angiographic demonstration of reversible total occlusion of one of the major epicardial coronary arteries is in itself enough for a diagnosis of coronary vasospasm.

If, however, angiography reveals only moderate vasoconstriction, as occurs more frequently in the daily clinical practice of provocation testing, other indexes of

Table 22.1 Potential advantages and disadvantages of spasm provocation testing in the catheterization laboratory and at the bedside

	Advantages	Disadvantages
Provocation test during angiography	Angiographic demonstration of reversible vasoconstriction	Relatively late and insensitive ischemic markers (chest pain, electrocardiographic changes)
	Direct intracoronary injection of nitroglycerin	Invasive, perturbs vasomotor tone, radiation exposure
	Temporary pacemaker backup	Injecting contrast agent into the coronary circulation
		Continuous monitoring of the whole ischemic process is impossible
Bedside ergonovine echocardiography	Detection of regional wall motion abnormalities: a sensitive and specific marker of myocardial ischemia, continuous monitoring, early detection, and early termination of ischemia	Intracoronary injection of nitroglycerin impossible
	Noninvasive, does not perturb vasomotor tone	Temporary pacemaker backup is impossible
	Repeat and follow-up studies	Dependent on acoustic window

myocardial ischemia are necessary before a definite diagnosis of coronary vasospasm can be made. In the catheterization laboratory, the development of chest pain and electrocardiographic changes, well known as relatively late events in the ischemic cascade, are classic markers of myocardial ischemia. The usual 3- to 4- min wait after each injection of the drug before repeat angiography without sensitive monitoring of the ischemic cascade in the catheterization laboratory may also contribute to the potential danger of the procedure. This is because the development of serious arrhythmia or myocardial infarction depends on the duration of the preceding myocardial ischemia during spasm provocation.

In addition to concerns about disturbing vasomotor tone with the catheter and radiation exposure (around 10 milliSievert), injecting a contrast agent into the coronary circulation during a severe ischemic episode may increase the risk of the procedure. Myocardial imaging rather than angiography has been proposed as a more sensitive, more specific, and safer method of identifying coronary vasospasm by some physicians. The importance of intracoronary nitroglycerin for reversing intractable vasospasm that is not responsive to sublingual and intravenous nitroglycerin has been reported [19, 20], but other published investigations indicate that intracoronary nitroglycerin is not a prerequisite for spasm provocation testing [8–18].

The most important advantage of ergonovine echocardiography is its capacity for detecting regional wall motion abnormalities, which are sensitive and specific markers of myocardial ischemia, even before the appearance of chest pain or electrocardiographic changes. During ergonovine echocardiography, the wall of the left ventricle can be continuously monitored, with early termination of myocardial ischemia based on the detection of regional wall motion abnormality. This may improve the safety of the test since, less than half of the patients with definite wall motion abnormalities showed ECG changes suggestive of myocardial ischemia [8, 16]. A further multicenter investigation is needed to determine whether early detection and termination of myocardial ischemia based on regional wall motion abnormalities can completely obviate the need for temporary pacemaker backup. Continuous monitoring of the ventricular wall motion without interruption during ergonovine echocardiography can contribute to the detection of multivessel coronary spasms involving the right and left coronary arteries. This is almost impossible during invasive spasm provocation testing in the catheterization laboratory, as termination of spasm in one coronary artery territory is necessary. Simultaneous catheterization of both coronary ostia for demonstration of potential multivessel spasm is not a routine procedure due to low clinical feasibility.

22.6 Clinical and Prognostic Impact

Noninvasive ergonovine SE is an effective and reasonably safe way of diagnosing coronary vasospasm in routine clinical practice for patients visiting the outpatient clinic [16] or for those admitted to the coronary care unit under the clinical impression of unstable angina pectoris [15]. Although clinical usage of spasm provocation testing has decreased significantly in Western countries and spasm provocation testing is no

longer a routine diagnostic procedure, mortality and event rates are significantly higher with a positive result of ergonovine SE in patients with near-normal coronary angiogram or those with negative stress test results for significant fixed stenosis [22].

These results demonstrate the powerful prognostic implication of noninvasive ergonovine SE in routine daily practice for differential diagnosis of chest pain syndrome. The test positivity in absence of underlying fixed coronary stenosis is also a predictor of doubled likelihood to develop fixed, flow-limiting coronary stenosis at the site of coronary vasospasm after years or decades, as hypothesized in 1980 by Marzilli and Maseri of the Pisa group based on semi-anecdotal clinical evidence [23] and demonstrated by the Seoul group in 2022 in a study on 3556 patients with a median follow-up of almost 10 years [24].

Ergonovine test provides an effective and powerful means of risk stratification based on the presence of inducible ischemia in patients with no evidence of significant fixed coronary stenosis, either by direct invasive or noninvasive (by 64-slice computed tomography) coronary angiography or by noninvasive stress testing. Consideration of ergonovine SE for complete differential diagnosis of mechanisms of myocardial ischemia should be encouraged in various clinical scenarios involving patients with chest pain syndrome [21], such as patients with angiographically normal coronary arteries, and a history of angina at rest, aborted sudden death [25, 26], flash pulmonary edema [27], or suspected left ventricular apical ballooning syndrome [28]. The usefulness of the ergonovine test in monitoring the efficacy of antianginal therapy has been documented [29], but its clinical value remains uncertain. It is probably inappropriate to use the test in patients in whom the diagnosis is already established by clinical history or with concomitant ischemia in presence of angiographically documented coronary artery disease. The test can be less safe in patients with uncontrolled hypertension and previous stroke [30]. It is also important to consider vasospasm—and, if appropriate, vasospasm testing—in several clinical settings remote from the cardiology ward when ergometrine-containing or serotonin-agonist drugs are routinely given and may occasionally precipitate "out-of-the-blue" cardiological catastrophes mediated by coronary vasospasm: ergometrine given in the obstetric clinic to reduce uterine blood loss in the puerperium phase [31–36] or bromocriptine given for milk suppression [37–39], sumatriptan or ergometrine used in neurology for migraine headaches [40–42], 5-fluorouracil and capecitabine (an oral 5-fluorouracil prodrug) given as chemotherapy in (breast and colon-rectal) cancer [43–45], and, with increasing frequency, cocaine as a cause of chest pain in the emergency room [46]. Marijuana assumption may also cause coronary vasospasm [47]. In all these conditions, it is essential to think of vasospasm to recognize it.

22.7 Pitfalls

Ergonovine is not commercially available in some countries. The test should be done in a safe environment by an experienced cardiologist with well-accepted indications when there is no possibility of catheterization laboratory testing, which is the rule outside some academic centers with specific research interests in coronary vasomotion.

22.8 Clinical Guidelines

In out-of-hospital cardiac arrest, there is no evidence of heart disease in 5% of patients. According to 1997 guidelines, "ergonovine test during coronary angiography is recommended but not mandatory" [48]. Recent data from the Japanese Coronary Spasm Association suggest a 6% incidence of coronary vasospasm in survivors of out-of-hospital cardiac arrest from cardiac cause [49]. These patients who survived cardiac arrest are a high-risk population despite maximal medical therapy and should be identified. In the guidelines for the diagnosis of coronary spastic angina by the Japanese Circulation Society, drug-induced coronary spasm provocation testing with ergonovine (or acetylcholine) is recommended only with invasive evaluation during cardiac catheterization, with class 1 indication in patients in whom vasospastic angina is suspected based on symptoms, but in whom coronary spasm has not been diagnosed by noninvasive evaluation (including exercise ECG test, Holter, and hyperventilation test) [50]. Provocative testing with intravenous ergonovine is not recommended in patients without known coronary artery anatomy or in patients with high-grade obstructive lesions on coronary arteriography. Diagnostic tests proposed for suspected vasospastic angina are listed in Table 22.2 [51].

The European Society of Cardiology 2020 chronic coronary syndromes guidelines recommend against noninvasive testing for spasm with intravenous ergonovine due to the risks of such a procedure: "*intravenous administration of ergonovine for non-invasive tests should be discouraged due to the risk of triggering prolonged spasm in multiple vessels, which may be very difficult to manage and can be fatal*" [51]. The clinical embargo to ergonovine or ergometrine testing outside the catheterization laboratory continues due to the perceived risk, yet the observed risk in properly selected populations is lower than other widely used pharmacological stresses for the diagnosis of coronary artery disease, although this large-scale evidence on over 14,000 patients became available just after guidelines publication [20].

Noninvasive testing can be performed in the echo lab in appropriately selected patients by trained cardiologists, balancing the risk with the benefit of missing a

Table 22.2 Diagnostic tests in suspected coronary vasospasm

Recommendations	COR	LOE
An ECG is recommended during angina if possible	1	C
Invasive or noninvasive coronary arteriography is recommended in patients with characteristic episodic resting chest pain and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease	1	C
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of an increased heart rate	2a	C
An intracoronary provocation test should be considered to identify coronary spasms in patients with normal findings or nonobstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm	2a	B

COR class of recommendation, *LOE* level of evidence. (From [51], ESC guidelines 2020)

Table 22.3 Strong indications of coronary vasospasm testing

Class	1 (Strong Indication)
≥ 1 Criterion for VSA without Documented Episode by ECG and without CAD	v
ACS without Culprit Lesion	v
Unexplained Resuscitated Cardiac Arrest	v
Unexplained Syncope with Previous Chest Pain	v
Recurrent Rest Angina Following Successful PCI	v

ACS acute coronary syndromes, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *VSA* vasospastic angina

potentially life-threatening diagnosis. For the safe performance of stress testing outside the cardiac catheterization laboratory, an accurate selection of appropriate indications as proposed by the COVADIS group in 2017 is essential [52]. The first criterion is to assess the pretest probability of coronary vasospasm, which increases in presence of at least 1 of the 4 criteria:

1. Rest angina (especially between night and early morning).
2. Marked diurnal variation in exercise tolerance (reduced in the morning).
3. Hyperventilation can precipitate an episode.
4. Calcium channel blockers (but not beta-blockers) suppress episodes.

The pretest probability of vasospasm is very low (< 5%) with 0 criteria and very high (> 90%) with all 4 criteria. An additional, important criterion (not mentioned by guidelines) is the onset of angina after starting therapy with a drug with documented coronary vasospastic potential, such as 5-fluorouracil in colon cancer.

Other appropriate, strong indications are aborted sudden death, acute coronary syndrome with normal coronary arteries, unexplained syncope with antecedent chest pain, and recurrent rest angina following successful revascularization (Table 22.3).

In the recent 2020 recommendations of the American Society of Echocardiography, coronary vasospasm is recognized as one of the main mechanisms causing the development of wall motion abnormalities in the absence of significant angiographic coronary stenosis [53].

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Hyperventilation, Handgrip, Cold Pressor Stress Echocardiography

23

Ana Djordjevic-Dikic and Eugenio Picano

Keywords

Alkalosis · Coronary vasospasm · Ischemia

23.1 Hyperventilation Test

Hyperventilation has been mainly used in clinical practice as a provocative test for coronary artery vasospasm [1, 2]. The rationale for the use of hyperventilation testing for this purpose is based on the demonstration that, in susceptible patients, hyperventilation may trigger vasospasm of a major epicardial coronary artery associated with chest pain and ischemic electrocardiographic changes similar to those observed during spontaneous anginal attacks. Moreover, hyperventilation could provoke spasms of coronary small vessels that are more vulnerable to metabolic changes and responsible for microvascular angina and ischemic ECG changes [3].

Prolonged, vigorous over-breathing decreases plasma hydrogen ion concentration, leading to alkalosis, which can trigger coronary artery spasms. The increase in arterial blood pH reaches the peak at the end of hyperventilation, while ST-segment elevation usually develops during the recovery phase early after the end of the test when arterial pH is already decreasing toward baseline but is still significantly

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A. Djordjevic-Dikic (✉)
University Clinical Centre of Serbia, Cardiology Clinic, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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elevated compared to the basal values [4]. Tachypnea and hyperpnea cause lightheadedness, peripheral paresthesia, cramps, and syncope and may occur in severe cases due to decreased levels of ionized calcium in the blood (driven inside cells in exchange for hydrogen ions [H^+]).

Coronary spasm in this setting can ensue, with increases in intracellular concentration of calcium ions following a decrease in the concentration of hydrogen ions, which compete with calcium for active transmembrane transport [5] (Fig. 23.1). The increase in intracellular calcium concentration can, in turn, elicit a vasospastic constriction of smooth muscle cells in susceptible coronary epicardial arteries and microcirculation [5, 6]. Hyperventilation increases not only the heart rate which is a simple and potentially useful marker of the sympathetic reserve but also systolic blood pressure, reflected as an increased double product [4, 7, 8].

The patient hyperventilates for 5 min, with increased frequency (respiratory rate of 25 or higher per min) and depth of breathing (Fig. 23.2). The time window of positivity usually occurs 1–5 min after the end of hyperventilation, therefore without degrading the quality of echocardiographic imaging. Monitoring should last until 10 min after completion. The hyperventilation stress echocardiography (SE) test should be conducted in the early morning (when the vulnerability to vasospasm is highest in susceptible patients) after at least 48 h from the administration of vasoactive drugs.

The sensitivity of the test is markedly affected by the spontaneous activity of the disease; when spontaneous attacks occur frequently, a positive response to hyperventilation is observed in more than 80% of patients, while the sensitivity of the test decreases to 50% or less in patients with less active disease [9–13]. Since hyperventilation may produce chest pain and pseudo-ischemic changes in vasospasm, echocardiographic monitoring during the test can be particularly useful to demonstrate normal regional wall motion and thickening and therefore rule out the diagnosis of epicardial vasospasm, while microvascular spasm could still exist. In patients with variant angina, hyperventilation can also be used to predict the ability of antianginal

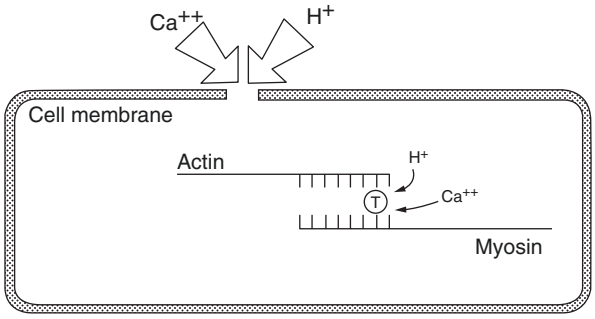

Fig. 23.1 The mechanism of contraction induced by alkalosis in a smooth muscle cell. With a reduced concentration of hydrogen ions, more calcium enters the cell from the outside and more intracellular calcium reaches the regulatory troponin site, triggering contraction. (Modified from [7], with permission)

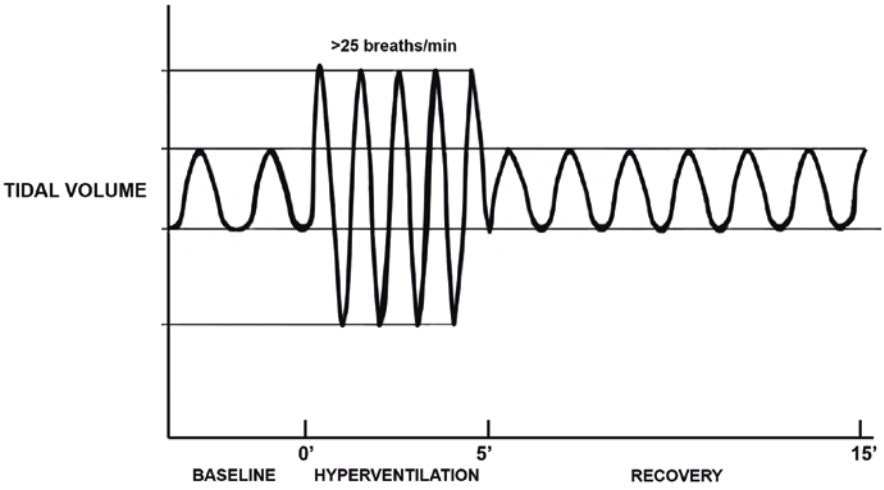

Fig. 23.2 Protocol of the hyperventilation SE test

Table 23.1 Tests for coronary vasospasm

	Hyperventilation	Ergometrine
Sensitivity	++	+++
Specificity	+++	+++
Safety	+++	++[+]
Imaging time	10 min	20 min

drugs to prevent spontaneous attacks and to select an effective medical treatment [11]; moreover, if the test yields negative results during long-term follow-up, this may indicate a spontaneous remission of the disease [11].

The hyperventilation test has shown excellent safety and satisfactory feasibility associated with good sensitivity (slightly lower than ergometrine) and specificity for the diagnosis of vasospastic angina. It is considered slightly safer than the ergonovine test because the stimulus to vasospasm wanes as soon as the intracellular pH returns to normal; however, one should be aware that the consequences of ischemia are largely independent of the form of provocation [14, 15]. The imaging time is shorter with hyperventilation (about 10 min) than with ergonovine (approximately 20 min) (Table 23.1).

It can therefore be a useful test for the diagnosis of vasospastic angina in outpatients and patients with contraindications to ergometrine such as arterial hypertension or previous stroke. It may unmask the vasospastic origin of symptoms in patients with syncope [16, 17]. A case of reproducible post-coital hyperventilation-induced coronary vasospasm, within minutes to hours of sexual activity, was described in a woman with chest pain and idiopathic recurrent pulmonary edema,

reproduced by hyperventilation test and abolished by calcium-antagonists and nitrates [18]. However, hyperventilation is demanding for the patient who may not be able to complete it and is contraindicated in epilepsy. In patients with typical symptoms, a positive response to hyperventilation is diagnostic, thus avoiding the need to perform ergometrine testing.

Hyperventilation testing can also be used to assess the efficacy of medical therapy, such as endothelium-protective estradiol supplementation or atrial natriuretic peptide infusion in variant angina [19, 20].

In the guidelines for the diagnosis of coronary spastic angina by the Japanese Circulation Society, non-invasive coronary spasm provocation testing with a hyperventilation test is recommended in patients suspected of having vasospastic angina with a low (class IIa) or high (class IIb) frequency of attacks, but in whom coronary spasm has not been diagnosed by non-invasive evaluation (including exercise-ECG test and Holter recording) [21] (Table 23.2).

The clinical suspicion is justified in presence of typical chest pain if any one of the following criteria is met:

1. Attacks occurring at rest, particularly between night and early morning;
2. Marked diurnal variation observed in exercise tolerance (particularly reduction in exercise capacity in the early morning);
3. Attacks induced by hyperventilation (hyperpnea);
4. Attacks suppressed by calcium channel blockers, but not beta-blockers.

The novel, promising approaches combine mild hyperventilation followed by exercise [22] where activation of α adrenergic receptors could elicit vasoconstriction and compete with metabolic vasodilatation [23]; or the cold pressor test [24] to enhance the test sensitivity for vasospasm detection. In the diagnosis of coronary vasospasm, there is a hierarchy of testing for stressor potency with ergometrine being the most potent, hyperventilation the intermediate, and exercise and cold pressor the least potent stressor [9] (Fig. 23.3).

An example of a positive test for wall motion abnormalities with hyperventilation + exercise is shown in Fig. 23.4.

An example of a positive test for wall motion abnormalities with hyperventilation followed by exercise is shown in Fig. 23.5.

Since hyperventilation acts differently than exercise and cold, the sensitivity for vasospasm critically increases with the combination of hyperventilation and either the cold pressor or exercise test. The algorithm for assessment of epicardial

Table 23.2 Indications of hyperventilation test[a]

Indication	Appropriate	Uncertain	Inappropriate
Low frequency of attacks	v		
High frequency of attacks		v	
Acute coronary syndrome			v

[a]Patients with suspected vasospastic angina not documented by ECG, Holter, or exercise test according to the Japanese Circulation Society

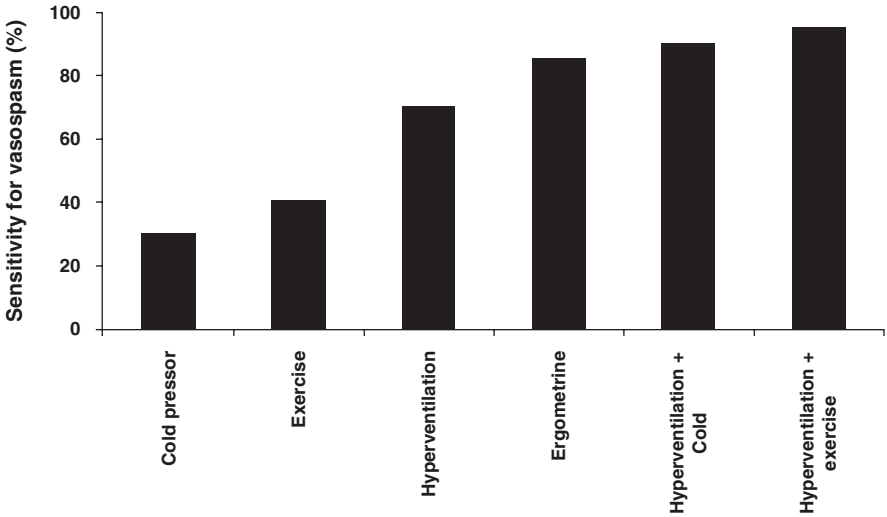

Fig. 23.3 The hierarchy of test sensitivity for the diagnosis of coronary artery disease. Cold and exercise are relatively weak stressors when used alone, but they can critically potentiate the sensitivity of hyperventilation

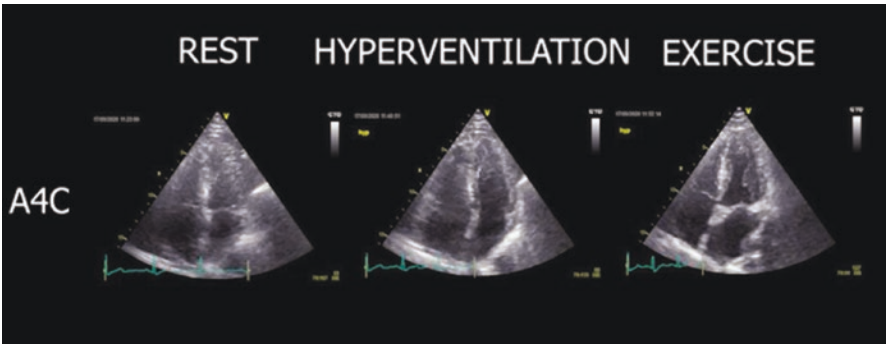

Fig. 23.4 Representative example of hyperventilation SE. The patient is a 57-year-old lady with a history of hypertension, and chief complaints of palpitations and occasional episodes of chest pain precipitated by cold air in the morning and after physical exertion. Coronary angiography showed normal coronary arteries. The patient was on therapy with bisoprolol, trimetazidine, acetylsalicylic acid, sartan, and diuretics at the time of testing. Left ventricular wall motion at end-systole recorded in the apical 4-chamber view was demonstrated at rest (left panel), peak hyperventilation (middle panel), and after hyperventilation + exercise (right panel). Regional wall motion is normal at rest and after hyperventilation, and apical akinesia appears after hyperventilation exercise. See accompanying video 23.1. (Video images courtesy of Dr. Prof. Ana Djordjevic-Dikic, Belgrade, Serbia. The video is available under the chapter's "Supplementary Material" on Springer Link)

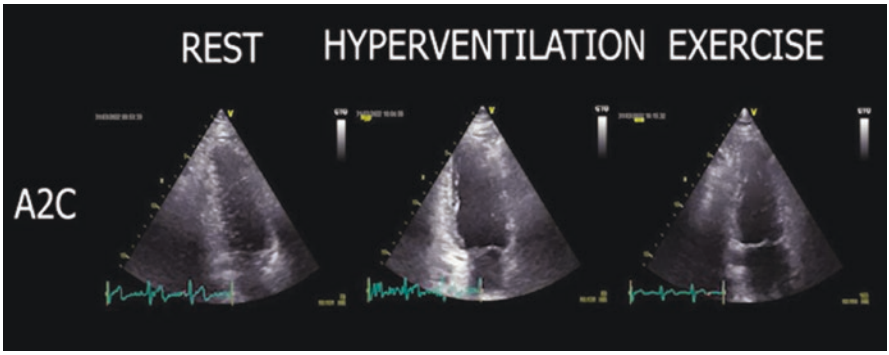

Fig. 23.5 Representative example of hyperventilation + exercise SE. The patient is a 52-year-old gentleman with typical chest pain for 3 years, which recently increased in frequency. Coronary angiography performed 2 years before testing showed normal coronary arteries. The patient was on therapy with amlodipine, trimetazidine, and statin at the time of testing. Left ventricular wall motion at end-systole recorded in the apical 2-chamber view was demonstrated at rest (left panel), peak hyperventilation (middle panel), and after hyperventilation + exercise (right panel). Regional wall motion is normal at rest, mild hypokinesis in the inferior wall appears after hyperventilation, with akinesia after hyperventilation exercise. See accompanying video 23.2. (Video images courtesy of Dr. Prof. Ana Djordjevic-Dikic, Belgrade, Serbia. The video is available under the chapter's "Supplementary Material" on Springer Link)

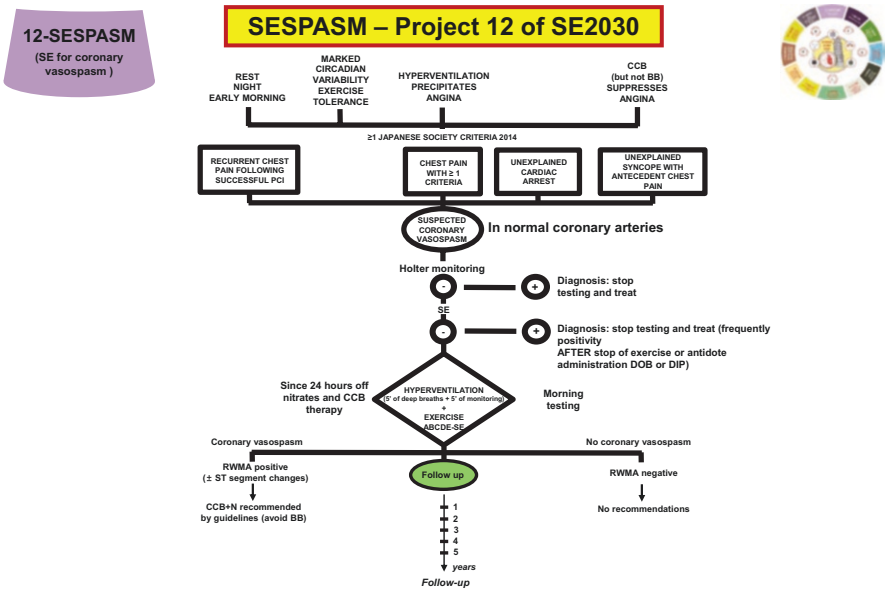

Fig. 23.6 The algorithm for spasm assessment

coronary and microvascular spasm is presented in the hyperventilation-exercise study for spasm (SESPASM) (Fig. 23.6), which is part of the bigger project for wider SE implementation of the SE study group 2030 [25, 26].

Table 23.3 Clues for the recognition of cardiac and non-cardiac conditions

	Microvascular disease	Variant angina	Non-cardiac chest pain
Pathogenesis	Small vessel alteration	Epicardial artery spasm	Esophageal spasm, etc.
Chest pain pattern	On effort, emotion, at rest	At night, with palpitations	Nitrate sensitive
Resting LV function	Normal	Normal	Normal
Hyperventilation-RWMA	Negative or hypokinesis	Positive (A-, dyskinesis)	Negative
Hyperventilation-CFVR	Flow reduction (−50%)	Flow absence	Flow increase (+150%)

CFVR coronary flow velocity reserve, *RWMA* regional wall motion abnormality

Hyperventilation has been used for decades as a test of epicardial coronary artery vasospasm, but coronary microvascular vasospasm can also occur and give symptoms, and it is more difficult to recognize than epicardial artery vasospasm. A hyperventilation test can help in this challenging task, especially with the assessment of coronary flow velocity reserve in the mid-distal left anterior descending artery. The normal response is an increase in flow (+150%), but the hyperemic response can be blunted or even reversed (−50%) in patients with the coronary functional microvascular disease [3]. Hyperventilation test induces ST-segment elevation with significant regional wall motion abnormality usually up to dyskinesia for transmural ischemia in variant angina. In coronary functional (vasospastic) small vessel disease, coronary flow velocity reserve can be even reduced from baseline, indicating a vasoconstrictive response associated with chest pain, ST-segment depression, and often accompanied by regional wall motion abnormality (usually hypokinesis indicative of subendocardial ischemia). More frequently, coronary flow velocity reserve is blunted compared to normal values (+150%) obtained with hyperventilation in normals with non-cardiac chest pain [25]. The role of non-invasive assessment of coronary flow velocity in patients with chest pain and nonobstructive coronary artery disease during provocative tests with vasodilators is recognized in the 2021 Guidelines of the American College of Cardiology/American Heart Association, Class of Recommendation 2b (“may be reasonable”), level of evidence C (expert opinion) [27]. Hyperventilation is therefore a powerful tool, largely underused for the functional characterization of patients with angina and normal coronary arteries (Table 23.3). The current approaches based on long and demanding invasive testing are necessary to identify the coronary vasospastic component [28], separating the sometimes coexistent epicardial coronary vasospastic and the small coronary vessel vasospasm [29], but a more practical non-invasive approach is needed, and hyperventilation testing might be helpful to achieve this elusive goal.

23.2 Handgrip SE

The handgrip is an isometric exercise stress test with hemodynamic effects on both systemic and coronary circulation. Handgrip induces sympathetic activation and catecholamine release resulting in increased afterload, preload, heart rate, and end-systolic wall stress with a modest increment in myocardial oxygen consumption.

In normal conditions, the coronary tone depends on the balance between vasoconstriction and vasodilation mediated by α- and β-receptors, respectively, and by endothelial function integrity. Conversely, atherosclerosis of the coronary arteries causes endothelial dysfunction with the loss of β-receptor vasodilatation response and predominance of the vasoconstriction effect mediated by α-receptors [30].

Owing to its ability to increase cardiac workload and vasoconstriction on atherosclerotic coronary arteries, handgrip has been proposed as a useful test to detect myocardial ischemia in patients with known or suspected coronary artery stenosis. However, handgrip has a low sensitivity and specificity for detecting the presence of coronary artery disease, if used alone. Isometric exercise has been proposed in addition to conventional stress tests, as it is easy to perform during echocardiography.

At present, no univocal or standardized study protocol has been defined yet. Usually, the maximum isometric muscular effort of the patient is preliminary measured. The subject holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required—the base should rest on the first metacarpal (heel of palm) while the handle should rest on the middle of four fingers. When ready, the subject squeezes the dynamometer at 50% of predetermined grip strength until exhaustion or up to 5 minutes.

Handgrip appears a safe and feasible additional test to standard stress protocol, which may be useful in daily clinical practice to improve diagnostic accuracy, decrease study duration, and avoid atropine administration with dobutamine [31, 32], exercise [33–35], and adenosine or dipyridamole [36, 37]. This may be particularly advantageous if we consider that atropine is contraindicated in some categories of patients (prostatic disease or glaucoma) and has been associated with potentially severe side effects. However, these data were obtained in relatively small series.

Outside the diagnosis of coronary artery disease, an isometric handgrip test can be useful as an alternative to exercising as a diastolic stress test and a test to evaluate inotropic reserve. The suggested protocol, in this case, is an isometric handgrip at 40% of maximal voluntary contraction. The increase in heart rate (with shortening of diastolic filling time) and the rise in systolic blood pressure (with delayed calcium handling and associated actin-myosin cross-bridge cycling) leads to a stress test of global left ventricular diastolic and systolic function [38]. The normal response is that E/e' does not change significantly and ejection fraction increases despite the increase in systolic blood pressure and afterload. In patients with heart failure and preserved ejection fraction, E/e′ rises disproportionately [39, 40]. In patients with initial systolic heart failure, ejection function falls during isometric handgrip [41]. The major limitation is that not all patients endure keeping the prolonged handgrip force.

23.3 Cold Pressor SE

The cold pressor test induces sympathetic tone activation with an increase in myocardial oxygen demand also due to pain sensation. In normal conditions, catecholamine release results in endothelial-dependent (through β-adrenergic receptor stimulation) and endothelial-independent vasodilatation (mediated by α2-adrenergic

activity on smooth muscle cell layer). In addition, flow-dependent vasodilatation secondary to endothelial increased nitric oxide release occurs [42].

In patients with coronary artery spasms due to endothelial dysfunction symptomatic of variant angina, an impairment of endothelial-dependent and flow-mediated vasodilatation or even paradoxical vasoconstriction can be unmasked by a cold pressor test [43, 44]. Coronary endothelial dysfunction can also be detected in Tako-Tsubo [45] or Kawasaki disease [46].

After baseline measurement of blood pressure, 12-lead ECG and standard two-dimensional echocardiography are performed. Subsequently, patients immerse their right (or left) hand in cold water (3 °C). The cold pressor test is stopped after 4 min. Blood pressure measurement and the 12-lead ECG are obtained immediately before withdrawing the hand from cold water. Continuous echocardiographic monitoring for assessing changes in regional wall motion is performed during the cold pressor test and the first 10 min after finishing the procedure. During the test, blood pressure measurements and 12-lead ECG are repeated every 2 min. In addition, flow mapping of the distal left anterior descending coronary artery by transthoracic Doppler echocardiography can also be performed to assess non-invasively coronary flow reserve soon after the cold pressor test.

However, the sensitivity of the cold pressor test alone in predicting variant angina is low. For this reason, a combination of hyperventilation for 6 min (as previously described) immediately followed by a cold pressor test for 2 min has been introduced to improve diagnostic accuracy. The combined test can induce coronary spasm, eliciting segmental wall motion abnormality, which allows the diagnosis of vasospastic angina and the identification of the involved coronary artery.

In the guidelines for the diagnosis of coronary spastic angina by the Japanese Circulation Society, non-invasive coronary spasm provocation testing with the cold pressor test is recommended (class IIb) in patients who are in stable conditions and suspected of having coronary vasospasm [21].

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Part IV

The Patients

24 Stress Echocardiography in Special Subsets of Angiographically Defined Patients: Normal Coronary Arteries, Single-Vessel Disease, Left Main, Chronic Total Occlusion, and Patients Undergoing Coronary Revascularization

Branko Beleslin and Eugenio Picano

Keywords

Chronic total occlusion · INOCA · Left main · Myocardial bridging · Triple vessel disease

24.1 Normal Coronary Arteries

In patients undergoing coronary angiography for investigation of chest pain, the incidence of normal or near-normal coronary arteriographic findings varies between 10% in men and 50% in women [1]. Not all nonsignificant stenoses are created prognostically equal, since coronary events are rare in patients with smooth, normal arteriograms, sixfold more frequent in patients with mild (0–20% stenosis), and 15-fold more frequent in patients with moderate (20–40% and still nonsignificant) lesions [2]. Even with the most conservative reading criteria, stress echocardiography (SE) positivity occurs in 10–20% of patients with angiographically nonsignificant coronary artery disease [3]. The presence of minor, nonsignificant coronary angiographic abnormalities is four times more frequent in patients with an abnormal SE than in patients with a normal one [3]. At long-term (9 years) follow-up, hard

B. Beleslin (✉)
University Clinical Centre of Serbia, Medical School, Cardiology Clinic, University of Belgrade, Belgrade, Serbia

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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events are more frequent in patients with positive SE results than in those with negative SE results [4]. Within the lower-risk subset of patients with negative SE by wall motion criteria, the risk is higher in patients with reduced coronary flow reserve assessed with flowmetry of the left anterior descending coronary artery [5] (Fig. 24.1). These patients have coronary microvascular angina, with a mechanical impairment during stress detectable with global longitudinal strain [6, 7] in absence of regional wall motion abnormalities.

The angiography-imaging mismatch of SE, i.e., false-positive responses occurring in patients with nonsignificant epicardial coronary artery disease, can be turned into a "prognostic match" when the long-term outcome is considered.

According to the 2019 guidelines of the European Society of Cardiology, SE plays a pivotal role in patients with ischemia with angiographically normal coronary arteries (INOCA) to establish whether regional wall motion abnormalities occur in conjunction with angina and ST-segment changes (class of recommendation 2a, level of evidence C) and for the assessment of coronary flow velocity reserve of the left anterior descending coronary artery to document the presence of coronary microvascular dysfunction with values <2.0 (class of recommendation 2b, level of evidence C) [8].

24.2 Myocardial Bridging

Myocardial bridging is defined angiographically as systolic compression (>50% lumen diameter decrease) of an intramyocardial segment of a normal epicardial coronary artery ("milking sign"). Patients with myocardial bridging are often

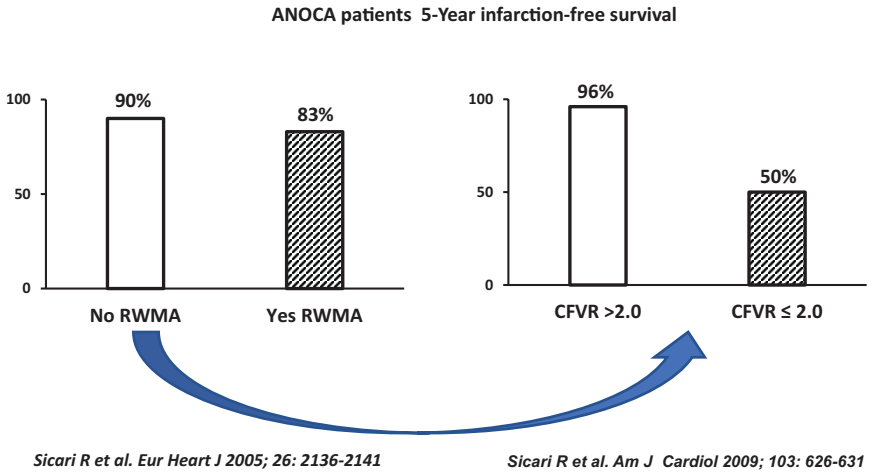

Fig. 24.1 Cumulative rates of survival free of hard cardiac events (death and nonfatal infarction) in patients with normal coronary arteries. The prognosis is worse in 10% of patients with inducible wall motion abnormalities (left panel). In the low-risk subset of patients with negative wall motion response, the prognosis is worse in 30% of patients with reduced coronary flow reserve (right panel) (modified from Sicari R et al. [4, 5])

asymptomatic, but this anomaly may be associated with exertional angina, acute coronary syndrome, cardiac arrhythmias, syncope, or even sudden death [9].

Although historically myocardial bridges have been diagnosed with invasive coronary angiography as a systolic compression, this technique has a low sensitivity. Cardiac computed tomography is the preferred noninvasive imaging modality because it can visualize the coronary artery as an intramural course, imaging the coronary lumen but also the vessel walls and the neighboring myocardium [10] (Table 24.1). Intravascular coronary ultrasound detects both the systolic compression (≥10% during the cardiac cycle) and a characteristic echo-lucent "half-moon" appearance in the tunneled vessel under the bridge. Transthoracic Doppler shows a peculiar flow pattern in the bridge segment with the "fingertip" phenomenon, characterized by a steep rise in the flow velocity at early diastole followed by a sharp deceleration and subsequent plateau. These flow patterns such as the diastolic fingertip pattern with no or decreased systolic antegrade flow can be explained by the systolic compression of the bridge segment and release of the vascular lumen during early diastole. The early diastolic spike is most probably due to the antegrade coronary flow meeting the still compressed (delayed relaxation) narrow bridge segment. The subsequent sharp deceleration in coronary flow velocity results from compression release and an increase in the vascular lumen. After the release of the compression, the lumen of the bridge segment remains unchanged in the second half of diastole and therefore corresponds to the plateau of the flow pattern at this phase [11]. Because of the systolic squeezing of the bridge segment, reversed antegrade flow may occur during this phase.

Anginal symptoms may be reproduced with exercise, pacing, dobutamine, or dipyridamole stress [12–14]. SE can be useful to assess the functional impact of these abnormalities—not always clinically meaningful. Symptomatic patients with myocardial bridging and evidence of ST-segment depression and effort angina during exercise-electrocardiography show frequent and reversible perfusion defects during dipyridamole SE. Perfusion changes are accompanied in one-third of cases by true wall motion abnormalities in the left anterior descending territory of bridging during stress and may show, in a subset, true inducible ischemia as a distinctive septal wall motion abnormality, named "septal buckling with apical sparing" [15].

This is well consistent with the concept that myocardial bridging can have a spectrum of functional responses, from fully normal wall motion and perfusion (in the majority of cases) to isolated perfusion defects (in 30% of cases) to more functional

Table 24.1 Imaging of myocardial bridging

TECHNIQUE	SIGN
Invasive coronary angiography	Systolic compression
CCTA	Intramural course
Doppler-TTE (rest LAD flow)	Fingertip diastolic pattern
SE	Septal buckling, apical sparing
CFVR	<2.0

CCTA coronary computed tomography angiography, *CFVR* coronary flow velocity, *LAD* left anterior descending

severe wall motion abnormalities. The documentation of inducible ischemia is also interesting from a pathological viewpoint since myocardial bridging should not cause ischemia as it primarily affects only systolic and not diastolic flow when subendocardial perfusion occurs [16]. However, at high heart rates, diastole shortens and the systolic contribution to coronary blood flow increases significantly. The presence of a focal functional abnormality in the septum suggests that the hemodynamic disturbance, and thereby, ischemia, is local in the myocardial bridge, involves at least one septal branch within the myocardial bridge segment, and recognizes the Venturi effect as the most likely hemodynamic mechanisms. With marked constriction, and especially during high flow states (associated with exercise or dobutamine or dipyridamole), coronary blood flow velocity increases and the perfusion pressure decreases within the narrowed myocardial bridge region, leading to focal ischemia and septal buckling [17]. SE also usually observes a characteristic apical sparing, which also can be reconciled with a Venturi effect since, distal to the bridge, the vessel area increases, resulting in a decrease in velocity and pressure recovery accounting for the normal function in the myocardial territory perfused by the postbridge left anterior descending coronary artery [18]. Although this is the most typical SE pattern, variations may occur, since the constriction may not be uniform within all bridges, it can be modulated by drugs (typically attenuated by beta-blockers and calcium channel blockers or enhanced by nitrates), and can change with time [19].

24.3 Single-Vessel Disease

The natural history of patients with single-vessel disease is generally benign, but heterogeneous. The 4-year infarction-free survival rate is higher for negative SE than for a positive SE result in medically, but not invasively treated patients. Moreover, a significantly higher 4-year infarction-free survival rate is found in invasively vs. medically treated patients with a positive, but not in those with a negative SE test result [20]. The prognostic value of SE test results outperforms the impact of the degree of stenosis (50, 75, 90, or 100%) and location of disease (left anterior descending, left circumflex, or right coronary artery), which are recognized as powerful prognostic predictors.

In patients with stable angina and severe single-vessel disease, the beneficial effect of revascularization on symptoms is predicted by the presence and extent of inducible ischemia at pre-intervention SE, not by results of treadmill testing or severity of anatomic stenosis, as shown by the placebo-controlled ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial [21].

24.4 Left Main Coronary Artery Disease

Significant left main artery stenosis is the single most prognostically important lesion involving the coronary arteries. In patients with left main coronary artery stenosis, regardless of the presence of symptoms, surgery can significantly improve survival as compared to medical therapy. Left main coronary artery disease is a formal contraindication to any further form of stress testing, and life-threatening complications due to extensive ischemia induced by stress have been described in patients with the left main disease [22]. Nevertheless, since testing is often done before coronary angiography, several series have reported on SE results in this subset of patients. The overall picture is that SE in the left main is reasonably safe with dipyridamole [23], exercise [24], or dobutamine, and more accurate than other stress imaging techniques as documented by a meta-analysis of 31 studies [25]. Although no pathognomonic response for left main coronary artery disease can be recognized, the SE pattern in the time and space domain is characterized by a shorter stress time, greater extent and severity of the induced regional wall motion abnormality, more frequent antidote resistance, and longer recovery time. All these conditions should raise the suspicion of left main equivalent coronary artery disease and warrant urgent coronary angiography. With the ABCDE SE protocol, the number of positive biomarkers increases with the increasing severity and extent of underlying coronary artery disease, and the left main disease or left main equivalent is more likely with 3 or more abnormal parameters (Fig. 24.2) [26].

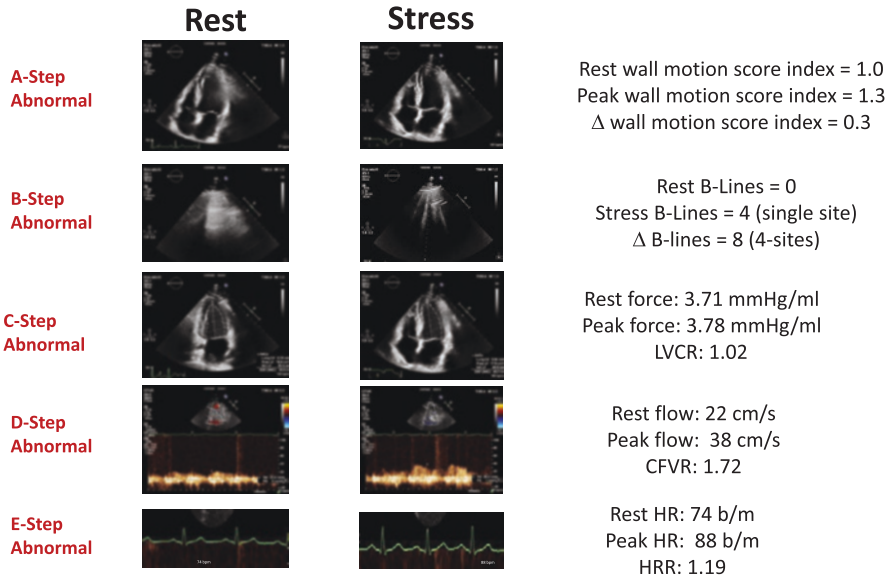

Fig. 24.2 A SE response pattern is compatible with a left-main or left-main equivalent underlying coronary artery disease. With dipyridamole stress, there is an abnormal response for all 5 steps of the ABCDE protocol, with a score = 5 highly suggestive of severe and extensive coronary artery disease (Courtesy of Prof. Quirino Ciampi, Benevento, Italy)

24.5 Patients with Chronic Total Coronary Occlusion

The complexity of the patient with chronic total coronary occlusion requires a comprehensive and dynamic assessment of all major factors possibly underlying symptoms, modulating risk, and representing a potential therapeutic target. The first-line imaging technique is resting transthoracic echocardiography, with or without ultrasound-enhancing agents. It is followed, when appropriate, by exercise or pharmacological (dobutamine or vasodilator) SE.

Coronary flow imaging can be directly assessed in the left anterior descending coronary artery with a high success rate with high-end instruments, broadband or high-frequency pediatric probes, second-harmonic imaging, dedicated machine settings specific for each vendor, and use of ultrasound-enhancing agents when needed [27]. The normal physiologic flow pattern in mid-distal left anterior descending is an anterograde flow, usually coded in red. The sign of flow inversion with the replacement of a normal anterograde with the retrograde flow coded in blue is a simple sign of coronary occlusion, highly specific to chronic total coronary occlusion in the left anterior descending [28]. The flow reflects the collateral flow from the ipsilateral or contralateral coronary artery. A normal anterograde flow does not rule out chronic total coronary occlusion of the left anterior descending artery, since if the collateral input is located proximally to the recording site, flow direction should be anterograde. The documentation of retrograde coronary flow is a hallmark of occlusion of the proximal left anterior descending artery, while the approach has an unsatisfactory success rate and sensitivity for left circumflex and right coronary artery occlusions [29]. The color flow information can be integrated with pulsed-wave Doppler, which shows at rest a negative (away) rather than positive (toward) flow from the transducer positioned in the apical window, with dynamic reduction or even flow inversion during vasodilator stress for the occurrence of coronary steal phenomena.

SE is also useful to assess and quantify the effects of arteriogenesis therapy enhancing coronary collateral circulation, for instance with a 2-week cycle of exercise potentiated with intravenous heparin before each exercise [30]. The anatomic improvement in coronary collateral circulation in coronary vessels with chronic total occlusion and stress-induced ischemia is paralleled by an improvement in regional and global wall motion quantified with peak wall motion score index or peak global longitudinal strain in the early recovery phase (Fig. 24.3).

The presence of a large region with viability or ischemia supports the dilatation of chronic total coronary occlusion. Coronary dilatation is less indicated in patients in absence of viability or with no, or little, inducible ischemia [31]. Physical or pharmacological SE can be performed with the ABCDE protocol to integrate with a simple test the assessment of several vulnerabilities of the patient beyond coronary occlusion [31]: ischemia (step A), pulmonary congestion (step B), left ventricular contractile reserve (step C), coronary microvascular dysfunction, and coronary flow reserve (step D) and chronotropic incompetence (with imaging-independent step E based on the electrocardiogram).

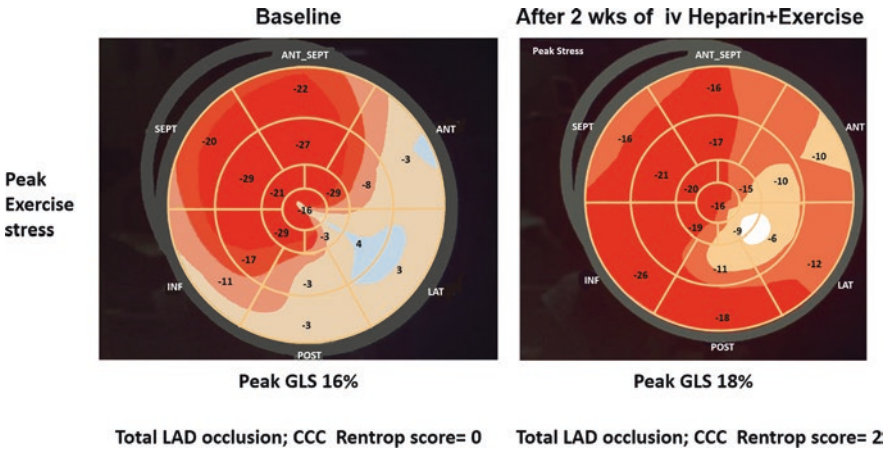

Fig. 24.3 Improvement of regional and global left ventricular function at peak exercise after coronary arteriogenesis therapy. Polar map of regional longitudinal strain immediately postexercise, before (left) and after (right) a 2-week cycle of therapy enhancing coronary collateral circulation (CCC) in a patient with chronic total occlusion of left anterior descending coronary artery and stress-induced angina and ischemia. The angiographic score of CCC improves from 0 (absent) to 2 (good) on a 0 to 3 Rentrop scale (modified and adapted from reference [30], Petrovic et al. 2020). Courtesy of Dr. Marija Petrovic and Prof. Ana Djordjevic-Dikic, Belgrade, Serbia

24.6 Patients Undergoing Coronary Revascularization

Coronary artery revascularization with either coronary artery bypass surgery or percutaneous transluminal coronary angioplasty is an effective therapeutic procedure in the management of properly selected patients with coronary artery disease. For patient selection and assessment of procedure efficacy, a functional evaluation of stenosis is useful. As stated by Dr. Gruntzig at the dawn of the angioplasty era, "imaging post-catheterization permits evaluation of the physiologic significance of an observed lesion and to determine the potential effect of dilatation on perfusion distal to the lesion." In addition, a pre-angioplasty imaging evaluation "provides a baseline for noninvasive postangioplasty monitoring of the procedure's success. As with the patient who has undergone bypass surgery, subjective symptoms are usually a good guide but are not sufficient for the longitudinal evaluation of the procedure" [32]. The practical impact of SE in assessing revascularization procedures has been shown both in coronary artery bypass surgery [33–37] and in coronary angioplasty [38–50]. The main tasks of physiological testing in revascularized patients can be summarized as follows:

1. Anatomical identification of disease and geographical localization, with the physiological assessment of stenosis of intermediate anatomical severity and identification of target lesion in multi-vessel disease.

2. Risk stratification to identify asymptomatic patients more likely to benefit, in terms of survival, from a revascularization procedure.
3. Identification of myocardial viability in the region with severe hypokinetic or akinetic segments at rest.
4. Following revascularization, identification of restenosis or graft occlusion or disease progression, with abnormal results also predictive of subsequent events.

The results of the revascularization procedure may be completely successful (with the disappearance of inducible ischemia) or partially successful (with persisting inducible ischemia).

The timing of postangioplasty SE varies widely, ranging from 24 h to 1 week in various studies [51–58]. All these studies demonstrated a comparable reduction in SE positivity rates, ranging from 70 to 100% before and from 10 to 30% after angioplasty. SE testing performed early after percutaneous transluminal coronary angioplasty does not seem to suffer from the reduced specificity that limits the usefulness of perfusion stress testing in this setting and can be linked to the transient reduction in coronary flow reserve for reversible microvascular damage.

The possible physiological benefit on the regional coronary reserve determined by revascularization appears to be the most likely explanation for the improvement in stress test results. A consistently positive SE test after angioplasty has an unfavorable prognostic implication, placing the patient in a subset at high risk for recurrence of symptoms, as also shown by a meta-analysis of 7 SE studies in over 5000 patients [59] and more recent studies in contemporary populations [60].

The limited, or even total, lack of improvement in the test response after angiographically successful angioplasty may have several explanations. The residual stenosis may be anatomically insignificant and yet hemodynamically important because there is a poor correlation between the percentage of lumen reduction and regional flow reserve, particularly early after angioplasty. Restenosis may be difficult to recognize on postangioplasty angiograms because of the apparent improvement in luminal dimensions secondary to extravasation of contrast into the media to the plaque, with fissuring and dissection. Sometimes, functional factors such as coronary hyper-tone or vasospasm are superimposed on organic stenosis and are not corrected, and may be worsened, by coronary angioplasty [61, 62].

The current indications for SE after coronary revascularization are summarized in Table 24.2 [63, 64]. However, a 2022 randomized trial shows no clinical benefit in clinical outcomes from active surveillance using functional testing over usual

Table 24.2 Indications to SE after coronary revascularization (PCI or CABG)

	COR
Prior coronary artery revascularization and new cardiac symptoms	2a
Asymptomatic patients after the expiration of the period for which the previous test was felt to be valid	2b

COR class of recommendations, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft

care among high-risk patients with previous percutaneous coronary intervention [65].

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25 Stress Echocardiography in Special Subsets of Electrocardiographically Defined Patients: Left Bundle Branch Block, Right Bundle Branch Block, and Atrial Fibrillation

Marco A. R. Torres and Eugenio Picano

Keywords

Atrial fibrillation · Septal beaking · Left bundle branch block · Right bundle branch block

25.1 Left Bundle Branch Block

Left bundle branch block (LBBB) is a frequent, etiologically heterogeneous, and diagnostically challenging entity. LBBB affects myocardial contraction, left ventricular diastolic filling, and coronary perfusion, although the presence and severity of these abnormalities vary based on the severity of the block and the underlying disease. Septal contribution to left ventricular systolic function is lost or attenuated with a resulting disproportionate workload placed on the left ventricular free wall, which may develop remodeling and later decompensation. Left ventricular isovolumetric contraction time is prolonged to maintain left ventricular ejection time, and the critical diastolic filling time is shortened in the LBBB compared to normal contraction. Septal work is reduced and septal perfusion is decreased to match the

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M. A. R. Torres (✉)
Itaipu Hospital—Unimed Leste Fluminense, Niteroi, Brazil

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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decreased regional myocardial demand. This regional hypoperfusion is not necessarily a sign of ischemia but more likely a physiologic, adaptive response of coronary autoregulation to the decreased septal work reducing regional oxygen demand. Uncoordinated contraction of the papillary muscles may contribute to mitral regurgitation [1].

Approximately 2% of patients referred for cardiac stress testing show stable or intermittent LBBB [2]. Although the LBBB is a recognized predictor of unfavorable cardiac outcomes [3, 4], the prognosis is primarily determined by the underlying cardiac pathology, including coronary artery disease, hypertension, idiopathic dilated cardiomyopathy, and aortic valve stenosis [5, 6]. The presence of an LBBB makes an ECG uninterpretable for ischemia and thus a stress imaging technique is necessary. The presence of an abnormal sequence of left ventricular activation determines increased diastolic extravascular resistance in the LBBB [7], with the lower and slower diastolic coronary flow, accounting clinically for the observed reduction in coronary flow reserve in patients with LBBB [8], a reasonable pathophysiological substrate of the stress-induced defect often observed by perfusion imaging in patients with normal coronary arteries [9].

The altered electrical activation also affects septal wall motion, which may range anywhere between a normal and a paradoxical movement. Normal thickening is observed in the presence of a less abnormal activation sequence (QRS duration <150 ms) and preserved contraction capability.

The paradoxical wall motion is more frequent, with a markedly abnormal activation sequence (QRS > 150 ms) and/or septal fibrosis.

Despite the difficulty posed by the abnormal wall motion (see Chap. 21, Fig. 21.4) stress echocardiography (SE) is the best option for the diagnosis of coronary artery disease [10–14]; it is more specific than perfusion imaging [10, 12] and its sensitivity is good, albeit reduced in the left anterior descending territory only in presence of a dyskinetic septum in the baseline echocardiogram [11].

The prognostic value of SE is excellent, additive when compared to clinical and resting echocardiographic variables, and especially pronounced in patients without previous myocardial infarction [13, 14]. The diagnostic and prognostic value of SE can be critically improved by adding the simultaneous evaluation of coronary flow velocity reserve in the left anterior descending artery [15] or myocardial perfusion with ultrasound-enhancing agents [16]. In practical terms, 20% of patients with LBBB show inducible wall motion abnormalities, and an additional 30% have isolated (without wall motion abnormalities) reduction in coronary flow velocity reserve. This isolated sign of coronary flow velocity reserve <2 allowed an effective risk stratification in patients missed by negative wall motion criteria, particularly in the case they had been tested under medical therapy, predicting a nearly eightfold higher annual mortality rate and a tenfold higher annual event rate when compared with coronary flow velocity reserve ≥ 2.0 [15].

The interpretation of regional wall motion and left ventricular cavity changes in patients with LBBB is easier with ultrasound-enhancing agents (Fig. 25.1).

The current guideline recommendations suggest using a cardiac stress imaging technique instead of an exercise electrocardiography since ECG is uninterpretable in these patients [17]. Among imaging techniques, SE is the first choice (Table 25.1) [18].

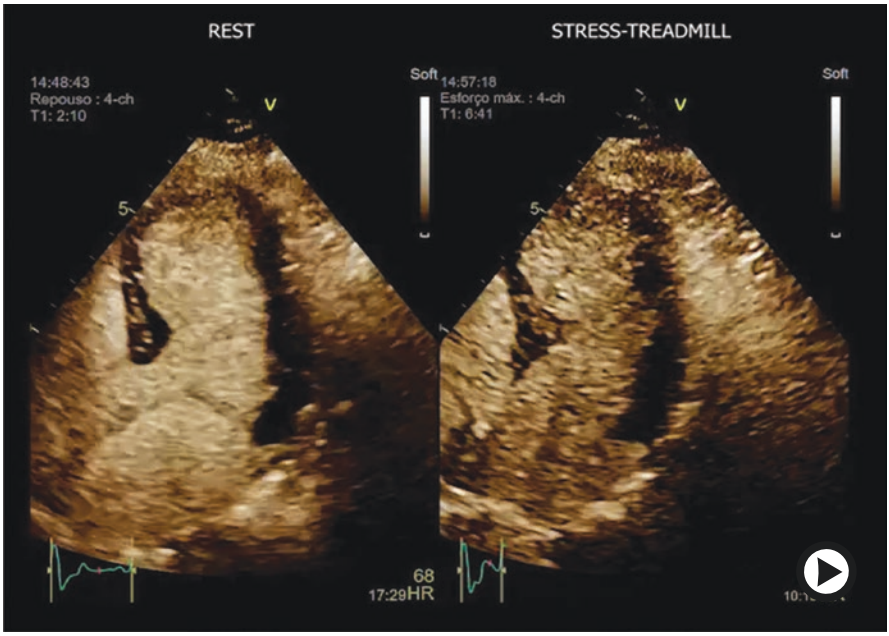

Fig. 25.1 Example of SE with ultrasound-enhancing agent at rest (left) and during treadmill stress (right panel) in a patient with LBBB. End-systolic frames are shown. The end-systolic cavity is smaller during stress, but regional wall motion is reduced in the antero-lateral wall during stress. See accompanying Video 25.1. (Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

Table 25.1 Recommendations for cardiac stress imaging in LBBB

	COR	LOE	Ref
SE is preferred over SPECT imaging because of its greater specificity and because of its greater versatility in detecting other cardiac conditions associated with LBBB	1	B	ASE 2020 [18]

COR class of recommendation, *LOE* level of evidence

25.2 Right Bundle Branch Block

Right bundle branch block is present in 2% of patients with chronic coronary artery disease and 3% of subjects referred for noninvasive assessment of coronary artery disease [1]. Although patients with right bundle branch block and no clinical evidence of cardiovascular disease generally have a favorable outcome [3, 6, 9], right bundle branch block in subjects with chronic coronary artery disease is predictive of a more severe left ventricular dysfunction, extensive coronary artery disease, and a mortality rate that is approximately twice as high [4]. SE is an excellent diagnostic choice since the right bundle branch block does not affect regional wall motion. In addition, it provides an efficient prognostic stratification, additive to simple resting electrocardiogram parameters such as left anterior fascicular block [19]. In populations referred to pharmacological SE testing, three levels of risk are identified: a low risk, in the case of no ischemia and no left anterior fascicular block (almost 50% of the entire population); an intermediate risk in the case of ischemia or left anterior fascicular block only; and high risk in the case of both ischemia and left anterior fascicular block [19].

25.3 Atrial Fibrillation

The prevalence of atrial fibrillation increases with the age of the population, being less than 1% in subjects under the age of 60 years and greater than 5% in those over the age of 70 years [20, 21]. Approximately 70% of individuals with atrial fibrillation are between 65 and 85 years old [22]. Coronary artery disease is one of the most common cardiovascular conditions associated with atrial fibrillation, present in 18% of chronic cases [23]. Although exercise electrocardiography is the cornerstone of noninvasive diagnostic techniques, in the presence of atrial fibrillation it shows several limitations. In particular, advanced age and other clinical conditions that limit the patient's functional capacity (including heart failure and chronic obstructive pulmonary disease) can reduce the feasibility of the test in patients with atrial fibrillation. In addition, atrial fibrillation is often associated with factors lowering the specificity of exercise-induced ECG changes, such as hypertension, left ventricular hypertrophy, and digitalis therapy.

Short diastolic intervals can contribute to false-positive responses during exercise testing in atrial fibrillation since diastolic perfusion of the subendocardium is impaired. SE is an effective modality for investigating atrial fibrillation patients. Despite the pronounced chronotropic response (and thus the lower doses administered), dobutamine SE provides useful diagnostic and prognostic information in these patients [23]. Moreover, the prognostic value of the test is comparable in patients with atrial fibrillation and sinus rhythm [24]. As for the safety of dobutamine stress in atrial fibrillation, conflicting results have been reported. While no dobutamine-induced adverse effects were observed in a series of 92 patients [25], a significantly greater occurrence of cardiac arrhythmias was described in 69 patients with atrial fibrillation compared to controls with sinus rhythm [24].

Atrial fibrillation can be also a complication of stress, relatively more frequent with dobutamine, during which it occurs in 1% of patients [25]. The risk of developing atrial fibrillation is higher (up to 10%) in patients with a history of atrial fibrillation, increased left atrial diameter, right bundle branch block, decreased heart rate, or high blood pressure [26]. Most patients return to sinus rhythm spontaneously within 1 h. Patients with persistent atrial fibrillation can be safely dismissed from the echocardiography laboratory to have outpatient follow-up within 24 h unless they have suboptimal heart rate control, hypotension, significant symptoms, or markedly abnormal findings on SE.

Vasodilator stress is better tolerated than dobutamine stress in atrial fibrillation. Heart rate reserve provides information on the cardiac sympathetic reserve, although the prognostically meaningful cut-off value of abnormality in patients with permanent atrial fibrillation is <1.17, i.e., lower than the 1.22 validated in patients in sinus rhythm [27].

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Stress Echocardiography in Special Subsets of Clinically Defined Patients: Elderly, Women, Outpatients, Chest Pain Unit, and Noncardiac Surgery

26

Miodrag Ostojic, Tamara Kovacevic Preradovic, Aleksandra Nikolic, and Eugenio Picano

Keywords

Elderly · Emergency department · Noncardiac surgery · Vascular surgery · Women

M. Ostojic (✉)
Department of Noninvasive Cardiology, Institute for Cardiovascular Diseases Dedinje, School of Medicine, Belgrade, Serbia

School of Medicine, University of Belgrade, Belgrade, Serbia

Medical School, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Institute for Cardiovascular Diseases "Dedinje", Belgrade, Serbia

University Clinical Center "Zvezdara", Belgrade, Serbia

Clinical Center Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

T. K. Preradovic
Clinic of Cardiovascular Diseases, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina
e-mail: tamara.kovacevic@medicolaser.info

A. Nikolic
School of Medicine, University of Belgrade, Belgrade, Serbia

Institute for Cardiovascular Diseases "Dedinje", Belgrade, Serbia
e-mail: nikolicdrsasa@gmail.com

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

E. Picano (ed.), *Stress Echocardiography*,
https://doi.org/10.1007/978-3-031-31062-1_26

26.1 Elderly Patients

Individuals over 80 years of age account for 4.7% of the total population in Europe, twice the proportion 20 years ago, and are projected to increase fivefold by the year 2040 in the United States [1]. It has been shown since almost 40 years ago that with aging even without risk factors for atherosclerosis by age of 70 years approximately 60% of coronary arteries' surface will be covered by atherosclerotic plaques. That surface of 60% covered by atherosclerotic plaques if smoking, hypertension, and diabetes are present will be reached much earlier (even with borderline cholesterol of 5.17 mmol/L) i.e., at age 64, 52, and 42 years, correspondingly. If just only cholesterol is increased up to 9.05 mmol/L that 60% surface will be reached approximately at age of 40 years, even without the presence of the risk factors [2].

In populations of contemporary patients studied by computed tomography coronary angiography, at age 70 years and over there was a small difference in the observed prevalence of significant coronary artery atherosclerosis in the asymptomatic versus typical angina group outlining the connection between aging and atherosclerosis which can be viewed, not only as a biological phenomenon but also as material fatigue described in mechanical machines [3]. Probably by some secular trends in delaying the process of atherosclerosis over time, the probability of coronary artery disease predicted by classical clinical criteria proposed by Diamond and Forrester in 1979 is overestimated in all subgroups (nonanginal chest pain, atypical and typical angina) in all age groups. The only exemption was found in asymptomatic patients where guidelines are not able to provide any probabilities, with an almost perfect trend of increase of observed significant plaques by increasing age. Those findings were considered in the European Society of Cardiology 2019 Guidelines on Chronic ischemic heart disease [4] and 2021 American College of Cardiology/American Heart Association guidelines [5].

For any given symptom, the pre-test likelihood of coronary artery disease increases markedly with increasing age. For instance, in subjects with nonanginal pain, the pre-test probability of disease in a man at the age of 50 years is 11% and increases to 24% at the age of 70 years (Table 26.1).

Exercise electrocardiography shows limited feasibility in old patients, mainly due to neuromuscular weakness, physical deconditioning, or neurologic, orthopedic, peripheral vascular, or respiratory limitations. In addition, test specificity declines as age increases because of repolarization abnormalities on resting electrocardiogram due to hypertension, left ventricular hypertrophy, or digoxin

Table 26.1 Pre-test probabilities of obstructive coronary artery disease in contemporary populations

	Typical angina		Atypical angina		Nonanginal pain		Dyspnea	
	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)	Women (%)	Men	Women
Age								
50–59	32	13	17	6	11	3	20	9
60–69	44	16	26	11	22	6	27	14
70+	52	27	34	19	24	10	32	22

From Knuuti et al., ESC Guidelines on chronic coronary syndromes 2019 [4]

intake [6]. Stress echocardiography (SE) has been found to confer an effective prognostic contribution in elderly individuals [7–16]. Pharmacologic SE provides useful prognostic information in patients >65 years of age. However, its prognostic value decreases with increasing age [11]. In particular, ischemia failed to add prognostic information in subjects >80 years of age, and in this subset, SE based on regional wall motion abnormality does not predict mortality [14]. Nevertheless, SE can offer much more than a simple evaluation of stress-induced regional wall motion abnormalities with a comprehensive approach, including coronary flow velocity reserve [15] and heart rate reserve [16]. The abnormal cutoff value for coronary flow velocity reserve in the left anterior descending artery is <2.0 across all age groups from 30 to 90 years [15]. The abnormal cutoff value for heart rate reserve decreases in patients with advanced age since the peak heart rate declines by 10 beats every decade beyond the age of 50. In elderly patients, an age-normalized index is more appropriate: 220-age [16].

The stratification strategy should be tailored and designed to patients' profiles. Elderly patients with positive SE test results tended to receive less coronary angiography and fewer revascularization procedures when compared to the overall population. Advanced age often directs physician's decision on therapeutic strategy, but this policy in time may adversely affect outcomes since an improvement of symptoms can be achieved by properly targeted interventions oriented by physiologic testing results. With current advances in surgical techniques and intraoperative myocardial protection, elderly patients with multi-vessel disease and even significant baseline dysfunction can undergo coronary artery bypass surgery or percutaneous coronary interventions with a low in-hospital mortality rate and an excellent short-term survival rate [1].

26.2 Women

For any given symptom, the pre-test probability of coronary artery disease is lower in women compared to men. For instance, in subjects with typical anginal pain, the pre-test probability of disease at the age of 65 years is 44% in men and 16% in women (Table 26.1). The diagnostic specificity of exercise electrocardiography and myocardial perfusion scintigraphy is lower in women than in men. Reduction of coronary flow reserve for coronary microvascular dysfunction (mostly affecting female patients), hormonal influences for exercise testing, and breast attenuation for the nuclear technique are potential explanations. In contrast, echocardiography combined with exercise or pharmacologic agents provides similar sensitivity, but a better specificity as compared to exercise electrocardiography [17, 18] and perfusion scintigraphy [19]. In women, the prognostic value of SE is high, like that in men [20]. In patients with chest pain of unknown origin, a normal test is associated with a <1% event rate at 3 years of follow-up [21]. Moreover, stress-induced ischemia adds prognostic information on top of clinical and exercise electrocardiography data [22]. In contrast to the ECG stress test and perfusion imaging, SE based on regional wall motion abnormality shows no difference in diagnostic and prognostic accuracy between males and females. When exercise electrocardiography gives positive or ambiguous results, SE

is warranted [23]. The choice of an imaging test in this setting should consider radiologic exposure. The radiation burden for perfusion scintigraphy ranges between 200 and 500 chest X-rays. The corresponding cancer risk is 37% higher in women than in men, mainly because of the high radio sensitivity of the breast [24]. Recommendations from the European Society of Cardiology suggest using nonionizing imaging techniques, especially in highly vulnerable subjects such as younger women [25]. Radiation exposure is explicitly mentioned by the 2021 American College of Cardiology/American Heart Association guidelines as a limiting factor for women who are pregnant, post-partum, or of child-bearing age: "*In all cases for a test deemed clinically necessary, the lowest effective dose of ionizing radiation should be used, including considerations for tests with no radiation exposure (e.g., echocardiography, cardiac magnetic resonance)*" [5].

26.3 Outpatients

In industrial countries, outpatient investigations account for more than 85% of the increasing costs of the total workload. The prognosis for patients with a normal exercise ECG and a low clinical risk for severe coronary artery disease is excellent [26]. SE does not replace stress ECG as a screening method for both clinical and economic reasons. However, in patients with nondiagnostic or ambiguous test results, SE testing in selected patients can be effectively performed in outpatients, with excellent safety and risk stratification capability [27–30]. According to the European Society of Cardiology 2019 guidelines on stable angina, a stress imaging test for risk stratification is especially recommended in patients with an inconclusive exercise-ECG (Class I, Level of evidence B) [4].

26.4 Emergency Department

In the United States, more than six million people go to emergency departments because of acute chest pain [31]. Some of these patients have coronary artery disease, and roughly 2–10% have myocardial infarction. However, most of them have conditions unrelated to cardiac disease. All these patients will undergo diagnostic testing and will be observed over time and eventually admitted to a cardiology department. Therefore, inappropriate admission of noncardiac chest pain is an enormous, avoidable cost for society and a loss of time for the patient. Unnecessary admission to the coronary care unit costs over 2000 dollars per day and imposes both undue stress and potential morbidity on patients [31]. Several strategies have been proposed to effectively assess these patients. One strategy is anatomy-driven and based on coronary computed tomography angiography [32, 33]. The alternative approach is ischemia-driven and based on functional testing with SE [34–49]. Studies performed on thousands of patients with different physical and pharmacological tests consistently show the high negative predictive value of a negative test based on regional wall motion abnormality and the low rate of positivity, around 5% in contemporary populations (Table 26.2).

Table 26.2 Prognostic value of SE in patients presenting with chest pain to the emergency room

Author, year	References	Stress of choice	Number of patients	Mean follow-up (months)	Negative predictive value (%)	Rate of positivity
Trippi et al., 1996	[34]	Dobutamine	139	3	98.5	8/139 (6%)
Colon et al., 1998	[35]	Exercise	108	12.8	99	8/108 (7%)
Gelejinse et al., 2000	[36]	Dobutamine	80	6	95	36/80 (45%)
Orlandini et al., 2000	[37]	Dipyridamole	177	6	99	5/177 (3%)
Buchsbaum et al., 2001	[38]	Exercise	145	6	99.3	5/145 (3%)
Bholasingh et al., 2003	[39]	Dobutamine	377	6	96	26/377 (7%)
Bedetti et al., 2004	[40]	Dipyridamole	552	13 ± 2	98.8	50/552 (9%)
Conti et al., 2005	[41]	Exercise	503	6	97	99/503 (20%)
Nucifora et al., 2007	[42]	Dobutamine	100	2	110	20/110 (18%)
Hong et al., 2011	[43]	Dobutamine	569	12–25	94.5	53/569 (9%)
van der Zee et al., 2011	[44]	Dobutamine	524	9.4 years	NA	23/350 (7%)
Hartlage et al., 2012	[45]	Dobutamine	255	299 days	99	2/166 (1%)
Shah et al., 2013	[46]	Exercise or dobutamine	811	1 year	12	98/802 (12%)
Innocenti, et al., 2014	[47]	Exercise or dobutamine	626	854 days	98	159/626 (25%)
Gurunathan, et al., 2018	[48]	Exercise	191	3 years	97	9/191 (5%)
Cortigiani, et al., 2022	[49]	Dipyridamole	658	7 years	95	20/658 (3%)

Out of ten patients—who were otherwise ready for discharge—at least one has true myocardial ischemia detected by SE. This patient can be identified and referred to coronary angiography to be revascularized. The negative predictive value of a negative SE test is based on regional wall motion abnormality and is further improved if coronary flow velocity reserve and heart rate reserve are added to stress-induced regional wall motion abnormality [49]. A normal wall motion with blunted coronary flow velocity reserve and heart rate reserve identifies an intermediate risk (Fig. 26.1).

SE is equally effective and associated with less downstream resource utilization than noninvasive computed coronary angiography with no difference in long-term cardiovascular outcomes [50–54]. Given the largely overlapping diagnostic and prognostic yield of the techniques, practical aspects such as radiation exposure, cost, and environmental impact become critical for decision-making [55].

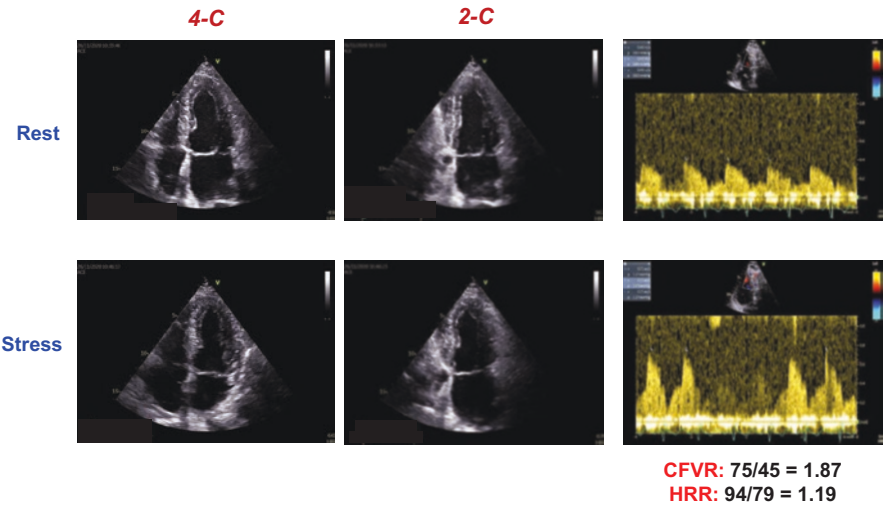

Fig. 26.1 A SE response pattern associated with intermediate risk. With dipyridamole stress, regional wall motion is normal, the end-systolic volume is decreased during stress, but coronary flow velocity reserve (CFVR) is reduced (1.87, normal >2.0) and heart rate reserve is blunted (1.19, normal >1.22). (Courtesy of Lauro Cortigiani, MD, Lucca, Italy)

26.5 Noncardiac Surgery

Perioperative ischemia is a frequent event in patients undergoing major noncardiac vascular or general surgery and coronary disease is known to be the leading cause of perioperative mortality and morbidity following vascular and general surgery [56]. The diagnostic/therapeutic corollary of these considerations is that coronary artery disease—and therefore the perioperative risk—in these patients should be identified in an effective way preoperatively. This is not feasible in an accurate way with either clinical scores (such as Detsky's or Goldman's score) or rest echocardiography, only. SE with either dipyridamole or dobutamine indicates that these tests have a high and comparable negative predictive value (between 90 and 100%), allowing a safe surgical procedure [57–71]. A negative test result is associated with a low incidence of cardiac events and allows a safe surgical procedure. The updated European Society of Cardiology guidelines recommends imaging stress testing before high-risk surgery in patients with more than one clinical risk factor and poor functional capacity (Class I, Evidence C) [72, 73]. There are three essential steps for this approach: define the surgery risk; define the functional capacity of the patient; and define the clinical risk of the patient.

The criteria for high-risk surgery are described in Table 26.3.

The criteria to define functional capacity are described in Table 26.4.

The items of the revised cardiac risk index are defined in Table 26.5.

The take-home message can be summarized with the combination of poor functional capacity (metabolic equivalents <4 or inability to climb 2 flights of stairs) and

Table 26.3 Risk categories of noncardiac surgery

Low (<1%)	Intermediate (1–5%)	High (>5%)
Breast	Intraperitoneal	Aortic surgery
Carotid asymptomatic	Carotid symptomatic	Major vascular surgery
Dental	Cholecystectomy	Duodenal surgery
Thyroid	Peripheral angioplasty	Pancreatic surgery
Orthopedic minor	Hip and spine surgery	Total cystectomy
Gynecology minor	Head and neck surgery	Pulmonary transplant
Urologic minor	Renal transplant	Liver transplant
Superficial surgery	Intrathoracic nonmajor	Adrenal resection
Reconstructive	Endovascular aneurysm repair	Pneumonectomy

Table 26.4 MET equivalents and functional capacity in daily life activities

METS	Functional capacity	Daily activities	Treadmill Bruce stages	Supine bicycle stages
1–4	Poor	Take care of yourself	<1	25–50 W × 2′
5–10	Good	Climb 2 flights of stairs	1–3	75–100–125–150 W × 2′
>10	Excellent	Strenuous sports (soccer, swimming, singles tennis)	4–7	200–225–250 W ×2′

Table 26.5 Revised cardiac risk index

Risk factors	Points
History of ischemic heart disease	1
A high-risk type of surgery	1
History of congestive heart failure	1
History of cerebrovascular disease	1
Pre-op treatment with insulin	1
Pre-op serum creatinine >2 mg/dL	1

Table 26.6 SE in the context of noncardiac surgery

Condition	COR	Source
Before noncardiac high-risk elective noncardiac surgery in patients with poor functional capacity and a high likelihood of CAD or high clinical risk	1	ESC 2022 [57]
Before noncardiac high-risk elective noncardiac surgery in asymptomatic patients with poor functional capacity and previous PCI or CABG	2a	ESC 2022 [57]
Before noncardiac intermediate-risk elective noncardiac surgery in asymptomatic patients when ischemia is of concern in patients with clinical risk factors and poor functional capacity	2b	ESC 2022 [57]
Stress imaging is not recommended routinely before noncardiac surgery	3	ESC 2022 [57]

CABG coronary artery bypass graft, *CAD* coronary artery disease, *COR* class of recommendation: 1: is recommended; 2a: should be considered; 2b: may be considered; 3: is not recommended, *ESC* European Society of Cardiology, *PCI* percutaneous coronary intervention

revised cardiac risk index >1 leading to considering functional stress testing according to the European Society of Cardiology guidelines 2022 [57] (Table 26.6).

According to the European Society of Cardiology 2022 guidelines, cardiac stress testing is always inappropriate in a low-risk surgery, whatever the patient's risk.

Cardiac stress imaging is always inappropriate in a patient with good or excellent functional capacity, whatever the surgery risk. This recommendation is re-emphasized in the American Society of Echocardiography SE guidelines 2020 [74].

In these patients, there are multiple sources of vulnerability beyond ischemia, and therefore, a comprehensive SE protocol evaluating the patient above and beyond inducible ischemia for instance through heart rate reserve and coronary flow velocity reserve can be especially informative. In the study project SE 2030, the ABCDE protocol is performed for risk stratification before moderate- or high-risk noncardiac surgery (such as liver transplant or noncardiac vascular surgery) in patients with poor functional capacity (<4 metabolic equivalents) and/or revised cardiac risk index >1 [75].

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Diastolic Stress Echocardiography

27

Albert Varga, Gergely Ágoston, and Eugenio Picano

Keywords

B lines · Contractile reserve · Preload reserve · Pulmonary congestion

27.1 The Invasive Diagnosis of Heart Failure with a Preserved Ejection Fraction

The increase of left ventricular filling pressures is the most important determinant of dyspnea (shortness of breath) and prognosis in patients with chronic heart failure, independent of the values of left ventricular ejection fraction (EF). Left ventricular filling pressures are traditionally obtained invasively by right cardiac catheterization which allows measuring pulmonary capillary wedge pressure (PCWP) as an indirect estimate of left atrial pressure [1]. The reference standard for the diagnosis of heart failure with preserved ejection fraction (HFpEF) is right heart catheterization at rest followed by invasive exercise testing if resting intracardiac pressures are normal (Table 27.1). The diagnosis is suspected based on dyspnea, natriuretic peptides, and normal EF > 50%, but these criteria lack specificity and a confirmatory test is needed. Invasive right heart catheterization is considered the diagnostic gold standard [2].

These criteria apply to patients with unexplained dyspnea and without any significant valvular disease (> mild stenosis, > moderate regurgitation), constrictive pericarditis, primary cardiomyopathy, or heart transplant. The invasive approach

A. Varga (✉) · G. Ágoston
Institute of Family Medicine, Szeged University Medical School, University of Szeged, Szeged, Hungary
e-mail: varga.albert@med.u-szeged.hu

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Table 27.1 Invasive diagnostic criteria for HFpEF

	Diagnostic criteria
Resting PCWP	≥15 mmHg
Exercise PCWP	≥25 mmHg

PCWP pulmonary capillary wedge pressure

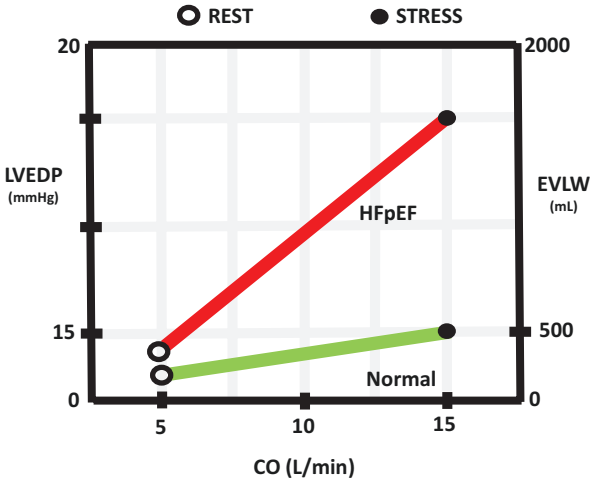

Fig. 27.1 The increase in cardiac output associated with stress and the corresponding variation in left ventricular end-diastolic pressures (LVEDP, left *y*-axis) and extravascular lung water (EVLW, right *y*-axis). The slope is flat in the normal subject and steep for a patient with HFpEF

establishes the concept that alterations in pulmonary pressures can be absent at rest and only apparent after provocative maneuvers capable to stress the system, showing an increase in filling pressures and consequent pulmonary congestion provoking dyspnea suggestive of left heart disease [3]. The simplest and most physiological stress is exercise determining a threefold increase in cardiac output with little or no increase in filling pressures and no increase in pulmonary congestion in healthy normal subjects, while the same increase in cardiac output determines a steep rise in left ventricular filling pressures and extravascular lung water in HFpEF (Fig. 27.1).

Patients with left ventricular diastolic dysfunction may have a similar hemodynamic profile at rest as healthy subjects with normal left ventricular diastolic function. With exercise, however, healthy subjects can increase cardiac output without increasing left ventricular end-diastolic pressure significantly, because of increased myocardial relaxation, which results in more efficient early diastolic suction with a minimal rise in left ventricular diastolic pressure. Reduced myocardial relaxation is one of the earliest manifestations of left ventricular mechanical dysfunction. Relaxation properties are substantially reduced in all forms of myocardial disease, including myocardial ischemia, hypertensive heart disease, hypertrophic cardiomyopathy, and HFpEF. Patients with left ventricular diastolic dysfunction display a deficiency in enhancing myocardial relaxation during exercise compared with healthy subjects who present a normal enhancement of exercise-induced myocardial relaxation. Accordingly, patients with left ventricular diastolic dysfunction may achieve the required cardiac output only at the price of increasing left ventricular

end-diastolic pressure, because a sufficient early suction mechanism for normal left ventricular filling during early diastole is not available. In this view, diastolic stress can be particularly useful in patients reporting unexplained dyspnea but presenting normal left ventricular systolic function and normal left ventricular filling pressures at rest.

However, the application of diastolic stress with the invasive approach has practical and conceptual limitations. It is invasive, risky, technically complex and is therefore highly impractical for routine clinical examinations [4]. In addition, it completely misses nondiastolic cardiac causes of dyspnea which require a different treatment. This is especially important in HFpEF since the substantial heterogeneity in phenotypes may explain the lack of therapeutic success of conventional heart failure therapies. In this setting, resting transthoracic echocardiography and stress echocardiography (SE) can be of help in refining the diagnostic criteria in the screening phase, identifying the underlying heterogeneous pathophysiological mechanisms of disease, and characterizing the different phenotypes of the syndrome, which represents the key step to tailoring the right therapy in the right patient [5]. This approach may eventually allow replacing invasive with noninvasive examinations.

27.2 SE for Recognizing Nondiastolic Causes of Dyspnea

There are different causes of dyspnea with a normal left ventricular that mimic HFpEF but recognize different causes and require a different treatment. Some of them are easily recognized with resting transthoracic echocardiography, such as valvular heart disease, pericardial constriction, high cardiac output failure, and infiltrative cardiomyopathies such as amyloid or adult congenital heart disease such as status post repaired tetralogy of Fallot or obstructive left-sided lesions [6]. Other conditions require a SE since they are associated with dynamic conditions absent at rest and elicited during stress. They can be recognized during a standard SE test (Table 27.2) and are (in descending order of frequency) stress-induced inducible ischemia, chronotropic incompetence, severe mitral regurgitation, dynamic left ventricular obstruction, and genuine reduced global left ventricular systolic dysfunction

Table 27.2 Refining population with pseudo-HFpEF with stress echo

Cause	Frequency (%)	When to suspect
CAD	10–30	High pre-test CAD probability
CI	5–10	High heart rate at rest
Severe MR	1–5	Mild-moderate MR at rest
Severe LVOTO	1–5	Super-normal EF at rest
Reduced LVCR	1–5	Reduced resting GLS

CAD coronary artery disease, *CI* chronotropic incompetence, *EF* ejection fraction, *GLS* global longitudinal strain, *LVCR* left ventricular contractile reserve, *LVOTO* left ventricular outflow tract obstruction, *MR* mitral regurgitation

Table 27.3 Probability of coronary artery disease with dyspnea as chief complaint [7]

Age (years)	Men (%)	Women (%)
30–39	0	3
40–49	12	3
50–59	20	9
60–69	27	14
70+	32	22

not reflected by load-dependent EF but detectable as reduced force-based or strain-based contractile reserve, usually associated with abnormal resting values of global longitudinal strain.

The most frequent cause is myocardial ischemia and underlying coronary artery disease. Dyspnea can be an anginal equivalent, and recent European Society of Cardiology 2019 guidelines assign a pre-test probability to dyspnea as the presenting symptom only slightly lower than typical anginal pain [7], especially in males of advanced age (Table 27.3).

Chronotropic incompetence is more frequent in patients with high resting heart rates and other causes of autonomic unbalance such as diabetes or chronic kidney disease. Dynamic left ventricular outflow tract obstruction is typical of hypertrophic cardiomyopathy, but it may occur in 5% of patients with left ventricular hypertrophy or sigmoid septum. EF can be normal but the left ventricular contractile reserve can be abnormal, as shown by a blunted contractile reserve, more frequent in presence of abnormal resting values of global longitudinal strain [8]. All these nondiastolic causes can be unmasked by exercise tests and allow to have a more focused therapeutic target for the treatment of dyspnea [9].

27.3 Resting Transthoracic Echocardiography to Diagnose HFpEF

In about 80% of patients initially suspected as having HFpEF, the screening phase reveals no obvious cause of dyspnea and the diagnostic workup must continue to include structural parameters and functional parameters, such as *E* wave velocity by pulsed-wave Doppler and *e′* by tissue Doppler or pulmonary artery systolic pressure (PASP) from tricuspid regurgitant velocity (TRV) jet [10].

The resting transthoracic echocardiography approach by the American Society of Echocardiography 2019 is based on *E*/*e′*, TRV, and left atrial volume index (Table 27.4) [11].

In the clinical assessment, transthoracic echocardiography is integrated with simple information derived from patient history and physical examination to generate a score (from 0 to 9) mirroring the pre-test probability of HFpEF (Table 27.5). A score of 0–1 is associated with a low (<20%) probability of disease. Intermediate values (2–4) are associated with an intermediate (30–70%) probability of disease. High values (5–9) are associated with a high probability of disease (from 80% to >95%) [12].

Table 27.4 TTE for diagnosis of diastolic dysfunction

E/*e*′ average	• 14
Septal *e*′ (or lateral *e*′), cm/s	• < 7 (or lateral <10)
TRV (m/s)	• 2.8
LAVI (mL/m^2)	• 34

LAVI left atrial volume index, *TRV* tricuspid regurgitant velocity jet. Interpretation: >50% abnormal: diastolic dysfunction; 50% abnormal: indeterminate; <50% abnormal: normal [11]

Table 27.5 Probability of HFpEF with a clinical noninvasive score (Reddy 2018) [12]

Score letter	Clinical variable	Cutoff values	Points
H1	Heavy	BMI >30 kg/m^2	**2**
H2	Hypertensive	≥2 antihypertensive drugs	**1**
F	Atrial fibrillation	Paroxysmal or persistent	**3**
P	Pulmonary hypertension	Doppler PASP >35 mmHg	**1**
E	Elder	Age > 65 years	**1**
F	Filling pressure	Doppler *E*/*e*′ > 9	**1**
H2FPEF score			**Sum (0–9)**

BMI body mass index, *PASP* pulmonary artery systolic pressure

The six clinical and echocardiographic variables that constitute the H2FPEF score include the following: (1) a body mass index >30 kg/m^2 (H); (2) the use of ≥2 antihypertensive drugs (H); (3) the presence of atrial fibrillation (F); (4) pulmonary hypertension defined as PASP >35 mmHg (P); (5) an age >60 years (E); and (6) elevated filling pressures evident from *E*/*e*′ > 9 (F). The presence of paroxysmal or persistent atrial fibrillation yields three points, a body mass index >30 kg/m^2 yields two points, and all the other criteria listed above yield one point. A score ≥ 5 (corresponding to a probability >85% compared to the right heart catheterization diagnostic gold standard) will be considered diagnostic for HFpEF.

This simple clinical score is useful but neglects biomarkers such as cardiac natriuretic peptides and structural indices such as left atrial volume index, left ventricular mass index, and relative wall thickness. The index proposed in 2019 by the European Society of Cardiology also includes these indices to build a more comprehensive score integrated with simple biomarkers such as cardiac natriuretic peptides and resting transthoracic echocardiography variables to generate a pre-test probability score ranging from 0 (no disease) to >5 (disease) as shown in Table 27.6.

The main parameters are again TRV-derived PASP and *E*/*e*′, with similar cutoff values at rest as in the Mayo score but with the inclusion of the values of the same parameters during stress (average *E*/*e*′ ≥ 15 units, two points, and TRV > 3.4 m/s, one additional point only if the *E*/*e*′ criterion is present). Diastolic SE is less useful for diagnostic purposes with a resting score ≥5 (diastolic dysfunction present), useless with a score ≤1(diastolic dysfunction unlikely), and indicated for scores 2–4 (diastolic dysfunction indeterminate) [3].

Table 27.6 Probability of HFpEF integrating functional, morphological, and clinical chemistry biomarkers

Variable	Cutoff values rest	Cutoff value stress	Points
BNP (pg/mL)	35–80 (SR)		1
	>80 (SR)		2
Wall thickness (mm)	≥12		1
Average *E*/*e′*	9–14		1
	≥15	≥15	2
GLS (%)	<16		1
LAVI (mL/m^2)	29–34		1
	>34		2
TRV (m/s)	>2.8	>3.4 (*E*/*e′* ≥ 15)	1

Corresponding values for NT-pro-BNP are 105–240 (score 1) or >240 pg/mL (score 2) for patients in sinus rhythm (SR). Cutoff values for both BNP and NT-proBNP are higher for patients with atrial fibrillation (AF) compared to those in SR

27.4 Diastolic SE Response Patterns

In all patients and especially in those with a low-to-intermediate probability of HFpEF disease, diastolic SE can offer clear advantages over invasive examinations and can be used to confirm or exclude the diagnosis and characterize different phenotypes of the disease. Current recommendations encourage the use of pulsed tissue Doppler for calculating the ratio between the preload-depending transmitral *E* velocity and the average of septal and lateral velocities of the earliest diastolic motion (*e′*) of the mitral annulus. A healthy subject has a considerable reserve that can support increased demand from exercise and stress, but when one has significant left ventricular diastolic dysfunction, the normal reserve is significantly reduced, producing shortness of breath. This reduced "diastolic" reserve capacity can be better identified by a stress test designed specifically to assess this reserve.

Early diastolic mitral flow velocity *E* is sensitive to preload (and therefore increases with increasing left ventricular filling pressure) and *e′* velocity (which is reduced in all the different kinds of left ventricular diastolic dysfunction) is relatively not sensitive to preload. The *E*/*e′* ratio has been shown to have a reasonably accurate correlation with invasive left ventricular filling pressure at rest [13] but is less accurate with exercise [14–16]. Changes in mitral and pulsed-wave tissue Doppler septal velocities after maximal (mean heart rate = 153 bpm) treadmill exercise in healthy subjects of middle age (Table 27.7) correspond to an increase of both *E* and *e′* velocities, without significant variation of *E*/*e′* ratio [10].

Of note, although both transmitral *E* velocity and mitral annular *e′* velocity are more vigorous and increase in young subjects, *E*/*e′* ratio is almost identical in older and younger healthy subjects [11]. Hence, the same normal value of *E*/*e′* (<10 for normal left ventricular filling pressure using average *e′*) can be used as a noninvasive estimate of left ventricular filling pressure for all subjects regardless of their

Table 27.7 Mitral and tissue Doppler septal velocities with exercise in healthy subjects

Variable	Baseline	Post-exercise
E peak velocity (cm/s)	73 ± 19	90 ± 25
A peak velocity (cm/s)	69 ± 17	87 ± 22
Deceleration time (ms)	192 ± 40	176 ± 42
e′ (cm/s)	12 ± 4	15 ± 5
E/*e′* ratio	6.7 ± 2.2	6.6 ± 2.5

Modified from Nagueh SF et al., J Am Soc Echocardiogr 2009 [10]

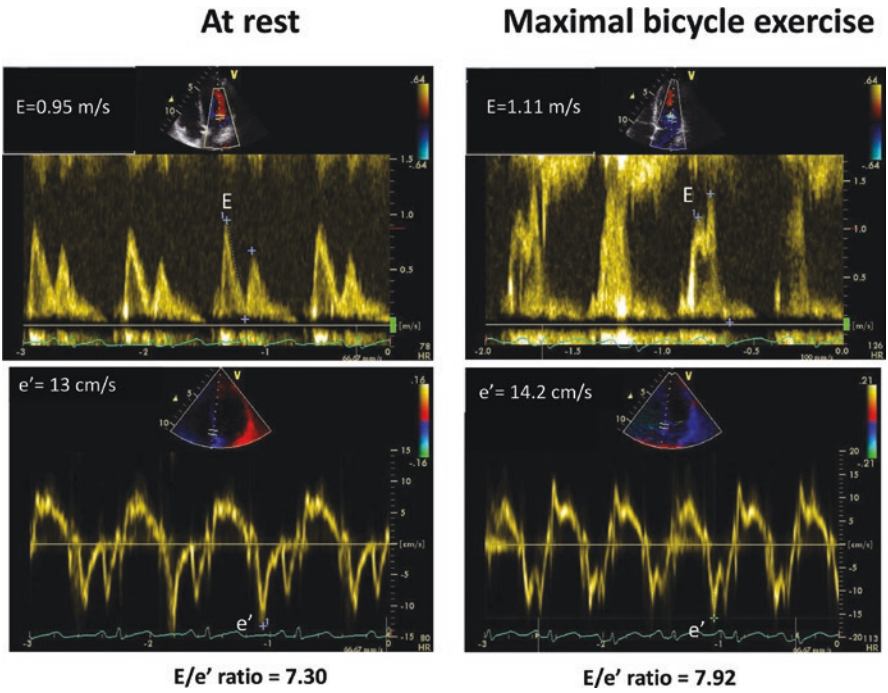

Fig. 27.2 A typical normal (at rest)—normal (post-exercise) response. (By courtesy of Professor Maurizio Galderisi)

age. On the other hand, in patients with left ventricular delayed relaxation, the exercise-induced *e′* velocity increase is much less than that of transmitral *E* velocity such that the *E*/*e′* ratio increases.

An example of the normal pattern response is shown in Fig. 27.2.

An example of the normal-to-abnormal pattern response is shown in Fig. 27.3.

The abnormal response to stress in a patient with normal or indeterminate findings at rest is an important option to unmask mechanisms of left ventricular diastolic dysfunction and heart failure**,** especially in patients with unexplained dyspnea [16].

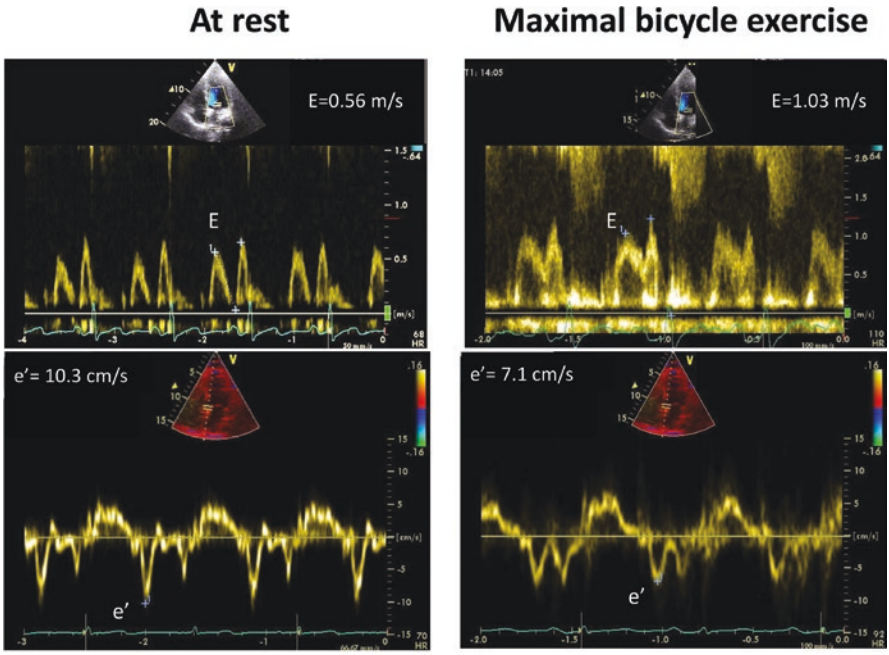

Fig. 27.3 A typical normal (at rest)—altered (post-exercise) response in a patient with unexplained effort dyspnea. (By courtesy of Professor Maurizio Galderisi)

27.5 Additional Parameters to Be Evaluated by Diastolic SE

Continuous-wave Doppler signal of tricuspid regurgitation can be additionally evaluated to provide quantitative information on PASP increase induced by exercise. Upper normal PASP is 35 mmHg (TRV >2.8 m/s) at rest and 50 mmHg (TRV >3.4 m/s) with exercise [3], but the value is dependent on flow increase, and a large increase in cardiac output is associated with higher values of PASP which are perfectly normal [17, 18].

When TRV is not available, as it happens in 50% of patients during stress, PASP can be assessed with pulmonary flow acceleration time. During exercise, acceleration time shortens and a value <100 ms is suggestive of pulmonary hypertension [19, 20].

PASP is an index of hemodynamic congestion, but an earlier sign more specific for pulmonary congestion and increased PCWP is B lines. The timing and severity of pulmonary congestion are nicely mirrored by the presence and severity of B lines which have a clear prognostic value in these patients both at rest and during exercise [21, 22]. B lines appear during exercise but also with dobutamine or vasodilators [23], which are also stressors of diastolic function. The left atrial volume index may increase during stress, instead of the normal physiological response of volume

reduction or mild dilation, and an increase in function is best evaluated with peak atrial longitudinal strain [24]. Left atrium mechanical properties have an impact on the exercise hemodynamics in HFpEF. The impaired value of the left atrial reservoir strain is associated with abnormal hemodynamics during the exercise [25, 26]. Other important mechanisms of diastolic heart failure are the reduced left ventricular contractile reserve detectable with global longitudinal strain despite normal EF values [27], the reduced preload reserve, and the lack of increase of left ventricular end-diastolic volume during early stages of exercise [28], the abnormal coronary microvascular function with angiographically normal coronary arteries [29], and the altered autonomic function with reduced cardiac sympathetic reserve [30]. All these aspects contribute to disease progression and adverse outcomes and can be evaluated with comprehensive physical or pharmacological SE [31–33].

27.6 Why Exercise Is the Best Modality for Diastolic Stress Echo

Any stress on the heart, including simple sinus tachycardia, is also powerful diastolic stress since the positive lusitropic (enhanced left ventricular relaxation) effects of adrenergic stress (or exercise) induce better left ventricular filling in a shorter time. However, exercise is the most physiological and therefore best modality for diastolic stress echo. The normal diastolic response to exercise includes an initial stage corresponding to left ventricular end-diastolic volume increase (increased preload) and left ventricular end-systolic volume reduction (increased contractility), a plateau at intermediate to high-stress level, up to a point when left ventricular diastolic reserve is exhausted and left ventricular filling declines. This drop occurs at lower heart rates in the presence of left ventricular diastolic dysfunction: the lower the diastolic left ventricular filling, the lower the stroke volume, and, for any given level of left ventricular systolic dysfunction, the worse the prognosis.

Exercise SE can be performed by either semi-supine bicycle or treadmill, with the first to be preferred because of the possibility of obtaining better imaging. The quantitative assessment of the E/e' ratio and PASP during semi-supine exercise should be performed at rest, at intermediate stages, at peak stress when possible, and soon after the end of the exercise. The rationale of performing this assessment after the exercise completion is based on the observation that the increase in E wave velocity remains stable for a few minutes after the exercise cessation and that the delayed recording of the transmitral pattern avoids the problems in measuring appropriately E peak velocity deriving from the fusion of E and A wave velocities at faster heart rates, i.e., at the maximal exercise.

Diastolic SE has been also performed with dobutamine infusion but the changes in E/e' obtained using this stressor do not predict changes in left ventricular filling pressures [34, 35].

Vasodilators are also powerful diastolic stress. Heart rate increases minimally but coronary vasodilation reduces left ventricular compliance in vulnerable patients, possibly due to the increase in blood content of the myocardium (4% at rest, and

10% of myocardial volume under maximal vasodilation). Consequently, there is an increase in PCWP and an increase in B lines after dipyridamole in patients with HFpEF, even when regional wall motion and left ventricular contractile reserve is normal [36, 37].

Preload SE has been proposed to estimate the left ventricular end-diastolic pressure–volume relationship during a preload augmentation maneuver by measuring the changes in transmitral flow pattern velocity and left atrial volume changes during leg-positive pressure, obtained by a leg massage machine which can maintain a constant loading pressure around the legs for 5 min. By using this method, a setting of 90 mmHg has been applied because this pressure does not significantly increase either heart rate or systolic blood pressure. Left ventricular diastolic dysfunction can be induced and a restrictive pattern (*E* velocity deceleration time <200 ms) is an independent predictor of all-cause mortality [38].

Whatever the stress used, the increase in cardiac output is associated with a distinct pattern in healthy subjects compared to HFpEF patients. The two most distinct features are the disproportionate increase in filling pressures and lung water during stress in HFpEF compared to normal [39] (Fig. 27.4). The slope of this line can vary according to various conditions since—for any given increase in pressure [40]—the lung water accumulation will be steeper in presence of inflammation, reduced plasma albumin, impaired lymphatic drainage efficiency, or acute rather than slow pulmonary wedge pressure changes [41]. The same result can be obtained with a preload stress test (such as leg-positive pressure), a vasodilator test (impairing ventricular stiffness with an erectile effect on myocardium), or a dobutamine test (increasing cardiac output and stressing the diastole with the increased heart rate).

Based on established (TRV and *E*/*e*′) and emerging (B lines, end-diastolic volume reserve, cardiac output, left atrial volume, acceleration time when TRV is not feasible) parameters, the recommended protocol for exercise SE can be summarized

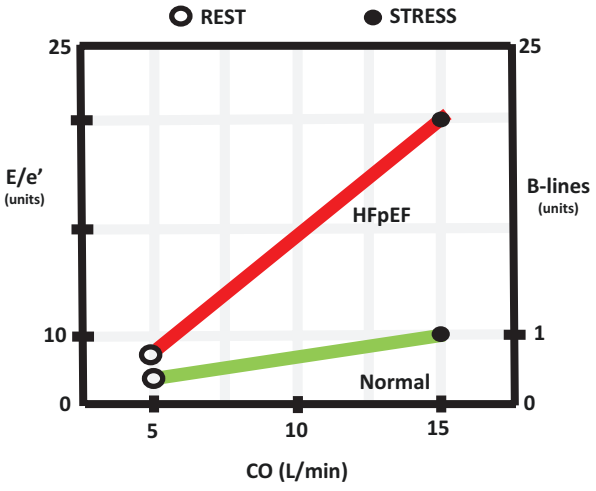

Fig. 27.4 The increase in cardiac output (*x*-axis) associated with stress and the corresponding variation in *E*/*e*′ (left *y*-axis) and lung B lines (right *y*-axis). The slope is flat for the normal patient and steep for patients with HFpEF

Table 27.8 General protocol of exercise SE in HFpEF

	2D	LUS	CWD	PWD	TDI	STE	ECG	BP
Parameters	EDV, ESV, LAV	B lines	TRV	*E*, AcT	*e′*	GLS	HR	SBP
Steps								
1—Rest	v	v	v	v	v	v	v	v
2—Low load	v		v				v	v
3—Peak	v		v	v			v	v
4—Early rec		v			v	v	v	v
5—Recovery	v						v	v

AcT acceleration time, *BP* blood pressure, *CWD* continuous-wave Doppler, *2D* 2-dimensional echocardiography, *ECG* electrocardiogram, *EDV* end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *GLS* global longitudinal strain, *HR* heart rate, *LAV* left atrial volume, *LUS* lung ultrasound, *PWD* pulsed-wave Doppler, *rec* recovery, *SBP* systolic blood pressure, *STE* strain echocardiography, *TDI* tissue Doppler imaging, *TRV* tricuspid regurgitant jet velocity

as follows (Table 27.8). The recommended time window for B lines is in the first minute of recovery when B lines increase compared to peak exercise and their imaging does not interfere with other peak stress parameters such as TRV [42].

27.7 Limitations of Diastolic SE

The value of the *E*/*e′* ratio is debated already at rest in patients with mitral valve disease and those with mechanical prostheses and regional wall motion abnormalities. The grading of diastolic dysfunction according to the usual criteria is not feasible in all patients since TRV can be obtained in one-half of patients during exercise [43]. TRV underestimates PASP in patients with severe tricuspid regurgitation. The same right atrial pressure at rest and peak stress is also a source of error since peripheral venous pressure may increase during exercise [44]. The *E*/*e′* is only moderately correlated to PCWP during exercise, and its technical feasibility is reduced at peak stress due to wave fusion and tachycardia [45]. Diastolic grading is time-consuming and complex and often leads to discordant or indeterminate results, with good inter-observer agreement only in normal or abnormal cases [46]. Simpler parameters such as B lines have outstanding feasibility, high reproducibility, and a tight relationship with changes in PCWP during exercise [47], but a larger experience is needed in HFpEF patients, also considering that B lines can have a dual hemodynamic origin, from increased PCWP in left heart failure and also from increased central venous pressure reducing lymphatic lung water drainage in right heart failure [1]. Finally, the current classification based on the resting values of EF ignores the underlying heterogeneity of pathophysiological mechanisms, since a preserved EF can be associated with a hypocontractile phenotype (more frequent with EF values between 50% and 60% and associated with impaired ventriculo-arterial coupling), and a hypercontractile phenotype, more frequent with values of EF > 60% and characterized by a reduced preload reserve and excessive LV afterload [48].

27.8 Guidelines and Recommendations

Any evaluation of patients with known or suspected HFpEF should start from resting transthoracic echocardiography to include assessment of TRV jet and PASP, left ventricular mass index, left atrial volume index, myocardial tissue velocity *e′*, and the ratio of early mitral inflow to tissue velocity *E*/*e′*. This package is recommended by both the current 2021 European Society of Cardiology heart failure guidelines [49] and the 2016 American Society of Echocardiography/European Society of Cardiovascular Imaging recommendations for the evaluation of left ventricular diastolic function [8].

The 2019 European Society of Cardiology recommendations in chronic coronary syndromes suggests using SE to rule out an ischemic origin of dyspnea in patients with a greater than 10% probability of disease based on clinical estimation [7]. The American Society of Echocardiography-European Association of Cardiovascular Imaging 2016 recommendations suggest excluding a cause of dyspnea other than diastolic dysfunction with a SE based on regional wall motion abnormality, mitral regurgitation, left ventricular outflow tract gradient, and heart rate response. When these nondiastolic causes are excluded, a SE focused on diastolic function is indicated (Table 27.9). The recommended parameters are *E*/*e′* and PASP derived from TRV. Specialty SE recommendations also mention the use of B lines and assessment of left ventricular end-diastolic volume reserve [8]. All documents recommend exercise as the first-line test, but the American Society of Echocardiography 2020 also recommends pharmacological tests when exercise is not feasible [50].

American Society of Echocardiography-European Association of Cardiovascular Imaging also recommends including cardiac output together with B lines, end-diastolic volume changes, contractile reserve (also with global longitudinal strain), PASP (from TRV or, when TRV is not available, acceleration time), *E*/*e′* and left atrial volume index. For calculation of cardiac output (stroke volume times heart rate), stroke volume can be estimated from a 2-dimensional assessment of end-diastolic volume and end-systolic volume [8].

The test can be performed in patients with suspected HFpEF (European Society of Cardiology-Acute Heart Failure score between 2 and 4 points) for primarily diagnostic purposes, and patients with established diagnosis (≥5 points) for risk stratification and regrading of severity. In the approach accepted in the SE 2030 study, SE is essential in the screening phase to identify extra-diastolic causes of dyspnea and

Table 27.9 Recommendations for SE in known or suspected HFpEF: when and how

	Class 1	Class 2a	
To rule out ischemia	**v**		ESC 2020 [7]
To rule out ischemia, MR, CI, dynamic LVOTO	**v**		ASE-EACVI 2017 [8]
HFpEF score 2–4	**v**		ESC-HFA 2019 [3]
Exercise first choice	**v**		ESC-HFA 2019 [3]
Pharmacological when exercising not feasible		**v**	ASE 2020 [50]

CI chronotropic incompetence, *LVOT* left ventricular outflow tract obstruction, *MR* mitral regurgitation

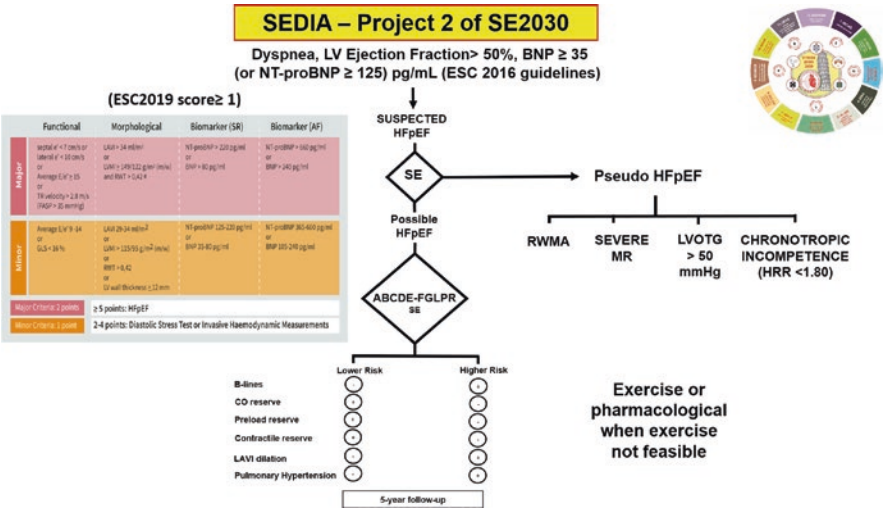

Fig. 27.5 The general protocol adopted for the study of SE in Diastolic heart failure (SEDIA) subproject of the SE 2030 study

later in the diagnostic phase to document the presence and severity of diastolic dysfunction. In the diagnostic phase, in addition to *E*/*e′* and PASP derived from TRV, SE evaluation may include B lines, cardiac reserve, coronary flow reserve, heart rate reserve, left atrial volume, pulmonary hemodynamics (with pulmonary flow acceleration time when TRV is unfeasible), and right ventricular function. Each variable establishes the evidence for a different phenotype and represents a biomarker of risk and a potential therapeutic target. Comprehensive diastolic SE accepted in the SE 2030 study network might allow a better understanding of this heterogeneous clinical syndrome (Fig. 27.5) [51].

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Stress Echocardiography in Hypertension

28

Jesus Peteiro and Eugenio Picano

Keywords

Arterial hypertension · Coronary flow velocity reserve · Heart rate reserve · Left ventricular hypertrophy

28.1 Background

Uncontrolled and prolonged elevation of blood pressure can lead to a variety of changes in the myocardial structure, coronary vasculature, and conduction system of the heart. The development of left ventricular hypertrophy, coronary artery disease (CAD), various conduction system diseases, and systolic or diastolic dysfunction of the myocardium, may manifest clinically as angina or myocardial infarction, cardiac arrhythmias (especially atrial fibrillation), heart failure with either reduced or preserved ejection fraction, and valvular heart disease. In patients with CAD and/or heart failure, blood pressure should be corrected if ≥140/90 and treated to target <130/80 mmHg (<140/80 in elderly patients, and >120/70 in heart failure). Patients with angina have a high prevalence of hypertension. Hypertension is an established risk factor for the development of CAD, almost doubling the risk [1]. Transthoracic

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J. Peteiro (✉)
CHUAC-Complexo Hospitalario Universitario A Coruna, CIBER-CV, University of A Coruna, La Coruna, Spain
e-mail: Jesus.Peteiro.Vazquez@sergas.es

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

E. Picano (ed.), *Stress Echocardiography*,
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Table 28.1 Rest and stress echocardiography for risk stratification in hypertensive subjects with normal resting left ventricular function

	Higher risk	Lower risk
Resting echocardiography		
LVMI (g m^{-2})	>115 (men), >95 (women)	≥115 (men), ≥95 (women)
LAVI (mm^2 m^{-2})	>34	≤34
DD (grade)	2–3	0–1
RWT	≥0.45	< 0.45
Stress echocardiography		
WMA	Yes	No
B-lines	≥ 2.0	<2.0
LVCR	Abnormal	Normal
E/*e*′	≥15	<15
CFVR	≤2.0	> 2.0
HRR	Abnormal	Normal

CFVR coronary flow velocity reserve, *DD* diastolic dysfunction (from 0 = absent to 3 = severe), *HRR* heart rate reserve, *LAVI* left atrial volume index (in apical biplane view), *LVH* left ventricular hypertrophy, *LVCR* left ventricular contractile reserve, *RWT* relative wall thickness, *WMA* wall motion abnormalities

echocardiography is especially helpful for initial risk stratification, and identifies four key variables of recognized prognostic value [2]: (1) left ventricular hypertrophy, especially of the concentric type; (2) left atrial dilatation, often occurring in the absence of valvular heart disease or systolic dysfunction and may correlate with the severity of diastolic dysfunction; (3) diastolic dysfunction, common in hypertension, and usually but not invariably accompanied by left ventricular hypertrophy [3]; and (4) systolic dysfunction (Table 28.1).

Stress echocardiography (SE) adds critically important pathophysiologic, diagnostic, and prognostic information to resting transthoracic echocardiography and identifies multiple vulnerabilities of the hypertensive patient above and beyond epicardial coronary artery stenosis, from diastolic dysfunction to impairment of cardiac and contractile reserve, from coronary microcirculation dysfunction to altered cardiac autonomic unbalance.

28.2 Pathophysiology

Arterial hypertension can provoke a reduction in coronary flow reserve through several mechanisms, which may overlap in the individual patient. The main mechanisms are CAD, left ventricular hypertrophy, and microvascular disease [4] (Fig. 28.1).

Abnormal coronary flow reserve has been demonstrated in patients with essential hypertension, despite the presence of angiographically normal arteries and the absence of left ventricular hypertrophy [5]. This observation has been attributed to the remodeling of both vascular and extravascular structures and coronary hemodynamic alterations. The former includes remodeling of intramural arterioles and interstitial fibrosis, and leads to a decreased density of vessels in the coronary

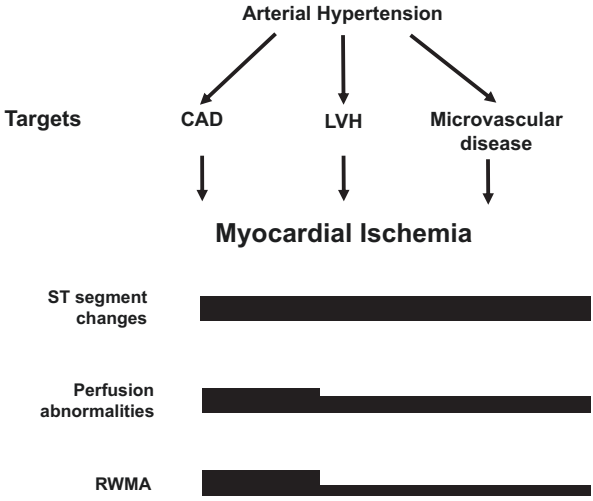

Fig. 28.1 Three main targets of hypertension: CAD, left ventricular hypertrophy (LVH), and microvascular disease. All three of these conditions can provoke stress-induced ST-segment depression, perfusion abnormalities, and, less frequently, transient regional wall motion abnormality. (Modified from Lucarini et al. [9])

microvasculature, whereas the latter is characterized by increased extravascular compressive forces and elevated systolic and diastolic wall stress, and impaired relaxation. Coronary microvascular dysfunction in patients with hypertension is not necessarily related to the presence or degree of left ventricular hypertrophy [6]. In general, arterial hypertension can be associated with multiple phenotypes [7], and only a comprehensive assessment with SE allows the capture of the complexity of cardiovascular involvement in arterial hypertension. When the comprehensive ABCDE SE protocol is applied in normotensives and hypertensives, the prognosis progressively worsens with the increasing score from 0 (all steps are normal) to 5 (all steps are abnormal) [8].

28.3 Diagnosis of CAD

The noninvasive diagnosis of CAD in hypertensive individuals is particularly challenging for the cardiologist since the coexistence of hypertension lowers the specificity of exercise electrocardiography and perfusion scintigraphy [9]. Experience with diagnostic tests in these patients led to the frustrating conclusion in the pre-SE era that "no noninvasive screening test has been found to adequately discriminate between hypertensive patients with and without associated atherosclerosis" [10]. Furthermore, all exercise-dependent tests also show a markedly lowered feasibility in hypertensive patients; severe hypertension during the resting condition is a contraindication to exercise testing, and even in mild to moderate hypertension, the first step of exercise can induce an exaggerated hypertensive response that limits effort tolerance. SE tests have a higher specificity than the electrocardiogram [11, 12] or perfusion stress testing, with similar sensitivity [13, 14].

As in normotensives, exercise can be performed on a bicycle or a treadmill. Peak exercise is preferred over postexercise imaging, given its higher sensitivity (Fig. 28.2).

Peak treadmill imaging is feasible and simple and the first choice compared to postexercise imaging. In addition, pharmacological stresses have significantly higher feasibility than exercise stress testing, especially with vasodilator testing, which does not evoke the often limiting hypertensive response that can be associated with dobutamine stress [16].

An exaggerated systolic blood pressure (SBP) rise has been considered a cause of wall motion abnormalities during exercise in absence of coronary lesions in old studies that evaluated exclusively patients submitted to angiography [17, 18]. However, recent studies evaluating a higher number of patients and without being subject to test verification bias have found that patients with exaggerated SBP responses are not more likely to have false-positive results than those with normal pressure responses [19, 20]. For cases of premature cessation of exercise due to exaggerated SBP, dipyridamole SE might be considered since there is little or no SBP rise during this stress [21].

Apart from symptoms that might suggest ischemia, hypertensive patients, particularly those with left ventricular hypertrophy, frequently complain of dyspnea

Fig. 28.2 Setting of peak treadmill exercise-echocardiography, preferred over the less sensitive and equally feasible postexercise imaging. (Modified from Peteiro et al. [15]). See accompanying Video 28.1. (See also https://www.youtube.com/watch?v=gnYRa6PoYVw. The video is available under the chapter's "Supplementary Material" on Springer Link)

that can be the result of either CAD, diastolic dysfunction, or a noncardiac disease. A diastolic stress test with exercise [22] is useful in this condition to rule out ischemia and to correlate dyspnea with parameters that suggest high filling pressures, such as an increased ratio of early diastolic transmitral velocity to early diastolic tissue Doppler velocity (E/e') [23, 24] or the change of a normal left ventricular inflow pattern or a pattern of altered relaxation to a pseudonormalized pattern during exercise [24]. An E/e' ratio >13–15 is considered abnormal [22–25].

28.4 Prognostic Stratification

During stress, we have three signals of potential value in hypertensive patients: ST-segment depression, wall motion abnormalities, and coronary flow reserve. The pathophysiological significance of stress-induced, ischemic-like electrocardiographic changes remains uncertain [26]. This stress pattern is often found in these patients with normal coronary arteries and hyperkinetic wall motion. The electrocardiographic changes may merely represent nonspecific, innocent alterations or may reflect true subendocardial hypoperfusion. Such ischemic-like electrocardiographic changes occurring with angiographically normal coronary arteries have been associated with a reduced coronary flow reserve [27], a higher incidence of spontaneously occurring or stress-induced ventricular arrhythmias [28], higher values of the left ventricular mass index, and when left ventricular mass is normal, more pronounced structural and functional changes in systemic arterioles [29]. Regression of structural changes of systemic arterioles achieved with any form of antihypertensive therapy is paralleled by the electrocardiographic negativity of a previously positive electrocardiographic stress test result [30, 31].

As with microvascular angina, resting and SE can be helpful for risk stratification in patients with chest pain and angiographically normal coronary arteries. The prognostic value of stress-induced wall motion abnormalities is strong and extensively documented. Hypertensive patients with inducible wall motion abnormalities (with or without underlying CAD) are at higher risk than those without [32–36].

The prognosis is worse when the stress-induced dysfunction is present on top of a resting regional wall motion abnormality [35]. In one study of hypertensive patients with normal coronary angiography, those with exercise-induced wall motion abnormalities leading to a decrease in left ventricular ejection fraction had five times higher cardiac mortality, and almost seven times higher cardiac failure during follow-up than those with a normal exercise echocardiogram [36].

Within the subset of hypertensive patients with no wall motion abnormalities, patients with reduced coronary flow reserve assessed are at intermediate risk. Patients with neither wall motion abnormalities nor coronary flow reserve reduction are at the lowest risk [37].

When compared to other stress imaging techniques with comparable prognostic values, such as myocardial perfusion scintigraphy, SE has four clear advantages: lower cost (approximately 1:3) compared with perfusion scintigraphy; higher specificity (which avoids useless coronary angiographies) [13, 14], also maintained in

challenging subsets such as patients with right bundle branch block [38]; additive prognostic value over other parameters obtained with a resting echocardiogram, before stress, such as left ventricular hypertrophy [39]; and lack of radiation exposure [40].

Prognostic stratification and efficient diagnosis based on the integrated use of rest and SE can be achieved in hypertensives.

In hypertensive patients with normal coronary arteries and coronary microvascular damage (reduced coronary reserve without wall motion abnormalities), a subnormal increase in global longitudinal strain is consistent with true ischemia during stress [41].

The excessive blood pressure increase can be a limiting sign leading to premature interruption of testing, but it is also associated with a significantly lower risk of mortality and major adverse cardiac events, probably as an expression of the increased left ventricular contractile reserve, calculated as force (SBP/end-systolic volume) reserve [42]. Diastolic function evaluated as E/e' also adds to the prognostic value of stress-induced wall motion abnormality and ejection fraction in normotensives and hypertensives, again suggesting that the versatility of echocardiography is underused in the current practice of SE [43].

28.5 Pitfalls

The main pitfalls for SE in hypertensives are a reduction in the feasibility of stress testing due to limiting excessive blood pressure rise with exercise or an increase in the frequency of limiting side effects such as atrial arrhythmias with dobutamine. The diagnostic markers suffer from a reduction in specificity, more modest with wall motion abnormalities (which may occur especially in the apical region with excessive blood pressure rise) and more pronounced with perfusion changes, since the reduction in coronary flow reserve may occur independently of coronary artery stenoses due to left ventricular hypertrophy and/or microvascular disease.

28.6 Clinical Guidelines

Arterial hypertension has multiple targets of end-organ damage, and a comprehensive SE is ideally fit to assess the multiple potential vulnerabilities of the hypertensive patient: functional significance of epicardial coronary artery stenosis, pulmonary congestion, diastolic function, left ventricular contractile reserve, coronary microcirculatory function, and cardiac autonomic balance. Stress-induced wall motion abnormalities are more specific for angiographically assessed coronary artery stenosis, also in presence of a stress-induced hypertensive response, whereas coronary microcirculatory abnormalities are frequently found with angiographically normal coronary arteries, with or without associated left ventricular hypertrophy. The presence of moderate to severe resting arterial hypertension is a specific contraindication to exercise and dobutamine testing [44] (Table 28.2).

Table 28.2 Contraindications to stress imaging modalities in hypertensives

	Exercise	Dobutamine
Grade 3 systemic hypertension (office SBP >180 mmHg)	v	v
Grade 2 systemic hypertension (office SBP 160–180 mmHg)		v

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Stress Echocardiography in Diabetes

29

Jaroslaw D. Kasprzak and Eugenio Picano

Keywords

Contractile reserve · Coronary flow velocity reserve · Coronary microcirculation · Sympathetic innervation

29.1 Background

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in patients with diabetes. Approximately one-half of deaths are attributed to coronary artery disease in diabetic patients, whose risk of myocardial infarction or cardiac death is two- to fourfold greater than in nondiabetic patients [1]. Moreover, cardiac events are as frequent in diabetic patients without evidence of CAD as in nondiabetic patients with known CAD [2]. Recent studies with electron beam computed tomography have shown that subclinical atherosclerosis is common in patients with diabetes, and studies with myocardial perfusion scintigraphy (with single-photon emission tomography) or stress echocardiography (SE) have shown that 25–50% of asymptomatic diabetic patients have ischemia during exercise or pharmacological stress and that a substantial proportion of these patients go on to develop major cardiovascular events within several years [2, 3]. The increased risk associated with diabetes calls for effective prevention and risk stratification strategies to optimize therapeutic interventions [3]. Asymptomatic diabetic patients include a subset of individuals at high risk of cardiovascular disease who would benefit from improved

J. D. Kasprzak (✉)
Department of Cardiology, Medical University of Lodz, Bieganski Hospital, Lodz, Poland

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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risk stratification beyond that possible with risk factor scoring systems alone [4]. Exercise testing is of limited value in the diabetic population because exercise capacity is often impaired by peripheral vascular [5] or neuropathic disease [6]. Furthermore, test specificity on electrocardiographic criteria is less than ideal because of the high prevalence of hypertension and microvascular disease [7]. Stress imaging, and in particular SE, can play a key role in the optimal identification of the high-risk diabetic subset, also with the potential of identifying the different dilated and restrictive phenotypes [8].

29.2 Pathophysiology

Diabetes mellitus can provoke cardiac damage at four levels: coronary macrovascular disease, autonomic neuropathy, direct cardiomyocyte damage (suggested as more prevalent in type 1 diabetes), and coronary microvascular disease (Fig. 29.1). These syndromes are rarely found in isolated form in individual patients, but more often overlap and potentiate each other. Diabetes mellitus induces coronary structural, macroangiopathic [9], and functional microvascular abnormalities [10], which are associated with coronary endothelial dysfunction and impairment in coronary flow reserve, even in the absence of epicardial CAD [11]. Left ventricular systolic function at rest and during dobutamine can be impaired in diabetic patients even in presence of normal ejection fraction, and this incipient dysfunction can be detected

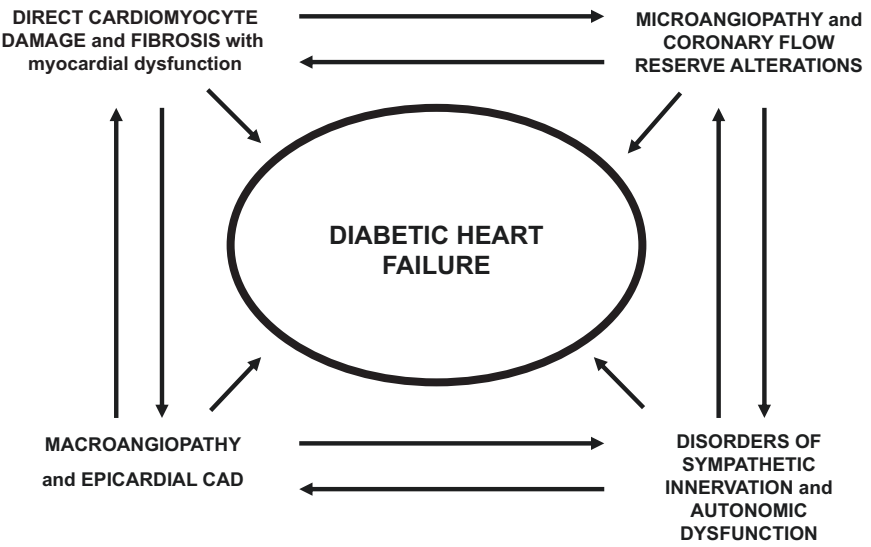

Fig. 29.1 The four aspects of damage in the diabetic heart: direct cardiomyocyte damage, coronary microangiopathy, coronary macroangiopathy, and autonomic neuropathy. The four pathways—albeit pathogenetically distinct—cross-talk. For instance, microangiopathy may codetermine neuropathy—through vasa nervorum involvement—and at the coronary level, may impair coronary flow reserve, amplifying the impact of epicardial coronary artery stenosis

with the assessment of global longitudinal strain with deformation imaging [12]. Functional recovery after the dobutamine challenge is also altered in diabetics [13] as documented by longitudinal strain measurements.

29.3 Diagnosis of CAD

The coronary microangiopathy component can amplify the effects of coronary macroangiopathy, which is a major complication of diabetes. Coronary, cerebral, and peripheral vascular diseases are the causes of death in 75% of adult diabetic subjects. The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to SE in the detection of CAD in asymptomatic (and symptomatic) diabetic patients [14–21]. The typical behavior of microvascular disease during stress testing is the frequent induction of ST-segment depression and perfusion abnormalities, with a true reduction in coronary flow reserve without regional or global wall motion changes [8]. In practical terms, this means that in patients with normal baseline ECG results, the negative predictive value of a maximal exercise ECG is satisfactory, but in all patients with positive or ambiguous ECG and/or chest pain findings, a SE test is warranted. In diabetic patients, SE has shown a higher specificity than perfusion imaging but suffers from a higher rate of false-positive results, possibly due to the coexistence of nonvascular myocardial damage in many patients [21].

29.4 Prognostic Stratification

Risk stratification of diabetic patients is a major objective for clinical cardiologists, given their increased risk for CAD and cardiovascular mortality [1]. Resting echocardiography is already important for this purpose since there is a distinct "diabetic cascade" (Fig. 29.2) with higher risk levels—and higher degrees of cardiomyopathic involvement—identified by left atrial dilatation [22], diastolic dysfunction [23], and impaired longitudinal shortening of the myocardium [24], which may all coexist with normal ejection fraction [25].

SE has shown powerful risk stratification capabilities in diabetics. In patients with overt resting ischemic cardiomyopathy, the presence of myocardial viability recognized by dobutamine echocardiography independently predicts improved outcomes following revascularization in nondiabetics as well as in diabetic patients following revascularization [26]. Also, in patients with normal resting left ventricular function, a clear refinement of prognosis can be obtained with SE, first and foremost based on classical wall motion abnormalities [27–32], which place the patients in a high-risk subset for cardiovascular events. The incremental prognostic information provided by SE is highest in patients with intermediate-to-high threshold positive exercise electrocardiography test results [33]. However, in diabetic patients—differently from nondiabetic subjects—a negative test result based solely on wall motion criteria is associated with a less benign outcome of 3–4% yearly

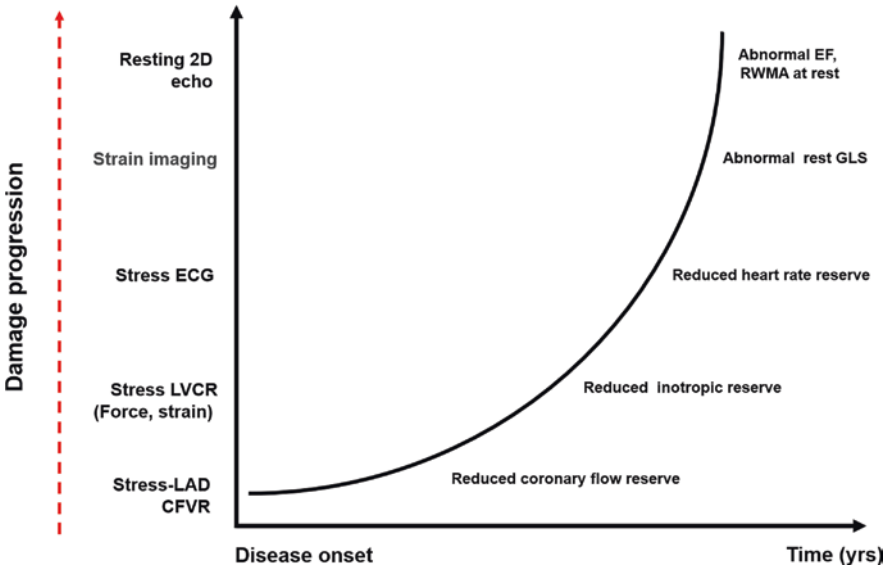

Fig. 29.2 Cardiomyopathy cascade. In the sequence of events, changes in diastolic function and alterations in the longitudinal function of the left ventricle (such as reduction in global longitudinal strain) may precede by years the reduction of resting ejection fraction. Coronary, contractile, and chronotropic reserve during stress is impaired at an earlier stage than resting indices. (Adapted and modified from Picano E [25])

mortality [30, 32]. In these patients, coronary flow reserve evaluated simultaneously with wall motion during vasodilation stress testing by transthoracic Doppler echocardiography adds independent prognostic information [34]. In particular, a normal coronary flow reserve is associated with tighter glycemic control [35] and better long-term event-free survival in unselected diabetic patients [36] as well as in diabetic patients with angiographically normal coronary arteries [37]. Explanations for reduced coronary flow reserve in the absence of stress-induced wall motion abnormalities include mild-to-moderate epicardial coronary artery stenosis, severe epicardial artery stenosis in presence of antiischemic therapy, and severe microvascular coronary disease in presence of patent epicardial coronary arteries [34]. Further stratification in patients with negative wall motion response can be obtained by evaluation of left ventricular contractile reserve and heart rate reserve. The risk is lowest in patients with the absence of regional wall motion abnormalities, with normal contractile reserve, coronary flow velocity reserve, and heart rate reserve [38, 39]. Concomitant abnormal coronary flow velocity reserve (<2) and left ventricular contractile reserve (<1.1) are related to a ninefold increase in cardiovascular events in diabetic patients with nonischemic dipyridamole stress [38]. This stratification with the comprehensive SE protocol is best achieved with vasodilators [40] including the key variable of coronary flow velocity reserve [41] but is also possible with exercise or dobutamine stress with a focus on left ventricular contractile reserve [42]. A cold pressor test was also proposed as a protocol for

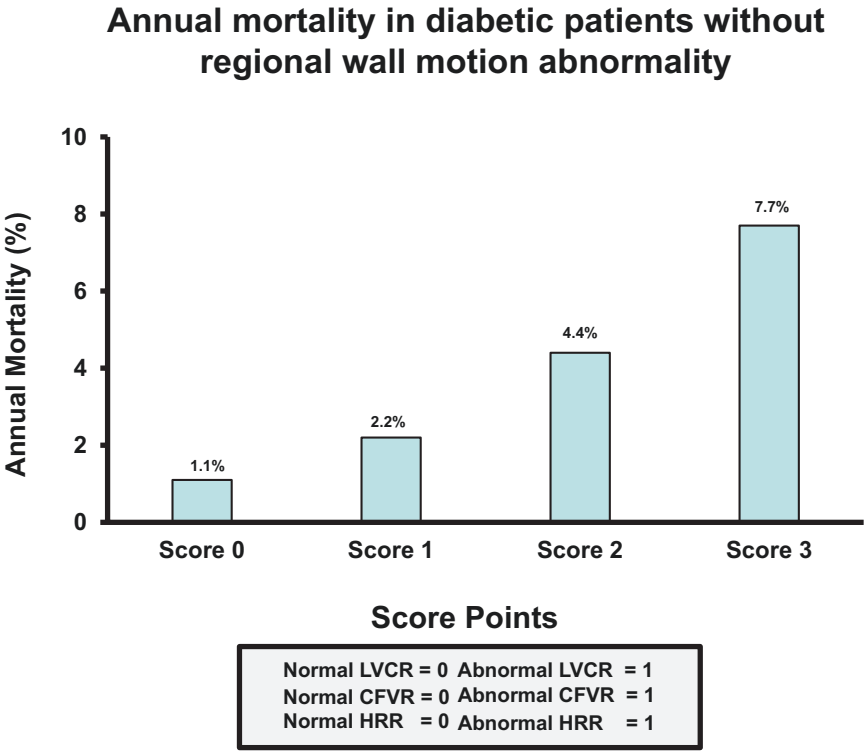

Fig. 29.3 Risk stratification in diabetes. The annual mortality rate in diabetic patients without inducible regional wall motion abnormalities. The risk is lowest in patients with normal left ventricular contractile reserve, coronary flow reserve, and heart rate reserve. The risk is highest when all three reserves are abnormal. (From the original data of Cortigiani et al. [39])

the assessment of microvascular dysregulation expressed as abnormal coronary flow velocity reserve [43]. Functional stress testing may include a comprehensive assessment of risk and evaluation of the vulnerabilities of the patient beyond coronary artery stenosis and inducible ischemia, such as contractile reserve, coronary microvascular function, and cardiac autonomic balance (Fig. 29.3).

29.5 Pitfalls

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, autonomic or peripheral neuropathy (both sensory and motor), and vascular disease [44]. For those unable to perform an exercise test, pharmacological stress testing may be required.

Importantly, a normal SE in a diabetic patient signifies severalfold higher cardiovascular risk as compared to a normal study in a nondiabetic population.

29.6 Clinical Guidelines

According to the latest 2019 guidelines of the European Society of Cardiology on diabetes [45], coronary computed tomography angiography or functional imaging (including exercise or pharmacological SE) may be considered (class of recommendation 2b) in asymptomatic patients with diabetes mellitus for screening of CAD. A recent European Association of Cardiovascular Imaging document on the detection of myocardial dysfunction highlights the role of SE in documenting microvascular coronary disease [46]. Comprehensive SE is especially suited to identify the different phenotypes of disease, with alterations in sympathetic innervation through heart rate reserve, reduced systolic function with altered contractile reserve, restrictive pattern with pulmonary congestion and rest and stress B-lines, and predominant coronary microvascular disturbance with alterations in coronary flow velocity reserve. SE has low cost, no radiation, and little environmental impact, and these features are especially attractive in patients in need of serial evaluations over time [47] since the warranty period of a functional test expires after 1 year [48].

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Stress Echocardiography in Hypertrophic Cardiomyopathy

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Eszter Dalma Pálinkás, Maria Grazia D'Alfonso, Fabio Mori, Iacopo Olivotto, and Eugenio Picano

Keywords

Coronary flow velocity reserve · Left ventricular outflow tract obstruction · Myocardial ischemia · Pulmonary congestion

30.1 General Concepts

Hypertrophic cardiomyopathy (HCM) is the most common monogenic disease of the myocardium, with a 1:500 prevalence in the general population worldwide, although often misdiagnosed or neglected [1]. HCM is defined by the presence of increased left ventricular wall thickness ≥15 mm by any imaging modality in one or more left ventricular myocardial segments that are not solely explained by abnormal loading

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E. D. Pálinkás (✉)
Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary
e-mail: palinkaseszti@hotmail.com

M. G. D'Alfonso · F. Mori
Department of Cardiology, Careggi University Hospital, Florence, Italy
e-mail: dalfonsomg@aou-careggi.toscana.it; morif@aou-careggi.toscana.it

I. Olivotto
Pediatric Cardiology Unit, Meyer Children's Hospital IRCCS, Florence, Italy

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
e-mail: iacopo.olivotto@unifi.it

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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conditions and occurs in the absence of other detectable causes [2]. A lower threshold for wall thickness (i.e., ≥13 mm) is adopted in first-degree relatives of patients with the unequivocal disease. Clinical diagnosis is customarily made with two-dimensional echocardiography by detection of increased wall thickness, usually in the presence of a small left ventricular cavity after suspicion has been raised by the clinical profile or as a part of screening [2]. In most patients, HCM is caused by mutations in genes encoding contractile proteins of the cardiac sarcomere, Z-disk, and intracellular calcium handling pathways [3]. A minority of cases are caused by inherited metabolic and neuromuscular diseases, which are most common in pediatric cohorts, or so-called phenocopies such as amyloidosis or Fabry disease. In over one-third of patients, however, the genetic basis of the disease remains unresolved. To date, hundreds of different mutations have been associated with HCM (>90% affecting myosin-binding protein C, beta-myosin heavy chain, and troponin T), and many families exhibit "private" mutations which have not been previously described. Adding to the genetic complexity of the disease is the fact that many of these variants, suspected to cause disease, do not meet the requirements for pathogenicity, and are necessarily classified as "variants of unknown significance" [4]. Despite over two decades of research in the field, attempts to correlate genotype with phenotype, disease severity, and outcome have yielded inconsistent and overall disappointing results, although some clinically relevant associations have been observed [5, 6].

HCM is often characterized by a stable and uneventful clinical course and may be diagnosed late in life [7]. However, about 50% of patients experience symptoms related to effort or meals, 25% develop atrial fibrillation, and 15% progress toward left ventricular dysfunction and heart failure, including 5% ultimately developing end-stage disease (Fig. 30.1).

In addition, the condition is associated with a 0.5–1% annual risk of sudden cardiac death. Prior history of cardiac arrest is an obvious indicator of risk representing a clear-cut indication for the implantable cardioverter-defibrillator (Share registry). In primary prevention, however, arrhythmic risk prediction proves extremely challenging, due to the low event rate and low-positive predictive accuracy of risk factors identified to date. Current recommendations include individual multiparametric assessment comprising age, family history of sudden death, unexplained syncope, multiple-repetitive nonsustained ventricular tachycardia, elevated left ventricular outflow tract (LVOT) gradients (at rest or during Valsalva), massive left ventricular hypertrophy, abnormal pressure response to exercise, complex genotype, apical aneurysm, end-stage disease, and diffuse late gadolinium enhancement >20% [2].

Resting echocardiography provides a wealth of information in HCM patients [7], and adds to clinical risk stratification by identifying additional markers of risk such as massive left ventricular hypertrophy (>30 mm), intraventricular obstruction (>30 mmHg), progressive wall thinning, and declining systolic function over serial evaluations and the presence of left ventricular apical aneurysms [8]. Left atrial dilation and restrictive left ventricular filling pattern may also help to identify high-risk subsets. Extensive intramyocardial fibrosis identified by cardiac magnetic resonance as late gadolinium enhancement has proven of some utility in predicting cardiovascular mortality, heart failure-related end-points, and sudden cardiac death [9] (Fig. 30.2).

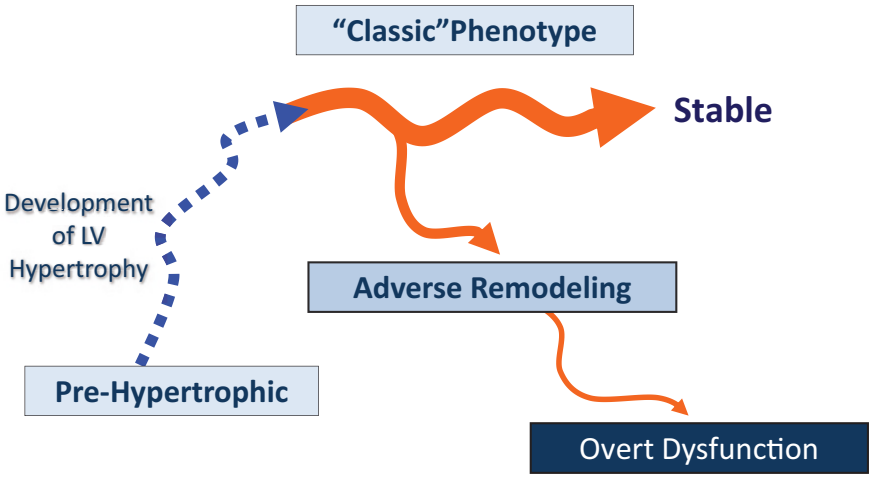

Fig. 30.1 Stages of HCM. The thickness of the orange lines reflects the prevalence of each stage in HCM cohorts. The prevalence of nonhypertrophic HCM is unknown. (From Olivotto et al., [7])

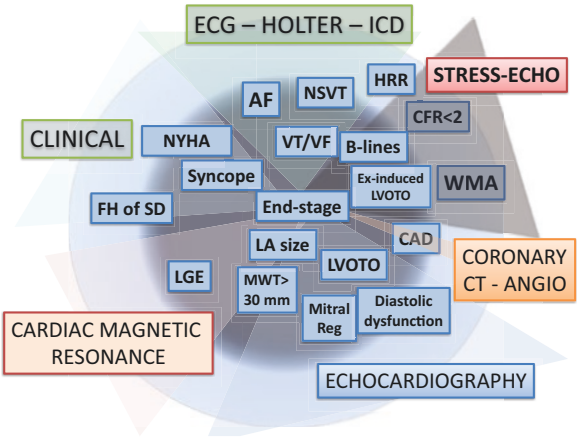

Fig. 30.2 Contribution of SE to risk stratification in HCM. All listed features have been shown or suspected to predict adverse outcomes in HCM. *ABPR* abnormal blood pressure response to exercise, *AF* atrial fibrillation, *CAD* coronary artery disease, *CFR* coronary flow reserve, *FH* family history, *HRR* heart rate reserve, *ICD* implantable cardioverter-defibrillator, *LA* left atrial, *LGE* late gadolinium enhancement, *NYHA* New York Heart Association functional class, *MWT* maximum wall thickness, *NSVT* nonsustained ventricular tachycardia, *WMA* wall motion abnormalities, *Reg* regurgitation, *SD* sudden death, *VT/VF* ventricular tachycardia/fibrillation

Table 30.1 Clinically relevant information derived from rest and SE in HCM

	Rest TTE	SE
Wall thickness, mitral leaflets, papillary muscles	x	
LVOTG and SAM	x	x
Mitral regurgitation	x	x
LV systolic function (EF, force)	x	x
LV diastolic function (*E*/*e′*)	x	x
LAVI	x	x
B-lines	x	x
PASP (hemodynamic congestion)	x	x
Heart rate reserve and recovery		x
Functional capacity		x
Myocardial ischemia (ECG changes)		x
BP response to exercise		x
Coronary flow velocity reserve		x
Diastolic reserve		x

BP blood pressure, *e′* early diastolic mitral annular velocity, *E* early mitral inflow velocity, *ECG* electrocardiogram, *EF* ejection fraction, *LAVI* left atrial volume index, *LV* left ventricular, *LVOTG* left ventricular outflow tract gradient, *PASP* pulmonary arterial systolic pressure, *SAM* systolic anterior motion of the mitral valve

Despite the comprehensive clinical and pathophysiological information provided by genetic testing, clinical evaluation, and multiparametric imaging in resting conditions, stress echocardiography (SE) remains an essential step in patients with HCM, to assess relevant features including functional capacity, presence, and extent of provokable obstruction, myocardial ischemia, coronary flow reserve, mitral regurgitation, pulmonary pressures, lung congestion, exercise-induced arrhythmias, heart rate reserve, and blood pressure response to exercise (Table 30.1). All these clinical, electrocardiographic, and echocardiographic variables represent a substantial contribution to clinical management and risk stratification [10].

Additional steps of potential importance in HCM patients are exclusion/assessment of mid-ventricular obstruction, right ventricular outflow obstruction, evaluation of clinical relevance of coronary myocardial bridging, and exclusion-assessment of associated conditions including atherosclerotic coronary artery disease. The integration of clinical and exercise SE information allows tailored lifestyle recommendations and indications for the appropriate level of activity, including clearance for noncompetitive sports for active individuals.

30.2 Pathophysiology

Clinical and hemodynamic response to exercise or pharmacological stress in HCM is complex, resulting from the interplay of several different and not mutually exclusive pathophysiological mechanisms: (1) dynamic LVOT obstruction, (2)

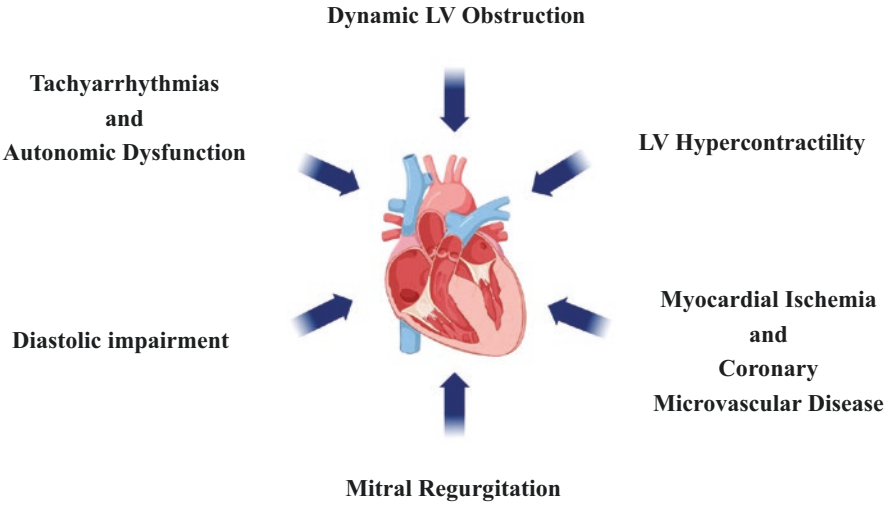

Fig. 30.3 The main pathophysiological mechanisms of disease in HCM. Each of the mechanisms may identify a distinct phenotype, and potentially an actionable therapeutic target

abnormally increased left ventricular function, (3) myocardial ischemia and coronary microvascular dysfunction, (4) diastolic dysfunction and restrictive physiology, (5) functional mitral regurgitation, and (6) tachyarrhythmias and altered cardiac autonomic nervous system balance (Fig. 30.3). Each variable is clinically important and can be captured during a comprehensive SE.

30.2.1 Dynamic Left Ventricular Obstruction

Most HCM patients have the propensity to develop intraventricular gradients under a variety of physiological conditions. Such dynamic obstruction generally occurs at the left ventricular outflow, produced by the systolic anterior motion (SAM) of the mitral valve causing ventricular septal contact [11]. LVOT obstruction is a pathophysiological conspiracy caused by the concomitance of marked mitral leaflet elongation, hypercontractile small or normal-sized left ventricle, abnormally positioned papillary muscles, small LVOT dimensions, and abnormally directed anterograde flow in systole due to septal hypertrophy, leading to the SAM of the mitral valve [12]. The dynamic obstruction may occur at different sites besides LVOT, including the mid-ventricle (due to interposition and septal contact of the anterior papillary muscle) and the right ventricular outflow tract (due to a sphincter-like mechanism occurring at the level of the crista supraventricularis). Fixed, anatomic obstruction due to sub-aortic membranes should be carefully excluded. Each of these mechanisms should be systemically assessed, since management strategies may differ, particularly when interventions aimed at relieving LVOT

obstruction are considered. Dynamic assessment of LVOT obstruction (at rest, during bedside maneuvers, and exercise) holds important prognostic information and plays a pivotal role in the assessment of symptoms.

By convention, LVOT obstruction is defined as an instantaneous peak Doppler LVOT pressure gradient ≥30 mmHg at rest or during physiological provocation (i.e., Valsalva maneuver). A gradient of ≥50 mmHg is usually considered the threshold at which LVOT obstruction becomes hemodynamically important and invasive treatment may be appropriate. Up to one-third of patients have an obstruction at rest (peak instantaneous gradient >30 mmHg), another third have a labile, physiologically provoked gradient (<30 mmHg at rest and physiologically provoked gradient >30 mmHg), and only one-third have true nonobstructive forms (rest and physiologically provoked gradient <30 mmHg) [13].

Of note, while not all patients with HCM have LVOT gradients, it is also true that not all subjects with stress-induced gradients have HCM [14, 15]. Significant gradients can be observed during exercise or dobutamine in patients with Syndrome X or hypertension, athletes, Tako-tsubo syndrome, congenital heart diseases, following cardiac valve surgery, or in acute myocardial infarction, and can be precipitated by dehydration, reduction in preload and left ventricular cavity size, and/or increase in left ventricular contractility [16].

30.2.2 Left Ventricular Hypercontractility

Left ventricular function at rest can be supernormal in the early phase of the natural history of HCM, with a contraction "too good to be normal." Left ventricular function at rest can be markedly abnormal in late and irreversible stages of advanced disease. At the initial stages of HCM, the peculiar pattern is a normal-increased value of baseline ejection fraction, with a blunted increase of force during stress, associated with downregulation of SERCA-2 mRNA, resulting in altered calcium handling which may contribute to reduced contractile reserve [17]. The identification of the contractile state of the left ventricle in HCM is especially relevant since in some mutations the earliest sign of the disease is a hyperdynamic contraction. For instance, the two most frequently mutated HCM genes encode β-cardiac myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3). Young carriers of either MYH7 or MYBPC3 mutation have shown hyperdynamic contraction and impaired relaxation that precede the appearance of myocardial hypertrophy. Two small molecules, mavacamten and aficamten, reduce contractility by decreasing the adenosine triphosphatase activity of the myosin heavy chain. The chronic administration of mavacamten in a transgenic HCM mouse model suppresses the development of left ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis indicating that hyperdynamic contraction is essential for HCM pathobiology [18]. In patients with symptomatic obstructive HCM (phases 2 and 3 for mavacamten, phase 2 for aficamten), both molecules have shown efficacy in reducing resting and exercise gradients, reducing symptoms, and improving diastolic function and quality of life. Mavacamten has recently been approved by the FDA. In the

recent VALOR-HCM study, mavacamten treatment has been effective in reducing or postponing the need for invasive septal reduction therapies in symptomatic obstructive HCM patients [19].

30.2.3 Myocardial Ischemia and Coronary Microvascular Disease

Symptoms and signs of myocardial ischemia are often found in patients with HCM, but a significant angiographically assessed coronary artery disease is present in 20% of HCM patients and is associated with increased mortality [20]. Typical angina on effort associated with ECG changes and wall motion abnormalities may suggest epicardial coronary artery stenosis or, in younger patients, tunneling of the LAD [21, 22]. Significant ST-segment depression during stress often occurs in absence of coronary artery disease and wall motion abnormalities, but it is associated with an increased risk for adverse outcomes with pharmacological and physical stress, both in adults and young HCM patients [23, 24]. For the practical purpose of diagnosing coronary artery disease, all noninvasive markers of inducible ischemia are of limited value, with a specificity lowest for ST segment changes, intermediate for perfusion imaging, and higher but still insufficient for regional wall motion abnormality. Myocardial perfusion imaging with single-photon or positron emission tomography imaging shows perfusion abnormalities in >50% of HCM patients without coronary artery disease [2].

Myocardial ischemia is primarily due to coronary microvascular dysfunction**,** extensive remodeling of the intramural coronary arterioles, and blunted coronary artery reserve, occurring not only in the hypertrophied septum but also in the less hypertrophied left ventricular free wall [25, 26]. However, intrinsic molecular abnormalities of the cardiomyocyte, such as enhanced late sodium current leading to cytoplasmic calcium overload, have been shown to play an important role in increasing oxygen demand [2].

30.2.4 Diastolic Reserve and Restrictive Physiology

Diastolic dysfunction is an important component of HCM pathophysiology, although its severity and relevance of congestive symptoms may not be apparent from resting echocardiography [27, 28]; therefore, exercise echocardiography is crucial in unmasking reduced diastolic reserve and clarifying the cause of functional limitation. In the most severe cases, however, the diastolic function is severely impaired at rest. This peculiar phenotype, characterized by restrictive physiology, is subtended by severe and diffuse fibrosis of the left ventricle. Nonuniformity and dyssynchrony of left ventricular contraction and relaxation may also contribute to restrictive physiology. The molecular basis is a delayed inactivation from abnormal intracellular calcium uptake with diastolic intracellular calcium overload [29].

30.2.5 Mitral Regurgitation

Mitral valve enlargement can determine LVOT obstruction in HCM and might be stimulated by potentially modifiable biological valvular-ventricular interactions [30]. The SAM of the mitral valve is an indirect sign, and one of the mechanisms of dynamic obstruction and is in turn associated with variable degrees of functional mitral regurgitation, due to loss of leaflet coaptation, which is mid-to-late systolic and oriented laterally and inferiorly. In the elderly, posterior mitral annulus calcification, the anterior position of the mitral apparatus, and sigmoid septal morphology with decreased septal-aortic angle increase the likelihood of SAM and obstruction, which may develop in previously unobstructed patients [31]. Due to its dynamic nature, the severity of SAM-related mitral regurgitation varies with the degree of LVOT obstruction, may increase significantly during effort, and represents the main determinant of symptoms [32].

30.2.6 Autonomic Dysfunction and Chronotropic Incompetence

The cardiac autonomic function is impaired in HCM [33] and the abnormal heart rate recovery (an index of reduced vagal reserve) and the abnormal heart rate reserve (an index of reduced sympathetic reserve) are found in at least one-third of HCM patients [34]. An abnormal blood pressure response to exercise may be attributable to autonomics, but also diastolic filling abnormalities, or LVOT obstruction. The easiest index of altered cardiac autonomic function is heart rate reserve. HCM patients show reduced beta-receptors density and function, with an initial exaggerated response to sympathetic stimulation which may later progress to receptor desensitization [35]. A blunted heart rate reserve can be therefore considered a marker of reduced sympathetic reserve often associated with higher baseline levels of sympathetic activity which can be detrimental in HCM for many reasons. Increased sympathetic activity and increased cardiac norepinephrine may increase myocardial cell growth, disarray, and scarring, induce myocardial ischemia through alpha-adrenergic coronary constriction, and increase the rate of spontaneous depolarizations in myocardial cells with resulting electrical instability [36]. Iatrogenic chronotropic incompetence, due to the extensive use of beta-blockers or AV node blockers such as verapamil, has recently gained attention as a mechanism of reduced exercise capacity and limiting symptoms in HCM [37, 38]. This concept is now emerging also in HFpEF, where withdrawal of beta-blockers may improve patients' performance in selected cases [39]. The evaluation of chronotropic response to exercise and its impact on cardiac output and diastolic reserve should therefore be routinely part of a SE protocol.

30.3 Clinical Indications of Stress Exercise

According to the recent American College of Cardiology/ American Heart Association guidelines, in patients with HCM, exercise stress testing is reasonable to determine functional capacity and provide prognostic information as part of the initial evaluation

[2]. Furthermore, it also provides invaluable information during their long-term clinical course. Stress testing is very safe in HCM patients, even in the presence of resting LVOT obstruction [10]. As a rule, exercise testing is preferable to pharmacological stress in HCM patients, due to the high prevalence of false-positive findings in the latter, in terms of provokable obstruction, as well as the uncertain relevance of pharmacologically induced gradients to physiological conditions and patients' symptoms (Fig. 30.4).

However, SE, particularly when based on physiological exercise, provides useful information in virtually all HCM patients and is offered routinely in specialized centers unless the acoustic window is poor or the individual is clinically unstable or unable to exercise. In subjects with unfavorable profiles and congestive symptoms, exercise echocardiography may provide essential clues concerning arrhythmic risk, disease progression, presence of co-morbidity, response to treatment, and potential indication to advanced options such as transplant. Provokable obstruction, in patients who are nonobstructive at rest, may be useful in predicting symptomatic progression and outcome. In *asymptomatic*, active HCM patients who are nonobstructive at rest and have none of the established risk factors, negative SE serves the

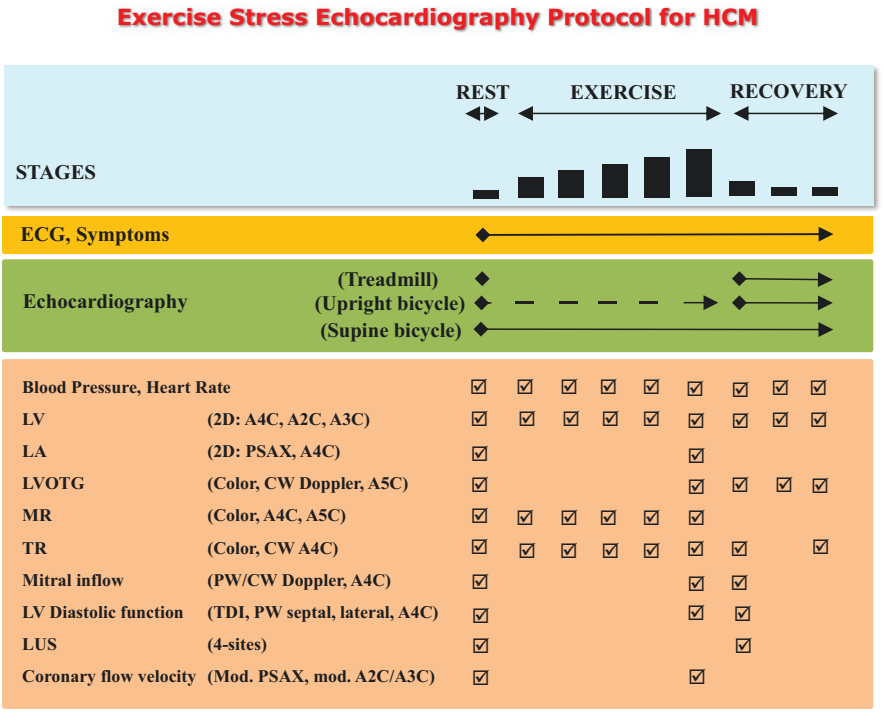

Fig. 30.4 Proposed protocol for exercise echocardiography in HCM. B-lines are assessed at baseline and the early recovery phase, 1–2 min after the stop of exercise. *2D* Two-dimensional, *A2C* apical two-chamber, *A3C* apical three-chamber, *A4C* apical four-chamber, *BP* blood pressure, *CW* continuous-wave, *ECG* electrocardiography, *LA* left atrium, *LUS* lung ultrasound, *LV* left ventricle, *LVOTG* left ventricular outflow tract gradient, *MR* mitral regurgitation, *PSAX* parasternal short-axis, *PW* pulsed-wave, *TDI* tissue Doppler imaging, *TR* tricuspid regurgitation

purpose of confirming a favorable clinical profile and providing reassurance concerning physical activity and other lifestyle issues such as pregnancy. Exercise echocardiography proves very useful in this context to provide tailored advice regarding safe levels of exertion depending on the workload at which SAM develops [38]. Furthermore, HCM patients who self-report as being asymptomatic often exhibit significant exercise limitation, to which they have grown accustomed, requiring appropriate investigation.

30.4 Interpretation of Findings

Based on the specific pathophysiological background, SE is key in eliciting critical clinical information in HCM patients, including (1) de novo provocation or exacerbation of dynamic LVOT pressure gradients, (2) blood pressure and left ventricular function response to exercise, (3) inducible regional wall motion abnormalities and reduction in coronary flow reserve, (4) restrictive pattern and diastolic reserve, (5) mitral regurgitation, (6) exercise-induced arrhythmias, heart rate reserve, and heart rate recovery, (7) pulmonary pressures and development of congestion, and (8) response to medical treatment and outcome of invasive procedures.

30.4.1 Dynamic Left Ventricular Obstruction

As previously discussed, dynamic obstruction occurring at the LVOT and/or midventricular level is common in active HCM patients and is the main determinant of exercise limitation and symptoms. Remarkably, severe provokable obstruction, occasionally leading to surgical myectomy or alcohol septal ablation, may be unsuspected at routine echocardiographic evaluation, due to a total lack of SAM of the mitral valve in resting conditions. Thus, in the absence of adequate evaluations by exercise echocardiography, the cause of symptoms may be misinterpreted and an opportunity for effective treatment is missed. An exercise-induced gradient greater than 50 mmHg is generally considered of "surgical" interest when associated with drug-refractory symptoms [40]. Dynamic gradients usually increase during effort and may persist or even increase during (early) recovery, following a fall in systemic resistance.

However, a subset has been recently described in which a paradoxical reduction in gradient is observed with effort, associated with preserved functional tolerance and favorable clinical profile [41]. Several factors influence the impact of provokable obstruction on functional capacity and symptoms, including precocity of gradient onset, degree of associated mitral regurgitation, time from last meal or alcohol consumption, and the concomitant presence of midventricular obstruction. The assessment of LVOT gradient after pharmacological or invasive intervention allows us to objectively document the efficacy of treatment in reducing the incidence and severity of exercise-induced LVOT gradients [42].

30.4.2 Increased Left Ventricular Function and Abnormal Blood Pressure Response

The left ventricular contractile function is especially important in HCM patients and is better defined with load-independent force (which also incorporates the value of LVOT gradient at rest and peak stress) rather than with ejection fraction. Force is the ratio of systolic blood pressure + LVOT gradient divided by the end-systolic volume of the left ventricle and provides a simple, load-independent index of left ventricular contractility. The possibility of incorporating a simple and reproducible biomarker of left ventricular contractility such as force in the SE assessment of HCM seems especially attractive as new molecular modifiers of contractility are now being tested in clinical studies. In one patient, the baseline level of left ventricular contractile state can be too high; in another patient (or in the same patient at a later stage of the natural history), the baseline level of contraction can be too low. In both cases, the left ventricular contractile reserve will be reduced [43]. The characterization of contractile function at rest and during stress with a load-independent index such as force or volume-independent index such as global longitudinal strain may pave the way to targeted intervention that a simple assessment of ejection fraction cannot allow, since the same values of rest ejection fraction and ejection fraction reserve can encompass a situation of abnormally increased, normal or abnormally decreased contractile state [44, 45].

30.4.3 Myocardial Ischemia and Coronary Microvascular Disease

For noninvasive identification of concomitant coronary artery disease, regional wall motion abnormalities in HCM patients are more specific than perfusion abnormalities and ST-segment depression, but also may suffer from false-positive responses, especially in presence of marked hypertrophy. Therefore, a negative test for regional wall motion abnormality is useful for excluding functionally significant coronary artery disease, or, in younger patients, tunneling of the left anterior descending coronary artery, but a positive test is less useful for including coronary artery disease and indicating ischemia-driven revascularization for symptomatic benefit. In patients with chest pain and positive SE for inducible regional wall motion abnormality, a noninvasive coronary computed angiography is indicated before referring the patient to ischemia-driven revascularization. Regional wall motion abnormalities occur in 6% of HCM patients and are a strong predictor of adverse outcomes even in absence of underlying coronary artery disease [46–48]. Coronary flow velocity reserve (CFVR) is reduced in about one-third of HCM patients. The measurement is equally reliable and substantially simpler with Doppler echocardiography in the mid-distal left anterior descending artery with vasodilators [49]. The feasibility is >95% in the general population and higher in HCM since the thick septum, the large coronary diameter, and the increased resting flow make the detection and sampling of coronary flow faster and easier even during exercise SE (Fig. 30.5).

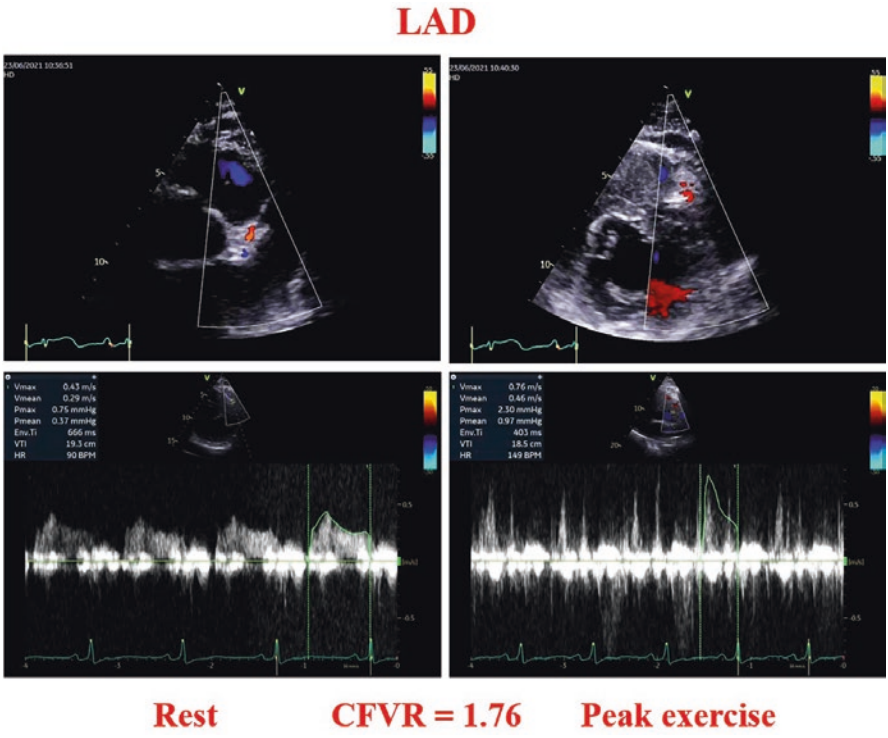

Fig. 30.5 CFVR in HCM with exercise stress. Upper row: color flow Doppler imaging of proximal and mid left anterior descending coronary artery at resting transthoracic echocardiography in HCM. Lower row: rest (left panel) and peak exercise (right panels) evaluation of coronary flow velocity in HCM: pulsed-wave Doppler tracing of coronary flow with measurement of peak diastolic flow velocity (rest = 43 cm/s; peak exercise = 76 cm/s). The CFVR is 76/43 = 1.76. (By courtesy of Attila Pálinkás, MD, Hódmezővásárhely, Hungary)

The presence and degree of impairment of CFVR are largely unrelated to the presence and degree of left ventricular hypertrophy and LVOT obstruction and are associated with reduced systolic function and functional capacity [48]. The reduction of CFVR shows a striking prognostic value, clearly superior to LVOT obstruction [49–52].

30.4.4 Restrictive Physiology and Diastolic Reserve

Restrictive physiology during exercise SE is detected as an abnormal increase in *E*/*e′* (reflecting reduced diastolic reserve) [28] and systolic pulmonary arterial pressure, with the recognized limitations of feasibility and accuracy, also due to the need to

sample *E*/*e*′ when mitral waves are not fused (in the recovery phase) and the presence of tricuspid regurgitant jet velocity to assess systolic pulmonary artery systolic pressure. A simple addition to confirming the increase in pulmonary capillary artery wedge pressure is the presence of B-lines by lung ultrasound, which are linearly related to extravascular lung water accumulation and an increase in left ventricular end-diastolic pressure. The appearance of B-lines is linearly, closely, and negatively correlated with maximal oxygen consumption on cardiopulmonary testing in heart failure patients and may usefully integrate the prognostic profiling of the patient, possibly indicating a personalized SE-guided approach to lung decongestion therapy. In HCM, patients with stress B-lines have a reduced left ventricular preload reserve, more severe mitral regurgitation, and increased left atrial volume index, *E*/*e*′, and pulmonary artery systolic pressure during stress (Fig. 30.6). Diuretics are generally considered contraindicated in HCM since they may induce dehydration which may induce worsening of obstruction. It is however accepted that they can be used in HCM patients with dyspnea and pulmonary congestion. The observation of B-lines might eventually drive a more personalized use of diuretics in selected patients showing moderate to severe pulmonary congestion at rest or during stress [53–55].

30.4.5 Mitral Regurgitation

Functional mitral regurgitation may worsen during exercise due to the combined effect of higher dyssynchrony of contraction, mitral leaflet distortion, deformation, and increased filling pressures, and it contributes to symptoms and worse outcomes [56].

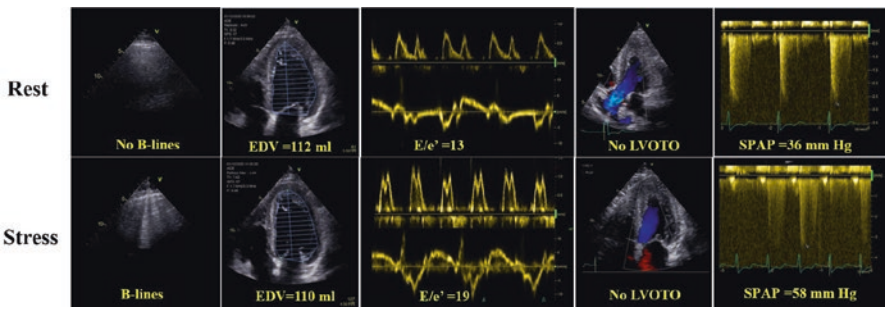

Fig. 30.6 Example of exercise B-lines in a nonobstructive HCM patient with exertional dyspnea and negative coronary angiography. During ESE B-lines were associated with reduced diastolic reserve, mirrored by falling EDV, increasing *E*/*e*′, and worsening pulmonary pressures during ESE. *E* early mitral inflow velocity, *e*′ early diastolic mitral annular velocity, *EDV* end-diastolic volume, *LVOTO* left ventricular outflow tract obstruction, *SPAP* systolic pulmonary arterial pressure. (Images by courtesy of José Luis de Castro e Silva Pretto, MD, Passo Fundo, Brazil)

30.4.6 Autonomic Dysfunction Mirrored in Heart Rate and Blood Pressure Response

Heart rate reserve is easily measured from one lead EKG (present by the protocol in the echo monitor) as the peak/rest heart rate ratio. In HCM, a reduced heart rate reserve is associated with a lower peak oxygen consumption at cardiopulmonary testing, a higher degree of myocardial fibrosis with delayed enhancement with cardiovascular magnetic resonance, and a worse outcome [57, 58]. A reduced heart rate reserve indicates a blunted sympathetic reserve and is associated with an increased risk of death in HCM, independent and incremental over regional wall motion abnormalities, and CFVR [59] (Fig. 30.7).

Heart rate reserve offers a continuous spectrum of responses to risks, from the lowest increases associated with the highest risk to the highest increases associated with the lowest risks. Abnormal blood pressure response to exercise is defined as exercise-induced hypotension (any decrease in systolic blood pressure below baseline in the absence of an initial rise with exercise, or a sustained decrease of >20 mmHg during exercise following an initial rise) or failure to increase blood pressure (a systolic blood pressure rise of less than 20 mmHg from baseline) [10]. This response is observed in up to one-quarter of HCM patients and is believed to identify hemodynamic instability secondary to autonomic dysfunction, LVOT obstruction, diastolic dysfunction, microvascular ischemia, and inappropriate

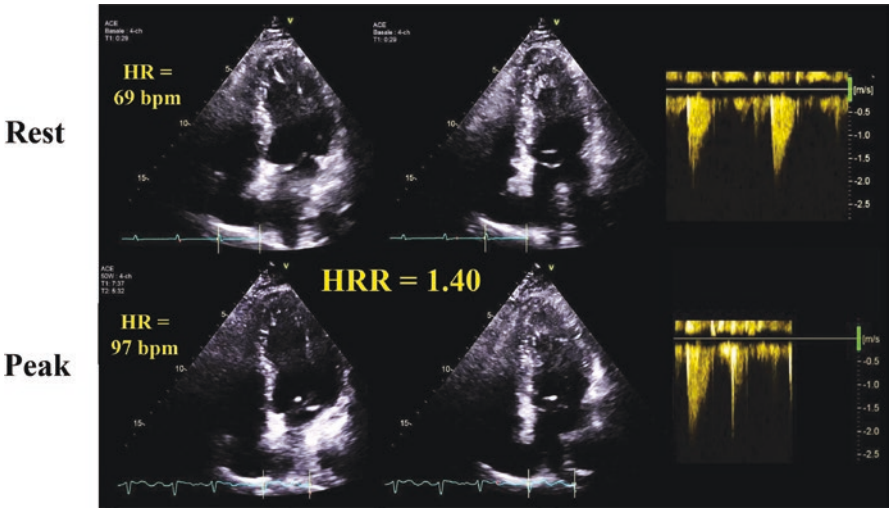

Fig. 30.7 Heart rate reserve (HRR) during exercise stress. Rest (upper panels) and peak stress (lower panels) evaluation of regional wall motion, left ventricular outflow tract gradient (LVOTG), and heart rate. Left panels: Normal wall motion at rest and peak stress. ECG lead shows a blunted HRR response (rest = 69 bpm; peak exercise = 97 bpm; HRR = 1.40). Right panels: continuous wave Doppler tracing of LVOTG (rest = 14 mmHg; peak exercise = 20 mmHg). During the exercise test, the patient shows normal regional wall motion, no significant LVOTG, and an abnormally reduced HRR

peripheral vasodilatation. Exercise-induced hypotension is an indication for interruption of stress testing and may require positioning the patient in the supine or Trendelenburg position, when symptomatic.

30.5 Response to Therapy

SE is gaining increasing importance in assessing HCM patients' responses to invasive and pharmacological treatment. Existing evidence is limited but consistent in highlighting the considerable benefits of surgical myectomy in terms of exercise hemodynamics and functional capacity [60]. Evidence following alcohol septal ablation is scarce, although symptomatic relief seems comparable [61]. Furthermore, obstructive patients benefit objectively from disopyramide therapy [62] and the recent EXPLORER-HCM trial has shown notable improvement in resting and stress cardiac structure and function after mavacamten administration [63] (Fig. 30.8). While documenting, objective improvement may not be necessary for clinical practice in patients with good symptom benefit, exercise SE following therapy remains crucial in patients with persisting symptoms to distinguish suboptimal procedural

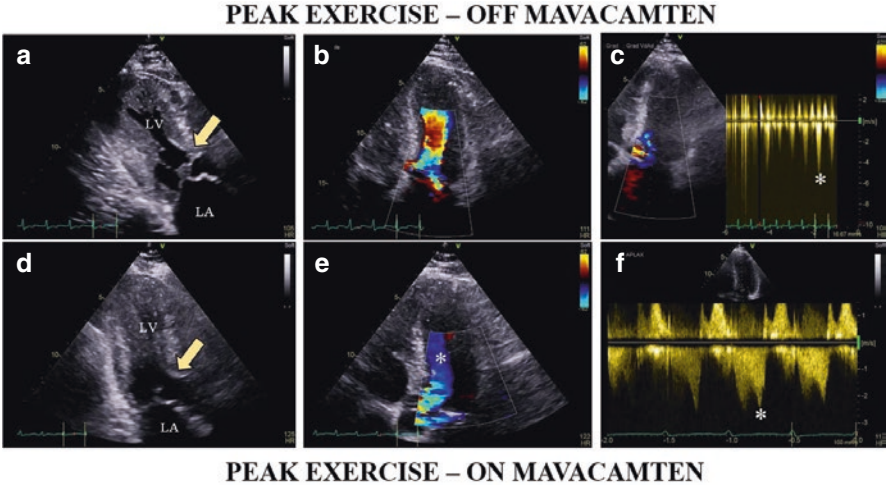

Fig. 30.8 Example of optimal response to myosin inhibition with mavacamten. Top panel: pretreatment, peak exercise at 50 W. (**a**) End-systolic frame 3-chamber view showing complete SAM with septal contact (arrowhead). (**b**): End-systolic frame in 5-chamber view showing midventricular and LVOT turbulence and functional mitral regurgitation. (**c**) Peak exercise gradient exceeding 100 mmHg. Bottom panel: posttreatment, peak exercise at 100 W. End-systolic frame 3-chamber view showing resolution of SAM (arrowhead). (**d**) End-systolic frame in 5-chamber view showing laminar flow in LVOT. (**e**) Peak exercise intraventricular gradient 13 mmHg (**f**)

results (i.e., persisting gradients on efforts) versus residual diastolic dysfunction. Finally, exercise SE has become a cornerstone for clinical trials evaluating novel pharmacological approaches to HCM.

30.6 Technical Issues and Pitfalls

In the vast majority of HCM patients, stress testing can be performed safely, including those with elevated LVOT gradients at rest who are normotensive and have no history of hemodynamic instability on effort. While HCM has long been considered a relative contraindication to stress testing, it is now well established that echocardiography during physiological exercise has minimal risk when performed in a controlled, supervised environment. Nevertheless, in a subset of HCM patients, stress testing is not feasible or advisable, due to the inability to exercise, severe congestive symptoms (New York Heart Association class ≥III), hemodynamic instability associated with elevated LVOT gradients at rest, known effort-induced arrhythmias, or severe comorbidities. Conversely, acoustic window quality is rarely a problem, given the young mean age of patients with HCM, and ultrasound-enhancing agents can be used when needed. Since many factors may affect LVOT gradient evaluation, a standardized approach is essential to have meaningful and comparable results across different laboratories. Consistently, it has been suggested that the most effective way to unmask a labile gradient is to perform echo monitoring while exercising in an upright position. This approach can be applied not only to HCM but also to other groups, such as athletes, in whom after an inconclusive exercise-ECG, the test of choice is exercise-echo. There are, however, relatively little data comparing the different protocols. As such, the ESC guidelines suggest that "*laboratories should develop and validate their protocol and ensure that staff is properly trained in the procedure*."

Pulmonary congestion with B-lines at lung ultrasound can be assessed in the early recovery phase since they persist for some minutes after cessation of exercise. Their changes during exercise mirror changes in left ventricular diastolic pressure and pulmonary capillary wedge pressure. They represent an easier and more feasible way to assess pulmonary circulatory changes than systolic pulmonary arterial pressure or *E/e′* [64]. A frequent pitfall during the effort involves the possibility of sampling MR instead of the left ventricular outflow tract. Therefore, the utmost care should be employed to avoid this source of misinterpretation also considering that high velocities can be a normal variant at a young age [65] and gradients can be found outside HCM in several conditions of high-flow state and dynamic obstruction, such as anemia or hypovolemia.

Coronary flow velocity can be obtained during the early stages of exercise, but it is much easier with dedicated vasodilator stress testing which also may be used to assess inducible ischemia and cardiac autonomic dysfunction as a blunted heart rate reserve (<1.22). In general, patients with HCM are exposed to serial imaging, and it is important to avoid cumulative damage from nephrotoxic iodinated agents or radiation exposure since the prognosis of the disease is generally benign and the cause

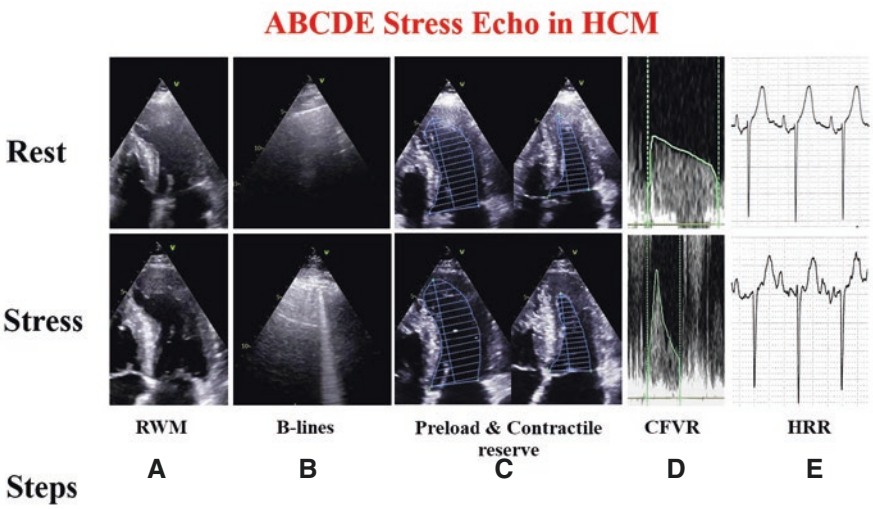

Fig. 30.9 An illustrative example of ABCDE SE in a 41-year-old nonobstructive symptomatic HCM patient. Rest images (upper panels) show (from left to right) a normal wall motion (step A), no B-lines (step B), normal EDV and ESV (step C), elevated resting coronary flow velocity in the left anterior descending coronary artery (step D), and normal heart rate (step E). During ESE (lower panels), the patient showed normal wall motion (step A), exercise B-lines (abnormal step B), reduced preload and contractile reserve (EDV rest-stress: 85–78 mL, delta EDV = −7 mL; LV force rest-stress: 6.1–9.3 mmHg/mL, LVCR = 1.52), borderline CFVR (CF rest-stress: 53–108 cm/s, CFVR = 2.04), and blunted heart rate reserve (HR rest-stress: 65–102 bpm, HRR = 1.57). No significant left ventricular outflow tract obstruction (LVOTG baseline 27 mmHg, peak stress 31 mmHg) or mitral regurgitation (mild MR at rest, unchanged during stress) could be detected during ESE. Exercise SE revealed chronotropic incompetence (abnormal step E) and diastolic dysfunction with pulmonary congestion (abnormal step B), reduced cardiac reserve (abnormal step C), and borderline coronary microvascular disease (step D). See also the corresponding Video 30.1. (Courtesy of Attila Pálinkás, MD, Hódmezővásárhely, Hungary. The video is available under the chapter's "Supplementary Material" on Springer Link)

of death in HCM is generally noncardiac in contemporary populations [66]. Whenever possible, comprehensive SE with ABCDE protocol helps to assess the many potential vulnerabilities of the patient (Fig. 30.9).

30.7 Guidelines and Recommendations

According to 2017 joint recommendations of the European Association of Cardiovascular Imaging-American Society of Echocardiography societies on SE beyond coronary artery disease, "*exercise SE is safe and commonly used especially in HCM patients with equivocal symptoms, to determine functional capacity before a corrective therapeutic procedure, and for individual risk stratification*" [67]. Exercise SE should be performed in symptomatic patients and is reasonable in asymptomatic patients without resting critical LVOT obstruction since the result of the exam can influence health advice or choices of therapies for concomitant conditions [2] (Fig. 30.10).

As recognized by 2020 guidelines of the American College of Cardiology/American Heart Association, in HCM "*echocardiography is the primary imaging*

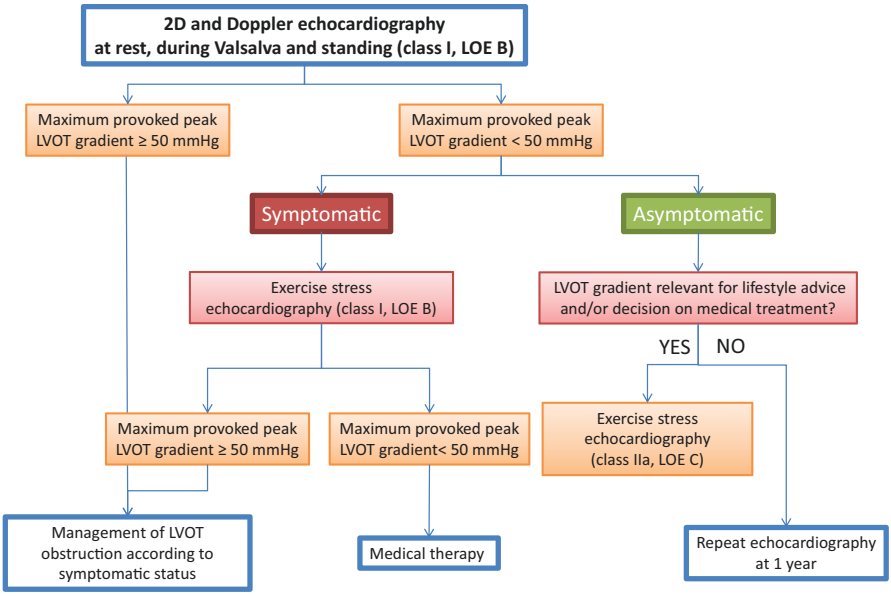

Fig. 30.10 Recommendations for the assessment and treatment of LVOT obstruction from the 2014 European Society of Cardiology guidelines on diagnosis and management of HCM . *LOE* level of evidence, *LVOT* left ventricular outflow tract. (Modified from Elliott et al., [1] and updated from Ommen et al. [2])

Table 30.2 LVOT obstruction in American Heart Association-American College of Cardiology 2020 guidelines

	CoR	LoE
Symptomatic, LVOTG (rest/Valsalva) <50 mmHg	I	B
Asymptomatic, LVOTG (rest/Valsalva) <50 mmHg	II a	C

CoR class of recommendation, *LOE* level of evidence

modality for the characterization of LVOT obstruction including the integral role of the mitral valve, determination of the maximal wall thickness, cardiac chamber dimensions, systolic function, and the presence of a left ventricular apical aneurysm, all inform phenotype severity and sudden cardiac death risk stratification" [2]. Exercise SE is recommended in symptomatic patients if bedside maneuvers fail to induce LVOT gradient ≥50 mmHg and is rated as class 1 ("*should be considered*"), level of evidence B ("*data derived from a single randomized clinical trial or large nonrandomized studies*"). The recommendation is class II a ("*can be considered*"), level of evidence C ("*consensus of opinion of the experts and/or small studies, retrospective studies, registries*"), in asymptomatic patients [2] (Table 30.2).

LVOT gradient determination is central to risk stratification and identification of threshold to septal reduction therapy (>50 mmHg in severely symptomatic patient's refractory to medical therapy) but is also extremely variable. The factors modulating LVOT gradient recognized by guidelines are reported in (Table 30.3) [2].

Table 30.3 Factors modulating LVOT obstruction

	Increase LVOTG	Decrease LVOTG
Postprandial state	x	
Fasting state		x
Volume depletion	x	
Squatting	x	
Pregnancy	x	
Alcohol consumption	x	
Beta-blockers off	x	
Beta-blockers on		x
Positive inotropes	x	
Upright exercise	x	
Semi-supine exercise		x

For all these factors, pharmacologic modulation of LVOT gradient with dobutamine can be misleading, and therefore "*determination of provocative LVOT obstruction and eligibility to septal reduction therapy is not advised with dobutamine.*" In addition, the septal reduction therapy can be ineffective, or even detrimental, on extra-septal factors which may underlie gradient induction with exercise in HCM, from papillary muscle dysfunction to mitral leaflet elongation.

Other useful information beyond the LVOT obstruction can be obtained during SE, since—according to 2017 recommendations—"*abnormal blood pressure response to exercise, blunted systolic and diastolic reserve, and worsened mitral regurgitation are associated with poor exercise capacity and outcome. SE is not indicated when a gradient >50 mmHg is present at rest*" [67]. According to an expert consensus of the European Association of Cardiovascular Imaging in 2015, "*SE can be used for functional imaging in HCM with coronary flow reserve assessment on the left anterior descending artery with concomitant wall motion analysis which provides diagnostic and prognostic information and may allow the distinction between obstructive epicardial coronary disease and microvascular ischemia*" [68]. Microvascular angina is identified by the combination of normal regional wall motion and blunted coronary flow reserve, while obstructive epicardial coronary artery disease shows a reduced flow reserve associated with regional wall motion abnormality. According to 2017 recommendations, vasodilation is the preferred modality for the evaluation of CFVR [67]. SE in this specific field requires specialized training to reach competence and sufficient volumes to maintain competence, and therefore patients in need of testing are better referred to SE laboratories embedded in comprehensive HCM centers [2].

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Stress Echocardiography in Dilated Nonischemic Cardiomyopathy

31

Jelena Čelutkienė and Eugenio Picano

Keywords

Contractile reserve · Coronary flow velocity reserve · Pulmonary congestion · Sympathetic reserve

31.1 Term and Epidemiology of Dilated Nonischemic Cardiomyopathy

The term dilated nonischemic cardiomyopathy (DNCM) is usually used for the syndrome of ventricular dilatation and systolic dysfunction without significant coronary artery disease. The true prevalence of DNCM is difficult to assess, mostly because of classification complexity and lack of systematic data collection. It depends on morphological and functional diagnostic criteria used for this entity in observational and clinical trials. The spectrum of etiologies includes hypertensive, arrhythmogenic, genetic, infectious, immune-mediated, toxic, metabolic, peripartum, and other rare diseases [1]. Moreover, recently accumulated evidence shows the interplay of genetic and extrinsic (i.e., toxic or overload) factors, for example, titin-truncating variants are associated with an increased risk of alcoholic [2], cancer-therapy-induced [3], as well as peripartum cardiomyopathies [4].

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J. Čelutkienė (✉)
Faculty of Medicine, Centre of Cardiology and Angiology, Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Centre for Innovative Medicine, Vilnius, Lithuania
e-mail: Jelena.Celutkiene@santa.lt

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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The syndrome of heart failure is the most frequent clinical presentation of DNCM [5]. The actual rate of deterioration is highly variable and depends on the nature and causes of the overload, the age of the patient, and many other genetic and environmental factors. Following a period of asymptomatic left ventricular dysfunction that can last more than a decade, survival after the onset of significant symptoms averages about 5 years [6].

31.2 Role of Stress Echocardiography in DNCM: General Approach

Stress echocardiography (SE) has an important role in the initial and advanced stages of DNCM, first for assessment of contractile reserve of the left ventricle (Fig. 31.1). In addition, this modality is ideally equipped to detect pulmonary congestion with B-lines and hemodynamic congestion with systolic pulmonary artery pressure estimates with provocation such as exercise [7].

The recent realization that therapies aimed at symptomatic heart failure may also improve outcomes in patients with asymptomatic left ventricular dysfunction has increased the importance of recognizing and treating patients before overt heart failure. In the early stage, in patients with yet normal left ventricular function, a reduced inotropic reserve can unmask initial damage. In advanced stages, SE complements resting echocardiography, identifying a heterogenous prognostic profile that underlies a similar resting echocardiographic pattern (Table 31.1).

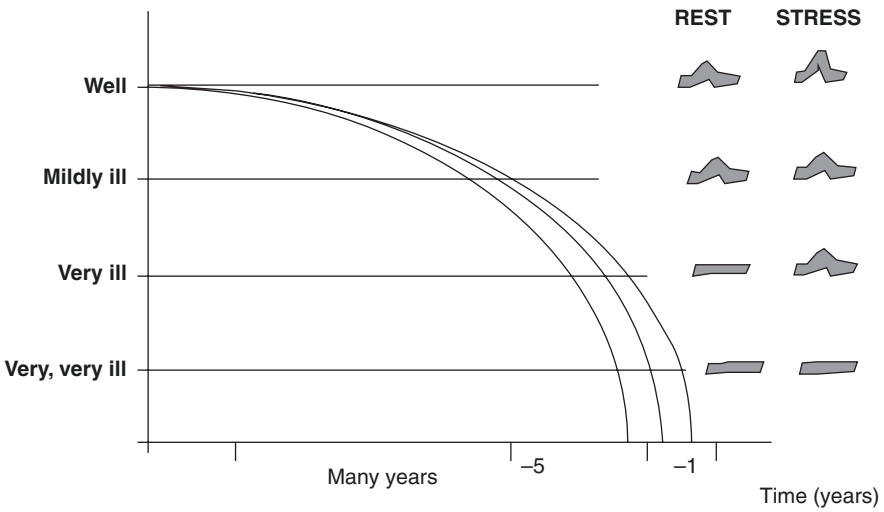

Fig. 31.1 SE in different stages of cardiomyopathy. At an early stage, baseline function is normal, but the inotropic reserve is depressed. At an advanced stage, the baseline function is depressed but there is an inotropic reserve. At a very advanced stage, the resting function is depressed, and the inotropic response is abolished. (Modified and adapted from Katz 2001 [6])

Table 31.1 SE response and the four stages of heart failure

Stage of heart failure	Structural heart changes	Resting global function (EF)	Longitudinal function (GLS)	Contractile reserve	Coronary flow reserve
At-risk	Absent	Normal	Normal	Normal	Normal
Preheart failure	Absent	Normal-reduced	Reduced	Normal-blunted	Normal-reduced
Heart failure	Overt	Reduced	Markedly reduced	Blunted or absent	Reduced
Advanced heart failure	Advanced	Significantly reduced	Markedly reduced	Absent	Markedly reduced

EF ejection fraction, *GLS* global longitudinal strain

31.3 Detection of Incipient Cardiomyopathy in Preserved Ejection Fraction

Some patients are exposed to potentially cardiotoxic conditions, such as chemotherapy for cancer or iron overload in thalassemia. The clinical natural history of these conditions is characterized by a relatively short interval between the onset of cardiac symptoms and end-stage cardiac failure. The detection of preclinical cardiac involvement can be important to start more aggressive therapy. There are two possible approaches for the early detection of incipient myocardial damage when the ejection fraction (EF) is still normal. The first possibility is to assess longitudinal function, impaired at an earlier stage of disease than EF, which may longer remain normal due to supernormal compensatory radial function. The selective early impairment of longitudinal function can be measured with reduced global longitudinal strain using deformation imaging. The early reduction in longitudinal function, with normal EF, has been described in several acquired conditions, from systemic sclerosis [8] to diabetic [9] or hypertensive [10] cardiomyopathy. Genetic cardiomyopathy also exhibits an early impairment of longitudinal function, detectable with reduced deformation in the left ventricle [11] or—in the case of early arrhythmogenic right ventricular cardiomyopathy—in the right ventricle [12].

The second approach is to assess the segmental and global contractile reserve during inotropic challenges. The rationale for applying SE in these conditions is that structural impairments of the myocardial wall can be subtle enough not to impair resting EF, but severe enough to blunt or even exhaust the contractile response to the inotropic stimulation. At low doses ($\leq$10 μg kg^{-1}/min), dobutamine selectively stimulates β-1 myocardial receptors, determining a mild, sustained inotropic stimulation with little if any effect on either systemic hemodynamic parameters or loading conditions. With these low dobutamine doses, regional wall function shows a blunted increase in the percentage of systolic thickening, or in peak systolic velocity on myocardial velocity imaging, which helps detect early damage. The blunted regional cardiac contractile reserve has also proved useful in

detecting subtle forms of cardiac involvement in several diseases, such as doxorubicin chemotherapy [13], thalassemia [14], and hypertrophic [15] or diabetic cardiomyopathy [16]. Genetic cardiomyopathy also exhibits a blunted increase in longitudinal function, detectable with deformation in the left ventricle [14] or—in the case of early arrhythmogenic right ventricular cardiomyopathy—in the right ventricle [17].

In all these conditions, the reduction in myocardial contractile reserve observed with dobutamine stress may be accompanied by impaired coronary flow reserve, best detected today by vasodilator stress combined with pulsed-wave Doppler in the mid-distal left anterior descending coronary artery [18]. The reduction of coronary flow reserve at an early clinical stage, when symptoms are absent or minimal and left ventricular EF is normal at baseline [19], has been described in several clinical conditions such as systemic sclerosis [20], diabetes [21], or hypertensive [22] heart disease. Contractile reserve focuses on the myocytes, whereas coronary flow reserve assesses coronary microcirculation. Both impaired contractile reserve and decreased coronary flow reserve are therefore very early markers of initial cardiomyopathy, at a stage when lifestyle modification or drugs are more likely to be efficacious in slowing, stopping, or reversing the downward trajectory of the disease.

31.4 The Value of Contractile Reserve in Patients with a Reduced EF

DNCM is a condition that predominantly affects ventricular systolic function. Nevertheless, indices of global systolic dysfunction as measured at rest are inadequate for depicting the severity of the disease and are poorly correlated with symptoms, exercise capacity, and prognosis. In contrast, the assessment of contractile reserve during stress, rather than baseline indices, is an important means of quantifying the degree of cardiac impairment and refining prognostic prediction [23].

The contractile reserve of the left ventricle is especially important in patients with reduced resting EF and can be identified with several parameters: an increase in EF >10% or with an increase of global longitudinal strain >2% or wall motion index improvement >0.20 or with a reduction of end-systolic volume >10% during stress. A preserved left ventricular contractile reserve identifies DNCM patients with a better prognosis and greater improvement after medical or device therapy [24–36]. Patients with a left ventricular contractile reserve are three times more likely to be responders to cardiac resynchronization therapy [37–49]. The

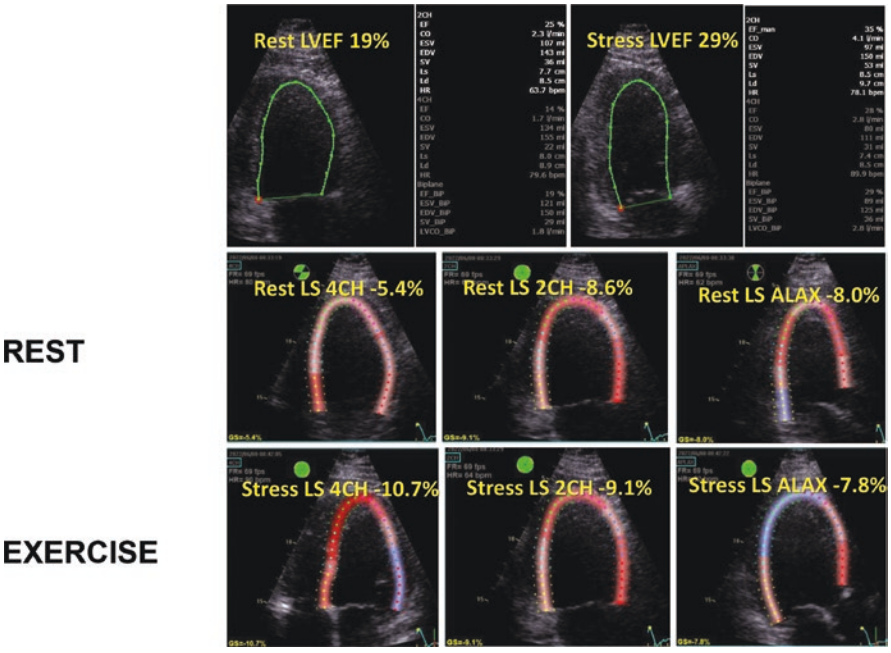

Fig. 31.2 An example of a patient with left ventricular contractile reserve during exercise stress. A 77-year-old man diagnosed with hypertensive heart disease and left bundle branch block underwent exercise echocardiography before cardiac resynchronization therapy implantation. An increase in left ventricular EF from 19% to 29% at 75 W was observed. End-systolic volume decreased from 121 to 89 mL. Global longitudinal strain increased from −7.3% to −9.2%. (By courtesy of Prof. Jelena Čelutkienė, Vilnius, Lithuania)

more benign response pattern with left ventricular contractile reserve is accompanied by a reduction of left ventricular systolic volume during exercise SE (Fig. 31.2).

The same pattern is found with dobutamine SE (Fig. 31.3).

The less benign response pattern with the absence of left ventricular contractile reserve is shown in a lack of reduction, or even dilatation, of left ventricular systolic volumes during stress. In patients with DNCM, a lack of increase in left ventricular function is associated with higher mortality. The information on the contractile reserve is usually obtained with dobutamine but is equally sensitive and prognostically relevant with dipyridamole infusion, showing an excellent concordance with contractile reserve assessed with dobutamine [50, 51].

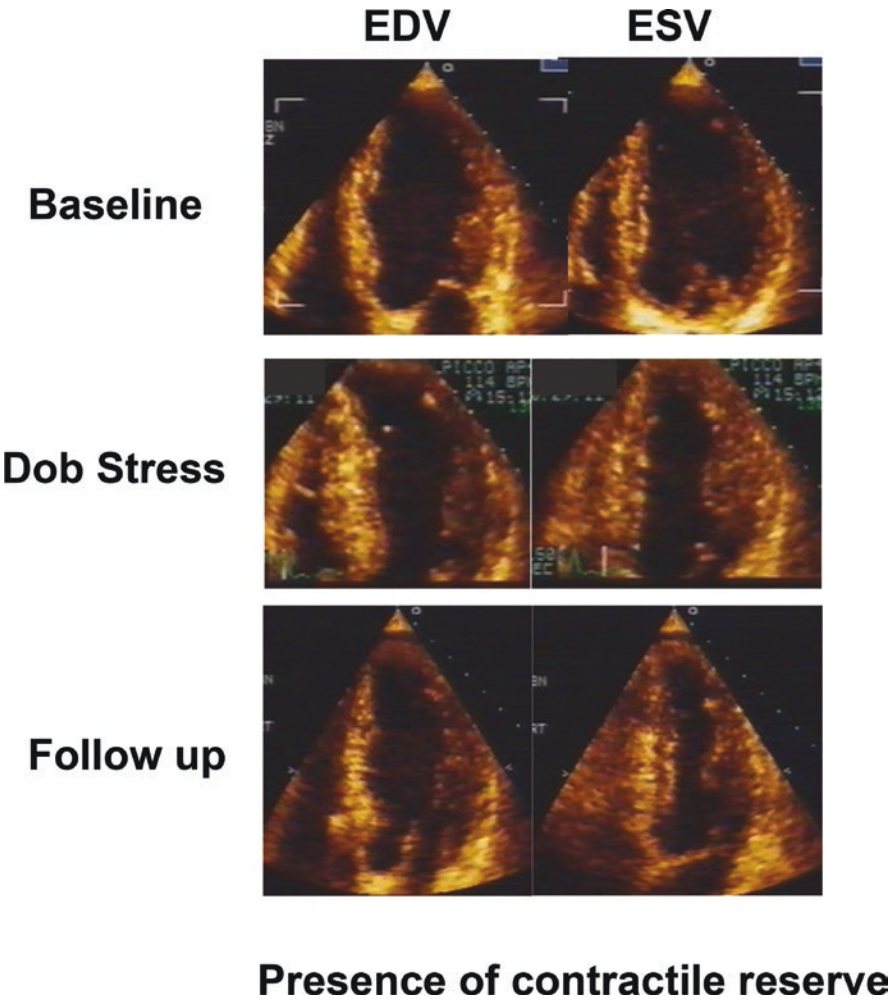

Fig. 31.3 An example of a patient with left ventricular contractile reserve. Echocardiographic apical four-chamber view at rest, at peak stress, and follow-up after cardiac resynchronization therapy of a patient with contractile reserve (*CR+*). EDV, end-diastolic volume; ESV, end-systolic volume. At baseline, a dilated left ventricle with acute reduction of end-systolic volume following dobutamine and after cardiac resynchronization therapy. (By courtesy of Prof. Quirino Ciampi, Benevento, Italy)

31.5 Combination of the Contractile, Coronary, and Chronotropic Reserve During SE

Left ventricular contractile reserve is of paramount importance in DNCM, but it is not the only and probably not even the most important parameter derived from SE. In addition to left ventricular contractile reserve, coronary flow velocity reserve

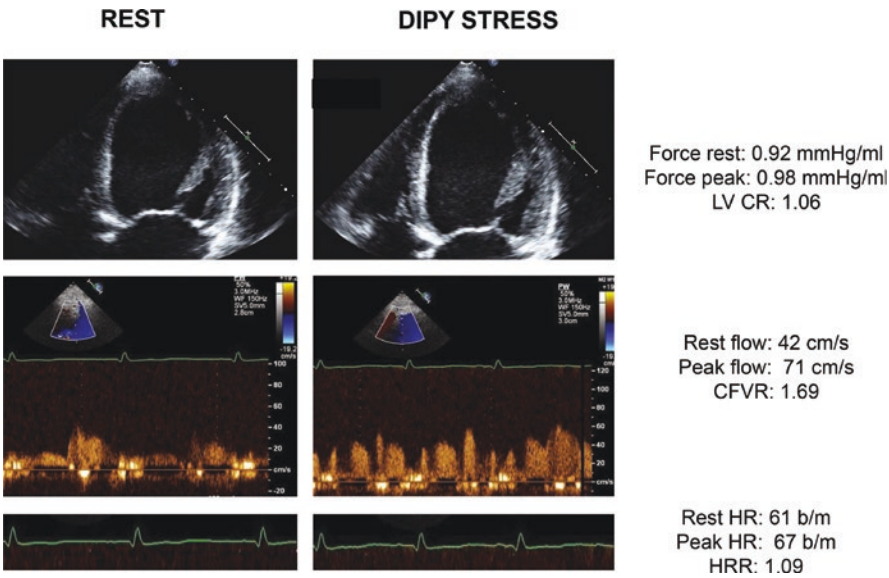

Fig. 31.4 Dipyridamole SE with abnormal score 3 in a patient with DNCM. Left column: rest. Right column, stress. From top to bottom: dilated end-systolic volume at rest which does not decrease during stress. Force (systolic blood pressure/end-systolic volume) is reduced at rest (0.92 mmHg/mL) and remains almost unchanged during stress (0.96 mmHg/mL) with abnormal left ventricular contractile reserve (1.06, with abnormal value with dipyridamole <1.10). Middle panels: blunted increase of pulsed-wave Doppler peak diastolic flow (rest = 42 cm/s; stress = 71 cm/s; CFVR = 1.69). Lower panels: abnormal heart rate reserve. Heart rate rest = 61; peak = 67 bpm; heart rate reserve (67/61) = 1.09 (abnormal value with dipyridamole <1.22). *CFVR* coronary flow velocity reserve, *HRR* heart rate reserve, *LVCR* left ventricular contractile reserve

and heart rate reserve are of established importance in predicting outcomes in these patients and can be derived from physical or pharmacological SE. The evidence base is extensive for coronary flow velocity reserve [52–56]. The three responses on contractile, coronary, and chronotropic reserves can easily be combined in one vasodilator stress [57]. The most benign response is a score of 0 with normal contractile, coronary, and chronotropic reserves. The more malignant response is scored 3, with all three abnormal responses (Fig. 31.4).

A reduced coronary flow velocity in the territory of the left anterior descending coronary artery can also coexist with a dilated and hypocontractile left ventricle, without contractile reserve during stress, but normal chronotropic reserve, with a global intermediate risk score of 2 (Fig. 31.5).

In a cohort of 610 patients with nonischemic heart failure (340 patients had EF <50%), the 4-year mortality was 1% in patients with a score of 0 consistent with normal contractile, coronary, and chronotropic reserves. Mortality increased progressively to 8%, 22%, and 33% in patients with score = 1, score = 2, and score = 3,

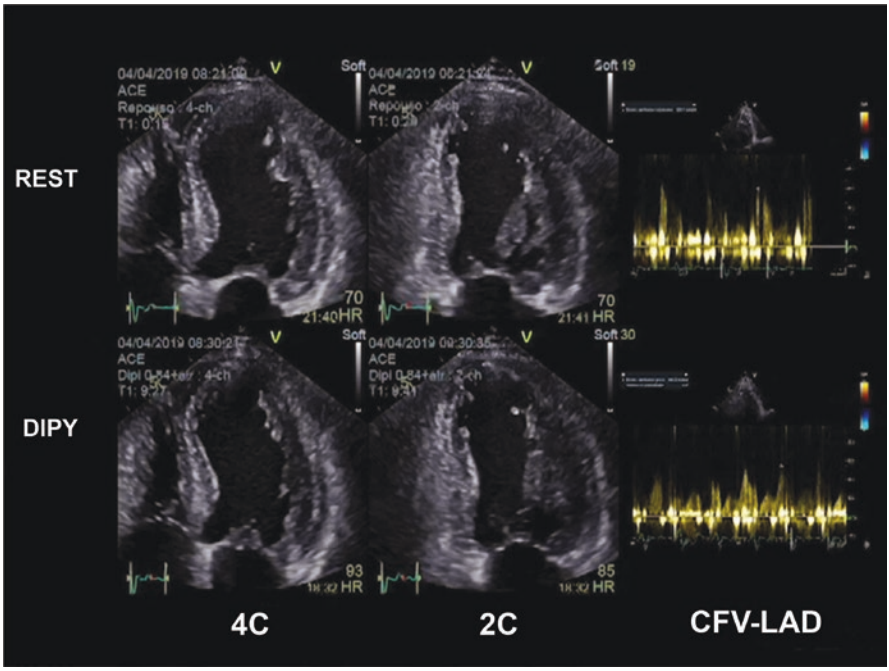

Fig. 31.5 The abnormal response of a dilated left ventricle with reduced resting function, without significant contractile and coronary reserves. *Upper panels*, rest. *Lower panels*, peak dipyridamole stress. *Left panels*: apical four-chamber (4C) view; *Middle panels*: apical two-chamber view (2C); *Right panels*: pulsed-wave Doppler of peak flow velocity in LAD. End-systolic frames are shown. The left ventricle is dilated at rest and the end-systolic volume does not decrease during dipyridamole. The coronary flow reserve is abnormal (peak/ rest = 28/24 cm/s = 1.16, normal values with dipyridamole >2.0). The heart rate reserve is normal (peak/ rest = 93/70 = 1.32, normal values with dipyridamole >1.22). See accompanying Video 31.1. (Video images courtesy of José Luis Pretto, MD, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

respectively, corresponding to abnormal contractile, coronary, and chronotropic reserves and their combinations. Each of the three—contractile, coronary, and chronotropic reserves—adds independent and incremental prognostic value and all of them can be obtained in a one-stop-shop [57].

The test can be even more comprehensive in individual patients with additional diagnostic parameters (Table 31.2).

Stress B-lines are a marker of lung water and alveolar-capillary membrane distress directly affecting the membrane efficiency for gas exchange. There is an inverse, tight, linear correlation between the anaerobic threshold assessed with cardiopulmonary testing and the number of peak exercise stress B-lines [58].

Table 31.2 Prognosis in dilated cardiomyopathy: key parameters beyond EF

Step	Technique	Parameter
A	2D	WMSI
B	Lung ultrasound	B-lines
C	2D, strain imaging	Force, GLS, ESV
D	Pulsed-wave Doppler	CFVR
E	ECG	HRR
F	Color Doppler	MR grade
L	2D	LAV
P	CW, pulsed, and tissue Doppler	PASP, *E*/*e′* ratio
R	M-mode	TAPSE

2D two-dimensional, *CFVR* coronary flow velocity reserve, *CW* continuous wave, *ECG* electrocardiogram, *ESV* end-systolic volume, *GLS* global longitudinal strain, *HRR* heart rate reserve, *LAV* left atrial volume, *MR* mitral regurgitation, *PASP* pulmonary artery systolic pressure, *TDI* tissue Doppler imaging, *TAPSE* tricuspid annular plane systolic excursion, *WMSI* wall motion score index

31.6 Pitfalls of SE in Dilated Nonischemic Cardiomyopathy

The risk of life-threatening complications during pharmacological stress (especially dobutamine) is higher in presence of severe resting left ventricular dysfunction [59]. Exercise is always preferred in patients capable to exercise. Vasodilator stress is the most convenient option to test coronary flow reserve simultaneously with contractile and chronotropic reserves [60].

31.7 Clinical Guidelines

Echocardiography is a key technique in DNCM since serial examinations are needed in these patients from the sub-clinical, early phase to the overt, advanced heart failure [61]. The required information is not limited to left ventricular function and volumes, but also pulmonary congestion and diastolic function, coronary microvascular disease, cardiac sympathetic imbalance, secondary valvular disease, pulmonary hypertension, and right ventricular function [62]. Testing for the contractile reserve is useful to predict outcomes and therapeutic benefits [63]. Data with a systematic application of comprehensive SE according to ABCDE protocol are limited to date, but the SE 2030 study is likely to fill the gap in the next years [64].

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Stress Echocardiography in Angina with Nonobstructive Coronary Arteries

32

Attila Palinkas and Eugenio Picano

Keywords

Coronary flow velocity reserve · Coronary microcirculation · Global longitudinal strain · Normal coronary arteries

32.1 Definitions and Epidemiology

The clinical syndrome of "angina and no obstructive coronary artery disease" (ANOCA) is defined by two features: (1) Stable, chronic (several weeks or longer) symptoms suggesting ischemic heart disease such as chest discomfort with both classic and atypical features in terms of location, quality, and inciting factors. (2) Absence of flow-limiting obstruction by coronary angiography (invasive or computed tomographic angiography) as defined by any epicardial coronary artery diameter reduction ≥50% or fractional flow reserve <0.8 [1].

This clinical definition is different from ischemia with no obstructive coronary artery disease (INOCA) which requires as a third, obligatory criterion the objective evidence for myocardial ischemia from the ECG or a cardiac imaging study (echocardiography, nuclear imaging, or magnetic resonance imaging) at rest or during stress (exercise, mental, or pharmacological) [1].

A different entity is a myocardial infarction with angiographically normal coronary arteries (MINOCA), which also requires the absence of obstructive coronary artery disease but in presence of the universal acute myocardial

A. Palinkas (✉)
Internal Medicine Department, Elisabeth Hospital, Hódmezővásárhely, Hungary

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Table 32.1 Clinical syndromes with chest pain and normal coronary arteries

	ANOCA	INOCA	MINOCA
Chest pain	Present	Present	Present
CAD	Absent	Absent	Absent
Troponin rise	Absent	Absent	Present
Ischemia stress	Absent	Present	Present or absent

infarction criteria with an elevated cardiac biomarker, typically a cardiac troponin >99th percentile of the upper reference level with a rise and fall in the level on serial assessment [1].

The main criteria for differential diagnosis are shown in Table 32.1.

MINOCA is found in 10% of all myocardial infarctions, ANOCA in >50% of patients referred to coronary angiography, and INOCA can be documented in about one-third of patients with ANOCA. Many patients with ANOCA suffer from cardiac extraischemic causes such as pericarditis, or noncardiac causes of chest pain, such as gastroesophageal reflux, asthma, psychiatric causes such as anxiety and panic attack, or osteoarticular disease with costochondritis [2]. In INOCA, the pathophysiology is heterogeneous. A significant central role is possibly played by coronary microvascular disease, coronary vasospasm, and altered cardiac autonomic function with disordered sympathetic innervation. Dynamic intraventricular obstruction increases coronary extravascular resistances and therefore can be considered a cause of functional coronary microvascular disease [3].

32.2 Coronary Microvascular Disease in ANOCA

Coronary microcirculation is a fundamental portion of the coronary artery tree, as it contains most of the coronary blood volume and represents the main regulator of coronary blood flow. Arterioles, capillaries, and venules originating from the major coronary artery branches and extending inside the myocardium, with a diameter of less than 300 μm, constitute the whole coronary microcirculation. Coronary microvascular impairment greatly contributes to the pathophysiology and outcome of many cardiac diseases. Different degrees of coronary microvascular impairment can be found both with and without epicardial obstructive atherosclerosis. Several conditions can be clustered together in the syndrome of microvascular disease (Table 32.2) [3].

Coronary microvascular alterations can be structural, functional, extravascular, and intravascular. In some of these conditions, the abnormalities of the microvasculature represent markers of risk and may determine myocardial ischemia, thus becoming important therapeutic targets [4].

Table 32.2 Clinical cardiac conditions characterized by coronary microvascular impairment

Coronary microvascular impairment in the presence of obstructive epicardial coronary artery disease	It may occur in the context of either stable coronary artery disease or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors
Coronary microvascular impairment in the presence of myocardial diseases	It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular) and is sustained in most instances by adverse remodeling of intramural coronary arterioles
Coronary microvascular impairment in the absence of obstructive coronary artery disease and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, diabetes and insulin-resistant states)
Iatrogenic coronary microvascular impairment	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization

Adapted from Camici and Crea [3]

32.3 INOCA: Not Only Coronary Microvascular Disease

The definition of INOCA has been used to encompass a broad range of conditions (Table 32.3). All ANOCA patients with the documented coronary microvascular disease have INOCA, but INOCA patients can recognize causes of ischemia differently from coronary microvascular disease.

Clinical history, electrocardiogram, and resting transthoracic echocardiogram are therefore essential for identifying patients with true coronary microvascular dysfunction ("cardiac syndrome X") that probably represents no more than 30% of all INOCA patients [5]. The term "syndrome X" (originally the Group X in the 1973 paper by Arbogast and Bourassa) was coined to stress the uncertainty over the pathophysiology of chest pain [6]. It remains unclear whether the chest pain in these patients is ischemic or nonischemic in nature. However, since the unknown factor (X factor) in the original definition was clarified by the evidence of a reduced coronary flow velocity reserve (CFVR) with angiographically normal coronary arteries, we can dismiss the term Syndrome X and define "coronary microvascular disease" for a subset of INOCA patients with reduced ($\leq$2.0) CFVR [7].

Takotsubo cardiomyopathy is clinically indistinguishable from an acute coronary syndrome, but myocardial involvement completely and rapidly recovers in a few days or weeks, making takotsubo cardiomyopathy a unique model of transient and completely reversible myocardial dysfunction, in the absence of significant coronary artery disease [8].

Table 32.3 Myocardial ischemia with "normal" coronary arteries: the spectrum of INOCA

Appropriate nosography	Findings
Minor, initial coronary artery disease (up to 30% stenosis)	Abnormalities of nonsmooth coronary arteries
Early possible cardiomyopathy	HFpEF, LV diastolic dysfunction, left bundle branch block
Variant angina Microvascular vasospasm	Coronary vasospasm of epicardial vessels Coronary vasospasm of small vessels
Secondary microvascular disease	LV hypertrophy, mitral valve prolapse, diabetes, hypertension, high blood cholesterol, amyloidosis
Dynamic LV outflow tract obstruction	LV outflow tract obstruction
Normal coronary microcirculation	Normal CFVR
Microvascular disease (cardiac syndrome X)	Reduced CFVR (< 2.0)
Takotsubo, ACS	Partially reversible acute microvascular damage

ACS acute coronary syndromes, *HFpEF* heart failure preserved ejection fraction, *LV* left ventricle, *CFVR* coronary flow velocity reserve

32.4 The Ischemic Cascade in Microvascular Disease

The typical pattern of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and perfusion abnormalities without regional wall motion abnormality (RWMA) (Fig. 32.1) [9].

The sequence of events is therefore strikingly different from the ischemic cascade found during stress testing in the presence of coronary artery stenosis (Table 32.4).

In these patients with small coronary vessel dysfunction, focal ischemia in small myocardial regions scattered throughout the myocardium and caused by prearteriolar dysfunction, might explain the paradox of angina and ST-segment depression provoked by physical or pharmacological stress. The site of abnormally elevated resistances (in patients with reduced coronary flow reserve) might be intramural, upstream from the endocardium–epicardium branching point, which is not visualized by coronary angiography [10].

The evidence that, despite ischemic-like stress-induced chest pain and ST-segment changes, left ventricular function remains normal during SE in INOCA patients, is not incompatible with true myocardial ischemia: indeed, it is well known that the presence or absence of abnormal wall motion is related to the amount of a critical mass of ischemic subendocardial tissue, and minor degrees of patchy strictly subendocardial myocardial ischemia [11] are less likely to produce regional wall motion abnormality. A regional dysfunction by two-dimensional echocardiography requires a critical ischemic mass of at least 20% of transmural wall thickness and about 5% of the total myocardial mass. For minimal flow reductions, abnormalities of regional

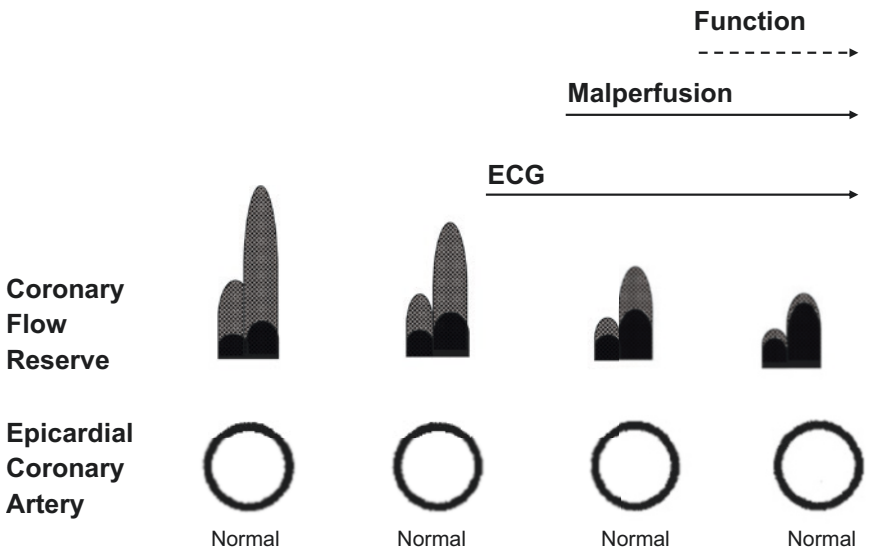

Fig. 32.1 The features of microvascular disease consist of normal epicardial coronary arteries (even when observed by intravascular ultrasound: *lower row*) and reduced coronary flow reserve (by Doppler tracing showing a spectrum of coronary hyperemic responses, from normal—*left* to abolished—*far right*). Chest pain and ECG changes are frequent during stress, especially when flow reserve is reduced, whereas echocardiography changes (*dashed lines*) are only rarely observed. (Modified from Picano E et al. [9])

Table 32.4 Coronary artery disease versus INOCA cascade during stress testing

	Coronary artery disease	INOCA
Clinical models	Coronary stenosis	Microvascular disease
Epicardial coronary anatomy	Stenotic	Normal
Coronary flow reserve	Depressed	Depressed
Stress: Chest pain	Present	Present
Stress: ST depression	Present	Present
Stress: RWMA	Present	Usually absent
Experimental model	Yes	No

RWMA regional wall motion abnormality

systolic function are subtle and certainly below the threshold of detection by echocardiography. Indeed, even under ideal imaging conditions, a subendocardial infarction can be accompanied in 20% of cases by a normal/hyperkinetic regional and global wall thickening [12], for hypercontraction and tethering from subepicardial layer and contiguous segments which may compensate for a limited subendocardial dysfunction.

32.5 SE Patterns in INOCA

In coronary microvascular disease, the peculiar pattern during SE is the regional and global left ventricular hyperkinesia with ST-segment depression and chest pain, consistently observed during dipyridamole [13], exercise [14], and dobutamine [15, 16].

In some patients (<10%) however, an RWMA appears and is not an innocent finding. It is due to angiographically occult coronary artery disease (detectable with intracoronary ultrasound) or initial latent cardiomyopathy which will become manifest in subsequent years [17, 18]. These false-positive results are more frequent in patients with left ventricular hypertrophy and high values of systolic blood pressure during stress, and usually involve the apical region [19].

With last-generation ultrasound technology and advanced expertise, dual imaging (function and flow) SE provides simultaneous insight into regional and global left ventricular function and coronary flow reserve. Coronary flow reserve can be best measured during Doppler transthoracic vasodilator or dobutamine SE in the mid-distal left anterior descending coronary artery, semi-simultaneously with wall motion imaging. A normal (>2.0) CFVR is found in 70% of ANOCA patients (Fig. 32.2).

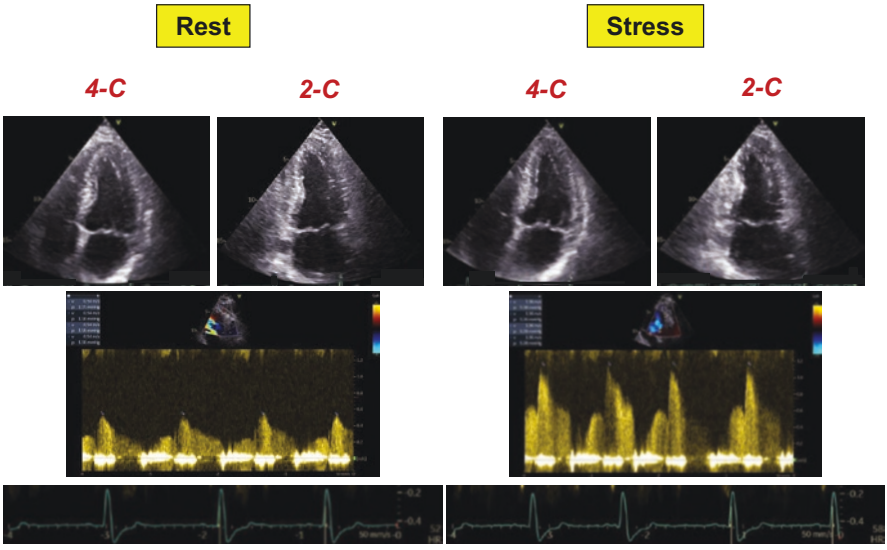

Fig. 32.2 Example of wall motion, coronary flow velocity reserve, and heart rate reserve assessment in patients with normal coronary arteries. Upper panels: end-systolic frames of apical four-chamber and two-chamber views showing normal function at rest and peak stress. Middle panels: Visualization of coronary flow in the mid-distal portion of the left anterior descending artery using pulsed-wave Doppler. Peak diastolic flow velocity was 54 cm s^{-1} under basal conditions (middle left panel) and 116 cm s^{-1} after dipyridamole infusion (middle right panel), with a normal CFVR value of 2.15. Heart rate reserve (lowest panels) is abnormal (rest = 52 beats/min; peak 58 beats/min; heart rate reserve = 58/52 = 1.11, normal values >1.22). (Courtesy of Dr. Lauro Cortigiani)

A reduced (≤2.0) CFVR can be found in 20% of ANOCA patients, in the absence of RWMA. However, the absence of RWMA does not necessarily imply that regional and global left ventricular mechanics are normal since subnormal increases in global longitudinal strain and subendocardial to subepicardial strain ratio can be observed in patients with coronary microvascular disease. Regional thickening and motion express radial function, which can be still normal when global longitudinal strain is impaired during less severe ischemia. When deformation imaging is applied to INOCA patients, an abnormal global longitudinal strain at rest or a reduced strain reserve during stress is observed in concomitance with the reduction in CFVR, suggesting that true ischemia occurs during stress [20–26].

In patients with INOCA, the cause of underlying ischemia can be coronary vasospasm of epicardial coronary arteries, unmasked by exercise, dobutamine, or dipyridamole stress, especially at the interruption of exercise or antidote administration. In these conditions, the diagnosis of vasospasm is easy and obtained by serendipity while testing the patient for coronary artery stenosis [27–29]. Other times, the test can be specifically targeted at vasospasm with ergonovine [30] or hyperventilation [31], eliciting coronary artery vasospasm and transmural ischemia detectable as RWMA.

In patients with left ventricular hypertrophy or young athletes, experiencing symptoms such as chest pain or syncope typically during exercise [32–34], a significant hyperdynamic contraction pattern with left ventricular intraventricular gradient during SE has been observed.

Due to the heterogeneity of underlying mechanisms, it is not surprising that the population of INOCA patients studied mostly under beta-blockers (which may exacerbate vasospasm) and with exercise or dobutamine stress (which may induce vasospasm) showed spontaneous improvements in angina and SE results, but the symptomatic improvement was not correlated with SE findings [35].

32.6 Prognostic Stratification

The prognosis of ANOCA patients is very heterogeneous, and this is not surprising considering the heterogeneity of underlying mechanisms. At long-term (9 years) follow-up, hard events are ten times more frequent in patients with inducible RWMA during SE than in those with negative SE results [36–38]. Within the lower-risk subset of patients with negative SE by wall motion criteria, the risk is higher in patients with reduced CFVR [39, 40].

In patients with ANOCA systematically tested for coronary vasospasm, the prognosis is worse in patients with vasospastic positivity during ergonovine echocardiography despite angiographically normal coronary arteries [41]. Only when all causes of true ischemia have been excluded, the patient can be assigned to a benign, likely noncardiac cause of chest pain. Interestingly, SE can identify an abnormal parameter also through nonimaging heart rate reserve since an abnormal heart rate

reserve identifies a reduced cardiac autonomic balance [42, 43] and offers prognostic information independent and incremental over RWMA and CFVR [44].

32.7 Current Guidelines and Perspectives

Current European Society of Cardiology 2019 and American College of Cardiology/American Heart Association 2021 guidelines on the management of stable coronary artery disease recommend performing SE for the detection of inducible RWMA in association with angina and ischemic ECG changes. Thus, in every patient with sufficiently typical chest pain in whom, despite abnormalities of the electrocardiogram and/or stress test results indicative of myocardial ischemia, coronary angiography fails to show fixed or dynamic obstructions in epicardial coronary arteries, the existence of primary coronary microvascular disease should be suspected. Noninvasive stress testing of CFVR in the left anterior descending artery is now an established option recommended (class 2b) by both European and US guidelines [45, 46]. A CFVR <2.0 strongly suggests coronary microvascular disease. If such criteria are satisfied, more invasive investigations can usually be avoided (Table 32.5).

Although guidelines suggest that testing in the catheterization laboratory may be more comprehensive, it requires separate testing for epicardial artery stenosis (fractional flow reserve <0.8), coronary artery vasospasm (intracoronary acetylcholine testing), coronary microcirculation (coronary flow reserve <2.0), and completely

Table 32.5 Investigations in patients with ANOCA

	COR	Source
Exercise or pharmacological echocardiography *should* be considered to establish whether RWMA occurs in conjunction with angina and ST-changes	2a	ESC 2020 [45]
Transthoracic Doppler echocardiography of the LAD with measurement of diastolic coronary flow velocity following intravenous vasodilators and at rest may be considered for noninvasive measurement of coronary flow reserve	2b	ESC 2020 [45], ACC/AHA 2021 [46]
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium-dependent and nonendothelium-dependent coronary flow reserve and detect microvascular/epicardial coronary vasospasm	2b	ESC 2020 [45], ACC/AHA 2021 [46]

ACC American College of Cardiology, *AHA* American Heart Association, *COR* class of recommendation, *ESC* European Society of cardiology

misses the possibility to detect left ventricular obstruction. Noninvasive testing outside the catheterization laboratory by hyperventilation or ergonovine echocardiography testing [41] is by far a more feasible and possibly safer option to identify vasospasm, but not endorsed by current guidelines' recommendations.

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Stress Echocardiography After Cardiac Transplantation

33

Leyla Elif Sade and Eugenio Picano

Keywords

Cardiac allograft vasculopathy · Coronary flow velocity reserve · Donor heart · Heart transplantation · Acute rejection

33.1 Background

Cardiac transplantation is an important treatment for end-stage cardiac disease with increasing worldwide volumes and expanding the marginal donor pool. Yet, rejection continues to be a major complication [1]. Rejection can be either acute or chronic. Acute rejection is a major problem within the first 3 years following cardiac transplantation, while the risk of chronic rejection which manifests as cardiac allograft vasculopathy (CAV), increases after the first year [1]. Primary graft failure, on the other hand, is a leading cause of mortality within the first month after transplantation but may manifest itself insidiously over the long term as well. Echocardiography is instrumental in monitoring all these three conditions (Fig. 33.1).

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L. E. Sade (✉)
Medicine, University of Pittsburgh Medical Center UPMC, Heart & Vascular Institute, Pittsburgh, PA, USA

Department of Cardiology, University of Baskent, Ankara, Turkey
e-mail: sadele2@upmc.edu

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Acute allograft rejection is characterized by inflammatory infiltration and edema within the myocardium and vessel wall leading to subtle or overt myocardial dysfunction and varying degrees of microvascular dysfunction [2, 3]. The reduction of the coronary vasodilatory reserve during rejection is thought to be secondary to metabolically or immunologically mediated decreased responsiveness of the vascular wall to vasodilator stimuli or ultrastructural abnormalities, such as interstitial edema or cellular infiltration [3].

CAV is the chronic manifestation of a rejection and is associated with poor long-term prognosis after heart transplantation [1]. CAV results from an immune-mediated mechanism and differs from atherosclerotic coronary artery disease in several aspects [4, 5].

Higher coronary flow velocities at rest together with blunted hyperemic flow responses are detected in patients with CAV [6, 7] and usually precede overt CAV observed by coronary angiography [8]. After transplantation, there is an increase in microvascular resistance because of the changes in myogenic tone and intimal thickening [9, 10]. Patients with increased resistance develop more severe blunting of fractional flow reserve and larger plaque volume [9, 11]. In addition, CAV is characterized by endothelial dysfunction and smooth muscle cell proliferation in the intima [5, 12], and inappropriate negative remodeling with progressive diffuse intimal thickening that leads to lumen loss and distal tapering of the epicardial vessels. Such vascular remodeling decreases vascular compliance and flow reserve [12, 13]. Also, the small-vessel disease is common in heart transplant recipients and contributes to the reduction in coronary flow reserve [13–15], and unfavorable outcomes [16]. More focal, localized stenosis can also develop even without warning angina due to denervation.

Consequently, the assessment of CAV requires a thorough evaluation of both macrovascular and microvascular coronary artery involvement. Yet, the clinical

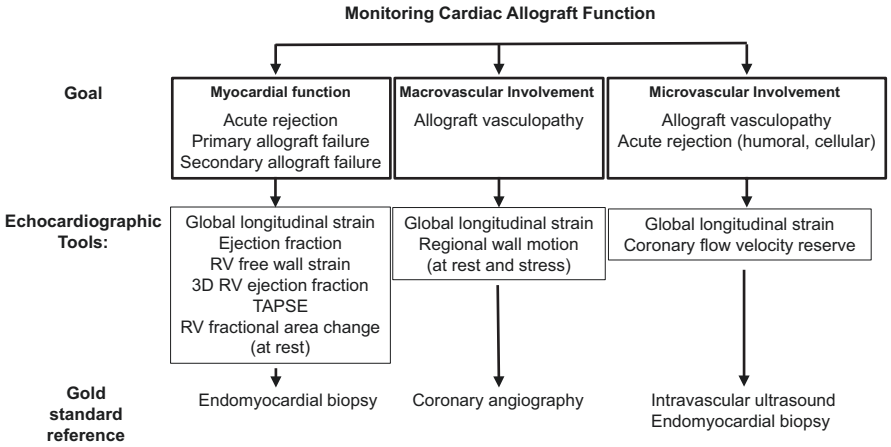

Fig. 33.1 Main strategies and echocardiographic tools for monitoring the allograft damage. *RV* right ventricle, *TAPSE* tricuspid annular plane systolic excursion

diagnosis of CAV is difficult due to silent ischemia of denervated allograft, thus, appropriate use of multimodality imaging seems reasonable, with echocardiography being the first step [17–19]. Although annual coronary angiography remains the most common approach to monitoring the development and progression of CAV, mild degrees of CAV may remain undetected by angiography [20, 21]. Using intravascular ultrasound, which is considered the reference standard to diagnose CAV, up to 75% of all cardiac transplant recipients have some evidence of CAV at 1 year, but only 10–20% show diseased coronary arteries by angiography [22]. Of note, the accuracy of stress echocardiography (SE) may vary in function of the reference standard used for comparison, and in many cases "false" positive result could be a misnomer given the microvascular involvement without obvious epicardial coronary disease unless intravascular ultrasound is used.

33.2 SE in Heart Transplantation

Pharmacological SE modalities are preferred over exercise SE in heart transplantation patients due to the blunted chronotropic response to physical exercise because of cardiac denervation. Pharmacological agents such as dobutamine, dipyridamole, and adenosine are all safe in heart transplant patients. Heart transplant recipients exhibit an augmented chronotropic response to beta-adrenergic stimulation by dobutamine and a poor response to atropine because ventricular denervation results in the upregulation of beta-adrenergic receptors and downregulation of muscarinic receptors [23].

33.2.1 Pharmacological SE for Detection of Acute Rejection

Conventional functional and morphological echocardiographic measures such as reduced ejection fraction, pericardial effusion, increased wall thickness, and echogenicity (by edema) are late manifestations of rejection and therefore not suitable for screening and early detection of rejection [24–27]. Yet, timely modification of immunosuppressive treatment can resolve structural and functional abnormalities induced by an acute rejection [28]. Quantification of myocardial deformation appears to be a more sensitive tool to detect allograft rejection as far as the same vendor is used for serial follow-up and patients are compared with their previous findings [28–31]. Because of the significant overlap of measurements between rejecting and nonrejecting subjects, no single cut-off could be defined so far as an indicator of rejection [24, 28–31].

During the acute rejection, coronary flow reserve can be acutely impaired with or without transient ST-segment depression or wall motion abnormalities during stress [3, 32, 33]. During SE, coronary flow reserve is measured as coronary flow velocity reserve (CFVR) in the mid-distal left anterior descending coronary artery. Microvascular dysfunction is associated with a history of rejection and underscores the importance of immune mechanisms [3, 34]. Antibody-mediated rejection targets

the endothelium of small vessels. However, the potential role of CFVR as a means of microvascular dysfunction for the diagnostic evaluation of acute allograft rejection needs further investigation. Rest and SE based on the detection of reversible regional wall motion abnormality remains insensitive to mild degrees of acute rejection [28, 32]. On the other hand, in patients with normal coronary angiography, and without significant intimal hyperplasia in vessels visualized by intravascular ultrasound wall motion abnormalities can be detected by dobutamine SE in 10% of the patients [21]. However, dobutamine SE does not allow for discrimination of the reason for the impairment of myocardial function, possibly due to myocardial damage, interstitial fibrosis, or microcirculatory dysfunction.

Inducible wall motion abnormalities that are not related to vasculopathy are transient and have usually a more benign course [8, 35]. Of note, no single echocardiographic variable or modality can be used as a stand-alone parameter for accurate and reliable detection of acute allograft rejection [24, 25, 36]. However, a stepwise approach with the use of multimodality imaging seems reasonable and cost-effective to reduce unnecessary endomyocardial biopsies [28, 37].

33.2.2 Pharmacological SE for Detection of Chronic Rejection

CAV is the hallmark of chronic allograft rejection. Regional wall motion abnormalities can be detected at rest or during pharmacological SE using dobutamine (or high-dose dipyridamole) in some subjects with CAV [38]. The typical normal response pattern of dobutamine SE in a patient without CAV is the absence of inducible regional wall motion abnormality (Fig. 33.2).

The typical abnormal response pattern of dobutamine SE in a patient with CAV is the presence of inducible regional wall motion abnormality (Fig. 33.3).

As in native coronary artery disease, dobutamine and high-dose dipyridamole tests have high feasibility and low incidence of side effects in heart transplant recipients. Diffuse intimal proliferation with distal tapering which is the characteristic feature of CAV may remain undetected by routine angiography unless serial comparisons are performed. Indeed, imaging with intravascular ultrasound has been shown to detect significant intimal thickening in almost two-thirds of the patients with apparently normal coronary angiograms [19, 36]. Consequently, conventional angiography is relatively insensitive and cannot exclude functionally relevant CAV [39–41], which can be captured by stress imaging. In the series that systematically evaluated coronary angiography and intravascular ultrasound, dobutamine SE demonstrated wall motion abnormalities in 44–50% of patients with a normal angiogram [21, 42]. If angiography is used as a reference method, these findings are deemed false-positive dobutamine stress tests and therefore explain the relatively low specificity of the stress tests compared to angiography [42–46]. Overall, sensitivity and specificity of dobutamine SE ranged from 0% to 100% and from 49% to 100%, respectively, in different studies, depending on the pretest probability of CAV (old graft, old donor, etc.) and depending on the reference standard for CAV diagnosis [6, 8, 36, 40–53] (Table 33.1). A recent meta-analysis including 749 heart

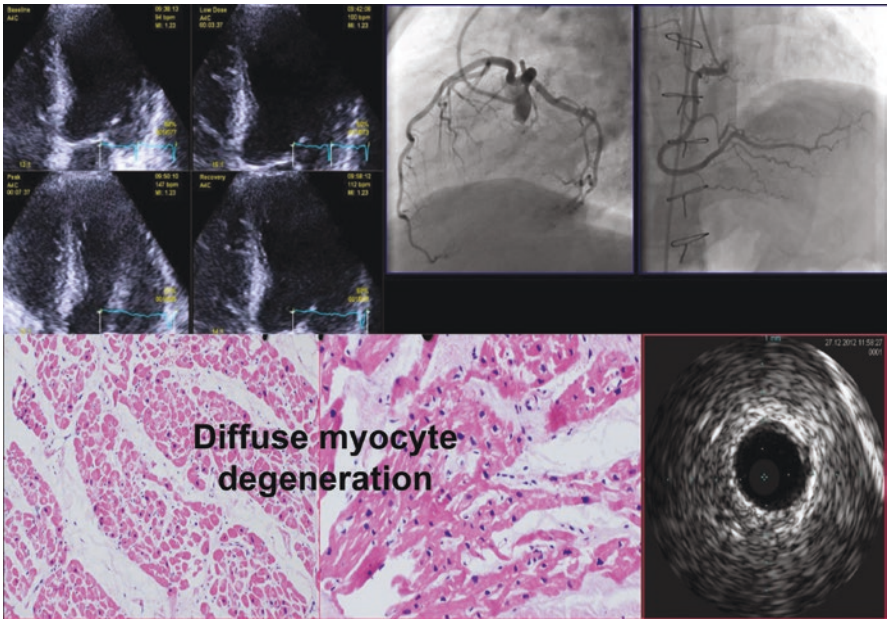

Fig. 33.2 Surveillance endomyocardial biopsy showing cellular degeneration (left lower panel) in an asymptomatic patient with a normal coronary angiogram (right upper panel) and intravascular ultrasound findings (right lower panel). End-systolic frames from the apical four-chamber view of dobutamine SE (left upper panel) show a normal regional and global increase in function, with a marked reduction of end-systolic volume at peak stress (peak). As expected, the dobutamine-induced increase in regional function is less marked in the basal inferior septum. See accompanying Video 33.1 with the apical four-chamber view at rest, low dose, peak dose, and recovery. (Video images courtesy of Professor Leyla Elif Sade, MD, Pittsburgh, USA, and Baskent University, Ankara, Turkey. The video is available under the chapter's "Supplementary Material" on Springer Link)

transplant recipients who underwent dobutamine SE studies, supported these observations and concluded that overall dobutamine SE has a limited sensitivity (60%) to detect early CAV but its specificity is much higher (85.7%) [54].

After all, patients with a high risk for CAV should not undergo a dobutamine SE, as this test has a high probability of false-negative results. A negative result in a high-risk patient does not preclude the need for coronary angiography. The addition of strain quantification has been proposed as a promising tool to increase the accuracy of SE in detecting CAV [55].

While dobutamine SE alone seems to be relatively insensitive to mild CAV and microvascular damage, the assessment of CFVR by transthoracic Doppler echocardiography is useful for detecting both macrovascular and microvascular involvement [8, 52, 53, 56]. CFVR can be impaired in the early stages of CAV before any coronary abnormality is discernible by coronary angiography [57, 58]. As CFVR measurements relate not only to epicardial vessel disease but also to the microcirculatory function, the choice of the sample vessel does not affect the

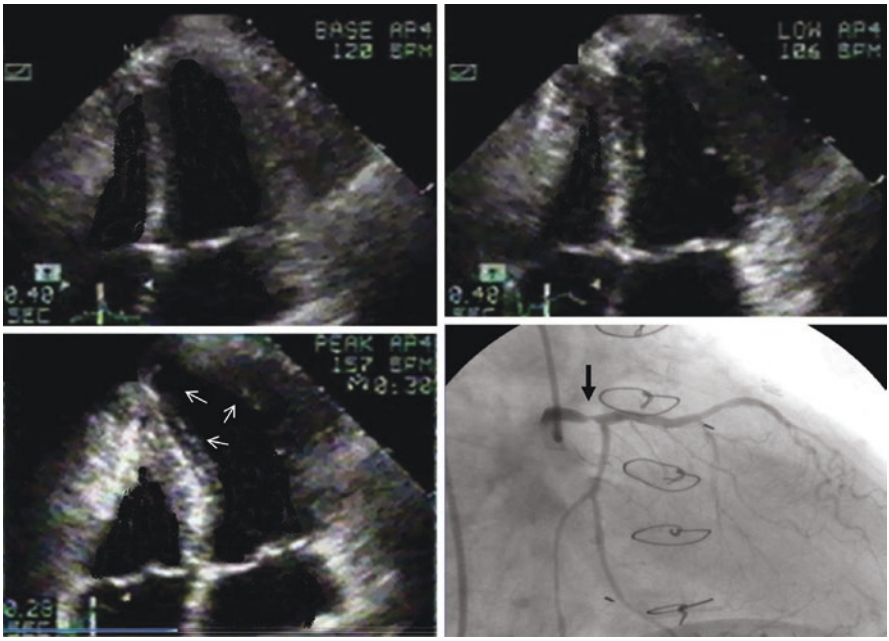

Fig. 33.3 Asymptomatic patient, 4 years after heart transplantation. End-systolic frames from the apical four-chamber view of surveillance dobutamine SE showed a normal regional and global function at rest (left upper panel) and after the low dose (right upper panel), with severe wall motion abnormality at peak dose (left lower panel) in the territories of the left anterior descending artery and left circumflex artery. Right lower panel: Coronary angiogram shows critical left main coronary stenosis (arrow). See accompanying Video 33.2 with the apical four-chamber view at rest, peak dobutamine dose, and recovery. (Video images courtesy of Professor Leyla Elif Sade, MD, Pittsburgh, USA, and Baskent University, Ankara, Turkey. The video is available under the chapter's "Supplementary Material" on Springer Link)

results. Higher coronary flow velocities at rest together with blunted hyperemic flow responses are typical in patients with CAV [6–9]. Coronary vasomotor capacity can be altered early as a consequence of immune-mediated microvascular damage, in the absence of flow-limiting stenosis in heart transplant recipients [9–11, 40, 56, 57]. Therefore, CFVR seems to be highly sensitive in contrast to SE based only on regional wall motion abnormality. It has been shown that CFVR predicts the development of angiographically evident CAV and becomes abnormal earlier than dobutamine SE based on regional wall motion abnormality in most of the patients [8] (Fig. 33.4).

Thus, while normal CFVR helps to exclude CAV (high negative predictive value but low specificity); the combination of CFVR with wall motion assessment (either with high-dose vasodilator stress or dobutamine) is encouraged to increase the specificity and overall accuracy to detect CAV [8, 53]. Additional evaluation of CFVR has been recommended as a tool to increase the prognostic value of conventional wall motion analysis by the 2009 European recommendation document on SE [38].

Table 33.1 Accuracy of pharmacological SE for CAV detection

Author, year, ref	Number of patients	Stress agent	Time post-HT (months)	Gold standard	Sensitivity	Specificity
Akosah et al., 1994 [47]	41	Dob	57 ± 5	CA	95%	55%
Akosah et al., 1995 [48]	45	Dob	58 ± 30	CA[a]	96%	53%
Derumeaux et al., 1995 [43]	41	Dob	40 ± 20	CA	86%	91%
Spes et al., 1996 [42]	46	Dob	46 ± 26	CA[a] IVUS	83% 79%	56% 83%
Derumeaux[b] et al., 1998 [49]	37	Dob	37 ± 20 56 ± 21	CA[a]	65% 92%	95% 73%
Spes et al., 1999 [44]	109	Dob	38 ± 37	CA[a]/ IVUS	72%	88%
Bacal et al., 2004 [50]	39	Dob	86 ± 31	CA	64%	91%
Rodrigues et al.[c], 2005 [45]	35	Dob	72 ± 32	CA	70%	96%
Eroğlu et al., 2008 [41]	42	Dob	72 ± 48	CA[a]	75%	79%
Sade et al.[d], 2014 [8]	23	Dob/ Dipy	46 ± 17	CA[a]	56% 100% 78%	64% 64% 87%
Chirakarnjanakorn et al., 2015 [46]	310	Dob	73–143	CA	28%	98%
Mahmoodurrahan et al., 2021 [51]	99	Dob	2.9–6.7	CA	3.2%	94%
Clerkin et al. 2016 [36]	154	Dob	2.7 ± 1.0	CA	0%	99&
Ciliberto et al. 1993 [52]	80	Dipy	27 ± 18	CA[a]	32%	100%
Tona et al.[c,d], 2006 [6]	73	Ado CFVR	96 ± 54	CA	82%	87%
Tona et al.[c] 2010 [40]	22	Ado CFVR	72 ± 48	IVUS	80%	100%
Pitchel et al. 2019 [53]	74	Dipy[e]	64 ± 43	CA	72.7%	49%

[a] Any coronary lesion including luminal irregularities
[b] The study examined the accuracy of SE in the same patient population at two-time points
[c] Contrast-enhanced studies
[d] Coronary flow reserve was assessed with dipyridamole or adenosine, CA coronary angiography, coronary stenosis >50% in at least one vessel
[e] CFVR and wall motion analysis were combined

The use of ultrasound-enhancing agents or myocardial quantification tools may increase the accuracy of SE for the diagnosis of CAV [6, 7, 34, 41, 45].

From a prognostic standpoint, a normal pharmacological SE result after heart transplantation has a high predictive value for an uneventful clinical course [7, 35, 50]. The value of the test seems to be at least comparable to that of a normal angiogram, and a normal pharmacological stress test has a high negative predictive value (in most studies >90%) that allows invasive diagnostic procedures to be safely

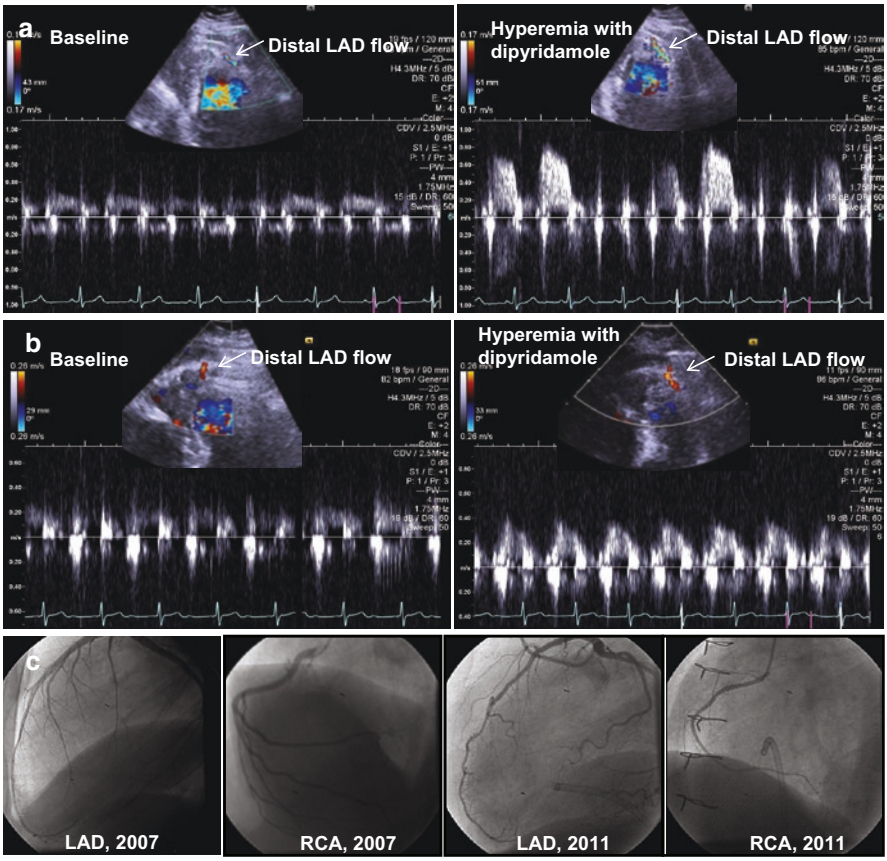

Fig. 33.4 (**a**) 1 year after transplantation, normal coronary flow velocity reserve (CFVR). Note the increase in baseline diastolic flow velocity from 30 to 90 cm/s under dipyridamole infusion yielding a CFVR of 3. (**b**) A patient with blunted hyperemic response to dipyridamole. Note that the baseline diastolic flow velocity increased from 25 to 40 cm/s yielding a CFVR of 1.6 after 4 years of transplantation. (**c**) Coronary angiograms of the patient in B, show significant distal tapering and diffuse narrowing in 2011 as compared to the older angiogram. Note that CAV could be overlooked without comparison with the previous angiogram. See accompanying Video 33.3. The color coronary flow signal is stronger (larger and brighter) at peak dipyridamole stress than at rest. (Video images courtesy of Professor Leyla Elif Sade, MD, Pittsburgh, USA, and Baskent University, Ankara, Turkey. The video is available under the chapter's "Supplementary Material" on Springer Link)

delayed in asymptomatic patients [6, 35, 53], especially if CFVR detectable by transthoracic echocardiography is also normal [8]. If the stress test is normal by both wall motion and CFVR criteria, invasive diagnosis can be delayed in asymptomatic patients (Fig. 33.5).

Positive SE should be followed by endomyocardial biopsy and conventional angiography. If the angiography appears normal, an intravascular ultrasound is warranted. This algorithm helps to avoid unnecessary cardiac catheterizations and to

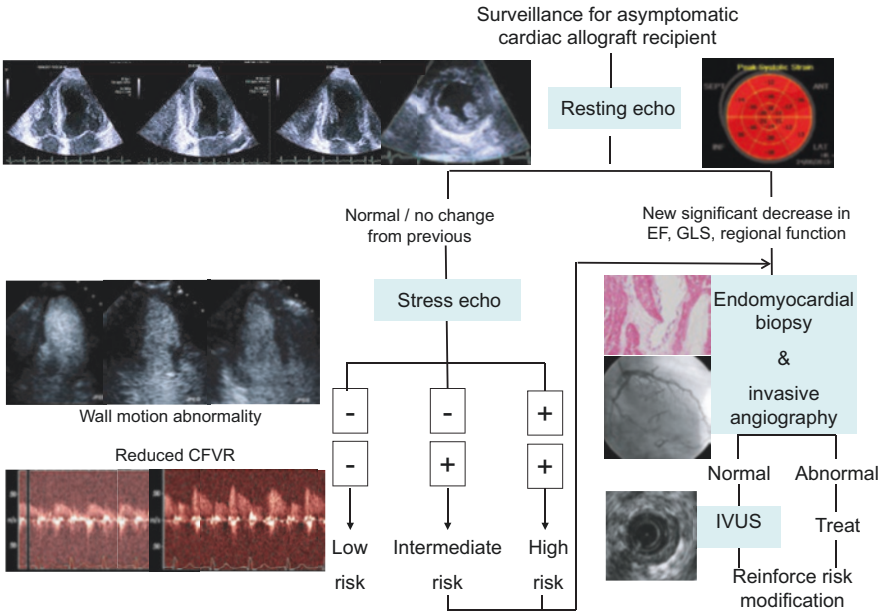

Fig. 33.5 A proposed diagnostic flow-chart in the surveillance of posttransplantation patients. Yearly testing with pharmacological SE may help to reduce the need for invasive studies. The reliability of pharmacological SE is stronger when the test response shows no wall motion abnormalities and normal coronary flow reserve in the left anterior descending artery during transthoracic vasodilation SE. *CFVR* coronary flow velocity reserve, *IVUS* intravascular ultrasound, *WMA* wall motion abnormalities

risk-stratify patients for closer follow-up of functionally relevant and/or progressive CAV. A noninvasive radiation-free follow-up is of particular importance in pediatric patients, in whom dobutamine SE was shown to be highly feasible and effective for diagnostic and prognostic purposes [58]. An endomyocardial biopsy that follows a positive stress test may have added value to explaining nonobstructive causes of positive SE.

33.3 Pharmacological SE for Recruitment of Donor Hearts

Organ donation has been a limiting step in this life-saving procedure. Heart donor shortage has been a social problem [59]. Patients who fulfill the criteria for heart transplantation have disproportionate waiting times to their mortality rate. To overcome organ shortage, the donor pool has been expanded by including marginal donors. This is introducing the risk associated with older donor age and age-related high prevalence of asymptomatic coronary artery disease and subclinical cardiomyopathy related to comorbidities. An alternative approach is based on pharmacological SE performed in marginal donors (aged >55 years) [60–63]. When resting and

SE results are normal, a prognostically meaningful underlying coronary artery disease or cardiomyopathy can be ruled out and the heart can be rescued and transplanted.

Another potential advantage of SE is that it can be helpful to evaluate contractile reserve which indicates reversible left ventricular dysfunction due to calcium excess or other effects of neurohumoral activation in donors who would otherwise be discarded due to resting wall motion abnormalities [64].

Transesophageal echocardiography may be needed when image quality is poor, particularly in ventilated patients. Contrast may also be needed when the left ventricular segments are poorly visualized however the potential pulmonary toxicity of contrast agents may preclude lung donation. Dipyridamole is the preferred stress agent in this setting because it is infused over a shorter period than dobutamine which makes it more convenient at the bedside. Furthermore, many potential donors may already be under inotropic support making the addition of dobutamine less effective and potentially harmful. Although certainly more data are needed with the use of SE to select marginal donors, a SE-driven way to select marginal hearts provides great potential to help solve the current mismatch between donor need and supply, with a very favorable cost-benefit profile [61, 63].

33.4 Pitfalls

As the transplanted heart is surgically denervated and remains without functionally relevant reinnervation in most patients, angina pectoris does not usually occur. Several noninvasive tests have limited value for the detection of CAV. This may be explained by some of the specific features of CAV and by the specific alterations of cardiac physiology in heart transplant recipients. For example, due to the high prevalence of conduction delays, altered repolarization, blunted heart rate response to exercise and limited exercise capacity may result in nondiagnostic exercise stress tests in transplant recipients. Diffuse CAV may remain under-detected by myocardial perfusion scintigraphy due to a lack of regional heterogeneity in perfusion defects. Coronary angiography may not be able to detect diffuse concentric thickening of the vessel wall. Intravascular ultrasound is the method of choice to detect alterations of the vessel wall and has emerged as the most sensitive invasive method for diagnosing CAV and plaque stability [65]. Although most investigators measure thickness and extension of intimal hyperplasia by intravascular ultrasound, no commonly accepted cut-off points or standardized definitions for CAV exist (minimal number of coronary segments and vessels necessary for valid diagnosis, grading by worst affected sites, or mean values). Furthermore, intravascular ultrasound has limitations in determining CAV with distal vessel involvement or at the microvascular level or functional CAV. Although coronary computed tomographic angiography is a reliable option to evaluate coronary arteries and vessel wall involvement, its use is limited for safety reasons during serial follow-up due to radiation and iodine contrast exposure. Other functional imaging tests should be considered in cases of

uncertainties about the diagnosis of rejection and CAV such as cardiac magnetic resonance with and without contrast. Imaging markers such as prolonged T2 time and increased T1 by cardiac magnetic resonance mapping, and flow reserve assessment are sensitive tools that complement echocardiography in a stepwise approach [17–19, 28].

One should be cautious when comparing sensitivities and specificities of SE between the studies. The accuracy of SE either by wall motion analysis or by coronary flow assessment varies considerably depending on the gold standard used and depending on the cut-off value adopted for CFVR. The sensitivity and negative predictive values decrease whereas the positive predictive value and the specificity increase when intravascular ultrasound is the gold standard instead of coronary angiography. Also, the cut-off value of CFVR differs from 2 to 2.9 in different studies. Posttransplant septal motion abnormalities are frequent in the first posttransplant year and may be misleading. These are expected to normalize during stress, however, any septal wall motion abnormality after the first year should raise the suspicion of CAV. In addition, normal resting values of global longitudinal strain are time-dependent due to graft aging.

33.5 Clinical Guidelines

Despite accumulating data, there have been no new updates in terms of imaging for allograft rejection and CAV in the guidelines. Data about the role of echocardiographic modalities can be read between the lines of the recommendation papers. This is basically due to the lack of systematic use of imaging among the centers in the follow-up of cardiac allograft recipients and because large series belong to retrospective analyses. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients recognize that SE "*may be useful for the detection of CAV in heart transplant recipients unable to undergo invasive evaluations*" [66]. The 2015 recommendations of the European Association of Cardiovascular Imaging in patients after heart transplantation suggest that pharmacological SE might be helpful in centers with adequate experience with the methodology, and coronary flow reserve might be combined with SE to improve the accuracy of the test—which can otherwise remain unsatisfactory if based only on wall motion abnormalities [67]. Prospective, large-scale outcome studies are needed to support more evidence-based, SE-driven surveillance of the transplanted heart with a comprehensive protocol that allows the combination of regional wall motion and CFVR in one test, with extremely high feasibility with either dobutamine or high-dose dipyridamole, as it has been shown in patients with chronic coronary syndromes [68]. More data are also needed for the SE-based rescue of hearts from marginal donors currently excluded from donation. The RESURGE (*Re*covery by *SE* of conventionally *u*nfit dono*r* *g*ood he*a*rts) study is a subproject of the SE 2030 international prospective multicenter study and plans to recruit at least 100 patients with the comprehensive SE protocol until the year 2025 (Fig. 33.6) [69].

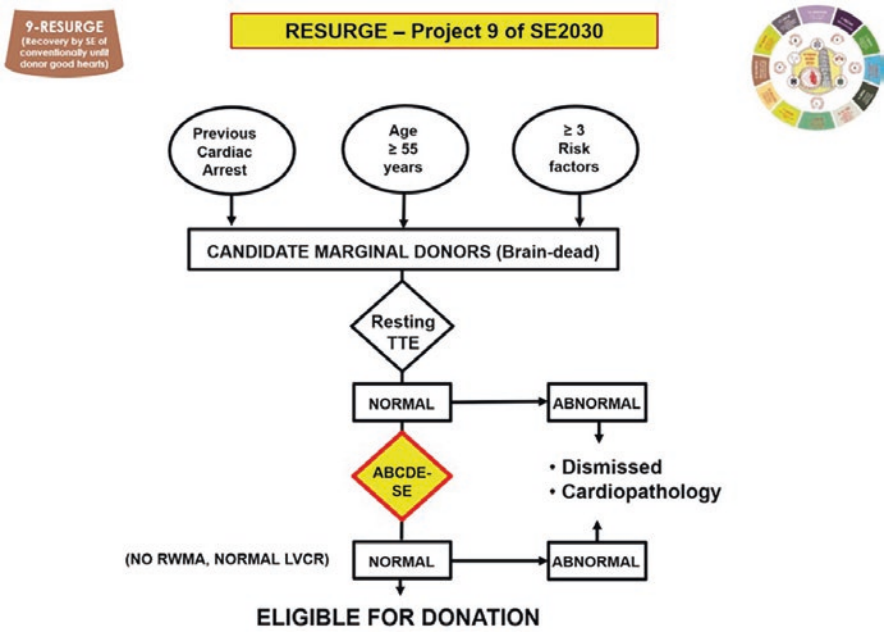

Fig. 33.6 The general protocol adopted for the study of *Re*covery by SE of conventionally unfit good donor hearts (RESURGE), a subproject of the SE 2030 study. (Modified from [69])

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Stress Echocardiography in Valvular Heart Disease

34

Francesca Bursi and Eugenio Picano

Keywords

Aortic stenosis · Mitral regurgitation · Pulmonary artery systolic pressure · Right ventricular function

34.1 Background

Major advances in diagnosis and risk stratification, combined with enormous progress in surgical valve replacement and repair, have led to improved outcomes for patients with valvular heart disease (VHD) over the past 30 years. Transcatheter techniques have gained ground for transcatheter aortic valve implantation, transcatheter edge-to-edge repair in secondary mitral regurgitation (MR), transcatheter valve-in-valve implantation after the failure of surgical bioprostheses, and transcatheter tricuspid valve interventions in inoperable patients. The most important indications for intervention in patients with hemodynamically significant aortic or mitral valve disease are the development of symptoms and left ventricular (LV) dysfunction. As symptoms may develop slowly and indolently in these chronic conditions, many patients are unaware of subtle changes in effort tolerance, even when questioned directly by their physicians. Hence, guidelines of both the American College of Cardiology (ACC) and American Heart Association (AHA) in 2020 and the European Society of Cardiology (ESC) in 2021 [1, 2] have placed renewed

F. Bursi (✉)
ASST Santi Paolo e Carlo Milano, Ospedale San Paolo, Dipartimento di Scienze della salute, Università degli Studi Statale di Milano, Milan, Italy
e-mail: francesca.bursi@asst-santipaolocarlo.it

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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emphasis on the role of exercise testing to provide objective evidence of exercise capacity and symptom status.

In addition, while rest Doppler echocardiography is the method of choice for assessing the severity of valvular disease, stress two-dimensional and Doppler echocardiography may be useful, if there is discordance between baseline measurements and physical examination, to assess dynamic changes in hemodynamics and may be used to guide the optimal treatment strategy [1]. Stress echocardiography (SE) has been recently expanded to the assessment of the hemodynamic consequences of valvular lesions during stress [3–9]. ESC 2021 guidelines underscore that exercise echocardiography has a diagnostic role as it may identify the cardiac origin of dyspnea and provides prognostic information mainly for aortic stenosis (AS) and MR [2].

34.2 Aortic Stenosis

Severe AS is defined as an aortic valve area (AVA) ≤1.0 cm^2 compared to the normal value of 3.0–4.0 cm^2. The reduction of the AVA must be substantial before the pathologic disease becomes hemodynamically significant and, at a later stage, clinically significant. A minimal valve gradient is present until the orifice area becomes less than half of normal. The pressure gradient across the valve is related to the valve orifice area and the transvalvular flow [10] (Fig. 34.1).

The fundamental relationship between flow, gradient, and valve area is valid for all native and prosthetic valves and has important practical implications. The characterization of the transvalvular gradient must be accompanied by the definition of transvalvular flow to obtain the value of AVA. The pragmatic consequence of this simple hydraulic principle is that complete assessment of AS (and any valve stenosis) requires, at rest and during stress, the measurement of the transvalvular flow, transvalvular pressure gradient, and calculation of the AVA. If one of the three is missing, the study is incomplete. Except for the relatively rare

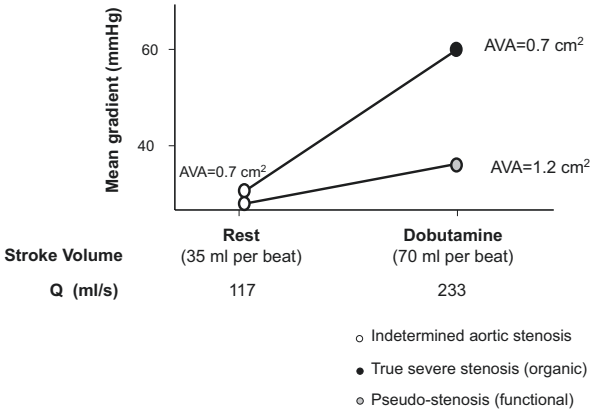


Fig. 34.1 Relationship between flow, gradient, and AVA. The same flow increase across the valve is associated with a modest increase in transvalvular gradients for AVA = 1.2 cm^2 and a marked increase for AVA = 0.7 cm^2

Table 34.1 The four hemodynamic categories of AS

	High gradient	LF, LG, rEF	LF, LG, pEF	NF, LG, pEF
LVEF (%)	Any	< 50	≥ 50	≥ 50
SVi (mL/m^2)	Any	≤ 35	≤ 35	> 35
mAVG (mmHg)	≥ 40	< 40	< 40	< 40
AVA (cm^2)	≤1	≤1	≤1	≤1
SE use	Not recommended	Recommended	Not recommended	Not recommended

AVA aortic valve area, *EF* ejection fraction, *LF* low flow, *LG* low gradient, *LV* left ventricular, *mAVG* mean aortic valve gradient, *SVi* stroke volume index

occurrence of a high-flow status condition [2], a high transvalvular gradient at rest is diagnostic for severe AS. Conversely, a low gradient at rest in presence of a reduced AVA cannot rule out the presence of a severe AS. A normal AVA at rest excludes severe AS, but a reduced AVA is not sufficient to confirm severe AS in presence of a reduced LV ejection fraction (EF) and/or reduced transvalvular flow. According to transvalvular flow, EF, and transvalvular pressure gradients, patients with reduced AVA are grouped into four broad categories identified by guidelines [2]: high-gradient AS; low-flow, low-gradient AS with reduced EF; low-flow, low-gradient AS with preserved EF; normal-flow, low-gradient AS with preserved EF (Table 34.1).

SE is recommended by guidelines in patients with low-flow, low-gradient AS with reduced EF.

34.2.1 Low-Flow, Low-Gradient Aortic Valve Stenosis with Reduced EF

Patients with severe AS (AVA ≤1.0 cm^2) and LV systolic dysfunction (EF <50%) often present with a relatively low-flow (indexed stroke volume ≤35 mL/m^2) and pressure-gradient (i.e., mean gradient <40 mmHg) (Fig. 34.2).

This entity represents a diagnostic challenge because it is difficult to distinguish between patients having true anatomically severe AS from those having pseudo-severe AS. In true-severe AS, the primary culprit is valve disease, and LV dysfunction is a secondary or concomitant phenomenon. The small and relatively fixed AVA contributes to raising afterload, decreasing EF, and reducing stroke volume. In pseudo-severe AS, the predominant factor is a myocardial disease, and the severity of AS is overestimated based on AVA because there is an incomplete opening of the valve due to a reduction in the opening force generated by the weakened ventricle. In both situations, the low-flow state and low-pressure gradient contribute to a calculated AVA that meets the criteria for severe AS at rest (≤1.0 cm^2). Hence, the resting echocardiogram does not distinguish between these two situations. Yet, this distinction is essential since patients with true-severe AS and poor LV function will generally benefit significantly from aortic valve intervention, whereas the patients with pseudo-severe AS will not [11–14].

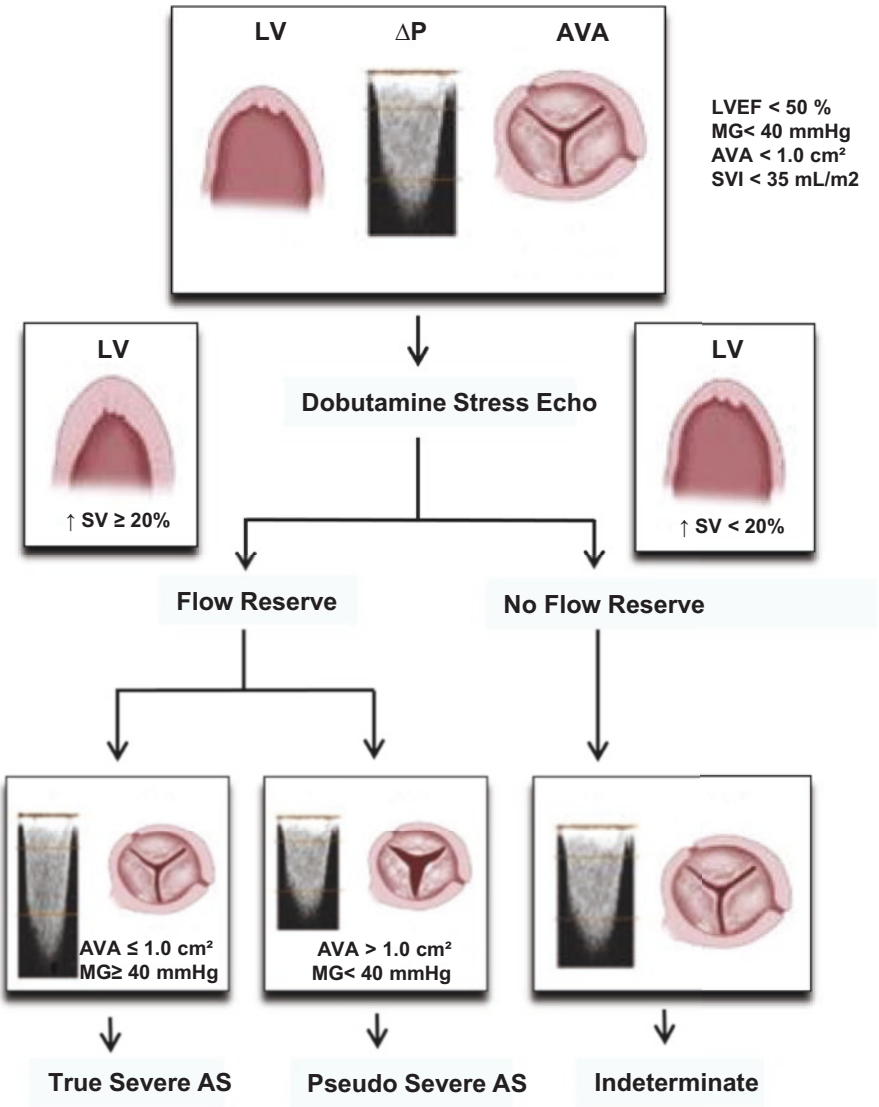


Fig. 34.2 Hemodynamic principles supporting the use of dobutamine SE in low-flow, low-gradient AS. At rest, the mean gradient is low regardless of the AVA because the transvalvular flow rate is low. The stroke volume (*SV*) is low at rest (≤35 mL/m^2) and may normalize following dobutamine. With the augmentation of flow with dobutamine, there is a marked increase in mean transvalvular pressure gradient (≥ 40 mmHg) in the case of true-severe stenosis (AVA ≤1 cm^2), whereas there is only a modest increase in gradient (< 40 mmHg) in the case of moderate stenosis (AVA > 1.0 cm^2). When there is no significant flow reserve or contractile reserve (SV increase <20% from baseline), the stenosis remains indeterminate

A SE by low-dose dobutamine is used in these patients to assess LV flow (contractile) reserve and aortic valve stenosis severity by measurement of AVA by continuity equation at baseline and during the infusion of the drug [1, 2, 10].

Three patterns are possible. During dobutamine, the typical pattern of pseudo-severe AS is the increase in flow reserve (stroke volume increase ≥20%) with a significant increase in AVA (to >1.0 cm^2) and a minor increase in transvalvular gradient (Fig. 34.3). Medical therapy optimization and echocardiographic follow-up are recommended [1, 2].

The typical pattern of true-severe AS is the increase in stroke volume (increase ≥20%) with unchanged AVA (≤1.0 cm^2) and a marked increase in transvalvular gradient (mean pressure gradient ≥40 mmHg or peak aortic jet velocity ≥4 m/s) at any flow (Fig. 34.4). Intervention for valve replacement is recommended (class 1 recommendation, level of evidence B, for ESC guidelines 2021) [1, 2].

The third pattern of indeterminate AS severity occurs in patients with a lack of contractile reserve with unchanged indexed stroke volume (increase ≤20%), unchanged AVA, and unchanged transvalvular gradient. In these patients, aortic calcium score by computed tomography may help to estimate the probability of stenosis severity [15, 16]. The absence of contractile reserve occurs in up to 30% of patients and is a predictor of high perioperative mortality after surgical aortic valve replacement (AVR). However, because this pattern does not predict late

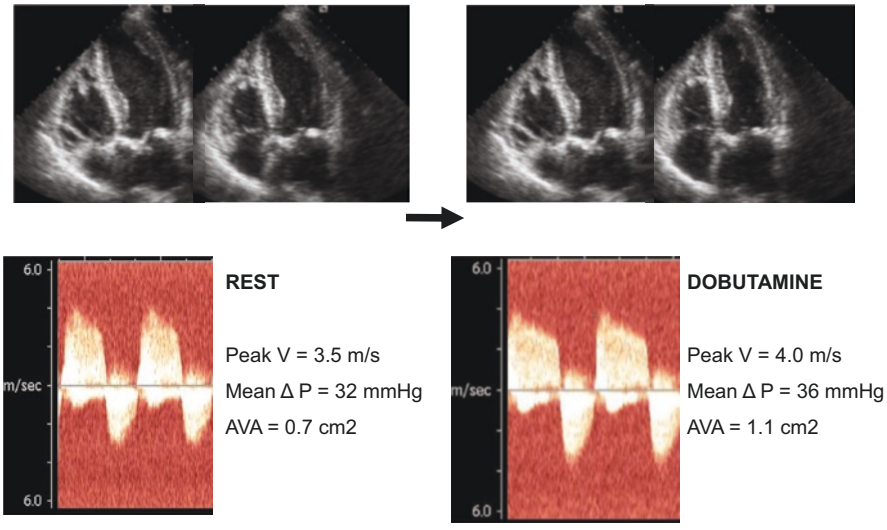


Fig. 34.3 Pseudo-severe AS response with dobutamine stress unmasked by dobutamine SE in a patient with reduced LV function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening (and increase in SVi). *Lower panels*: slight increase in pressure gradient (*ΔP*) and a significant increase in AVA

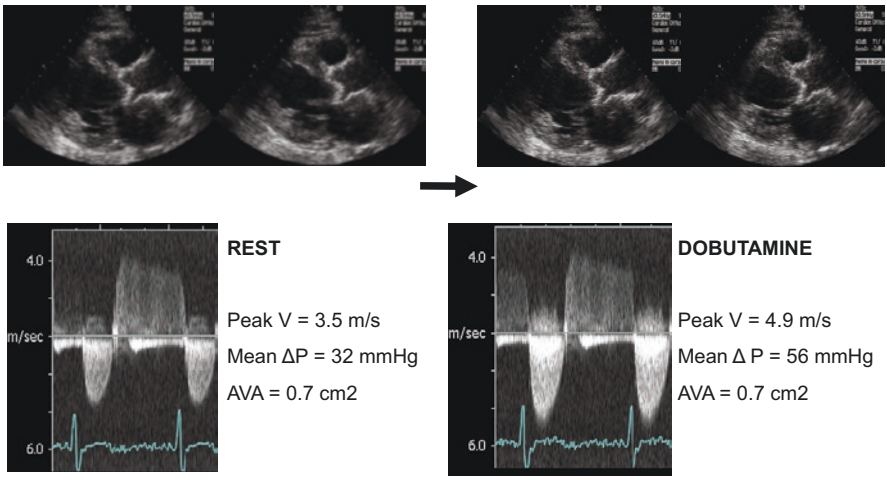


Fig. 34.4 True-severe AS response with dobutamine stress. Unmasked by dobutamine SE in a patient with reduced LV function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening (and increase in SVi). *Lower panels*: marked increase in pressure gradient (ΔP) and no increase in AVA

postintervention survival it should not contraindicate surgical or percutaneous interventions, which improve long-term prognosis and favor LV function improvement. In these symptomatic patients, intervention should be considered with a class 2a recommendation for ESC 2021 guidelines, especially when cardiac computed tomography calcium score confirms severe AS [2].

The main objective of dobutamine SE in the context of low-flow AS is to increase the transvalvular flow rate while not inducing myocardial ischemia. Hence, a low-dose protocol (i.e., 5 μg kg^{-1} min^{-1} increases up to 20 μg kg^{-1} min^{-1}) should be used for these patients. Moreover, it is preferable to use longer dobutamine stages (5–8 min instead of the 3–5 min generally used for the detection of ischemic heart disease) to ensure that the patient is in a steady-state condition during Doppler echocardiography data acquisition and before proceeding to the next stage, also for safety reasons [1, 2].

The increase in heart rate should also be taken into consideration given that it may predispose the patient to myocardial ischemia and at one point may override the inotropic effect, thereby limiting the increase in transvalvular flow.

In contrast to the stroke volume, the mean transvalvular flow rate (i.e., stroke volume/ejection time), which is, besides the AVA, the main physiological determinant of the increase in gradient, continues to increase at higher doses of dobutamine due to increase in heart rate. There is a high variability of flow rate response to dobutamine across individuals. During dobutamine SE, the persistence of

discordance between stress AVA (AVA ≤1 cm^2) and stress gradient (<40 mmHg) may hinder AS severity assessment. This occurs typically when there is a lack of contractile reserve with unchanged stroke volume. In these cases, it may be helpful to calculate the projected AVA at a normal flow rate (Q). The flow rate (Q) is obtained by SV/ejection time. The projected AVA at a standardized normal flow rate of 250 mL/s may be calculated by the formula: Projected AVA = AVA rest + (AVA change/Q change) × (250 − Q rest), where AVA rest and Q rest are the AVA and mean transvalvular flow rate measured at rest and AVA change and Q change are the absolute changes in AVA and flow rate measured during dobutamine infusion. A projected AVA ≤1.0 cm^2 is considered an indicator of true-severe stenosis [7, 18].

The recommended protocol for low-flow, low-gradient AS with reduced EF is shown in Table 34.2. Doppler tracings to assess flow and LV images are obtained at each dobutamine infusion stage. Care must be posed that the sample volume is placed in the same position in the LV outflow tract during the test.

Aortic valve gradient during stress should be obtained from the apical window, even if the highest resting gradient is obtainable from the nonapical window. LV apical view is optimized for Simpson's, regional wall motion assessment, and global longitudinal strain. The LV outflow tract diameter is measured at baseline and the same diameter is used to calculate the continuity equation AVA area at each stage. B-lines can be obtained in the recovery phase in the first 2 min after the cessation of exercise when pulmonary congestion is still present.

The endpoints for terminating the dobutamine test are (1) heart rate >220-age; (2) systolic blood pressure <80 or >220 mmHg; (3) significant increase in the LV outflow tract gradient; (4) ischemia detected by electrocardiographic criteria (>5 mm of flat or downsloping ST depression); (5) complex ventricular arrhythmias or rapid new atrial arrhythmias; (6) breathlessness, angina, dizziness, or syncope; and (7) maximum dose reached.

34.2.2 Aortic Valve Stenosis with Low-Flow, Low-Gradient, and Preserved Left Ventricular Function

Low-flow (SVi ≤35 mL/m^2) low-gradient (<40 mmHg) ("paradoxical") severe AS (AVA ≤1 cm^2 or indexed AVA ≤0.6 cm^2/m^2) can also be observed in patients with preserved LV EF (≥50%) [1]. This pattern shares many pathophysiological and

Table 34.2 Acquisition protocol for low-flow, low-gradient AS with reduced EF

	Rest	Dob-5	Dob-10	Dob-15	Dob-20	Recovery
1. EF (GLS)	v	v	v	v	v	
2. SV, CO	v	v	v	v	v	
3. AVG	v	v	v	v	v	
4. AVA	v				v	
5. B-lines	v					V

AVG aortic valve gradient, *AVA* aortic valve area, *CO* cardiac output, *Dob* dobutamine, with doses expressed in μg/kg/min, *GLS* global longitudinal strain, *SV* stroke volume

clinical similarities with heart failure and preserved LV EF. It is characterized by pronounced/exaggerated myocardial concentric remodeling, small LV cavity size, and restrictive pattern of LV filling. Symptomatic patients with paradoxical low-flow AS have a worse prognosis compared to patients with normal flow, but because there is evidence that AVR improves survival, intervention should be considered after careful confirmation of stenosis severity (ESC 2021 guidelines Class 2a indication, level of evidence C). Indeed, the management of this challenging entity starts with the confirmation of AS severity. Pseudo-severe paradoxical low-flow AS occurs in 30% of cases. The use of dobutamine SE is generally not recommended due to limited evidence available and the possibility of severe hypotension for induction of LV outflow obstruction. The possibility of severe AS is highly likely in presence of severe aortic valve calcification assessed by Agatston score with cardiac computed tomography (>3000 units in men, >1600 units in women).

34.2.3 Asymptomatic Severe Aortic Stenosis with High Gradient

Management of asymptomatic patients with severe AS, defined as peak velocity greater than 4 m/s and/or mean pressure gradient greater than 40 mmHg and/or AVA $\leq$1 cm^2 or indexed AVA $\leq$0.60 cm^2/m^2 [1, 2], remains a source of debate in subjects with normal LV function. The wide interindividual variation in the rate of progression and the outcome of the disease has recently prompted some authors to recommend early elective surgery in asymptomatic patients with severe AS. The rationale for using this approach is that if one applies a strategy of waiting for symptoms before recommending surgery, the patient may be operated on too late in the course of the disease at a stage in which myocardial damage is, at least in part, irreversible. In this regard, it is also important to emphasize that some patients, and especially elderly patients, may ignore or not report their symptoms, while others may reduce their level of physical activity to avoid or minimize symptoms. While exercise testing is contraindicated in patients with severe symptomatic AS, its principal role is to unmask symptoms in a significant proportion of patients with AS who claim to be asymptomatic, as these symptoms can predict outcomes. Reduced exercise tolerance, with the development of dyspnea or ST-segment depression, is associated with a worse outcome. In this respect, exercise electrocardiography testing is an important tool, and several studies have shown its prognostic value. In patients with asymptomatic severe AS, exercise echocardiography has been shown to provide incremental prognostic value beyond exercise testing alone [19]. Moreover, an increase in the mean transaortic pressure gradient of more than 20 mmHg, reflecting limited valve compliance or more severe stenosis, during exercise in asymptomatic patients was shown to be another predictor of symptom onset in the short term (Fig. 34.5) [2]. When the aortic valve is no longer compliant or in case of profound myocardial damage, a mismatch between afterload and contractility may occur during exercise, which is characterized by a limited

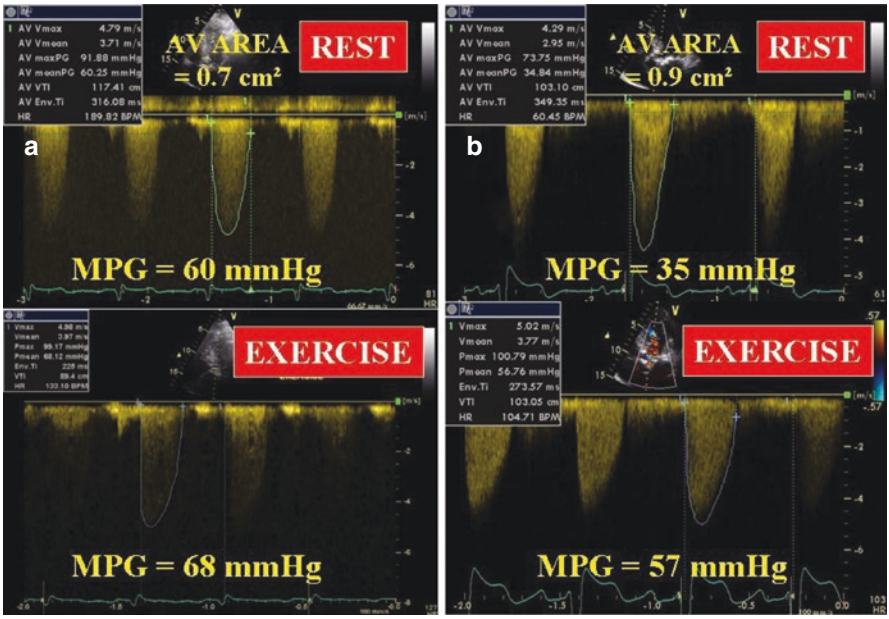


Fig. 34.5 Examples of exercise-induced changes in mean transaortic pressure gradient (MPG) in two asymptomatic patients with severe AS. (**a**) Modest increase in MPG (8 mmHg) with exercise. (**b**) Significant exercise-induced increase in MPG (22 mmHg). (By courtesy of Prof. Patrizio Lancellotti from Liege)

contractile reserve (small/no change in EF or global longitudinal function) [19]. These patients are at increased risk of cardiovascular events, yet the best cut-off values of changes in EF and global longitudinal strain remain to be determined. Similarly, patients who develop pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg, measured from the tricuspid regurgitant velocity) during the test displayed decreased survival rates [8]. However, more confirmatory data are needed to support the routine use of exercise echocardiography in the management of asymptomatic patients with severe AS. At present, exercise SE does not have a specific role in these patients, although exercise testing is mentioned in guidelines as it provides diagnostic and prognostic information [1, 2]. A fall in systolic blood pressure (≥20 mmHg in ACC/AHA and >20 in ESC document, respectively) and decreased exercise tolerance are indications of intervention (class 2a for both 2020 ACC/AHA and 2021 ESC guidelines). According to the 2021 ESC guidelines, in these patients, intervention should be considered (class of recommendation 2a) in presence of resting LV systolic dysfunction (EF < 55%) without another cause and is recommended if EF < 50% (class of recommendation 1) [2]. Stress testing with exercise is useful to identify patients who are truly asymptomatic since the underestimation of symptoms is common in VHD with patients limiting their level of activity over the years to adapt to the slow progression of valve disease.

The test protocol is outlined as follows. Pulsed wave flow in the LV outflow tract is recorded at rest, intermediate stages, and peak stress. LV outflow tract may serve for cardiac output calculation but also the timing of aortic valve closure for strain measurements. When recording velocities for pulsed-wave Doppler flow measurements, adjust the sample volume axial length to 5–7 mm. When measuring velocities, the outer edge of the dense (or bright) envelope of the spectral recording should be used. The LV outflow velocity is recorded from the apical five-chamber or long-axis view, with the sample volume positioned about 5 mm proximal to the aortic valve. Imaging at the intermediate stage is to be performed at the 25 W stage (low-level exercise). Aortic valve gradient during stress (25 W and peak) should be obtained from the apical window, even if the highest resting gradient is obtainable from the nonapical window.

34.3 Aortic Regurgitation

As is the case with AS and chronic MR, the development of irreversible LV dysfunction is a major concern in asymptomatic patients with severe aortic regurgitation (AR). In those with normal resting LV systolic function, an increase in LV EF during either exercise or pharmacologic stress before surgery indicates the presence of contractile reserve, and this may predict improvement in LV function after AVR [20]. The assessment of contractile reserve can be extended for the evaluation of patients with AR who have developed LV dysfunction. In these latter patients, exercise tolerance is an important predictor of the reversal of LV dysfunction and survival after AVR [21].

The development of symptoms during exercise testing is useful in predicting outcomes in patients with severe AR who are asymptomatic at rest. The validity of SE in predicting the outcome of patients with asymptomatic AR is limited mainly by the small number of available studies [1, 2].

The recommended protocol for asymptomatic severe AR is shown in Table 34.3. The increase in heart rate limits the quantification of AR severity.

Table 34.3 Acquisition protocol for severe aortic regurgitation without symptoms

	Rest	Low-intermediate	Peak	Recovery
1. EF, GLS	v	v	v	
2. PASP	v	v	v	
3. AR	v			
4. TAPSE	v		v	
5. B-lines	v			v

AR aortic regurgitation, *PASP* pulmonary artery systolic pressure, *TAPSE* tricuspid annular plane systolic excursion

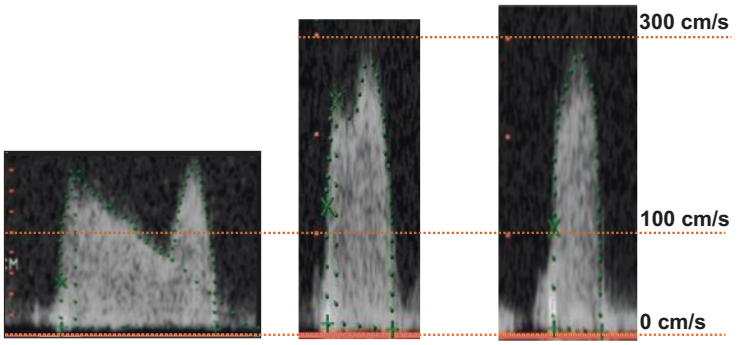
34.4 Mitral Stenosis

A baseline resting transthoracic echocardiography examination is usually sufficient to guide management in asymptomatic patients with mild-to-moderate mitral stenosis (MS) and in symptomatic patients with moderate-to-severe MS who are candidates for either percutaneous balloon valvuloplasty or surgical mitral valve repair or replacement. In some patients, a more detailed assessment of valve function and its hemodynamic consequences is needed, particularly when symptoms and Doppler findings are discordant. In asymptomatic patients with severe or clinically significant MS (mitral valve area ≤1.5 cm^2), exercise SE is useful to reveal symptoms, especially in sedentary patients [2]. In asymptomatic patients with a mitral valve area of ≤1.5 cm^2 and symptomatic patients with a mitral valve area >1.5 cm^2, the measurement of pulmonary artery pressures and mean transmitral pressure gradient during exercise SE may help distinguish those who could benefit from valvuloplasty or valve replacement from those who should be maintained on medical therapy [2, 22, 23]. As is the case with the aortic valve, the transmitral valve pressure gradient is related to the valve orifice area. However, it should be emphasized that the transmitral gradient is much more sensitive to the chronotropic conditions than that of the transaortic gradient and that these conditions may vary extensively from one patient to another. Moreover, for a given valve orifice area, patients with reduced atrioventricular compliance exhibit a more pronounced increase in pulmonary arterial pressure during exercise than those with normal compliance. The dynamic reserve of the mitral valve orifice area during exercise is affected by the mitral valve morphology, such as calcification, thickening, and leaflet mobility. Hence, the resting values of transmitral gradient or pulmonary arterial pressure do not necessarily reflect the actual severity of the disease. Exercise echocardiography may therefore be highly useful for confirming the severity of MS and assessing its consequences on the hemodynamic and symptomatic status of the patient under exercise conditions. Thresholds for hemodynamically significant MS on exertion have been established as mean transmitral gradient >15 mmHg (Fig. 34.6).

Also, pulmonary artery systolic pressure (PASP) >60 mmHg on exertion suggests severe MS, especially when it occurs at low-level exercise (Fig. 34.7) [6, 7]. The early exercise-induced relative increase in PASP correlated with a higher rate of exercise-induced symptoms and the need for valve intervention during follow-up in asymptomatic patients with mitral valve area ≤1.5 cm^2 [24].

B-lines can be present during exercise stress in patients with MS, mixed VHD, severe asymptomatic AR, or ischemic MR [25–27]. They indicate pulmonary congestion and are useful to link symptoms with a cardiac origin of dyspnea due to increased pulmonary capillary wedge pressure (Fig. 34.8).

Dobutamine SE has been less used in MS and is favored when exercise test is nonapplicable. A dobutamine-induced gradient >18 mmHg is a significant predictor of clinical deterioration, but changes in pulmonary pressures during dobutamine are unreliable and nonphysiologic for the dobutamine beta-2 receptors



	Rest	30-W exercise	Peak exercise
HR (b/min):	55	116	159
DFT (ms):	607	228	200
SV (ml):	66	59	57
Q_{mean}(ml/s):	109	259	284
ΔP (mmHg):	5	23	27
SPAP (mmHg):	40	62	69

Fig. 34.6 Exercise SE in a symptomatic patient with MS (mitral valve area: 1.2 cm^2) and relatively low-resting mean transmitral pressure gradient (*ΔP*). With exercise, there is a marked increase in the transvalvular gradient and systolic pulmonary arterial pressure (*SPAP*). In this patient, the exercise-induced increase in the mean transvalvular flow rate (Q_{mean}) was caused by the dramatic shortening in diastolic filling time (*DFT*). *HR* heart rate, *SV* stroke volume. (By courtesy of Prof. Patrizio Lancellotti from Liege)

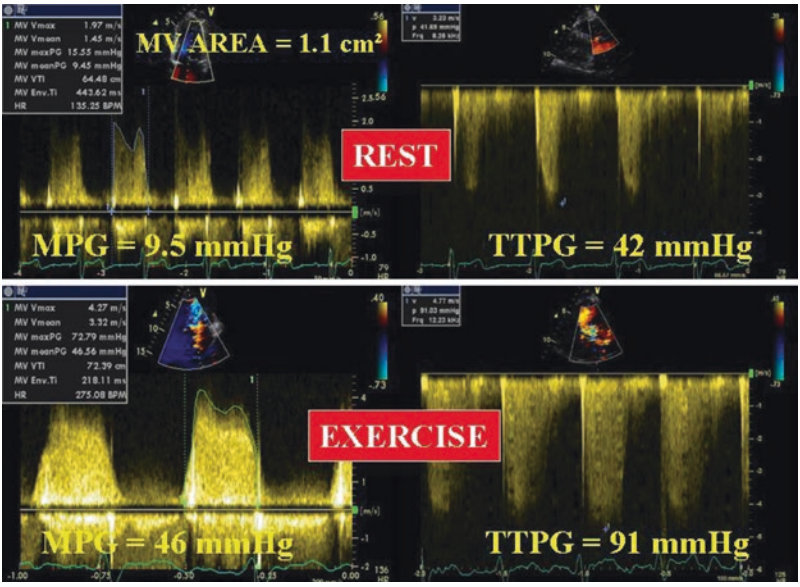


Fig. 34.7 Example of an asymptomatic patient with severe mitral valve stenosis but with moderately elevated mean transmitral pressure gradient (*MPG*) at rest. During exercise, the MPG increases markedly as does—the systolic transtricuspid pressure gradient (*TTPG*) indicative of pulmonary hypertension. (By courtesy of Prof. Patrizio Lancellotti from Liege)

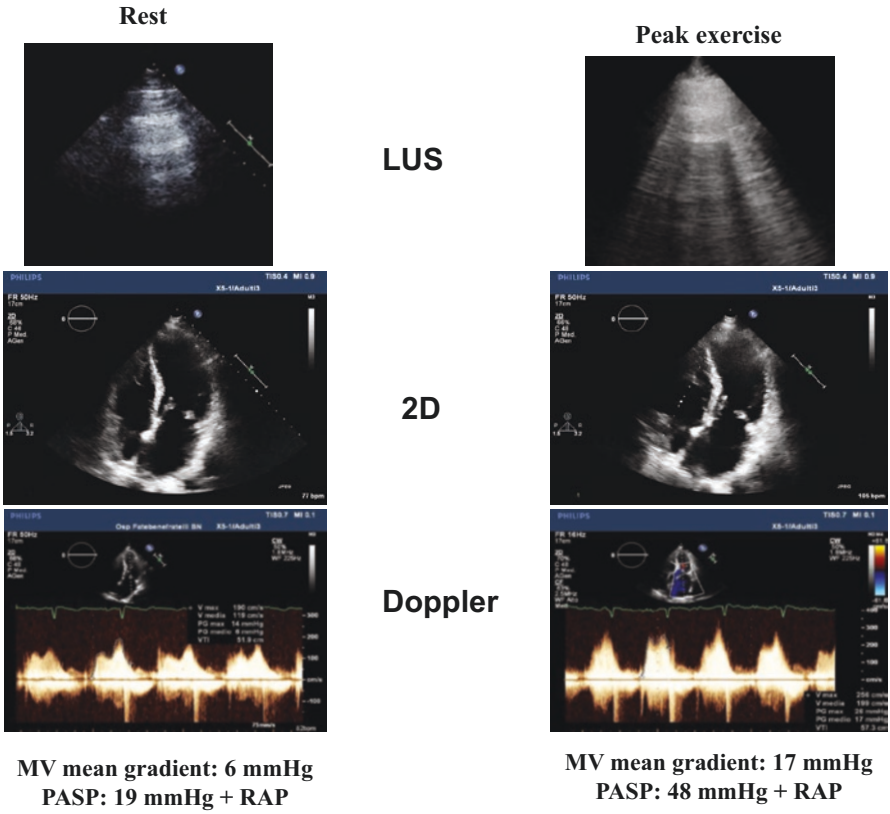


Fig. 34.8 A 49-year-old woman with New York Heart Association class 3, worsened in recent months. At rest (left panel), normal EF and normal PASP, with moderate MS (mean gradient = 6 mmHg). Lung ultrasound (LUS) shows normal A-lines (left upper panel) During exercise stress (right panel), the patient shows severe MS (mean gradient = 17 mmHg), abnormal PASP rise (48 mmHg + right atrial pressure), and four B-lines (right upper panel) in a single intercostal space (third intercostal space, the region between left mid-axillary and anterior axillary lines). (By courtesy of Quirino Ciampi, MD, Benevento, Italy)

stimulation with a decrease of pulmonary vascular resistances and fall of the pulmonary artery and wedge pressures masking the hemodynamic effects of the increasing gradient [28].

Above previously mentioned values, valvuloplasty or valve replacement is recommended, even for patients with apparently moderate MS at rest [6].

The recommended protocol for asymptomatic MS with an area of ≤ 1.5 cm^2 or symptomatic MS with an area >1.5 cm^2 is shown in Table 34.4.

The presence of symptoms is the driver of the management of MS. The indication for intervention is the presence of symptoms (class 1 indication). The use of SE

Table 34.4 Acquisition protocol for severe or asymptomatic nonsevere MS without symptoms

	Rest	Low-intermediate	Peak	Recovery
1. MPG	v	v	v	
2. MR	v	v	v	
3. EF GLS SV	v	v	v	
4. PASP	v	v	v	
5. TAPSE	v	v	v	
6. B-lines	v			v

GLS global longitudinal strain, *MPG* mean pressure gradient, *PASP* pulmonary artery systolic pressure, *SV* stroke volume, *TAPSE* tricuspid annular plane systolic excursion

application in MS is rated as class 1 with a level of evidence C for patients with discordant symptoms and stenosis severity [1].

34.5 Mitral Regurgitation

34.5.1 Primary (Organic) Mitral Regurgitation

The severity of primary MR can be reliably assessed by resting color-flow Doppler echocardiography with the use of semiquantitative or quantitative methods [1, 2]. Such information is useful to predict the development of LV dysfunction and symptoms. There is presently an important ongoing controversy on whether asymptomatic patients with severe MR should undergo early elective mitral valve repair versus watchful waiting. In selected patients in whom there is a discrepancy between symptoms and severity of MR, and especially in asymptomatic patients with severe MR, exercise SE may help to identify patients with subclinical latent LV dysfunction and poor clinical outcome. Worsening of MR severity (by ≥1 grade in patients with resting moderate MR), a marked increase in PASP (to ≥60 mmHg), the absence of contractile reserve (<5% increase in EF or <2% increase in global longitudinal strain), impaired exercise capacity, a limited right ventricular contractile recruitment (quantified by tricuspid annular plane systolic excursion <18 mm), and the occurrence of symptoms during exercise SE can be useful findings to identify the subset of high-risk patients [29]. Exercise capacity itself predicts worse outcomes in asymptomatic patients with significant myxomatous MR, and high-resting PASP and lower-resting LV EF predict worse outcomes [29]. Recommendations for early intervention in asymptomatic patients should only be made in those who are candidates for mitral valve repair and in experienced centers in which there is a high likelihood (>90%) of successful mitral repair without residual MR [2]. In the ESC 2021 guidelines, mitral valve repair is indicated in patients with exercise symptoms. Previous guidelines stated that repair may be considered in the case of exercise PASP ≥60 mmHg, but ESC 2021 explicitly recommends that right heart catheterization is systematically used to confirm pulmonary hypertension diagnosed by echocardiography when this is the only criterion to refer the patient to surgery [2].

Table 34.5 Asymptomatic severe or symptomatic nonsevere primary MR

	Rest	Intermediate	Peak	Recovery
1. EF, GLS	v	v	v	
2. MR	v	v	v	
3. PASP	v	v	v	
4. TAPSE	v	v	v	
5. MR CW	v	v	v	
6. E/e'	v			v
7. B-lines	v			v
8. LAV	v			v

E/e' the ratio of early transmitral diastolic flow velocity to early tissue Doppler imaging velocity of the mitral annulus, *GLS* global longitudinal strain, *MR CW* continuous wave Doppler of the MR, *LAV* left atrial volume, *TAPSE* tricuspid annular plane systolic excursion

Exercise SE has also been used to unmask the development of severe MR in patients with rheumatic mitral valve disease and only mild or moderate MR at rest [1]. The application of SE in asymptomatic patients with severe MR is rated as a class 2a recommendation with a level of evidence C [2].

The recommended protocol for asymptomatic severe or symptomatic nonsevere MR is shown in Table 34.5.

The imaging sequence usually follows a standardized approach, starting from two-dimensional four-, two-, and three-chamber views for assessment of regional and global LV function. Color-flow Doppler is necessary for the quantification of severity by the proximal isovelocity surface area (PISA) method and vena contracta, and continuous wave Doppler of the MR for quantification of severity by the PISA method. Continuous wave Doppler of the tricuspid regurgitant jet assesses the transtricuspid pressure gradient and estimates the PASP at the first stages of the exercise. Additional parameters are *E*/*e*′, B-lines, and left atrial volume and strain. They can be easily acquired in the early recovery phase since B-lines are still well detectable in the 2 min after test termination. *E*/*e*′ can be measured only when *E* and *A* waves are unfused, at a heart rate <110/min, typically present at rest and in the recovery phase. At peak, if PISA is not feasible, MR vena contracta is obtained.

34.5.2 Secondary (Functional) Mitral Regurgitation

Secondary MR is primarily a disease of the LV myocardium or left atrium and develops with an almost structurally normal mitral valve. Exercise SE is valuable in identifying hemodynamically significant MR in patients with LV systolic dysfunction, especially when ischemic heart disease is the underlying etiology. The magnitude of secondary MR varies dynamically by changes in loading conditions, annular size, and the balance of tethering versus closing forces applied on the mitral valve leaflets. Hence, the severity of MR assessed by resting echocardiography does not necessarily reflect the severity under exercise conditions. In patients with secondary MR, quantitative assessment of exercise-induced changes in the degree of MR is

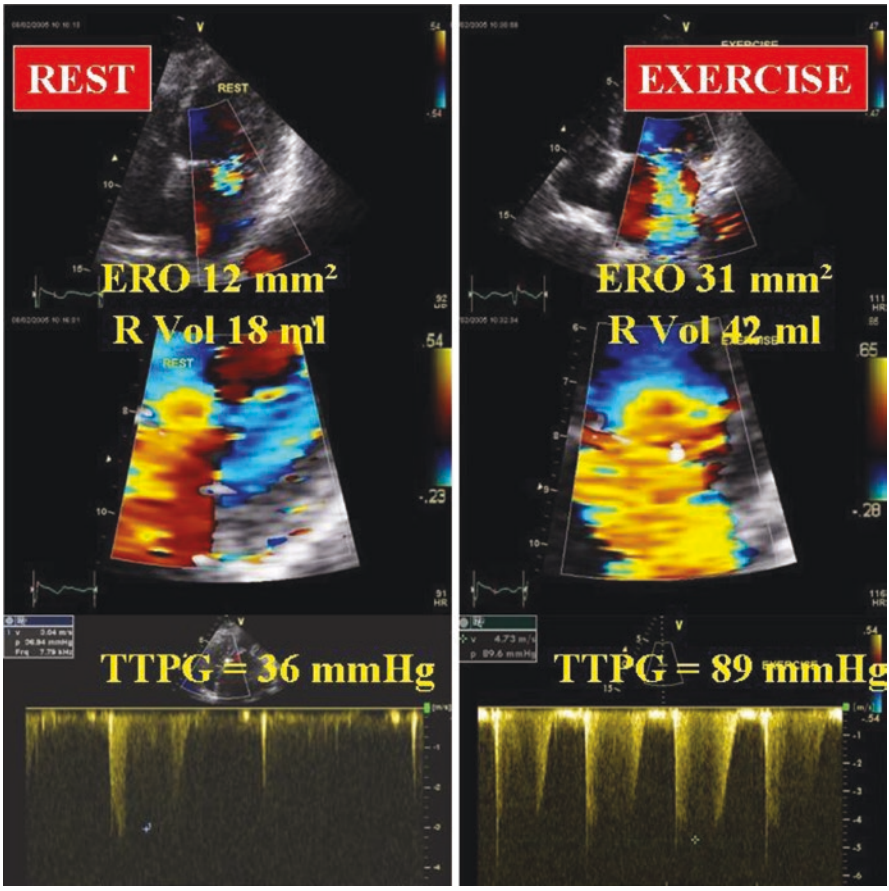


Fig. 34.9 Apical four-chamber view showing color-flow Doppler and the proximal flow-convergence region at rest and during exercise in a patient with a large exercise-induced increase in MR and estimated PASP. *ERO* effective regurgitant orifice, *RVol* regurgitant volume, *TTPG* systolic transtricuspid pressure gradient. (By courtesy of Patrizio Lancellotti, MD, from Liege, Belgium)

useful to unmask patients at high risk of poor outcomes. A ≥13 mm² increase in the effective regurgitant orifice area by Doppler or PISA method or an increase in PASP reaching at least 60 mmHg (Fig. 34.9) at peak exercise stress is predictive of increased morbidity and mortality. Of note, more than 30% of patients with secondary MR have a significant dynamic increase by >1 grade in MR during exercise. The effective regurgitant orifice at rest does not predict the effective regurgitant orifice at exercise. Hence, exercise SE provides important incremental information over resting echocardiography in patients with secondary MR [30].

Exercise SE in patients with secondary MR can provide useful information in the following situations: (1) patients in whom risk stratification is contemplated; (2) patients with exertional dyspnea out of proportion to the severity of resting LV

dysfunction or MR; (3) patients in whom acute pulmonary edema occurs without an obvious cause; (4) patients with moderate MR before planned surgical revascularization; and (5) persisting pulmonary hypertension after repair surgery [6]. Exercise SE is useful to establish the etiology of MR and assess myocardial viability [1]. There is currently no indication for pharmacologic SE to assess the severity or guide the management of secondary MR.

34.6 Asymptomatic Severe or Symptomatic Nonsevere Multivalve Disease

Combined stenosis and regurgitation or multiple valve disease may be concomitantly present in the same patient. However, there is little evidence to allow recommendations, the assessment may be particularly challenging because the presence of one valve disease may alter the hemodynamic of the other valve thus affecting calculations (i.e., MR may cause a low-flow state and lead to underestimating an AS). The main indication for SE, primarily exercise, is where there is a discrepancy between severity and symptoms. The exercise SE may be useful to unmask symptoms and to establish the mechanism responsible for their development but also the effect of the mixed valve disease on the ventricular function. Given the intrinsic complexity of the exam, an exercise semi-supine bicycle test with a prolonged duration of each exercise step allows systematic assessment of multiple valve lesions.

In the case of AS + AR, it is advised to follow protocol for AS, with the addition of qualitative and quantitative assessment of AR severity at baseline. In the case of MS + MR, it is advised to follow protocol for MS, with the addition of qualitative and quantitative (PISA) assessment of MR severity at rest and at peak exercise. In the case of AS + MR, it is advised to follow protocol for AS, with the addition of qualitative and quantitative (PISA) assessment of MR severity at rest and at peak exercise. Patients may have low-flow low-gradient AS although with normal EF. Of note in the presence of MR, dobutamine stress test should not be used to distinguish severe from pseudo-severe AS. An aortic calcium score may be more useful. In the case of AR + MR, it is suggested a qualitative and quantitative (PISA) assessment of MR severity at rest and peak exercise and a qualitative and quantitative assessment of AR severity at baseline. In the case of AS + MS, a low-flow state is often present and multimodality assessment using cardiac computed tomography aortic calcium score may be helpful. In AR + MS, measurement of the mitral area by pressure, half time, or continuity equation is not accurate.

34.7 Prosthetic Heart Valves

Echocardiography is the method of choice for evaluating prosthetic valve function. This evaluation follows the same principles used for the evaluation of native valves with some important caveats [30]. First, imaging of the valve occluder and assessment of transprosthetic flow is limited by reverberations and shadowing caused by

the valve components. Second, the fluid dynamics of mechanical prosthetic valves may differ substantially from that of a native valve. The flow is eccentric in monoleaflet valves and is composed of three separate jets in bileaflet valves, with the flow velocity potentially higher in the central orifice jet than in the two lateral orifice jets. Because most prosthetic valves are inherently stenotic, the effective orifice area (EOA) of a prosthetic valve is often too small for body size, a phenomenon known as prosthesis–patient mismatch. In the aortic position, prosthesis–patient mismatch is considered moderate when the indexed EOA is less than or equal to 0.85 cm^2/m^2 and severe when it is less than or equal to 0.65 cm^2/m^2 [30]. In the mitral position, the cut-off values are 1.2 and 0.9 cm^2/m^2, respectively. Prosthesis–patient mismatch has been linked to impaired exercise capacity, suboptimal symptomatic improvement, incomplete regression of LV hypertrophy and pulmonary hypertension, and increased cardiac events and mortality following valve replacement [31–35]. As opposed to normal functioning and well-matched prostheses or bileaflet mechanical valves with localized high gradient, the presence of valve stenosis or significant prosthesis–patient mismatch is generally associated with a marked increase in gradients and PASP, the occurrence of symptoms, and impaired exercise capacity on exercise SE [36, 37]. An absolute increase in mean gradient ≥20 mmHg in the aortic position suggests severe prosthesis dysfunction or prosthesis–patient mismatch (Fig. 34.10).

An absolute increase in mean ≥12 mmHg in the mitral position suggests severe prosthesis dysfunction or prosthesis–patient mismatch (Fig. 34.11).

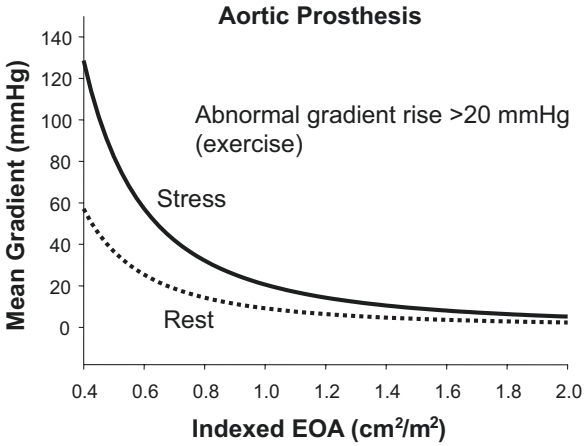


Fig. 34.10 Mean transprosthetic pressure gradient at rest (dotted lines) and during sustained physical exercise (continuous lines) as a function of the indexed EOA for aortic prostheses. Compared to patients who have large prosthetic EOAs, patients with small EOAs exhibit a major increase in transvalvular gradient with exercise (≥20 mmHg), thus suggesting the presence of severe prosthetic stenosis or prosthesis–patient mismatch in these latter patients

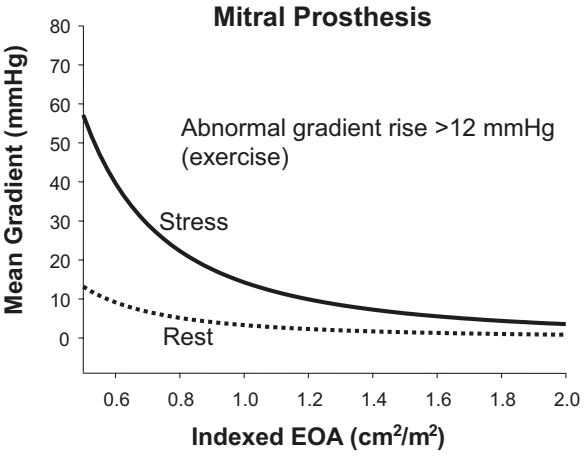


Fig. 34.11 Mean transprosthetic pressure gradient at rest (dotted lines) and during sustained physical exercise (continuous lines) as a function of the indexed EOA for mitral prostheses. Compared to patients who have large prosthetic EOAs and increase gradients only modestly during exercise and increased flow, patients with small EOAs exhibit a major rise in gradient (≥12 mmHg) with exercise, thus suggesting the presence of severe prosthetic stenosis or prosthesis–patient mismatch

High resting and stress gradients occur more often with biological rather than mechanical prostheses, stented rather than stentless bioprostheses, smaller (≤21 for aortic, and ≤25 for mitral) rather than larger prostheses, and mismatched rather than nonmismatched prostheses. Peak stress PASP ≥60 mmHg is consistent with the presence of a hemodynamically significant mitral prosthesis stenosis or regurgitation or mitral prosthesis–patient mismatch. As is the case in native aortic valves that have developed low-flow, low-gradient AS, dobutamine SE may also be useful in differentiating true prosthesis stenosis from pseudostenosis or prosthesis–patient mismatch in patients with prosthetic valves and low cardiac output. In the case of pseudostenosis with low output, the resting transprosthetic flow rate and thus the force applied on the leaflets are too low to completely open the prosthetic valve. During infusion of dobutamine, however, these patients manifest a substantial increase in the prosthesis EOA with the increasing flow rate, with no or minimal elevation in the prosthetic gradient. In contrast, true-severe prosthetic stenosis, or prosthesis–patient mismatch is associated with no significant increase in EOA and a marked increase in gradient with dobutamine, often with additional diagnostic changes (such as LV dysfunction or marked elevation in PASP) and symptoms.

Exercise or dobutamine SE cannot distinguish between acquired prosthesis stenosis and prosthesis–patient mismatch, as in both cases the EOA remains small and the gradient increases markedly with stress. In this situation, one should compare the EOA values obtained during SE with the normal reference values of EOA for the model and size of the specific prosthesis that has been implanted in the patient [1].

If the measured EOA is substantially lower than the normal reference EOA, one should suspect prosthesis dysfunction. If, on the other hand, the measured EOA is within the normal reference range, and the indexed EOA is low, one should consider the presence of prosthesis–patient mismatch.

34.8 Coronary Flow Reserve in VHD

Although SE is a widely accepted, accurate, and safe noninvasive technique to diagnose the presence and severity of coronary artery disease in patients without VHD, the use of stress testing to detect coronary artery disease is discouraged for the low diagnostic value and potential risks, especially in patients with severe AS [1]. In patients with severe AS and normal coronary arteries, the reduced coronary flow reserve is more closely related to the severity of the aortic valve stenosis than to the degree of LV hypertrophy [38]. The impairment of coronary flow reserve classically observed in AS may be caused by several factors including extravascular compression of the coronary microvasculature due to elevated LV diastolic pressures, a shortening of diastolic perfusion time, and an increase in myocardial metabolic demand resulting from the LV pressure overload. Of note, the reduction in coronary flow reserve is linked to cardiac natriuretic peptide release and predicts an impaired exercise capacity. In these

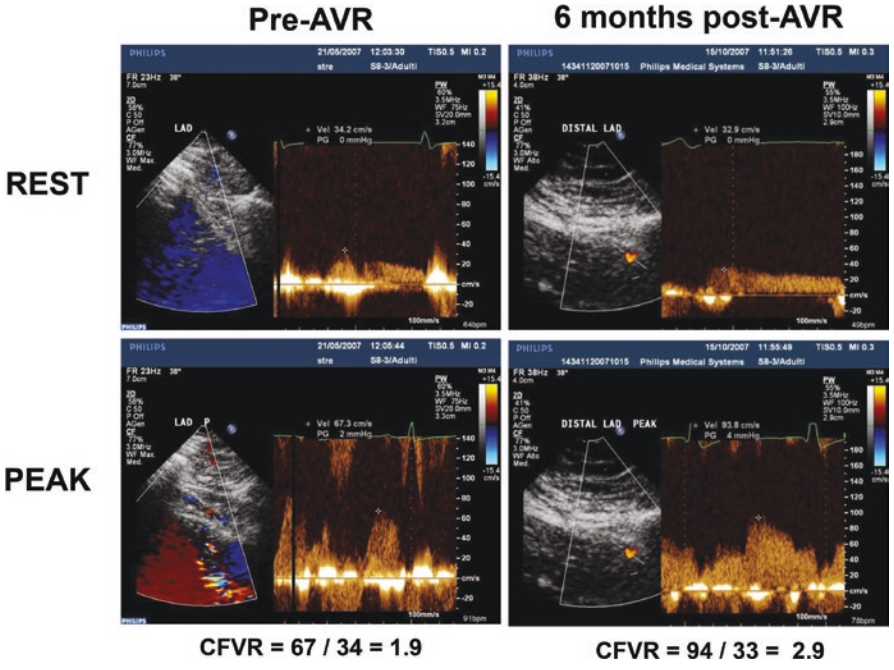


Fig. 34.12 Coronary flow velocity reserve (CFVR) assessed at rest and during adenosine administration by transthoracic SE in a patient with severe AS and angiographically normal coronary arteries before (left panel) and 6 months after (right panel) aortic valve replacement (AVR). In the postoperative assessment, LV hypertrophy is not yet regressed but CFVR substantially improved. (Courtesy of Dr. Fausto Rigo, Venice, Italy)

patients, the degree of coronary microvascular disease mirrored in a reduction of coronary flow reserve is related to exercise capacity, is reversible after valve replacement before regression of the LV hypertrophy and predicts outcomes better than the severity of valve stenosis [39–44]. SE can add this important variable to the assessment of VHD with an evaluation of coronary flow velocity reserve in the mid-distal left anterior descending coronary artery during vasodilator stress (Fig. 34.12).

It is increasingly clear that coronary microcirculation is impaired in VHD, and evidence is already available in AS, where it impacts myocardial remodeling, aortic flow patterns, and clinical progression [45].

34.9 Pitfalls

Despite the enormous potential information to be gained, SE lacks strong supportive evidence in VHD. Most recommendations are based on classes of evidence C ("consensus opinion of experts and/or small, retrospective studies"). Existing recommendations emphasize idealized cutoffs such as the stress-induced increase in EF >4% in AR, PASP values >60 mmHg with stress in MS or MR or AVA $\leq$1.0 cm^2 in AS [8]. The evidence supporting these simple cutoffs is not always robust, and they are vulnerable to artifacts, with limited reproducibility, known sources of error, and inadequate validation [1, 2].

Stress testing with exercise is useful to identify truly asymptomatic patients since the underestimation of symptoms is common in VHD with patients limiting their level of activity over the years to adapt to the slow progression of valve disease. However, exercise testing in symptomatic patients with severe AS (Stage D1, aortic velocity $\geq$4.0 m/s or mean pressure gradient $\geq$40 mmHg) is not indicated and could be harmful (contraindicated, class 3) for the risk of severe hemodynamic compromise. Exercise should be avoided for the high risk of complications, with a 1 in 500 rate of major complications including severe hypotension, cardiac asystole, ventricular tachycardia, and death [2]. According to the ACC/AHA 2020 guidelines, "*recording valve hemodynamics during exercise in AS is of limited value and does not show additive value for predicting clinical outcome when baseline measures of hemodynamic severity and functional status are considered*" [1].

Some SE applications in VHD are not so easy to execute and may not be safe if performed outside of a dedicated and experienced SE laboratory [46], and yet the recommended caseload for a level III echo competency includes 200 SE studies per year of which 25 need to be noncoronary indications [47], meaning that a laboratory can perform only 1 or 2 SE studies per year in low-flow low-gradient AS and remains competent.

SE is versatile, but sonographers cannot be experienced in all aspects of the technique. In the latest guidelines from the ACC/AHA, in all valve centers, both comprehensive (level 1) and primary (level 2), the imaging personnel requires a formalized position of "valve echocardiographer" to assess valve disease [1, 48]. In addition, the Doppler examination (at rest and even more during stress) requires meticulous attention to detail. The severity of the stenosis can be underestimated

when imaging is difficult or when the Doppler beam is not aligned in parallel with the direction of the high-velocity jet. The severity of the valve regurgitation may be overestimated or underestimated if the image or Doppler data quality is suboptimal. The general protocol should always consider and integrate nonimaging information, such as heart rate and blood pressure response and symptoms. A reduced frequency response, cardiac arrhythmias, a fall or inadequate rise in blood pressure, and the presence of dyspnea are important and should be integrated into the test response [48]. All images and loops are stored and analyzed offline after the test, and often no measurements are done during image acquisition.

The Doppler assessment of PASP—which is central in the evaluation of several conditions—has an imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in 15% of patients with inadequate tricuspid regurgitation jet, and is unreliable in massive tricuspid regurgitation. During stress, we still lack accepted cut-off values between normal and abnormal responses. PASP values are linearly dependent on cardiac output, and the multipoint pulmonary artery pressure-flow relationship is recommended. Postexercise measurements are unreliable because of the rapid return to the baseline of pulmonary hemodynamics [8]. Therefore, PASP assessment during stress was central for indication to treatment in previous guidelines but was taken out in the most recent release, and an invasive hemodynamic assessment is advised if this exercise hemodynamics information is needed [1, 2].

Mitral valve tip pulsed-wave Doppler and annular tissue Doppler in recovery can be obtained once E and A are unfused.

Prospective, large-scale outcome studies are needed to support more evidence-based, SE-driven treatment strategies. These studies should incorporate a more

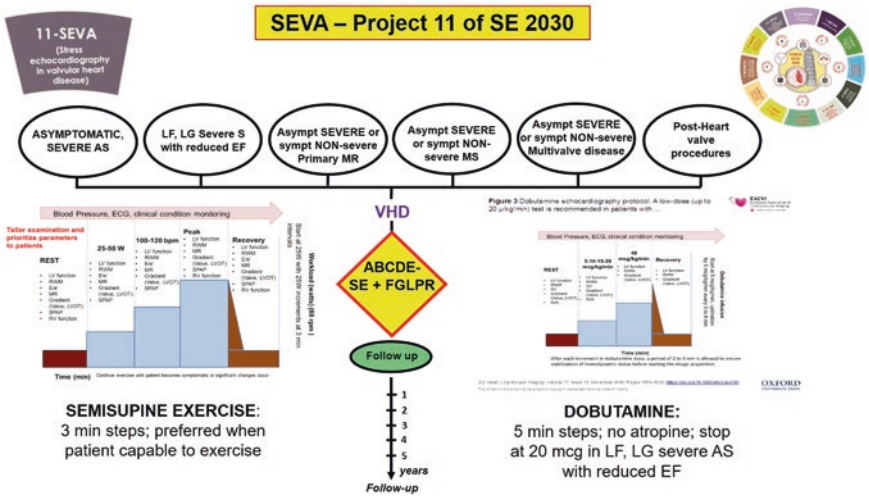


Fig. 34.13 The general protocol adopted for the study of SE in valvular disease (SEVA) subproject of the SE 2030 study

comprehensive assessment of the vulnerabilities of the patient with VHD, which extend well above and beyond the valve hemodynamics and are best assessed with a comprehensive protocol (Fig. 34.13).

The study of SE in VHD (SEVA) is a subproject of the large-scale, multicenter, international, prospective SE 2030 study which networks the experience of 30+ centers from 20+ countries collecting 10,000 patients spread over 12 different protocols with 5-year follow-up. The subproject on VHD will collect 500+ patients within the year 2025, and follow-up will continue until 2030 [49].

34.10 Clinical Guidelines and Recommendations

During the last decade, the evidence-base supporting the extensive use of SE in VHD has not increased as expected and as happened in other fields, such as coronary artery disease or heart failure. Therefore, SE paradoxically but inevitably lost ground in guidelines. Changes with a striking downgrading of previous recommendations were present in the ESC 2017 guidelines, which took out the evaluation of mean pressure gradient >20 mmHg at exercise in asymptomatic AS included with the class of recommendation 2b in 2012 ESC documents. A value of PASP>60 mmHg at exercise in asymptomatic primary MR was identified as the threshold for referral to surgery in 2012 ESC [7] and 2006 ACC/AHA guidelines [3], but this indication was removed from 2017 [7] and 2021 ESC [2] and 2020 ACC/AHA guidelines [1].

At present, SE is recommended in VHD for three main categories of applications characterized by a mismatch between resting transthoracic echocardiography findings and symptoms during exercise or activities of daily living: (1) Severe valve disease without symptoms; (2) Nonsevere single- or multivalve disease with symptoms; and (3) Symptomatic valve disease of indeterminate severity in the context of low flow. In all of these conditions, SE may provide unique information to match symptoms with the degree of cardiac involvement, for risk stratification and to guide decision-making, determining the optimal timing for surgery or percutaneous interventions [1, 8].

Low-dose dobutamine is the first choice in low-flow, low-gradient AS with reduced EF to separate true from pseudo-severe AS. For all other applications in VHD, exercise is the test of choice since it is the only physiological stress. Among stress exercise modalities, a semi-supine bike is recommended for obtaining Doppler data during exercise [8].

To ensure good quality data, it is recommended to prioritize data collection at peak stress. It is unlikely to achieve good data if there are too many measurements to be obtained at peak. Focus is kept on the primary aim of the study which is for hemodynamic assessment of valve disease. Hence, steps identifying the first-tier measurement for the specific patient are prioritized, followed by the remainder. At peak exercise, patients are typically already at or near their limit. Thus, peak acquisition is focused on no more than 6–7 items; second-tier measurement can be obtained at early recovery. However, when regurgitation or stenosis is severe at rest, there is no need to measure it at peak stress and acquisition should focus on LV

function and pulmonary pressures [4]. Ideally, ultrasound-enhancing agents should not be used for endocardial delineation as this may complicate Doppler imaging assessment (especially color, tissue Doppler, and pulsed-wave Doppler).

Stress testing for VHD accounts for 5% of the total caseload of SE laboratories [9]. By far, the two most frequent indications are for the assessment of asymptomatic severe or symptomatic nonsevere MR, and symptomatic low-flow, low-gradient AS with reduced EF [9].

The criteria of positivity present in the American Society of Echocardiography-European Association of Echocardiography and Cardiovascular Imaging recommendations 2017 are listed in Table 34.6.

The main indications of SE in VHD are summarized in Table 34.7.

Some other applications (AR, valve prostheses, mixed valve disease) are outside the guidelines for lack of supportive evidence, as emphasized by a recent document of the National Institute for Health Care and Excellence [50]. Despite the clinical relevance and the potential of SE in VHD, we have few studies, with small sample sizes (all but one <200 patients), from a limited number of highly productive groups, and with a methodology underusing the potential of the technique in the comprehensive state-of-the-art approach (Table 34.8).

For asymptomatic MR, research is recommended in prognostic studies to evaluate the impact of LV contractile reserve and PASP, while the value of peak exercise PASP>60 mmHg is considered sufficient for recommending intervention in a patient with symptomatic severe MR or moderate MR increasing to severe during exercise.

Table 34.6 Criteria for a positive SE application in the assessment of VHD

Valve assessment	Criteria for positive test results
Assessment of mild or moderate mitral regurgitation at rest in patients with symptoms	Increase in severity of mild or moderate MR to severe
Assessment of asymptomatic severe mitral regurgitation	Increase in PASP >60 mmHg. Lack of increase in LVEF ≥5% or global longitudinal strain ≥2%
Assessment of mild or moderate mitral stenosis at rest in patients with symptoms	Increase in the mean transmitral gradient ≥15 mmHg or estimated PASP ≥60 mmHg
Assessment low-flow, low-gradient AS, EF < 50%	MG >40 mmHg, AVA ≤1 cm^2, Δ-SV >20%
Assessment of asymptomatic severe aortic stenosis (AVA <1 cm^2)	Increase in mean transaortic gradient ≥20 mmHg
Assessment of asymptomatic severe aortic regurgitation	Lack of increase in LVEF ≥5% or exercise-induced reduction in LVEF
Equivocal aortic prosthetic valve PPM/ stenosis	Increase transvalvular gradient ≥20 mmHg
Equivocal mitral prosthetic valve PPM/ stenosis	Increase transvalvular gradient ≥12 mmHg

EF ejection fraction, *MG* mean aortic gradient, *PASP* pulmonary artery systolic pressure. Adapted from Lancellotti, Pellikka, et al. [8]

Table 34.7 The main indication to exercise test or SE in current clinical practice guidelines

Condition	COR	Accompanying statement
Symptomatic, severe (aortic max velocity >4 m/s, mean aortic gradient ≥40 mmHg, AVA ≤1cm^2) AS	3	Exercise testing should NOT be performed because of the risk of severe hemodynamic compromise [1]
Asymptomatic, severe AS	2a	Exercise is reasonable to confirm the absence of symptoms, but SE is not recommended because technically challenging and resting parameters adequate in most patients [1]
In patients with **suspected** low-flow, low-gradient severe AS with reduced EF (stage D2), low-dose DSE (≤20 μg/kg/min) is reasonable to further define AS severity and assess contractile reserve	2a [1] or 1 [2]	Dobutamine SE may be useful to distinguish severe AS with LV dysfunction due to afterload mismatch from primary myocardial dysfunction with only moderate AS [1]
For chronic primary MR (stages B and C) with symptoms, exercise SE may be reasonable	2a	MR may worsen during exercise, or filling pressures may become markedly abnormal, helping to demonstrate MR as the cause of symptoms [1]
Chronic secondary MR (stages B to D), exercise SE is useful to establish the etiology of MR and to assess myocardial viability	1	Although the presence of myocardial viability had no effect on survival in the STICH trial, there is a subset of patients with viable myocardium in whom the ischemic MR will respond to revascularization [1]
In rheumatic MS and a discrepancy between resting echocardiographic findings and clinical symptoms, exercise testing with Doppler is recommended to evaluate symptomatic response, exercise capacity, and the response of the mean mitral gradient and pulmonary artery pressure	1	Changes in valve gradients should be measured, as well as the estimated PASP. If the patient cannot exercise, increasing the heart rate with maneuvers such as leg lifts or sit-ups may be useful [1]

COR class of recommendations

Table 34.8 Evidence-base for SE in VHD [50]

Valve disease	Number of studies	Evidence level	Research need
Asymptomatic severe AS	9	Insufficient	Not prioritized
Symptomatic LF, LG AS	3	Sufficient	Not prioritized
Asymptomatic severe AR	0	Insufficient	Recommended
Asymptomatic severe MR	5	Sufficient	Recommended
Symptomatic, nonsevere MR	1	Insufficient	Not prioritized
Asymptomatic severe MS	0	Insufficient	Not prioritized
Symptomatic, nonsevere MS	0	Insufficient	Not prioritized

However, this indication is not shared by the ESC guidelines 2021, although it is stated that "*exercise echocardiography permits evaluation of changes in mitral regurgitant volume and pulmonary pressures during peak exercise and is particularly helpful in patients with discordant symptoms and regurgitation grade at rest*" [2].

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Stress Echocardiography in Cancer Survivors After Chemo- and Radiotherapy

35

Iana Simova, Martina Samardjieva, and Eugenio Picano

Keywords

Cancer · Chest radiotherapy · Coronary vasospasm · Left ventricular function

35.1 Introduction

Cardiac toxicity is one of the most concerning side effects of anticancer therapy with either radiotherapy or chemotherapy [1]. The gain in life expectancy obtained with anticancer therapy can be compromised by increased morbidity and mortality associated with its cardiac complications. There are four main reasons for applying stress echo (SE) in cancer survivors: (1) Safety. All patients but especially these patients who already suffered cancer should avoid any test with a known carcinogen such as ionizing radiation. Surveillance methods developed and largely practiced in the past based on blood pool radionuclide ventriculography or perfusion scintigraphy can exert detrimental effects on these vulnerable patients. (2) Need for serial testing. These patients are serially evaluated sometimes after a few days or weeks of therapy to assess acute changes and this can be done bedside at low cost and entirely by cardiologists only with ultrasound. (3) Comprehensive information. The effects of cancer therapy are multiple, variable, and largely unpredictable in the individual patient, and therefore testing cannot be restricted to one variable (coronary stenosis or left ventricular function) but might include all potential targets of cancer therapy, and these can be best done with the ABCDE+ protocol of comprehensive SE. (4)

I. Simova (✉) · M. Samardjieva
Cardiology Clinic, Heart and Brain Center of Excellence, Pleven, Bulgaria

Medical University, Pleven, Bulgaria

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Early detection of subtle damage during stress. If a resting assessment is integrated with a dynamic evaluation during stress, more subtle damage absent at rest can be more easily detected at an earlier, reversible, stage.

35.2 Radiation Therapy and the Heart

Cardiac patients are increasingly dying of cancer also due to the prognosis-changing diagnostic and therapeutic interventions based on ionizing radiation. The cumulative exposure to ionizing radiation is especially high in organs highly sensitive to radiation receiving the highest dose from cardiac procedures targeted on the chest [1], such as coronary angioplasty or chest computed tomography [2–7]. This is true in adults and even more in children with congenital heart disease, who suffer as adults of a three-fold increased risk of cancer when they received six or more ionizing test procedures after diagnosis of cardiac disease [8].

The reverse is true for cancer patients. Their prognosis was dramatically improved by radiation therapy, but this effective anticancer therapy also explains why cancer patients are increasingly dying of cardiovascular death. From the clinical viewpoint, five simple rules regulate the likelihood of heart damage after radiotherapy:

(1) The higher the cumulative dose, the higher the probability of radiation damage. For instance, the risk of major cardiac events in women after radiotherapy increases by 10% after receiving the dose of 2 Gray (Gy), 40% after 5 Gy, and 100% after 16 Gy [9]. Every dose should be carefully evaluated and justified, and not necessarily more dose is more beneficial. (2) The preexistence of risk factors for atherosclerosis multiplies the risk associated with any given dose. After 2 Gy, the risk of major cardiac events is 5% in a normotensive nondiabetic normocholesterolemic lean woman, and three-fold higher in a hypertensive diabetic and obese woman. (3) The target complication is more likely to develop in the organ—or organ region—receiving the highest dose. If the left breast is irradiated, the chance of developing a cardiac disease is three-times higher than if the right breast is irradiated. Even with left-sided irradiation, the right breast also carries some excess risk for the bystander effect, remote from the target tissue, due to systemic increase in inflammatory cytokines and oxyradical stress. (4) All tissues and cells of the heart are vulnerable and all may develop complications. The old myth is based on the law of Bergoniè and Tribondeau of the brain and heart radioresistance due to low mitotic index, and high tissue differentiation in these tissues is not valid. Both the brain and heart are highly radiosensitive organs, although the major effect on the heart is not cancer development but a variety of different effects involving possibly every single part and cell of the heart. In survivors of pediatric cancer treated with chest radiotherapy for leukemia or lymphoma, after 30 years the risk of developing myocardial infarction is increased five-fold, cardiomyopathy six-fold, valvular heart disease five-fold, and constrictive pericarditis six-fold [10]. With the evolution of less aggressive radiotherapy protocols, the risk of coronary disease declined significantly [11]. Surveillance in these patients should include a functional test with a comprehensive assessment of the heart. (5) Cardiotoxicity can come at any time in the natural history, and complications continue to develop after 10, 20, or 30 years

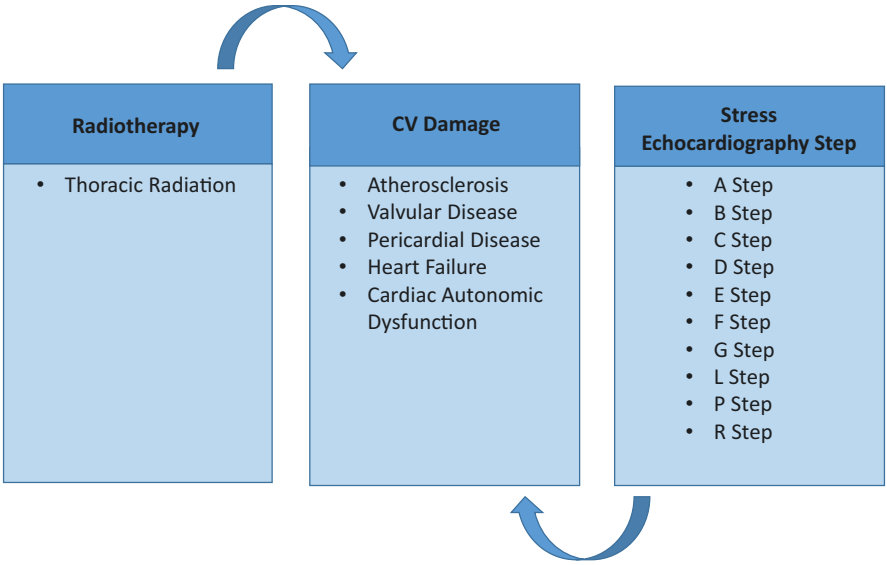

Fig. 35.1 Mediastinal radiation therapy and the pathways of cardiac damage. Each pathway can be detected via the comprehensive SE protocol at rest and during stress

Table 35.1 The risk of radiotherapy-induced heart disease

Chances of heart disease	Higher risk	Lower risk
Patient		
Age	<50 years	≥50 years
Risk factors	≥2	0 or 1
Chemotherapy	Yes	No
Preexisting disease	Yes	No
Radiotherapy		
Location chest	Anterior, left	Posterior, right
Shielding	No	Yes
Cumulative dose	≥30 Gy	<30 Gy
Daily dose	≥2 Gy/day	<2 Gy/day

from irradiation, as it may happen with radiation-induced cancer in heart patients, who may develop cancer after radiation exposure up to 40 years after the exposure. The radiation-associated cardiac disease manifests years or even decades after exposure to the chest with significantly higher morbidity and mortality (Fig. 35.1).

The main factors increasing the chances of radiation-induced heart disease are patient-related and radiotherapy-related (Table 35.1).

35.3 Chemotherapy and the Heart

The growing epidemic of cardiovascular disease in cancer patients has led to the development of multidisciplinary cardio-oncology units to reduce morbidity and mortality from cardiovascular disease in these patients and to improve cardiac

outcomes by reducing premature interruption of treatment due to cardiovascular events. In general, early detection of damage may lead to drug discontinuation or switching to alternative less toxic treatment and/or starting a cardiovascular treatment to mitigate cardiovascular damage once identified. Baseline risk stratification is appropriate for oncology patients before receiving the following cancer therapies: anthracycline chemotherapy, HER2-targeted therapies such as trastuzumab, vascular endothelial growth factor inhibitors, second and third-generation multitargeted kinase inhibitors for chronic myeloid leukemia targeting breakpoint cluster region-Abelson oncogene locus, multiple myeloma therapies (proteasome inhibitors and immunomodulatory drugs), rapidly accelerated fibrosarcoma, and mitogen-activated extracellular signal-regulated kinase inhibitors or androgen deprivation therapies [12]. The main risk factors determining cardiovascular risk before initiation of cancer therapies are the medical history of cardiovascular risk factors, lifestyle cardiovascular risk factors, cardiac biomarkers, previous cardiotoxic cancer treatment, and previous cardiovascular disease. The baseline cardiovascular risk assessment checklist is an echocardiogram, ECG, blood pressure, HbA1c, cardiac troponin, BNP or NT-proBNP, cholesterol profile, cardiac history, cancer treatment history, and cardiovascular risk factors. Applying a formal risk stratification strategy will allow clinicians to stratify cancer patients into low, medium, high, and very high risk of cardiovascular complications before starting treatment, to improve personalized approaches to minimize the risk of cardiovascular toxicity from cancer therapies [13].

35.3.1 Definition and Different Types of Cardiotoxicity

Cardiotoxicity is the damage to the cardiac structures leading to cardiac dysfunction and manifestations of heart failure. It occurs in cancer patients due to the relationship between anticancer therapy, cancer itself, and a history of concomitant cardiovascular disease. Cardiotoxicity includes reversible, irreversible, acute, chronic, and late-onset effects. The main classification known and used so far is the cardiotoxicity of Type 1 (irreversible)and Type 2 (reversible) [13]. The most common causes of type 1 cardiotoxicity are anthracyclines, while reversible cardiotoxicity has been observed with HER2 inhibitors such as Trastuzumab. There is much evidence of a link between cardiovascular disease and cancer, which has necessitated the introduction of terminology such as cardio-oncological syndromes (COS). A five-point COS classification system is used based on direct or indirect mechanisms in cardiovascular and oncological diseases that lead to the development of acute or chronic conditions (Table 35.2). In COS Type I (direct)—progressive development of cancer leads to cardiovascular disease. In COS Type II (indirect) —cancer-associated treatment causes cardiovascular disease. COS Type III (direct) —progressive scarring and remodeling of heart and kidney causes a pro-oncogenic environment, COS Type IV (indirect)—cardiovascular

Table 35.2 COS classification

Type I	The progressive development of cancer leads to CV disease
Type II	Cancer-associated treatment causing CV disease
Type III	Progressive scarring and remodeling of the heart and kidney cause a pro-oncogenic environment
Type IV	CV disease-associated treatment and diagnostics causing a pro-oncology environment
Type V	Systemic and genetic conditions cause both cancer and CV disease

COS cardio-oncological syndromes, *CV* cardiovascular
Modified from de Boer et al. [14]

disease-associated treatment and diagnostics causes a pro-oncology environment, and COS type V (secondary) —systemic and genetic condition causing both cancer and cardiovascular disease [14].

Early detection and prediction of cardiotoxicity in chemotherapy-treated patients is an important issue. Echocardiography and especially SE is one of the main techniques for the detection of subclinical cardiotoxicity. All steps in the SE ABCDE protocol have their place in a cancer patient, but here we add some more important components to evaluate. In these patients, the F, G, P, and R steps are important to capture the complexity of multifaceted damage (Fig. 35.2) [15]. Epicardial artery stenosis may be identified at a presymptomatic or asymptomatic stage as possible abnormalities of step A of SE because of endothelial dysfunction and smooth muscle cell proliferation leading to epicardial artery damage and accelerated atherosclerosis during radio and chemotherapy. Step B can detect lung congestion because of low-grade inflammatory changes and diastolic dysfunction. Myocardial fibrosis may lead to systolic and/or diastolic dysfunction altering step C, which is impaired also in the case of pericardial constriction. Coronary flow velocity reserve (or real-time myocardial contrast echocardiography) in step D can be altered because of microvascular injury and reduced myocardial capillary density. Cardiac autonomic balance (with heart rate reserve) step E can be altered because of neuronal cell inflammation and degeneration of the intrapericardial autonomic nervous system. This can lead to inappropriate sinus tachycardia. Step F and step G detect valve regurgitation and stenosis, respectively. Valvular heart disease is a common complication after radiotherapy and chemotherapy because of valve leaflet fibrosis and accelerated calcification. With step L, left atrial fibrosis and dysfunction can be detected. Step P can assess pulmonary artery systolic pressure (from tricuspid regurgitant jet velocity) and pulmonary wedge pressure (from E/e'). Significant alterations in the structure and function of the right ventricle are detected with step R (Table 35.3).

Coronary vasospasm can be induced by bleomycin, fluoropyrimidines, taxanes, VEGF inhibitors, and vinca alkaloids. Amyloid light-chain amyloidosis is frequently associated with multiple myeloma therapies. Androgen deprivation therapy is prescribed in 40% of men with prostate cancer and is associated with arterial hypertension, diabetes mellitus, and cardiac dysfunction [13].

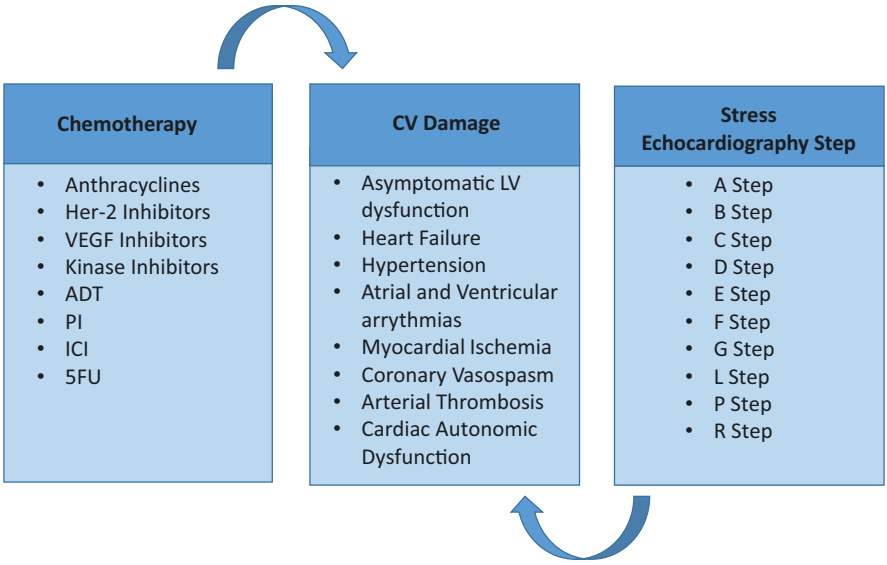

Fig. 35.2 Cancer chemotherapy and the pathways of cardiac damage. Each pathway can be detected via the ABCDE+ protocol at rest and during stress and can be preferentially hit by a specific drug. *VEGF* vascular endothelial growth factor, *ADT* androgen deprivation therapies, *PI* proteasome inhibitors, *ICI* immune checkpoint inhibitors, *5FU* 5 fluorouracil, *LV* left ventricle

Table 35.3 Targets of cancer chemotherapies

	HF	VHD	Arrhythmias	HPT	Arterial thrombosis	Ischemia-infarction	Venous thrombosis
Anthracycline	+++	++	+	+	–	–	–
HER-2 inhibitors	+++	++	+	+	–	++	–
VEGF inhibitors	+++	–	+	++	–	+	+
BCR-ABL inhibitors	++	–	+	+	+++	–	+
Multiple myeloma therapies	+++	–	+	+	–	–	+++
RAF and MEK inhibitors	+++	++	+	+	–	++	+

BCR-ABL breakpoint cluster region–Abelson oncogene locus, *HER-2* human epidermal growth factor receptor-2, *HPT* arterial hypertension, *HF* heart failure, cardiomyopathy, cancer-therapy-related cardiac dysfunction, *ICI* Immune checkpoint inhibitors, *KI* kinase inhibitors, *MEK* mitogen-activated extracellular signal-regulated kinase, *PI* proteasome inhibitors, *RAF* rapidly accelerated fibrosarcoma, *VEGF* vascular endothelial growth factor, *VHD* valvular heart disease. Modified from Alexander R. Lyon et al. [13]. ++, very high probability; ++, high; +, moderate probability of developing cardiovascular complications

35.4 Grading the Cardiac Damage

The grading is presently made based on ejection fraction (EF) and other ancillary parameters which may identify mild abnormality when EF is still in the normal range, with a particular value of the decrease over baseline (pretherapy) condition in EF, global longitudinal strain (GLS), and end-systolic volume. The cutoff for the normal EF is 50%. Cardiotoxicity is documented and cardioprotective therapy or change chemotherapy agents is suggested when there is a drop in EF by at least 10% from baseline or EF falls to a value below 50% [16]. GLS is an optimal parameter for detecting subclinical left ventricular dysfunction. In the best case, the measurements during chemotherapy should be compared with baseline values to avoid variations linked to vendors and software. If a baseline GLS is available, then a drop of <10% means that there is no evidence of subclinical left ventricular dysfunction. On the other hand, if there is a drop ≥15% from baseline GLS, a subclinical left ventricular dysfunction is present and a cardioprotective therapy with angiotensin-converting enzyme inhibitors and beta-blockers (carvedilol) is suggested. If baseline GLS is not available, the identification of subclinical left ventricular dysfunction is more challenging. During treatment, if the GLS is above the lower limit of age-specific and vendor-specific normal limit (absolute value above 16% or 19%, in absolute values), there is no evidence of subclinical left ventricular dysfunction, but if the GLS is below the lower limit of normality (for instance, <16% in absolute values), subclinical left ventricular dysfunction is present and a cardioprotective therapy could be started. Cardiotoxicity is more likely in presence of concomitant changes in left ventricular end-diastolic volume (>30 mL from baseline) and end-systolic volume (>30 mL from baseline), assessed with two-dimensional or, more accurately, three-dimensional echocardiography. There is still insufficient evidence on the interpretation of GLS during SE. A comprehensive SE might allow a more integrated and quantitative assessment of all parameters which can be affected asymmetrically by radiotherapy and chemotherapy. The grading is not adequate when the target is other than left ventricular function, for instance, coronary vasospasm, arrhythmias, valvular disease, or myocardial fibrosis. The damage to the right ventricle is assessed with tricuspid annular plane systolic excursion (<17 mm), fractional area change (<35%), right ventricular free wall strain (<20%), or right ventricular EF measured with three-dimensional echocardiography <45% [16].

35.5 Pitfalls of SE in Oncology Patients

There is a well-known variability of the method in estimating left ventricular function and the clinically significant variations should exceed the variability of the method. This implies that measurements should be done in controlled conditions (same machine for strain; same operator for EF) and with quantitative volumetric echo with biplane Simpson's rule to minimize variability. An EF by eyeballing with different operators with suboptimal endocardial visualization is the rule in a standard patient but cannot be acceptable in an oncology patient. The

EF should be expressed with simultaneous information on end-diastolic volume otherwise it can be misleading. This is true at rest and even more during stress, which can detect early subclinical damage as a lack of contractile reserve and lack of preload reserve.

35.6 Clinical Guidelines

Whenever possible, a baseline resting transthoracic echocardiography is recommended since echo gives the most information as a delta technique, when each patient acts as his/her control and all confounders are averaged out. As stated by the European Society of Medical Oncology recommendations 2020, "*nonionizing modalities may be most appropriate due to concern regarding cumulative radiation dose in cancer patients,*" who are already highly exposed to oncology diagnosis and follow-up programs [17]. For resting transthoracic echocardiography evaluation, the most appropriate modality for timely diagnosis of cardiotoxicity is volumetric echocardiography with Simpson's biplane method for measurement of EF, with contrast as needed. Modern methods such as 3D volume quantitation of the left ventricle and left atrium are more accurate and are recommended by the European Association of Cardiovascular imaging [17]. The assessment of GLS is crucial for the early detection of subclinical cardiotoxicity [17]. Diastolic function and left ventricular end-diastolic volume also should be assessed as a baseline, during and after anticancer therapy [17]. The study should be done during therapy when symptoms occur or before symptoms occur to detect subtle changes which may induce therapy withdrawal or down-titration of therapy when alternatives are possible. The timing of the examination is tailored to the baseline risk of the patient, and the known cardiotoxic potential of the treatment.

Patients on anticancer treatment with potential nonreversible (Type I) or reversible (type II) cardiotoxicity receiving anthracyclines and/or trastuzumab should perform serial monitoring of cardiac function. Echocardiography should be performed at baseline, third, sixth, and ninth months during treatment, and then at 12 and 18 months after the initiation of treatment [18]. The intensity of echocardiographic monitoring should be based on the individual risk of cardiotoxicity and requires an integrated evaluation by the cardio-oncology team [18]. At present, SE is recommended by the European Association of Cardiovascular Imaging and the Cardio-Oncology Council of the European Society of Cardiology in the cardiovascular imaging evaluation at baseline, and pretreatment, in patients with suspected angina [18].

For asymptomatic patients with a history of mediastinal chest radiation, the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19, 20], the National Comprehensive cancer network, and the guidelines of the European Society of Cardiology 2022 recommend that a SE should be considered (class of recommendation 2a) postchest radiotherapy every 5–10 years in asymptomatic patients who received >15 Gy mean heart dose [13].

The possible integration of SE in the surveillance strategy is now under evaluation in prospective studies (Fig. 35.3) [15].

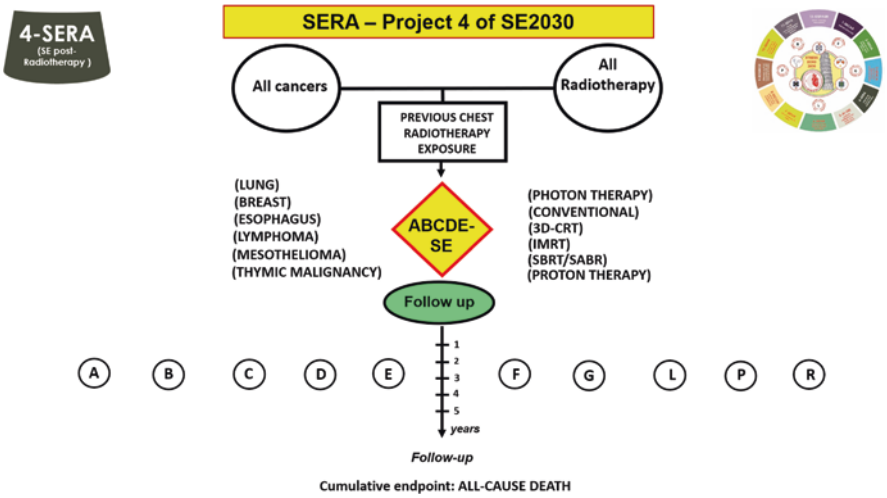

Fig. 35.3 The study flow-chart of the subproject SERA in SE 2030, adopting the comprehensive ABCDE+ protocol for surveillance of patients postradiotherapy

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Stress Echocardiography in Pulmonary Hypertension

36

Eduardo Bossone, Francesco Ferrara, and Eugenio Picano

Keywords

Acceleration time · Pulmonary hypertension · Pulmonary vascular resistance · Right ventricular function · Tricuspid regurgitant jet velocity

36.1 Definition and Classification

Pulmonary circulation can be the primary target of pulmonary vascular disease and the secondary target of a primary left heart or lung disease. Pulmonary hypertension (PH) can be precapillary or postcapillary. This distinction is only possible by invasive means. PH is defined by right heart catheterization criteria as a mean pulmonary arterial pressure (mPAP) > 20 mmHg [1]. A precapillary PH as can be found in idiopathic pulmonary arterial hypertension (PAH) is characterized by a normal pulmonary arterial wedge pressure (PAWP) < 15 mmHg and abnormal pulmonary vascular resistance (PVR) > 2 Wood units reflecting a primary abnormality of pulmonary arterioles upstream to the alveolar-capillary barrier. A postcapillary PH as can be found in left heart disease (heart failure, valvular disease) is characterized by an abnormal PAWP (> 15 mmHg) and normal PVR (≤2 Wood units) for a primary increase in pressure downstream to the alveolar-capillary barrier reverberating backward as a passive increase in pressure (Table 36.1).

The new cutoff value replaced the previous, more conservative criterion for an abnormal hemodynamic mPAP >25 mmHg, and re-introduced the definition of

E. Bossone (✉)
Department of Public Health, University of Naples Federico II, Naples, Italy

F. Ferrara
Cava de' Tirreni and Amalfi Coast Division of Cardiology, University Hospital, Salerno, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Table 36.1 Hemodynamic definitions of PH

	mPAP (mmHg)	PAWP (mmHg)	PVR (WU)	Condition
Non-PH	≤20	≤15	≤2	Healthy normals
Postcapillary	>20	>15	≤2	LHD
Mixed	>20	>15	>2	Advanced LHD
Precapillary	>20	≤15	>2	PAH, lung disease

LHD left heart disease, *PAWP* pulmonary artery wedge pressure, *mPAP* mean pulmonary artery pressure, *PH* pulmonary hypertension, *WU* Wood units

Table 36.2 Classification of PH

	Group 1	Group 2	Group 3	Group 4	Group 5
PAH	v				
LHD		v			
Lung disease			v		
CTEPH				v	
Unclear origin					v

CTEPH chronic thromboembolic PH, *LHD* left heart disease, *PAH* pulmonary arterial hypertension

exercise PH as mPAP/cardiac output (CO) slope between rest and exercise >3 mmHg/L/min [2]. The abnormal cutoff value of PAWP is >15 although the upper limit of normal is 12 mmHg [2].

Once a diagnosis of PH is made, it is mandatory to establish the underlying etiology, and the classification proposed by the World Health Organization identifies five pathophysiologically defined subgroups (Table 36.2) [3].

Each group includes several conditions. PAH in Group 1 is a rare condition and can be due to idiopathic, heritable, drug-induced, or conditions associated with connective tissue disease. Left heart disease in Group 2 is very common and can be due to heart failure with preserved or reduced ejection fraction or valvular heart disease. PH due to lung disease in Group 3 is common and can be associated with chronic obstructive or restrictive lung disease. PH in Group 1 is typically precapillary, and in Group 2 is typically postcapillary, but in the case of atypical PAH or advanced left heart disease, mixed forms are common. In Group 4 chronic thromboembolic PH, organized thrombi replace the intima of proximal or distal elastic pulmonary arteries. Group 5 includes forms of unclear or multifactorial origin, including splenectomy and sickle cell disease. Both Groups 4 and 5 are rare conditions. The distinction between precapillary and postcapillary forms of PH has important therapeutic correlates. Modern pulmonary vasodilator drugs are phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs. They have improved the prognosis of PAH but are deleterious in patients with postcapillary PH due to systolic and/or diastolic left ventricular dysfunction [4].

36.2 Resting Transthoracic Echocardiography

In all forms of PH, resting transthoracic echocardiography (TTE) provides unique information and is considered a first-line imaging test with an overview of systemic venous pressures, pulmonary hemodynamics, right and left heart structure, and function (Table 36.3) [5, 6].

Table 36.3 TTE findings in PH

TTE sign	Abnormal cutoff value	Clinical meaning
Pericardial effusion	Present	Elevated RA pressure
IVC diameter (subcostal view)	> 2.1 cm	Elevated RA pressure
IVC collapsibility	< 50% with sniff	Elevated RA pressure
RA area	> 18 cm^2	Elevated RA pressure
Dilated RV (base, A4C)	Basal RV/LV ratio > 1	Dilated RV
RV FAC%	< 35%	RV dysfunction
RV TAPSE	< 18 mm	RV dysfunction
RV systolic annular velocity	< 9.5 cm/s	RV dysfunction
RV strain	< 15%	RV dysfunction
TRV	> 2.8 m/s	Increased PASP
PA flow envelope	Mid-systolic "notch"	Increased PVR
PA ACT	< 105 ms	Increased PASP
B-lines	≥ 2	Pulmonary congestion
Septal wall ED (PSAX)	Flattening	RV volume overload
Septal wall ES	Flattening (D-shaped LV)	RV pressure overload

A4C apical four-chamber view, *ACT* acceleration time, *ED* end-diastole, *ES* end-systole, *IVC* inferior vena cava, *PA* pulmonary artery, *PASP* pulmonary artery systolic pressure, *PSAX* parasternal short-axis view, *PVR* pulmonary vascular resistance, *RA* right atrium, *RV* right ventricle, *TAPSE* tricuspid annular plane systolic excursion, *TRV* tricuspid regurgitant velocity

The resting physiological range of SPAP is dependent on age and body mass index and may be as high as 40 mmHg in older (>50 years) or obese subjects [7]. The presence of signs of PH with a normal left heart, normal E/e′ ratio, and normal left atrial volume are suggestive of precapillary PH [8, 9].

36.3 Exercise SE

Exercise stress echo (SE) can evaluate the right ventricular function, pulmonary artery systolic pressure (PASP) with tricuspid regurgitant velocity (TRV) or acceleration time (ACT), and PVR (pressure/flow) with an estimate of CO obtained with Doppler or two-dimensional method. The key variables can be measured with different methods, each one with its strengths and weaknesses [10–12]. The right ventricular function can be estimated with M-mode, two-dimensional, real-time three-dimensional methods, tissue Doppler, or strain-derived methods. The methodology is described in detail in Chap. 10 (Step R, right ventricular function), and the main differences between the principal methods are summarized in Table 36.4.

PASP can be estimated with either TRV [12, 13] or ACT [14–18]. The methodology is described in detail in Chap. 9 (Step P, pulmonary pressure), and the main differences between the two parameters are summarized in Table 36.5.

The reported feasibility to measure exercise TRV is variable, ranging from 60 to 100%. This may be explained by differences in exercise protocols (supine or semi-supine bicycle, tilted or fixed table, upright, and treadmill), training, use of an ultrasound-enhancing agent, and experience of center and operators. The RIGHT-Net study found a TRV feasibility rate of 85% at peak exercise. In healthy subjects, lower TRV feasibility (72%) has been found. Patient populations with different

Table 36.4 Different approaches for assessment of right ventricular function

Parameter	TAPSE	FAC	RV EF
Type of function	Longitudinal	Radial	Both
Imaging mode	M-mode	Two-dimensional	Three-dimensional
Unit of measurement	mm	%	%
Feasibility stress	> 95%	> 60%	> 50%
Heart rate degrades	No	Mild	Marked
Main advantage	Simple	Accurate	Very accurate

EF ejection fraction, *FAC* fractional area change, *RV* right ventricle, *TAPSE* tricuspid annular plane systolic excursion

Table 36.5 Different approaches for assessment of PASP

Parameter	TRV	ACT
Type of flow	Pathologic	Physiologic
Flow direction	Retrograde	Antegrade
Doppler mode	Continuous-wave	Pulsed-wave
Projection	Apical	Parasternal
Unit of measurement	m/s	ms
PASP increase	Velocity rises	Interval shortens
Feasibility during stress	60–90%	>90%
Heart rate dependence	No	Yes (> 110 b/m)

PASP pulmonary artery systolic pressure

Table 36.6 Different approaches for assessment of CO

Imaging mode	Two-dimensional	Doppler	None
SV calculation	EDV—ESV	VTI	Exercise-time
Unit of measurement	ml	cm/s	Minutes
Feasibility stress	> 90%	> 80%	100%
Main advantage	Simple	Accurate	Very simple

EDV end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *VTI* velocity time integral. To calculate SV with Doppler, VTI is multiplied for the cross-sectional area estimated from the diameter of the left ventricular outflow tract

clinical conditions may strongly influence feasibility which may be associated with different grades of tricuspid regurgitation (mild, moderate, severe) [12].

CO can be estimated with two-dimensional or Doppler methods, or even estimated through the proxy of exercise time [19]. The methodology is described in detail in Chap. 3 (Step C, contractile reserve) and the main differences are summarized in Table 36.6.

The best combination can be obtained in each laboratory based on local expertise and the technology available. The minimum set of parameters adopted in the multicenter SE 2030 study include tricuspid annular plane systolic excursion for right ventricular function, TRV and ACT when TRV is unfeasible for PASP, and exercise time for CO when Doppler or two-dimensional estimates are difficult to obtain or too lengthy [20].

Table 36.7 Progressive stages of disease identified by transthoracic and SE

Stage of disease	Absent	Initial	Overt	Advanced
RV function				
Rest	Normal	Normal	↓	↓↓
Stress	↑↑	↑	↔	↓
PASP				
Rest	Normal	Normal	↑	↑↑
Stress	↔↑	↑↑	↑↑	↔
TAPSE/PASP				
Rest	Normal	Normal	Abnormal	Abnormal
Stress	↔↑	↓	↓↓	↓↓↓

PASP pulmonary artery systolic pressure, *RV* right ventricle, *TAPSE* tricuspid annular plane systolic excursion

In the natural history of PH, changes occur during exercise at an earlier stage compared to resting changes, and therefore SE shows a clear potential to identify these changes at a less severe and more reversible stage [21]. In normal conditions, all parameters are normal at rest and during stress, with preserved contractile reserve of the right ventricle and a small increase in PASP for a large increase in right ventricular function leading to optimal right ventricular/PASP coupling. When the disease progresses, parameters become abnormal only during stress at an early stage but also at rest in an advanced stage (Table 36.7).

36.4 Clinical Applications of SE in PH

The clinical applications of SE in known or suspected PH vary according to the clinical condition and diagnostic question and may encompass the spectrum of disease, from the super-fit athletes with primarily diagnostic applications up to patients with established PH in whom exercise is applied for mainly prognostic applications.

In healthy subjects and especially in athletes, right ventricular fatigue detectable as a reduced systolic function after strenuous exercise or an impaired contractile reserve at peak stress is an early sign of right ventricular disease or simply of a maladaptive response to training limiting the performance [22, 23].

Heritable PAH is most commonly due to heterozygous mutation of the bone morphogenetic protein receptor II (BMPR2) gene on chromosome 2q33, detectable in 80% of cases with familial aggregation of the disease. In patients at risk for PAH as the genotype positive-phenotype negative carriers of the mutation, the development of PH with exercise increases seven times the risk of subsequent long-term (six years) development of clinically overt PH [24, 25].

Connective tissue disease, and in particular systemic sclerosis, can lead to secondary PAH and this is more likely in patients with exercise-induced PH [26, 27].

This application is especially appealing since TTE and lung ultrasound also provide prognostically critical information on left ventricular function, right ventricular contractile reserve, and interstitial lung fibrosis detectable as dry B-lines with lung ultrasound [28, 29].

High-altitude pulmonary edema is a life-threatening disease that occurs in 10% of subjects climbing at 4500 m above sea level. Patients at risk for this condition can be identified at sea level with exercise during a hypoxic challenge (breathing a low oxygen concentration) determining an exaggerated rise in PASP [30, 31].

Recently, exercise echocardiography was considered in the advanced diagnostic algorithm of heart failure with preserved ejection fraction. In cases of diagnostic uncertainty, an average E/e′ ratio during exercise ≥15 with a peak TRV >3.4 m/s may confirm the diagnosis [32].

Current American and European guidelines do not formally include exercise-induced PH as a criterion that may indicate surgery in valvular heart disease [33, 34]. However, an abnormal exercise-induced increase of PASP may provide additional and incremental prognostic information [35, 36], although more data are needed [37].

In patients with established PH at rest, the presence of a preserved right ventricular contractile reserve during exercise or dobutamine SE is a major prognostic determinant [38–40].

36.5 Methodology

The general methodology in presence of known or suspected PH is shown in Table 36.8. All measurements performed at baseline must be repeated at peak stress, but at an intermediate load measurement of PASP must be attempted for three reasons: first, TRV can be measured at intermediate load only; second, most hemodynamic changes occur in the early steps of exercise; and third, at least two stress points are necessary to build the slope of the pressure-output curve, theoretically and practically more informative than flow-dependent pressure alone.

Table 36.8 Acquisition protocol for PH

	Technique	Rest	Intermediate	Peak	Recovery
1. TRV	CW-Doppler	v	v	v	
2. ACT	PW-Doppler	v	v	v	
3. TAPSE	M-mode	v	v	v	
4. EF, LAV, RAV	2D	v	v	v	
5. B-lines	LUS	v			v

ACT acceleration time, *CW* continuous wave, *EF* ejection fraction, *LAV* left atrial volume (and strain), *LUS* lung ultrasound, *PW* pulsed-wave, *RAV* right atrial volume, *TAPSE* tricuspid annular plane systolic excursion, *TRV* tricuspid regurgitant velocity

The ratio of early transmitral diastolic flow velocity to early tissue Doppler imaging velocity of the mitral annulus (E/e′) is also potentially useful but often difficult to record at high heart rate for mitral waves fusion, with decreased accuracy in the prediction of left ventricular filling pressures during exercise.

36.6 Pitfalls

The assessment of TRV is difficult in a significant percentage of patients (20–50%) during exercise and the success rate is increased substantially with integration with the ACT of the physiologic flow in the outflow tract of the right ventricle. An increase only in TRV may be caused simply by a normal hyperdynamic response to exercise with the increased pulmonary flow, and a more robust assessment of pulmonary hemodynamics is possible by integrating measurements of PASP and flow (CO or its proxy of minutes of exercise). The upper normal limit of invasive or noninvasive mPAP/CO relationships is 3 mmHg/L/min [41, 42].

Doppler-derived signals are strongly angle-dependent, and therefore a variety of windows should be interrogated to ensure that peak signals are obtained, and the same window should be used for rest and stress imaging. When a faint signal is obtained, signal reinforcement with hand-agitated saline or contrast is helpful [43, 44]. The reproducibility of continuous-wave Doppler signal measurement is higher if only dense signals, not faint and fluffy signals associated with higher velocities, are considered [45]. Moreover, the measurement of right atrial pressure from the inferior vena cava during exercise is very difficult. For this reason, often an arbitrary value of 5 or 10 mmHg is assumed for right atrial pressure at exercise. However, this assumption may result in an underestimation of peak exercise PASP [46, 47].

Some applications are of great potential interest but clinical evidence is missing. Among these applications, the assessment of coronary flow velocity reserve in the right coronary artery is an index of right coronary microcirculation (Fig. 36.1), which is impaired early in right ventricular overload [48, 49] and can be assessed noninvasively with a high success rate, only slightly less than left anterior descending coronary artery [50, 51].

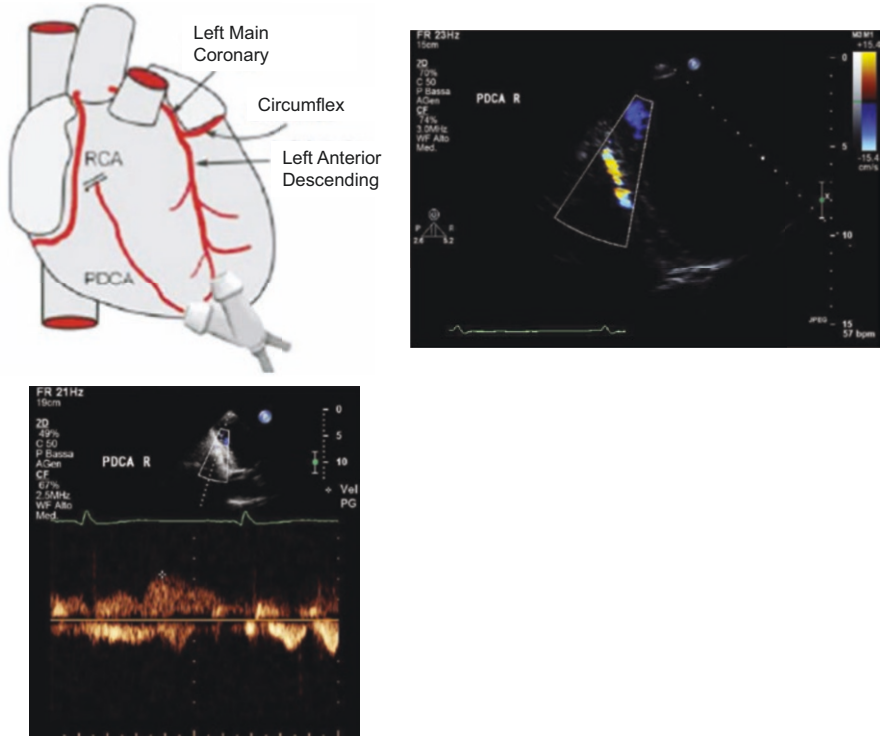

Fig. 36.1 *Upper left panel*: artist's drawing illustrating transducer beam orientation to the posterior descending coronary artery. The mid-distal tract is imaged from a modified apical two-chamber view with counterclockwise rotation and anterior angulations of the probe. *Upper right panel*: The corresponding echocardiographic image of posterior descending color flow. *Lower panel*: the corresponding pulsed Doppler flow signal at rest, on which the peak diastolic flow velocity is measured. The variation in diastolic flow velocity between rest and peak vasodilation (following adenosine or dipyridamole infusion) gives an index of coronary flow reserve. (Courtesy of Fausto Rigo, MD, Venice, Italy)

36.7 Clinical Guidelines

The main applications of PASP are in athletes, heart failure with preserved or reduced ejection fraction, valvular heart disease, congenital heart disease, and suspected or known PAH. The upper limit of normal is 43 mmHg, and an increase above this limit raises suspicion of preclinical disease in subjects screened for heritable PAH with BMPR2 mutation. The upper limit of normal is up to 60 mmHg in well-trained athletes for the increased CO leading to an increase in PASP and also in presence of normal pulmonary vascular reserve. For all other conditions, the upper cutoff value is set >60 mmHg, with the caveats of flow-dependence and limited feasibility during exercise which may lead to the integration of TVR with ACT (Table 36.9) [52].

Table 36.9 Cutoff value of exercise PASP in different conditions

	Exercise PASP (mmHg)	Reference
Normals	< 43	Rudski 2018 [5]
Trained athletes	< 60	Rudski 2018 [5]
HFpEF	> 60	Lancellotti 2017 [52]
HFrEF	> 60	Lancellotti 2017 [52]
VHD	> 60	Lancellotti 2017 [52]
PAH	> 60	Lancellotti 2017 [52]

HFpEF heart failure preserved ejection fraction, *HFrEF* heart failure reduced ejection fraction, *PAH* pulmonary arterial hypertension, *VHD* valvular heart disease

In 2021 European Society of Cardiology guidelines on HFpEF, a peak exercise value of TRV > 3.4 m/s is considered abnormal [32, 53]. In 2022 European Society of Cardiology guidelines on PH, exercise Doppler is recommended (class 2b) in symptomatic patients with systemic sclerosis or with chronic thromboembolic PH [2]. Exercise Doppler echocardiography is not recommended in other forms of PH because of uncertainty about cutoff values and their prognostic meaning [53].

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Pediatric Stress Echocardiography

37

Michael Henein and Eugenio Picano

Keywords

Children · Congenital heart disease · Kawasaki disease · Tetralogy of Fallot

37.1 Background

The rationale for applying stress echocardiography (SE) in children is not different from the application of the technique in adults. Sick children may need cardiac stress imaging as additional investigations, and SE is becoming more commonly used in the pediatric population [1]. To perform these procedures adequately, proper training of personnel and staffing of the pediatric stress laboratory is required to ensure the safety of patients and that the desired testing information is obtained. For these reasons, pediatric stress testing should remain an integral part of pediatric cardiology training [2]. The versatility of SE is ideally suited to tailor the most appropriate test to the individual patient, with specific signs used to address the particular diagnostic question in the individual patient (Fig. 37.1).

The 3 distinct populations are children or young adults with congenital heart disease [3, 4], adult patients with congenital heart disease [5–8], and children or adults with pediatric heart disease different from congenital heart diseases, such as familial homozygous hypercholesterolemia [9] or Kawasaki disease [10]. In all these conditions, resting transthoracic echocardiography has an essential role and

M. Henein (✉)
Department of Public Health and Clinical Medicine Units: Section of Medicine, Umeå University, Umeå, Sweden
e-mail: michael.henein@umu.se

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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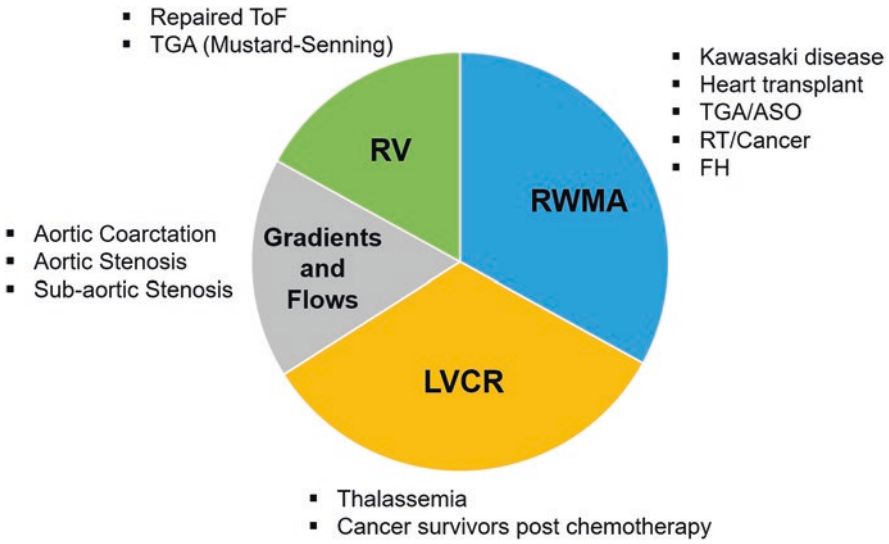

Fig. 37.1 The main targets of SE in pediatric patients. *ASO* arterial switch operation, *FH* familial homozygous hypercholesterolemia, *LVCR* left ventricular contractile reserve, *RT* radiotherapy, *RV* right ventricle, *RWMA* regional wall motion abnormalities, *TGA* dextro-transposition of the great arteries

SE has an important and expanding role, which is now increasingly recognized by guidelines and recommendations [3–10].

As with adults, the first target of SE in children and young adults is myocardial ischemia and its main sign of regional wall motion abnormalities. There are several patient populations for whom SE can be used to detect ischemia in children and young adults. The top six indications listed in decreasing order of frequency in the experience collected at Boston Children's Hospital between 2006 and 2017 are [3]: (1) Kawasaki disease, 32%; (2) Transplant Coronary Artery Disease, 22%; (3) Transposition of Great Arteries After Surgical Repair/status post arterial switch operation, 17%; (4) radiation therapy of the chest for cancer, 16%; (5) the anomalous origin of a coronary artery, 9%; and (6) familial homozygous hypercholesterolemia, 4%. The pathological correlates are different in the different conditions: genuine atherosclerosis in familial homozygous hypercholesterolemia; atherosclerosis-like accelerated coronary artery disease in transplanted heart cardiac allograft vasculopathy and radiation therapy; coronary inflammatory disease in Kawasaki disease; functional abnormalities for anatomic disorders in Transposition of great arteries/status post arterial switch operation and anomalous origin of coronary arteries. The final common pathway of these heterogeneous alterations is the vulnerability to myocardial ischemia which can be detected as regional wall motion abnormality (and reduced coronary flow velocity reserve) by SE.

37.2 Ischemia-Producing Conditions: Kawasaki Disease

Kawasaki disease is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Advances in clinical therapies (with intravenous immunoglobulin and aspirin) have reduced, but not eliminated, the incidence of coronary artery abnormalities in affected children. Today, Kawasaki disease is the most common cause of acquired cardiovascular disease in children in the USA, and coronary artery aneurysms or ectasia develops in 20% of untreated children and may lead to ischemic heart disease or sudden death [10]. According to 2017 American Heart Association guidelines on Kawasaki disease, cardiac stress testing for reversible ischemia is indicated to assess the presence and functional consequences of coronary artery abnormalities in children with Kawasaki disease and coronary aneurysms (evidence level A). Irrespective of the chosen stress modality, diagnostic accuracy for identifying coronary artery disease is high and comparable, with exercise or pharmacological stress-induced wall motion abnormalities representing a highly specific marker of coronary artery involvement, with excellent overall diagnostic accuracy [11–15]. The guidelines conclude that "the selection of modality for surveillance for inducible myocardial ischemia should take into account the expertise of the institution, with a preference for physiological stress with exercise over pharmacological stress, and minimizing the cumulative radiation dose and risks to the patient" [10]. Therefore, the historic use of methods such as myocardial perfusion scintigraphy [16], and positron emission tomography evaluation of coronary flow reserve [17] although informative, should be minimized [10]. If inducible ischemia is present, further imaging is suggested, usually with invasive coronary angiography to determine the presence of coronary stenosis and occlusions [10].

In adolescent Kawasaki disease survivors, dobutamine SE provided long-term prognostic information, which was strongly stratified based on the peak wall motion score index in the initial SE [18]. Stress-induced wall motion abnormalities were observed not only in the patients with fixed coronary artery stenoses but also in those with non-stenotic coronary artery lesions such as giant aneurysms, in whom the coronary flow is sluggish and the risk for thrombosis is high. These findings suggest the influence of dynamic coronary stenosis superimposed on any degree of fixed stenosis or microvascular changes due to systemic vasculitis and reducing coronary flow reserve. Therefore, the anatomic information provided by coronary arteriography and the functional information on inducible ischemia provided by SE may diverge. For the prediction of clinical outcome, the response to SE is even better than that of coronary anatomy, since it evaluates the functional significance of coronary artery lesions that are responsible for the latent vulnerability of myocardial ischemia [18].

At present, it appears reasonable to propose a very simple diagnostic algorithm in these patients, who must be screened with resting transthoracic echocardiography to detect coronary artery morphological anomalies, which are the cornerstone of

diagnosis and risk stratification (from class I, low risk, to V, high risk). A positive SE is frequently found in the high-risk class; therefore, it appears appropriate to use it in class IV and V patients [10, 19].

The fundamental information obtained with regional wall motion abnormality during SE can be further enriched with the use of advanced imaging techniques such as longitudinal function assessment with mitral annulus plane systolic excursion [20], cyclic backscatter variation with tissue characterization techniques [21], and perfusion changes with myocardial contrast echocardiography [22]. Each of these markers has a valuable rationale. Long-axis function can detect minor forms of ischemia, unable to affect the radial function and regional systolic thickening, since longitudinal fibers run in the subendocardial layer, thus abnormalities accurately reflect subendocardial ischemic dysfunction, known to appear before the transmural ones. Studies have shown that the longitudinal function can be impaired when radial motion is normal or even supernormal [20]. Cyclic backscatter variation is proportional to intramural contractility, and higher in the subendocardium than in the subepicardium, mirroring the well-known intramural contractility gradient. Therefore, minor forms of subendocardial hypoperfusion may impair subendocardial function and blunt cyclic backscatter variation without a detectable impairment in regional systolic thickening [21]. Finally, myocardial contrast echocardiography evaluates myocardial perfusion heterogeneity, which is more sensitive (albeit less specific) than regional wall motion abnormalities as a marker of myocardial ischemia [22]. Coronary flow velocity reserve allows the detection of coronary microvascular dysfunction and subcritical forms of epicardial coronary artery disease unable to induce regional wall motion abnormality during stress [23]. In Kawasaki disease, the impairment in coronary flow reserve is largely independent of epicardial coronary artery lesions and aneurysms, again suggesting primary coronary microcirculation impairment [24]. The reduction of coronary flow reserve can be either diffuse or branch-specific [25, 26].

37.3 Ischemia-Producing Conditions: Transplant Coronary Artery Disease

The leading cause of death after the first year of cardiac transplant is coronary artery disease, occurring in up to 43% of patients at 3 years following transplant [27]. This form of coronary disease, also known as graft coronary disease, differs from classical atherosclerosis in both histologic and angiographic features and it progresses much more rapidly. Because the disease is diffuse and usually involves small vessels it makes coronary arteriography an unreliable diagnostic technique—a matter that turned physicians to other modalities, such as SE. A total of seven SE (with dobutamine or exercise) studies, including over 250 patients [28–33], showed excellent diagnostic value [28–32] and prognostic capability [33, 34] since patients with positive test results had a sixfold higher risk of subsequent cardiac events. Thus, SE is recommended for the detection of cardiac allograft vasculopathy in children with heart transplants [35, 36].

37.4 Ischemia-Producing Conditions: Transposition of Great Arteries After Surgical Repair

Relatively young patients with transposition undergo an arterial switch operation, to allow the left ventricle to function as the systemic pump [37]. The arterial switch operation, which includes coronary artery transfer, is the surgical procedure of choice for the transposition of the great arteries. Mortality and clinical long-term outcome depend largely on adequate perfusion through the transferred coronary arteries [38]. Late deaths can be related to coronary occlusion, and intravascular ultrasound assessment, late after arterial switch operation, revealed proximal eccentric intimal thickening in most coronary arteries, suggesting the development of early atherosclerosis in reimplanted coronary arteries [39]. These patients tend to have a consistently reduced coronary flow reserve [40]. Only anecdotal reports present in the literature on a total of 34 patients from two studies—one with dobutamine [41], the other with transesophageal atrial pacing [42]—suggest that a stress-induced regional wall motion abnormality or reduced left ventricular long-axis function portends a negative prognosis.

Coronary flow reserve could be impaired—even in the absence of anatomic epicardial coronary artery disease—in children 5–8 years after the switch operation, which is mirrored by reduced vasodilation following nitrates, an endothelium-independent vasodilator stimulus [43].

37.5 Ischemia-Producing Conditions: Radiation Therapy to the Chest After Cancer

Chest irradiation with radiotherapy is required for the cure of several childhood cancers, including leukemia to Hodgkin's and non-Hodgkin's lymphoma. In the long term, cardiac disease is the most frequent treatment-related noncancer cause of death. Cardiac disease can include a broad range of alterations, from coronary artery disease (the most frequent) to heart failure, valvular disease, pericardial disease, and cardiac autonomic dysfunction with cardiac arrhythmias [44]. In this setting, SE can help to identify different targets of disease although the most established application is the detection of coronary artery disease through stress-induced regional wall motion abnormality. The likelihood of coronary artery disease after chest radiotherapy is higher with a high total dose (≥20 Gray), large cardiac volume (≥50% of the heart), concomitant chemotherapy, and younger age at exposure [45, 46].

For asymptomatic patients with a history of mediastinal chest radiation, a joint document of the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommends a screening transthoracic echocardiography and SE at 10 years after mediastinal radiation therapy and serial exams every 5 years thereafter [46–48]. The National Comprehensive Cancer Network has similar period recommendations for SE [49]. As stated by the European Society of Medical Oncology recommendations 2020, "nonionizing modalities may be most appropriate due to concern regarding cumulative radiation dose in cancer patients," who are already highly exposed to oncology diagnosis and follow-up programs [50].

37.6 Ischemia-Producing Conditions: Anomalous Origin of a Coronary Artery

Anomalous aortic origin of coronary arteries is a congenital heart anomaly in which one coronary artery arises from the opposite sinus (the left coronary artery from the right coronary sinus, or the right coronary artery from the left sinus). The initial segment of the abnormal artery courses between the great arteries and is usually located within the aortic wall. These anomalies are far from rare, affecting 0.1% to 0.3% of the population, and carry a high risk of sudden cardiac death. Anomalous origin of the left and right coronary arteries from the opposite sinus may cause sudden death in athletes. Anomalous aortic origin of a coronary artery is the second leading cause of sudden cardiac death in young athletes in the USA. In patients with anomalous right coronary artery, especially if asymptomatic, a negative SE for wall motion criteria is sufficient to postpone surgery and avoid activity restrictions. Postoperative SE may provide reassurance to asymptomatic patients engaged in competitive sports.

SE is usually negative also in patients with anomalous origin of the left coronary [51]. In patients with anomalous left coronary artery, especially if symptomatic, the risk of mortality may be sufficiently high that a negative stress test should not dissuade the prudent physician from recommending surgery or activity restriction. However, data are very limited to support evidence-based recommendations.

The European Society of Cardiology guidelines 2020 recommends that assessment of stress-induced ischemia using imaging modalities is the key to decision-making (level of recommendation I, class of evidence C) [8].

37.7 Ischemia-Producing Conditions: Familial Homozygous Hypercholesterolemia

Familial homozygous hypercholesterolemia is diagnosed through genetic confirmation (sometimes elusive) and clinical criteria, consisting of untreated LDL-cholesterol values >500 mg/dL with either cutaneous or tendon xanthoma before age 10 years or untreated elevated LDL-cholesterol level consistent with heterozygous familial hypercholesterolemia in both parents [9].

Familial homozygous hypercholesterolemia is characterized by accelerated atherosclerosis especially at the level of the aortic root and the aortic valve, determining aortic stenosis and regurgitation. Anatomic stenosis of epicardial coronary arteries and functional abnormalities of coronary microcirculation are frequent and the latter can be used as an early and partially reversible biomarker of disease [51–53], also useful to monitor the effects of therapy such as LDL-apheresis [54, 55].

37.8 Valve and Intraventricular Gradients

Several studies have been performed in native stenotic aortic, pulmonary, and prosthetic valves during high-flow states to unmask an abnormally high increase in gradients. The transvalvular gradient increases with increasing flow rates, the higher

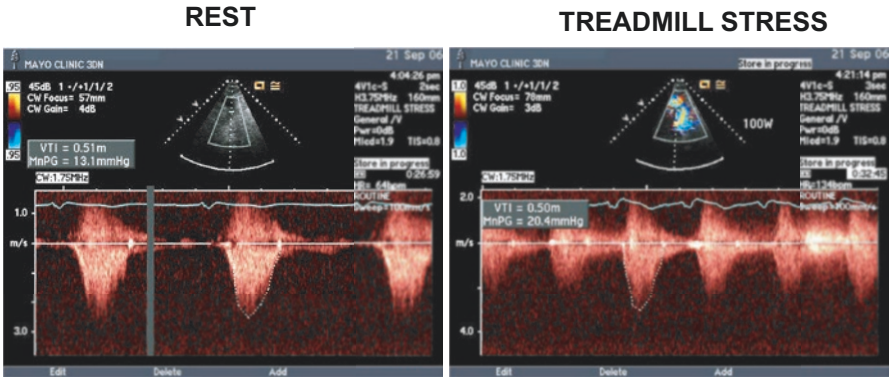

Fig. 37.2 Transcoarctation gradients from the suprasternal window before (left panel) and after treadmill (right panel). There is an increase in mean gradient (from 13 mmHg at rest to >20 mmHg at peak exercise) with diastolic run-off at peak exercise, indicating coarctation. (By courtesy of Patricia Pellikka, MD, Mayo Clinic, Rochester, USA)

the transvalvular flow, the higher the pressure gradient. A moderately and a severely diseased native valve, and a normal or abnormally functioning prosthesis, may display similar gradients at rest, but the marked rise in mean gradients during stress in the latter is to be distinguished from the fairly flat gradient response of the moderately diseased native or normally functioning prosthetic valves. The rationale of this application is very strong, but systematic data, especially in children, are still conspicuously lacking to date [56]. A similar application evaluates the development of intracardiac gradients in young athletes or patients with hypertrophic cardiomyopathies, in whom dobutamine or exercise can unmask an intraventricular obstruction unapparent at rest and which may have prognostic and therapeutic implications [3].

The measurement of gradients is especially important in left-sided heart obstructive lesions: aortic valve disease, subvalvular and supravalvular aortic stenosis, and coarctation of the aorta. According to 2008 American College of Cardiology Foundation/American Heart Association guidelines for adults with congenital heart disease, patients with subaortic stenosis, resting peak gradients less than 50 mmHg and symptoms of breathlessness and fatigability should be investigated with exercise Doppler to determine whether the gradient increases with exertion. In aortic coarctation, SE-Doppler is valuable and is targeted at obtaining the rest and exercise suprasternal notch continuous wave Doppler coarctation gradient, including the diastolic profile. In the follow-up post-correction, the mean gradient >20 mmHg with diastolic run-off is indicative of re-coarctation [4] (Fig. 37.2).

37.9 Contractile Reserve

The impairment of contractile reserve may involve the left or right ventricle. The left ventricle is targeted by cancer chemotherapy and mediastinal irradiation and by thalassemia major. The right ventricular function is prognosis-limiting in Mustard or Senning operation after the transposition of great arteries [57]. Patients with

normal ejection fraction at rest can have a subtle alteration in left ventricular function. This initial impairment can be detected as a reduction in long-axis function detected by mitral annular plane systolic excursion or tissue Doppler imaging [57]. Alternatively, initial myocardial damage can be detected as a blunted contractile response to inotropic stress, such as dobutamine or exercise. The early detection of subtle damage inapparent in resting conditions is especially important to adopt targeted preventive and therapeutic measures. More than 50% of childhood cancer survivors develop asymptomatic left ventricular dysfunction and 5% of them progress to clinically overt heart failure [58]. The blunted left ventricular contractile reserve has been described in anthracycline-treated long-term survivors of childhood cancer [59, 60] or thalassemic patients at an early stage of the disease [61]. At a more advanced stage, left ventricular function can be depressed and the inotropic challenge can restore normal function in patients who might have a better cardiac outcome if cardiotoxic chemotherapy is discontinued (Fig. 37.3).

The assessment of the contractile reserve of the right ventricle is of great importance. The long-term problems that are associated with repaired transposition of the great arteries depend on the type of repair. The oldest patients have intra-atrial repair, either Mustard or Senning type, in which venous return is directed to the contralateral left ventricle through an atrial baffle. As a consequence, the right ventricle supports systemic circulation.

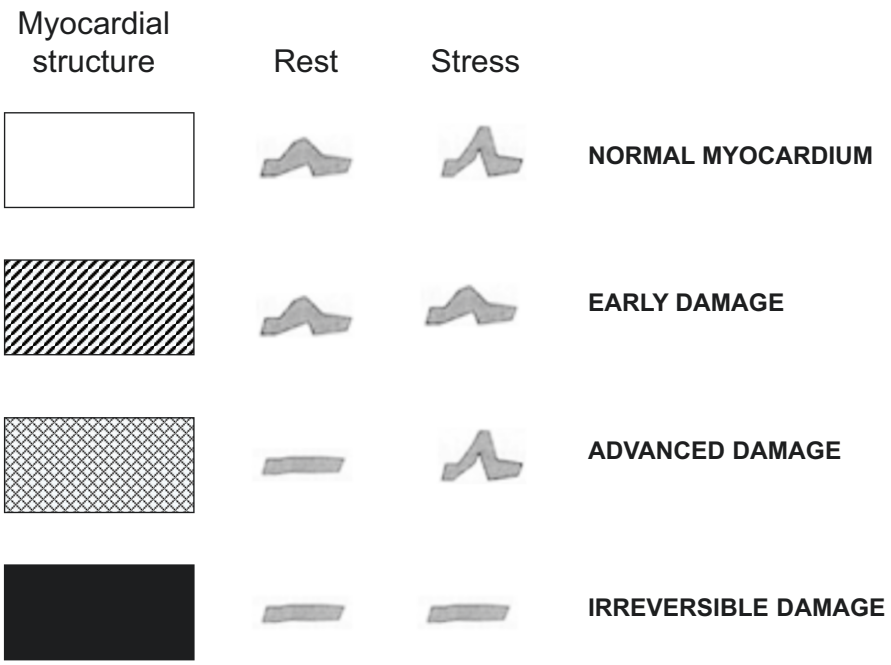

Fig. 37.3 Different stages of severity of myocardial damage in cardiomyopathy, due to, for instance, thalassemia or cardiotoxic chemotherapy

In patients with Mustard or Senning repair, right ventricular dysfunction and pulmonary hypertension are potential complications. Patients with exertional symptoms, angina-like chest discomfort, or breathlessness could be physiologically assessed by SE. There is a close relationship between right ventricular function and exercise tolerance assessed by cardiopulmonary exercise testing in these patients. Right ventricular function becomes very abnormal at a fast heart rate, demonstrating disturbances similar to those seen in patients with coronary artery disease, suggesting a possible underlying ischemic dysfunction [62]. These findings are consistent with those found in dilated cardiomyopathy in whom right ventricular dysfunction has been shown to predict exercise capacity as well as prognosis.

In patients with Mustard repair for transposition of the great arteries [62] or repaired tetralogy of Fallot [63], impaired exercise tolerance can be predicted by right ventricular long-axis function at baseline and during stress [29, 40].

37.10 Exercise Echocardiography in Long QT Syndrome (LQTS)

In addition to the pivotal application of SE in the above congenital and pediatric condition, it has proved to be a vital investigation in explaining the cardiac pathophysiology in patients with LQTS and in identifying predictors of cardiac events. LQTS mutation carriers are at an increased risk of ventricular tachycardia, recurrent syncope, or even sudden cardiac death. These patients present with marked dispersion of myocardial repolarization and prolonged action potential duration, resulting from dysfunction of cardiac ion channels, which contribute to arrhythmia [64].

Until recently, LQTS was considered a purely electrical phenomenon with clearly overlooked mechanical and hemodynamic consequences. This was mainly based on the observation that patients with LQTS usually have normal global left ventricular ejection fraction. Various recently developed imaging modalities, including myocardial Doppler, speckle-tracking echocardiography as well as experimental magnetic resonance imaging, demonstrated abnormal cardiac mechanics [65–68]. Myocardial disturbances are in the form of prolonged contraction and increased systolic dispersion, particularly in symptomatic LQTS carriers [69]. However, prolonged and discordant myocardial contraction may result in a disproportionate shortening of left ventricular filling time, which adversely affects cardiac output, particularly during exercise/stress, as previously shown in patients with dilated cardiomyopathy [70]. The underlying mechanism for the compromised cardiac output is inadequate stroke volume increase during stress, which itself may be an additional trigger of symptoms [71]. Recently, the valuable use of exercise testing in the assessment of LQTS carriers has moved from pure focus on the behavior of electrical parameters, such as QTc, to overall mechanical cardiac response including filling time, stroke volume, and regional left ventricular times relations changes.

In a group of LQTS carriers, exercise Doppler echocardiography has shown clear evidence for longer QTc and shorter filling time, at rest, compared to age and gender-matched controls. At peak controlled bicycle exercise test, QTc increased further and remained longer than controls at recovery. QTc and filling time inversely correlated ($r = -0.398$, $P = 0.001$), with greater fall in filling time in LQTS carriers than in controls ($-23 \pm 10\%$ vs. $+2 \pm 3\%$, $P < 0.0001$). Filling time also correlated with stroke volume ($r = +0.27$, $P = 0.001$), which increased more in controls than in LQTS carriers ($+32 \pm 4\%$ vs. $+2 \pm 1\%$, $P < 0.05$). These differences were more pronounced in symptomatic LQTS carriers who had shorter filling times and smaller stroke volume at peak exercise and during recovery compared to asymptomatics ($P < 0.05$) [72].

Further detailed analysis of cardiac dysfunction studied electromechanical coupling heterogeneity in the same group of LQTS carriers as shown by the electromechanical window. The electromechanical window proved to be negative, at rest, in LQTS carriers compared to age, gender, left ventricular ejection fraction, and heart rate matched controls (-42 ± 22 vs. 17 ± 5 ms, $P < 0.0001$). Furthermore, the electromechanical window became more negative at peak exercise (-89 ± 43 vs. 16 ± 7 ms, $P = 0.0001$) and recovery (-65 ± 39 vs. 16 ± 6 ms, $P = 0.001$), particularly in symptomatic patients, but remained unchanged in controls. In addition, the electromechanical window proved to be a stronger predictor of arrhythmic events than QTc (Area under Curve: 0.765 vs. 0.569, $P < 0.001$). Of interest, beta-blockers did not affect the electromechanical window at rest but made it less negative at peak exercise (beta-blockers: -66 ± 21 vs. no-beta-blockers: -113 ± 25 ms, $P < 0.001$) [73].

Diastolic cardiac function is not spared in LQTS carriers. The same group of LQTS carriers proved to have prolonged and markedly dispersed myocardial contraction delayed early relaxation phase and significantly shorter filling time at rest and all exercise phases. Unlike controls, these electromechanical disturbances deteriorated further with exercise, during which an additional decrease of the left ventricular diastolic myocardial function and attenuated stroke volume was demonstrated. Such abnormal responses to exercise were seen to a greater extent in symptomatic patients and the LQTS type 1 subgroup and improved with beta-blocker therapy. Worsening myocardial contraction dispersion at peak exercise proved to be the strongest discriminator for previous clinical events, and its discriminating power excelled further by adding early relaxation delay [74].

Finally, using speckle-tracking echocardiography regional left ventricular function response to exercise and its impact on stroke volume has also been reported. At peak exercise, patients had longer time to left ventricular longitudinal early diastolic strain rate (E_{SR}) at all three left ventricular segments: basal ($p < 0.0001$), mid-cavity ($p = 0.03$), and apical ($p = 0.03$) whereas at rest such difference was noted only at the basal region ($p = 0.0007$). Patients also developed reversed apicobasal relaxation sequence with early relaxation onset occurring later at the base than at the apex, both at rest (49 ± 43 vs. -29 ± 19 ms, $p < 0.0001$) and at peak exercise (46 ± 38 vs.

−40 ± 22 ms, $p < 0.0001$), particularly in symptomatic patients (69 ± 44 vs. 32 ± 26, $p < 0.0007$). Furthermore, reversed apicobasal relaxation sequence correlated with longer QTc interval, lower early diastolic strain rate, and attenuated left ventricular stroke volume [75].

37.11 Radiation Exposure in Children: Implications for Imaging Strategy

For any given radiological effective dose, the risk for some organs, including the brain, is 3–4 times higher in children than in adults [76] (Fig. 37.4).

Children are at substantially higher risk than adults because they have more rapidly dividing cells and a greater life expectancy, allowing the clinical manifestation of radiogenic cancer with long latency periods of decades. Thus, an infant or child patient has a longer lifetime risk for developing radiation-induced cancers than adult patients. At the age of 15–20 years, grown-up congenital heart disease patients have already cumulated an effective dose exposure corresponding to 20–40 milliSievert, with an estimated lifetime attributable extra-risk of cancer of 1 in 10 to 1 in 100 [77]. The average child in the USA will have seven medical imaging tests involving radiation by the time he or she reaches the age of 18. About 1 in 4 children had 2 or more imaging tests involving radiation and about 1 in 7 children had at least 3 tests [78]. The chest is the most frequently evaluated region of the body in children [79]. Scans are computed tomography in 8% of children and are often done without adjusting exposure parameters to weight, resulting in up to 50% of the dose being unnecessary [80].

Among pediatric cardiology patients with congenital heart disease, fluoroscopically guided diagnosis and interventions account for 3.5% of all radiological examinations performed and 84% of their total collective dose [80]. In the USA, this issue

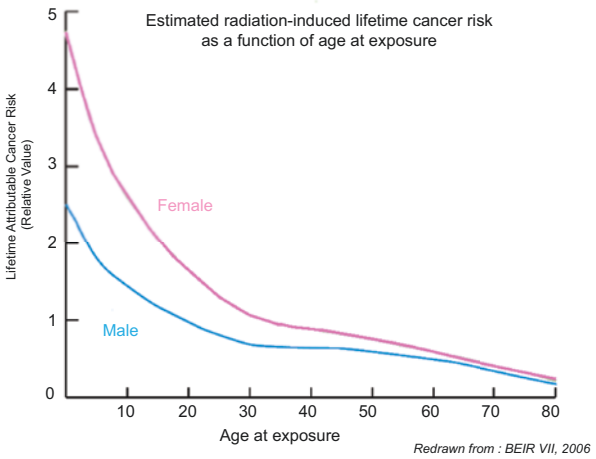

Fig. 37.4 The attributable lifetime risk for a single small dose of radiation according to age at the time of exposure. The oncologic, stochastic risk is about 38% higher in women than in men, and 400% higher in children aged <1 year than in adults. (Adapted from ref. [76])

of radiological responsibility was addressed with the Image Gently, Step Lightly Campaign, especially focused on the risks of unnecessary and excessive medical radiation exposure from interventional radiology administered to pediatric patients [80]. The cancer risk from medical radiation in children is not only based on extrapolations and estimates but also direct epidemiological evidence in populations exposed to medical radiation [81], including heart patients. In a study of 24,833 adults with congenital heart disease, the risk of cancer increased by more than 300% if the patient had received ≥6 procedures with ionizing radiation [82]. The cumulative medical radiation dose in children with congenital heart disease is high (up to the dose equivalent of 5000 chest x-rays in 1 out of 50 patients) [82]. Radiation exposure leaves acute and permanent damage, detectable hours and decades after exposure, in the chromosomes of circulating lymphocytes of patients [83]. The radiation-induced DNA damage is likely responsible for the observed increased risk for cancer in adulthood [84]. Another source of concern is the brain and atherosclerotic effects of early radiation exposure since these patients are at higher risk of developing a chronic multisystem disease in adulthood, including early dementia and premature atherosclerosis which have a complex, multifactorial origin and significantly contribute to morbidity and mortality in these adult patients [85].

Until 15 years ago, the dose and risks associated with common examinations in adult and pediatric patients were ignored by pediatricians and cardiologists [86, 87] who underestimated 500 times the dose of myocardial perfusion imaging or a chest computed tomography. There is little question that with the restoration of radiological awareness and mandatory incorporation of radiation doses in digital health records [88, 89], SE will become the technique of choice in children, and will help patients to achieve the benefits of the highest diagnostic standards without the long-term oncogenic risks of radiation exposure. The overarching recommendation of the 2019 American Heart Association guidelines (introducing a variation versus the previous 2008 release) is that "strategies to limit and monitor radiation exposure are recommended during imaging of patients with adult congenital heart disease, with studies not involving ionizing radiation chosen whenever appropriate" [4]. This is the obvious consequence of a new culture of safety and radiological awareness which is reinforced by general cardiology guidelines [4, 64, 78]. The doses associated with the most common pediatric cardiology doses and interventions are reported in Table 41.5 [4, 76, 90, 91].

37.12 Pitfalls

Suboptimal image quality due to restricted acoustic windows is associated with postoperative changes in pediatric and adult congenital heart disease, and ultrasound-enhancing agents are commonly needed to obtain interpretable images [4].

A focused competence for the pediatric population should ideally be an integral part of the high-volume SE laboratory. Diagnostic questions raised by children are extremely variable and require a versatile approach of highly trained personnel. Pediatric SE is best performed in teamwork—between an adult cardiologist trained

in SE and a pediatric cardiologist directly involved in the treatment of the patient. Together, the two cardiologists discuss the indications, perform the examination, and use the results in light of the clinical context [4].

37.13 Clinical Guidelines for SE in Pediatric and Congenital Heart Disease

Since the advent of neonatal repair of complex lesions in the 1970s, an estimated 85% of children with congenital heart disease today usually survive into adult life, and in the next decade, almost 1 in 150 young adults will have some form of adult congenital heart disease [4]. Guidelines recommend that diagnostic imaging procedures should be performed in a regional adult congenital heart disease center with appropriate experience in congenital heart disease and a laboratory with appropriate personnel and equipment [2, 3]. In general, we need stronger evidence to support more widespread use of SE in these patients, who can benefit most from the unique assets of the method, especially its radiation-free nature and versatility of the information provided. The main applications are summarized in Table 37.1. The indication to SE testing is probably appropriate in several

Table 37.1 Application of stress echo in children and adult congenital heart disease patients

	COR	Parameter	Ref
Aortic subvalvular, valvular; supravalvular stenosis, aortic coarctation			
Routine surveillance (every 2–5 years) in asymptomatic unrepaired or (every 12 months) in asymptomatic repaired	2a	Mean gradient	ACC/AHA, 2020 [6]
Evaluation due to changes in clinical status and/or new coronary symptoms	2a	Mean gradient	ACC/AHA, 2020 [6]
Repaired TOF, repaired TGA	2b	RV function, RVOT obstruction	ACC/AHA, 2020 [6]
TGA post-switch operation	2a	RWMA	ACC/AHA, 2020 [6]
Coronary anomalies			
The search for inducible ischemia is essential before decision-making	1	RWMA	ESC, 2020 [8]
Adult survivors should have noninvasive ischemia testing every 3–5 years	1	RWMA	ACC/AHA, 2020 [6]
Detection of cardiac allograft vasculopathy	1	RWMA	ISHLT, 2010 [35]
Kawasaki disease			
Coronary lesion severity class IV, V	2a	RWMA	AHA 2017 [10]
Every 2–3 years if the patient has symptoms suggestive of myocardial ischemia or signs of LV dysfunction			
Coronary lesion severity class III	2a	RWMA	AHA 2017 [10]

(continued)

Table 37.1 (continued)

	COR	Parameter	Ref
Coronary lesions I, II—asymptomatic	2a	RWMA	AHA 2017 [10]
Homozygous familial hypercholesterolemia			
Symptoms/signs of myocardial ischemia or valve dysfunction	1	RWMA	ESC, 2014 [9]
Childhood cancer survivors post-chest radiotherapy			
After 10 years in asymptomatic and every 5 years thereafter	1	RWMA	ACC/AHA, 2020 [6]

ACC American College of Cardiology, *AHA* American Heart Association, *COR* class of recommendation, *ISHLT* International Society Heart Lung Transplantation, *RV* right ventricle, *TGA* transposition of great arteries, *TOF* tetralogy of Fallot

conditions with 2 main indications: (1) routine surveillance in asymptomatic patients, every 2–5 years pre-op and every 12 months postoperatively; (2) evaluation (either pre-op or post-op) due to changes in clinical status and/or new concerning signs or symptoms. Adult congenital heart disease patients often need repetitive imaging, making them vulnerable to radiation-induced cancer; hence, modalities using ionizing radiation, nephrotoxic iodine contrast, or gadolinium potentially accumulating in the brain should be minimized [6]. All types of risks should be minimized in children with the preferential use of ultrasound. The class of recommendation is 1 and the level of evidence is moderate quality obtained with meta-analysis of non-randomized studies [4]. Whenever possible, exercise is the stress test of choice, since it is extremely well tolerated in children and it requires no sedation, needle stick, radiation exposure, gadolinium, or iodine contrast administration and can be considered for children age 6 or older [3].

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Stress Echocardiography in Athletes and Extreme Physiology

38

Rodolfo Citro and Eugenio Picano

Keywords

Athletes · B-lines · Coronary flow velocity reserve · Environment · Speckle tracking

38.1 Athletes and Extreme Physiology

Cardiac adaptation to regular exercise or strenuous exercise involves the whole cardiovascular system and can be different in ordinary environments and extreme settings. The interpretation of cardiac imaging findings requires a comprehensive understanding of exercise-induced cardiac remodeling which may mimic and overlap with findings suggestive of pathology, both at rest and during stress [1]. Cardiac adaptations to regular exercise are especially striking in competitive athletes, defined by the American Heart Association/American College of Cardiology as an individual "*who participates in an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training*" [2]. In this context, resting transthoracic echocardiography and stress echo (SE) are essential to identify and test each link of the complex chain leading to adequate or extraordinary performances of the athlete (Table 38.1).

R. Citro (✉)
Cardiology Department and Echocardiography Lab, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Table 38.1 Clinically relevant information derived from rest and SE in athletes

	Rest TTE	SE
Wall thickness	v	
LVOT gradient	v	v
LV systolic function (EF, GLS)	v	v
LV diastolic function (E/e′)	v	v
Hemodynamic congestion (PASP, B-lines)	v	v
LAV and function (ST analysis)	v	v
Mitral leaflets, papillary muscles	v	
RWMA	v	v
CFVR in LAD		v
HR reserve and recovery		v
Dynamic mitral regurgitation		v
RV function	v	v

CFVR coronary flow velocity reserve, *EF* ejection fraction, *GLS* global longitudinal strain, *HR* heart rate, *LAD* left anterior descending, *LAV* left atrial volume, *LV* left ventricle, *LVOT* left ventricular outflow tract, *PASP* pulmonary artery systolic pressure, *RWMA* regional wall motion abnormality, *RV* right ventricle, *ST* speckle tracking, *TTE* transthoracic echocardiography

SE can be especially important in the clarification of the 4 gray zone imaging findings in competitive athletes for use in differentiating physiologic remodeling from disease:

1. Thick left ventricular walls, differential diagnosis with hypertrophic cardiomyopathy, and SE response with preserved contractile strain reserve, cardiac synchronicity of contraction, and coronary flow velocity reserve (CFVR) in physiologic hypertrophy [3, 4].
2. Dilated left ventricular chamber, differential diagnosis with idiopathic/familial dilated cardiomyopathy, and SE response with preserved preload reserve and contractile reserve in physiologic dilation [5, 6].
3. Dilated right ventricular chamber, differential diagnosis with arrhythmogenic cardiomyopathy, and SE response with preserved right ventricular functional reserve in physiologic dilatation [7, 8].
4. Hyper-trabeculation of the left ventricle, differential diagnosis with non-compaction cardiomyopathy, and SE response with normal reserve of global and regional longitudinal strain [9, 10].

38.2 Comprehensive SE

Each step of a comprehensive SE protocol can be abnormal for specific reasons in athletes, with different phenotypes identified by different signs.

38.2.1 Regional Wall Motion Abnormalities

After extreme effort, a regional wall motion abnormality can even occur in absence of underlying coronary artery stenosis, due to an extraordinarily high increase in oxygen demand [11, 12]. Myocardial bridging has been described as a cause of wall motion abnormalities without detectable epicardial stenosis [13, 14]. Another possible cause is epicardial artery vasospasm, favored by cocaine, caffeine, and energy drinks [15, 16]. Abuse of androgenic-anabolic steroids increases the vulnerability to premature atherosclerosis, myocardial infarction, and coronary vasospasm [17, 18]. Coronary angiography is mandatory in the presence of inducible regional wall motion abnormality since the most likely cause is premature coronary artery disease.

38.2.2 B-Lines

B-lines are the sign of pulmonary congestion and accumulation of extravascular lung water. The two main causes are a direct increase in permeability of the alveolar-capillary membrane for alteration of the alveolar-capillary barrier or an increased pulmonary artery wedge pressure with increased filtration and unbalance of Starling forces. The appearance of B-lines during peak exercise was inversely correlated with resting global longitudinal strain and positively correlated with peak systolic pulmonary artery pressure in 350 endurance athletes, including long-distance cyclists, middle-distance swimmers, and middle-distance runners [19]. Exercise B-lines were more frequent in competitive bodybuilders with a long history of anabolic-androgenic steroid use [20].

38.2.3 Cardiac and Contractile Reserve

Cardiac chamber enlargement enables a large stroke volume which leads to an increase in cardiac output. Left ventricular stroke volume rises as a direct consequence of an increased end-diastolic volume and a reduction of end-systolic volume [21]. The increase of cardiac reserve (cardiac output) can be preferentially due to the recruitment of preload reserve (increased end-diastolic volume) or contractile reserve (decrease in end-systolic volume), combined with the increase in heart rate (chronotropic reserve). Cardiac output can increase up to fivefold in untrained subjects. In elite athletes, the increase in cardiac output can be eight times the baseline value, with a physiologic increase in pulmonary pressures above the normal range. An absent or subnormal increase in myocardial contractility during stress may be a marker of an underlying disease (e.g., dilated cardiomyopathy, arrhythmogenic cardiomyopathy, left ventricular non-compaction) in endurance athletes with ventricular dilatation and mildly reduced left ventricular ejection fraction at rest [6].

38.2.4 Speckle Tracking

Variation of strain analysis during peak and post-exercise reflects the structural adaptation of athletes' hearts in response to the hemodynamic demands of intense training. Normally there is an increased global longitudinal strain during exercise that corresponds to increased contractility in response to intense physical activity [22]. Longitudinal deformation is only one of the many ways the heart adapts to increased stroke volume; moreover, athletes belonging to different disciplines showed variable circumferential, radial shortening, and torsional motion contributions to stroke volume in response to different exercises [23].

38.2.5 Doppler-Based SE

Athletes show supernormal values of coronary flow reserve, due to physiologic hypertrophy and an increase in coronary microvascular density and epicardial artery vasodilatory capacity (Fig. 38.1) [24, 25].

38.2.6 EKG-Based Heart Rate Reserve

Generally, the functional hallmark of an athlete's left ventricle is a rapid switch from parasympathetic to sympathetic activation during exercise, which enhances myocardial contractility and a heart rate increase which is generally increased in athletes. Long-term use of androgen anabolic steroids leads to altered cardiac autonomic modulation with consequent abnormal heart rate reserve [26].

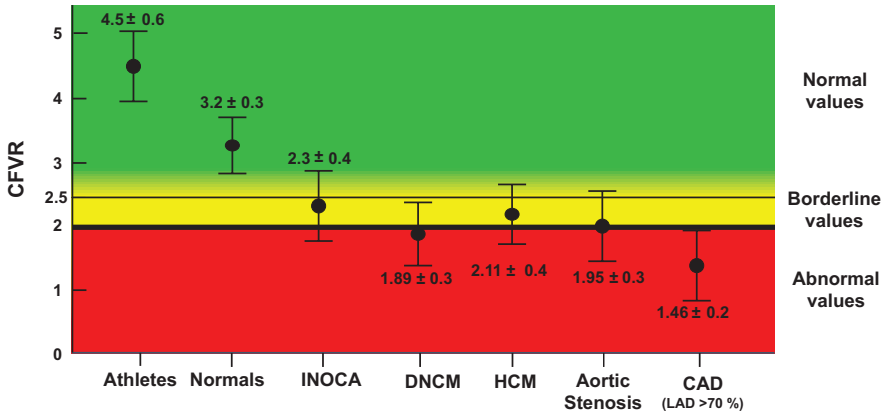

Fig. 38.1 The spectrum of clinical conditions with normal coronary arteries and reduced CFVR in the left anterior descending artery by transthoracic vasodilatory SE. *CAD* coronary artery disease, *CFVR* coronary flow velocity reserve, *DNCM* dilated nonischemic cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *INOCA* ischemia with angiographically normal coronary arteries. (Redrawn and modified from Rigo F, Venice-Mestre, Italy [25])

38.2.7 Arrhythmic Risk Stratification

Some cardiovascular disorders including cardiomyopathies, cardiac ion channel diseases, ventricular pre-excitation syndromes, nonischemic left ventricular myocardial fibrosis, anomalous coronary arteries, and arrhythmogenic right ventricular cardiomyopathy could present negative history, unremarkable physical examination, and normal resting ECG. The stress test is a "second-line" strategy to identify the occurrence, morphology, and complexity of ventricular arrhythmias, arising during the exercise stress test, which may be the only phenotypic manifestation of underlying disease [27]. One clinical manifestation in athletes of nonischemic left ventricular scar could consist of exercise-induced, repetitive, premature ventricular complexes with right bundle branch block [28].

38.2.8 Valvular Heart Disease

Trivial/mild valvular regurgitation is quite common in the general population, including athletes. In case of more than mild valvular heart disease, SE may be helpful to simultaneously assess functional capacity, the hemodynamic response to exercise, myocardial ischemia, and arrhythmias as well as dynamic changes in valvular disease severity. Clinical and echocardiographic follow-up should be repeated every 6 months or 2 years depending on the symptoms and degree of valvular pathology [29].

38.2.9 Mitral Valve Prolapse

The assessment of left ventricular contractile reserve may be useful to improve risk stratification and clinical decision-making in athletes with asymptomatic mitral regurgitation due to valve prolapse. Exercise may unmask the presence of signs and symptoms and may evaluate functional capacity in athletes that have equivocal symptoms. Athletes with mitral valve prolapse should undergo annual evaluations, including an echocardiogram at rest and during exercise that simulate the burden of exercise that they must face [30].

38.2.10 Left Ventricular Outflow Tract Gradient

Left ventricular outflow tract gradient or mid-ventricular obstruction can occur in athletes physiologically due to high-flow conditions in asymptomatic subjects or can be associated with symptoms (such as dyspnea of syncope or near-syncope) or ischemic-like ECG changes. It usually decreases with beta-blockers with amelioration of symptoms in symptomatic patients [31].

38.2.11 Atrial Volumes

In athletes, atria are larger than normal at rest, but their volume decreases, and function increases more than normal during exercise [32, 33]. However, a strenuous and prolonged agonistic exercise is associated with bi-atrial (and especially right atrium) dilation with decreased function [34].

38.2.12 Pulmonary Pressure

During exercise, there is a pseudo-abnormal rise in systolic pulmonary artery pressure simply due to the supernormal increase in cardiac output since pulmonary pressure is flow-dependent, and its value increases during high-flow conditions [35, 36]. However, it is possible that exercise-induced remodeling involves cardiac chambers and pulmonary circulation, which may show an increase in estimated pulmonary vascular resistances [37].

38.2.13 Right Ventricular Function

The right ventricle is particularly susceptible to hemodynamic stress (especially to high-volume loads). Although the right ventricular systolic function at rest is not different between athletes and controls, right ventricular enlargement and diminished systolic function in high-level endurance athletes after highly intensive and/or repetitive exercise may occur. This phenomenon is commonly known as "right ventricular fatigue" [38–40]. However, whether these primarily temporary effects may result in chronic right ventricular failure is still a matter of debate.

38.3 Ecological SE

Ultrasound scanner miniaturization is a reality, and our imaging devices are smaller and smaller with laptops and even smartphones being used. Although their image quality cannot rival that of high-end systems, this miniaturization will allow diagnosis anytime, anywhere, and of virtually anything (from left ventricular function to pulmonary edema). This technological innovation is especially promising in the SE field since it holds the potential of a paradigm shift from the artificial reality of the cardiac stress testing lab to the real world. Extreme psychological, environmental, and physical challenges cannot be reproduced in the cardiac stress laboratory with any physical or pharmacological stress. A prototype of this cultural and methodological transition from an artificial, indoor to outdoor, ecologic stress is represented by lung ultrasound in extreme physiology settings, such as high-altitude trekking [41–44] or deep underwater apnea diving [45–48].

Fig. 38.2 B-lines by portable lung ultrasound in 3 different outdoor and indoor settings: on a boat in Sharm-El- Sheik, Egypt, to scan elite apnea divers soon after emersion (left upper panel); in Nepal, in a tent to scan trekkers to identify high-altitude pulmonary edema at a subclinical stage (left lower panel); just after the arrival of the marathon or ultramarathon (right upper panel); indoor in the mountain medicine lab during a hypoxic challenge with exercise (right lower panel). In the middle, lung sonography with a portable echo shows no B-lines at rest (upper panel), B-lines soon after diving (middle panel), and return to baseline 24 h after diving (lower panel). (By courtesy of Lorenza Pratali, MD, [42], and Francesca Frassi, MD [45])

An example of ecologic SE in extreme environments is shown (Fig. 38.2). B-lines are detected by lung ultrasound well before the development of clinically overt pulmonary edema in apnea divers, high-altitude trekkers, and marathon or ultramarathon runners.

The theater is no longer the large and comfortable SE lab, crowded with nurses, doctors, and fellows-in-training, armed with last-generation, high-end, costly, and heavy ultrasound instruments with all sorts of technological options. In this artificial world, patients are scanned while lying quietly in the most suitable position for ultrasound imaging and with all equipment and personnel readily available for treating any sort of complications. The new theater for ecological stress is a hostile environment, often with limited space and time available for meaningful image acquisition with a pocket-size machine, usually with the doctor playing the role of cardiologist, nurse, and technician at the same time. Yet, the information available is probably greater with ecological stress outdoors than in a controlled setting in the hospital, where some conditions—for instance, mental stress, psychological discomfort, environmental aggression with urban pollutants, or extreme physiology conditions—cannot be reproduced. In the next years, SE will go outdoors, and a new physiological and clinical window of opportunity will be opened for the technique (Table 38.2).

Table 38.2 From indoor to outdoor SE

SE	Indoor	Outdoor
Instrument	High-cost, heavyweight	Low-cost, lightweight
Subjects	Sick or suspected sick	Well or worried well
Theater	SE lab	Desert, sea-boat, mountain
Stress type	Exercise or drugs	Extreme physiology
Echo scan	Comprehensive	Focused
Main target	Wall motion	B-lines
Stress	Artificial	Ecologic (real life)

38.4 Post-COVID-19 Assessment

Cardiovascular involvement is a frequent and well-known complication of COVID-19 and subclinical myocardial injury may precipitate arrhythmias and even sudden cardiac death during moderate-to-high physical exertion [49, 50]. According to current recommendations, SE may be useful to further stratify the risk of athletes recovering from COVID-19 and abnormal primary screening results (EKG, troponin testing, resting echocardiography) before returning to play and should be performed in case of persistent or new-onset cardiovascular symptoms [51–54]. Exercise SE can help recognize myocardial injury and/or subclinical myocarditis in young athletes who recovered from COVID-19, thus contributing to the optimization of recovery time and safe return to play [55].

38.5 Limitations

Transthoracic echocardiography is the initial test in athletes. Exercise SE is the test of choice when an exercise test is warranted. Nevertheless, ultrasound has limitations in these subjects and should be completed by other imaging techniques when needed. Transthoracic echocardiography does not allow imaging of coronary artery anatomy, and coronary computed tomography angiography is indicated when congenital coronary anomalies, bridging, or coronary artery stenosis are suspected. Cardiac magnetic resonance provides unique information on myocardial fibrosis and inflammation and is indicated when cardiomyopathy or myocarditis is still suspected after the ultrasound examination. Cardiac magnetic resonance also provides a better definition of right ventricular anatomy, function, and structure, and is indicated when right ventricular involvement is suspected, or to characterize aortic morphology, since some portions of the ascending aorta may be inaccessible to transthoracic echocardiography.

38.6 Clinical Guidelines

SE is recommended in athletes with ventricular arrhythmias and intermediate probability of coronary artery disease, in individuals with symptoms, and in asymptomatic patients at high risk [56, 57]. Other applications beyond wall motion are

Table 38.3 Recommendations for SE in athletes in guidelines

	COR	Ref
Athletes with ventricular arrhythmias and an intermediate probability of CAD	1	ESC 2015 [56]
Asymptomatic, > 35 years who have a very high risk of cardiovascular disease (SCORE > 10%, strong family history or familial hypercholesterolemia) and want to engage in high to very high-intensity exercise	2b	ESC 2020 [57]
Symptomatic, abnormal findings on clinical examination, abnormal or uninterpretable ECG, or abnormal exercise test	1	ESC 2020 [57]

CAD coronary artery disease, *COR* Class of Recommendation

suggested for hypertrophic cardiomyopathy patients without obstructive gradients at rest and in patients with congenital heart disease since left ventricular outflow obstruction or systemic atrioventricular valve regurgitation can become more severe during exercise (Table 38.3).

An optimized diagnostic approach for these subjects should minimize or avoid ionizing radiation exposure with scintigraphy or coronary computed tomography angiography since these patients are young and especially sensitive to the long-term effects of radiation on cancer and atherosclerosis. In addition, these patients are more likely to benefit from a comprehensive approach, since there are multiple sites of vulnerability and the gray zone between physiology and disease is decreased when the resting evaluation is coupled with a dynamic evaluation during exercise.

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Stress Echocardiography Post-COVID-19

39

Antonello D'Andrea, Francesco Sabatella, and Eugenio Picano

Keywords

Coronary microcirculation · COVID-19 · Pulmonary hypertension · Vaccines

39.1 Transthoracic Echocardiography and Lung Ultrasound in COVID-19 Infection

Transthoracic echocardiography (TTE) with lung ultrasound plays an essential role in the acute phase of COVID-19 infection since the presence of B-lines identifies early the interstitial syndrome of lung involvement, useful for diagnosis and risk stratification of COVID-19 pneumonia. B-lines from COVID-19 share the features of acute respiratory distress syndrome, and therefore they can be differentiated from cardiogenic B-lines due to pulmonary edema from heart failure for several features. Briefly, the pleural line is smooth in cardiogenic B-lines and bumpy and fragmented in COVID-19 interstitial syndrome [1]. Left ventricular function is abnormal in cardiogenic B-lines and normal in COVID-19 B-lines. Stress echocardiography (SE) is useful after SARS-CoV-2 infection, in the chronic phase mainly for symptomatic patients and asymptomatic patients with some resting abnormalities to assess the right ventricular-pulmonary unit and the left heart, both possible targets of long COVID-19.

A. D'Andrea (✉) · F. Sabatella
Department of Cardiology, Umberto I Hospital, Nocera Inferiore (Salerno), University of Campania "Luigi Vanvitelli", Caserta, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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39.2 COVID Acute Phase

Acute cardiovascular abnormalities are observed in half of all COVID-19 patients and may range from right ventricular wall motion abnormalities to interstitial lung disease with alveolar-capillary distress [1], global left ventricular contractile dysfunction, and coronary microvascular abnormalities [2]. Cardiac autonomic dysfunction is often present [3]. In addition, pulmonary hypertension is a recognized risk factor in the short term [4], and valves are a possible target since myocardium and valve stromal fibroblasts are rich in angiotensin-converting enzyme 2 which is the receptor for SARS-CoV-19 [5]. The clinical picture can be complicated by the frequent coexistence of cardiovascular comorbidities.

In some cases, the SARS-CoV-2 can cause direct damage to myocytes mediated by stimulation of the angiotensin-converting enzyme 2, which is expressed on myocytes and vascular endothelial cells, acting as a receptor for SARS-CoV-2 and as a "gateway" for the virus in these cells. Another hypothesized mechanism is myocardial damage induced by hypoxia and activation of the innate immune response with the release of pro-inflammatory cytokines. The subsequent inflammatory storm is also termed cytokine release syndrome, associated with the activation of the adaptive auto-immune system which can induce vascular and myocardial inflammation and an excess of blood clotting, with consequent episodes of diffuse thrombosis and shock. As a result of systemic hyper-inflammation and pro-thrombotic state, patients with COVID-19 pneumonia can rapidly develop severe complications such as respiratory failure, renal failure, or liver dysfunction, which can affect both thromboembolism and bleeding status. This infection is therefore associated with high morbidity and mortality largely due to respiratory failure, with microvascular pulmonary thrombosis perhaps playing an important pathophysiological role, like in other models of viral pneumonia. The increase in pulmonary artery pressure is a common condition among patients with severe COVID-19 pneumonia and cardiac injury and is linked to a higher risk of in-hospital mortality when associated with right ventricular dysfunction [6]. Severe COVID-19 infection is also associated with coronary microvascular dysfunction and cardiac autonomic unbalance.

39.3 COVID Chronic Phase

The chronic phase of COVID-19 infection can determine the Post-Acute Sequelae of SARS-CoV-2 (PASC) syndrome, which is defined as a set of recurring signs and symptoms about a month after SARS-CoV-2 infection. PASC-cardiovascular syndrome is defined as a wide range of signs and symptoms without pathological findings in standard diagnostic tests. Common symptoms include tachycardia, exercise intolerance, fatigue, palpitations, chest pain, and dyspnea. Exercise intolerance and tachycardia are the most frequent symptoms. In a prospective cohort of 247 patients with COVID-19 home-isolated, 30% described fatigue and 15% dyspnea up to 6 months [7].

A potential mechanism of exercise intolerance and excessive tachycardia in COVID-19 is deconditioning, associated with inactivity due to home isolation. On the other hand, PASC-cardiovascular disease involves an extensive group of cardiovascular diseases that include myocarditis and other forms of myocardial injury, pericarditis, new or worsening myocardial ischemia, microvascular dysfunction, nonischemic cardiomyopathy, increased thromboembolic risk, cardiovascular sequelae secondary to lung disease, and new onset of arrhythmia such as atrial fibrillation, premature ventricular contractions, and non-sustained ventricular tachycardia. In addition, postural orthostatic tachycardia syndrome has been described after SARS-CoV-2 infection [8–11].

39.4 SE Activity During the Pandemic Period

The SARS-CoV-2 pandemic has severely impacted the global health systems, challenging their capacity to provide essential healthcare services. Clinical practice has been strongly influenced at different levels. Regarding SE, both in the first and second waves of the pandemic we have seen a dramatic drop in the number of SE tests. In the United Kingdom, for example, data from sites confirm the overall reduction of the number of tests provided per month equal to 55%, with a reduction in the number of sessions and of patients in each session [12]. During the second wave of the pandemic, SE has been practiced almost at the same level as in the pre-COVID era. Some sites had replaced exercise stress tests with pharmacological stress. In other centers, to reduce the risk of contagion, patients had to wear level 2 Personal Protective Equipment, a swab test 2 or 3 days before an appointment was made, and screening questionnaires have been requested. In Italy, we observed a reduction of the activity in echocardiographic laboratories and especially in stress tests with an 83% reduction compared to pre-COVID-19 levels [13]. Among the noninvasive tests, exercise SE is the one at the highest risk of contagion due to the large generation of aerosols. Some precautions and habits in clinical practice must be considered [14]. It should start with determining the clinical benefit in those symptomatic patients in whom the infectious status has not been clarified. Limiting accompanying visitors, frequent hands washing, wearing masks, limiting contact time, and sanitizing instruments between examinations are all valid indications of the correct management of routine practice. For the safety of health care professionals, administering screening questionnaires about symptoms suggestive of SARS-CoV-2 infection and temperature checks are recommended.

Aerosol-generating procedures such as stress exercises should be performed in a room with good air circulation with negative pressure [15]. To reduce the spread of the disease and minimize patient and physician contact, a SE should be performed only if there is a reasonable clinical indication and it is important to know if the exam is decisive in patients not tested for SARS-CoV-2, to protect the medical team and any other patient (if tests are performed in emergency departments, for example). In order to limit the risks of contagion in hospital environments, patients with COVID-19 should be isolated from other patients in dedicated rooms, and SE should be executed in this

specific location. Patients not hospitalized must be screened for infection before the beginning of the exam: testing for COVID-19 is highly recommended before stress exercise. In some hospitals have been established different rooms and machines for patients with suspected infections. Cardiac imaging scan times should be minimized, and the images must immediately focus on the clinical question. The number of physicians and nurses taking part in the examination should be reduced to a minimum. If possible, especially during the pharmacological stress test, it would be safer to measure blood pressure with an automatic sphygmomanometer. Frequent hand washing is a good way to reduce contagion among the medical team. The increased risk for aerosolization during SE makes it necessary to use Personal Protective Equipment such as gloves, head covers, eye shields, and face masks.

The use of surgical masks for patients during stress testing may be considered. A stress test with a surgical facemask is a feasible procedure and does not negatively affect the functional capacity of our patients [16, 17].

About the devices to be used, such as a cover on probes and machine consoles, the possible reduction in the quality of the image must be considered. The virus is sensitive to most disinfectants, so machines and probes must be cleaned between exams (if the institution has isolation rooms, the machine should be cleaned inside the room and in the hall again). To reduce the risk of transmission, also phones, desktops, monitors, and keyboards should be frequently cleaned.

In waves of intense epidemiological pressure, pharmacological stress should be preferred over exercise (within the limits of clinical appropriateness). Among the exercise stress tests, a bicycle protocol is preferred since it is associated with lower peak ventilations per minute compared to a treadmill.

39.5 Post-COVID SE

The versatile platform of comprehensive SE is ideally suited to identify functional abnormalities, stratify prognosis, and personalize treatment in this complex and expanding population of patients with status post-COVID-19 and/or with persisting symptoms after resolution of clinical disease ("long COVID-19") (Table 39.1).

SE can find an indication in post-COVID-19 surveillance. In the clinical spectrum of long COVID-19 syndrome, there is a high burden of cardiopulmonary symptoms including breathlessness, palpitations, chest pain, and fatigue. Establishing the weight of the myocardial injury and cardiac sequelae of COVID-19 in determining these symptoms is often challenging. SE may identify and quantify the heart involvement in this setting of patients [18]. Recumbent or semi-recumbent exercise (e.g., rowing, cycling) is recommended for initial evaluation for PASC- cardiovascular syndrome patients who experience tachycardia, exercise/orthostatic intolerance, and deconditioning [19].

Global contractile function, coronary microvascular abnormalities, cardiac autonomic dysfunction, and pulmonary hypertension are the most frequent pathological features that can be studied with the ABCDE-FG plus LPR-SE protocol [19].

ABCDE-FG plus LPR-SE is an ideal protocol for evaluating functional impairment, assessing the prognosis, and planning a personalized treatment pathway in

Table 39.1 Rest and SE in patients post-COVID-19 infection

	Rest TTE	SE
Wall thickness	v	
Resting LVOTG	v	
LV systolic function (EF)	v	
LV diastolic function (E/e′)	v	
PASP (hemodynamic congestion)	v	
LAVI	v	
Mitral leaflets, papillary muscles	v	
RWMA		v
B-lines		v
LVCR		v
CFVR		v
HRR		v
MR		v
LVOTG		v
LAVI		v
PASP		v
RV function	v	v

CFVR coronary flow velocity reserve, *EF* ejection fraction, *HRR* heart rate reserve, *LAVI* left atrial volume index, *LVOTG* left ventricular outflow tract gradient, *MR* mitral regurgitation, *PASP* pulmonary artery systolic pressure, *RWMA* regional wall motion abnormalities, *RV* right ventricle

this population that is expected to increase. Although in some cases the feasibility of the examination depends on the quality of the acoustic window, the great versatility of SE allows us to evaluate a series of parameters beyond the simple evaluation of inducible ischemia in coronary artery disease, providing a complete view of cardiovascular functional status [20].

Each step carries information and represents a potential target for a selective therapeutic approach. Regional wall motion abnormalities are the expression of thrombotic occlusion of a previously existing atherosclerotic plaque or the extreme expression of cardiac autonomic dysfunction with sympathetic overactivation and reversible Tako-tsubo-like cardiomyopathy [21, 22]. More subtle and frequent abnormalities may be the expression of myocarditis later evolving into myocardial fibrosis and more frequently affect basal segments, differently from the Tako-tsubo pattern [23]. Pulmonary congestion or lung interstitial fibrosis is mirrored by wet or dry B-lines respectively [24]. Global left and right ventricular function simply measured with ejection fraction and tricuspid annular plane systolic excursion has a major impact on outcome [25]. The spectrum of subtle alterations induced by COVID-19 also may include coronary microvascular disease [26], cardiac autonomic dysfunction [27], valvular disease [28], pulmonary hypertension [29], and associated right ventricular dysfunction [30, 31]. A comprehensive approach like the one provided by comprehensive SE allows an integrated evaluation of these challenging patients. The evaluation by rest TTE can be performed in all patients and a selective SE evaluation in patients with symptoms or resting TTE abnormalities at 4 weeks to 4 months after the acute infection (Fig. 39.1).

The possible integration of SE in the surveillance strategy is now under evaluation in a prospective study of the SE 2030 project (Fig. 39.2) [18].

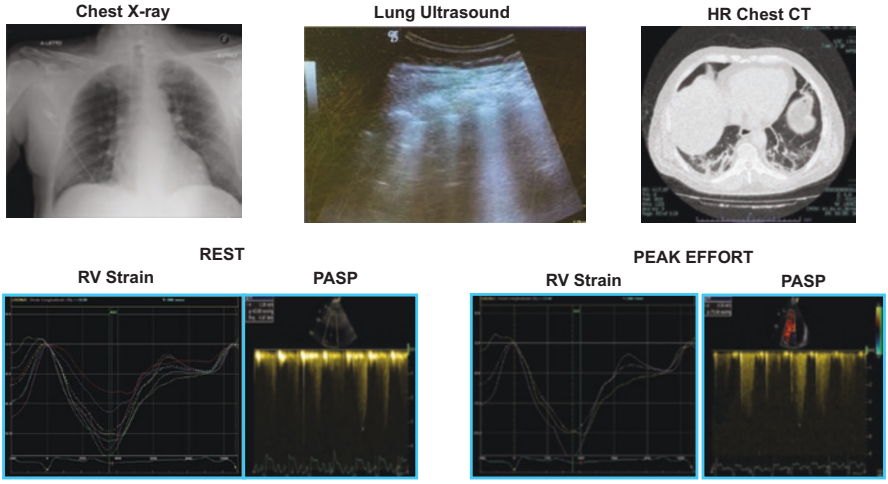

Fig. 39.1 Multimodality imaging approach in a 42-year-old patient with interstitial pneumonia as the main clinical manifestation of COVID-19 infection. In the acute phase, both the chest X-ray and the chest computed tomography scan show bilateral multifocal alveolar opacities associated with consolidation areas with patchy distribution, mainly peripheral-subpleural, with lung ultrasound B-lines. At a 6-month follow-up, resting TTE shows a normal right ventricular strain with mildly elevated pulmonary artery systolic pressure, estimated from tricuspid regurgitant jet velocity. During semi-supine exercise, dyspnea occurs together with a reduced right ventricular contractile reserve (right ventricular strain from rest = 13 to peak stress = 12%) and a significant increase in pulmonary artery systolic pressure (from rest = 43 to peak stress = 75 mmHg)

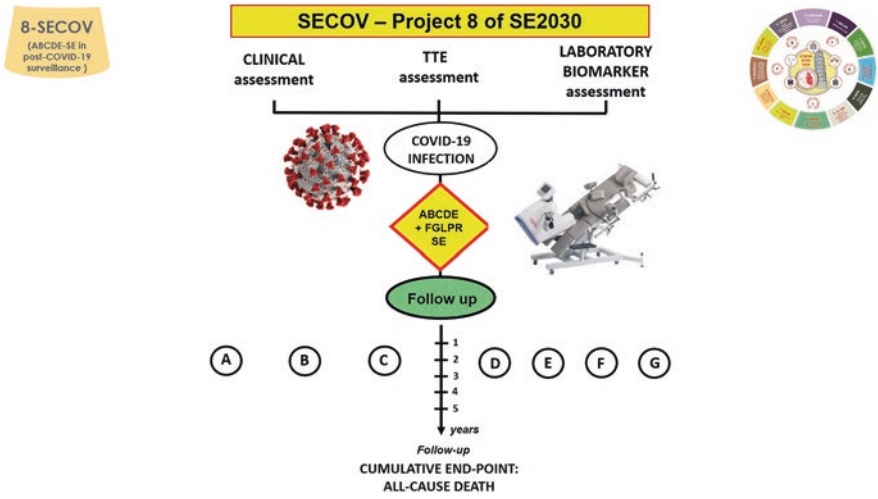

Fig. 39.2 The study flowchart of the subproject SECOV in SE 2030 adopts the comprehensive ABCDE+ protocol for surveillance of patients with cardiovascular symptoms post-COVID-19

39.6 Post-COVID Myocarditis

Acute myocarditis is defined as a pathological condition characterized by cardiac symptoms, increased C Troponin levels, alterations in the electrocardiogram (abnormalities of ventricular repolarization, arrhythmias), and left ventricular wall motion abnormalities at rest echocardiogram despite normal epicardial artery flow. In the under-20 population, the incidence is estimated to be about 450 per million [32]. It can be due to COVID-19 infection or COVID-19 vaccines, and many other infective and noninfective causes, such as bacteria, fungi, viruses, drugs, toxins (such as ionizing radiation), and immune-mediated causes (acute graft rejection). The real impact of SARS-CoV-2 infection on the prevalence of myocarditis is debated. Fulminant myocarditis is, fortunately, a rare occurrence.

Post-COVID-19 myocarditis is a serious complication of viral infection that presents with a wide spectrum of clinical manifestations, from cardiogenic shock to subclinical or asymptomatic patient involvement with cardiac abnormalities detected with cardiac magnetic resonance [33]. Clinical presentation varies from fatigue, dyspnea, chest pain, and palpitations to (infrequent) hemodynamic instability and cardiogenic shock. Data from prospective studies show that myocardial dysfunction, also detected with an evaluation of biventricular longitudinal strain, seems to be present in up to 40% of patients hospitalized for COVID-19 infection [34]. Male predominance has been reported [35].

Myocarditis following COVID-19 mRNA vaccination is a rare complication usually occurring 3–4 days after the second dose, especially in young male adults [36]. The exact incidence is not known and varies according to the sex and age of the population under consideration.

Data from US Vaccine Adverse Event Reporting System show an incidence of 40.6 cases per million in male individuals aged 12–29 years and 2.4 cases per million in male individuals aged >30 years. Rates in female individuals were 4.2 and 1.0 cases per million respectively [37]. Analogously an Israeli study reported 136 cases of definite or probable post-vaccination myocarditis [36]. Important evidence was observed in another report where the incidence of postvaccination myocarditis after at least one dose of a COVID-19 mRNA vaccine was 21 cases per million for the all-comer population and 107 cases per million for male individuals aged 16–29 years [38]. The observed male predominance also notified in other reports [39] may be related to sex hormone differences in immune response [40]. The most frequent symptoms are represented by chest pain (described as discomfort or oppressive) and dyspnea that occur after 4–5 days after the administration of the vaccine. Clinical features mimic those of disease related to other causes, with troponin elevation, and electrocardiographic abnormalities with ST-segment elevation; only a small percentage of patients show a reduction in ejection fraction, compared with abnormalities shown on cardiac magnetic resonance, found in all patients. Most patients have a mild clinical course, with spontaneous resolution of symptoms with or without therapy [41]. Although further studies are needed to fully understand the mechanisms underlying the pathological process, molecular mimicry (between the spike protein of SARS-CoV-2 and self-antigens), autoantibody

formation, immune dysregulation with activation of natural killer cells in some individuals with genetic predisposition, and a dysregulated cytokine and immune response to mRNA are assumed to play a role [42, 43].

The extent and severity of damage are adequately assessed by TTE, but the chances of reversibility of damage are optimally assessed with the evaluation of contractile reserve [44]. The presence of contractile reserve predicts functional improvement and safe weaning of ventricular assist devices [45, 46]. The same pattern of the contractile reserve with dobutamine associated with better outcomes has been found in patients with peripartum cardiomyopathy and baseline severe left ventricular dysfunction [47–49].

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Part V

The Society

Economic Sustainability of Cardiac Imaging

40

Clara Carpeggiani and Eugenio Picano

Keywords

Cost · Cost-benefit · Cost-effectiveness · Direct cost · Externalized cost

40.1 Cardiac Imaging Impact on Healthcare Cost

Healthcare payment is a subject on the mind of virtually every citizen today. The overuse of medical imaging is an area where expenses can be cut without undermining the quality of care [1]. Imaging is a major culprit for several reasons. For instance, diagnostic imaging tests are performed to protect against malpractice exposure, a high-cost diagnostic procedure is used for patients at low risk for the condition, a diagnostic test is applied despite no expected impact on the course of the treatment or there may simply be a lack of communication and inadequate exchange of information among physicians. As a result, more than 95 million high-tech scans are done each year in the USA, and medical imaging (including computed tomography, magnetic resonance imaging, and positron emission tomography scans) has ballooned into a $100-billion-a-year industry in the United States, with Medicare paying for $14 billion of that [1]. In the last years, some techniques fell precipitously for cost containment and radiation concern issues. In Canada, the number of single-photon emission tomography sites (mainly used for cardiological applications) fell from 603 in 2007 to 330 in 2017 [2]. In the USA, the single-photon emission tomography studies at Mayo Clinic rose by 300% from 1992 to 2003 and fell by 300% from 2003 to 2012 [3]. In Australia, the stress scintigraphy/

C. Carpeggiani (✉)
CNR, Biomedicine Department, Institute of Clinical Physiology, Pisa, Italy

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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stress echocardiography (SE) ratio in the public healthcare service was 1/1 in 2003 and 1/10 in 2015 [4]. Increasing concerns about radiation exposure and the sustainability of the healthcare system were the main drivers of the observed reduction in myocardial perfusion imaging scintigraphy cardiac imaging and symmetrically promoted the use of techniques less expensive and radiation-free such as SE [4]. Concerns about economic sustainability further increased in the COVID-19 era, characterized by an acute >50% reduction of all forms of cardiac imaging, and more pronounced for more expensive testing, with a relative increase in the overall appropriateness of indications [5].

40.2 Comparative Costs of Cardiac Imaging

No cardiac imaging examinations are free, and they all imply a financial cost and a risk. Referring to the 2012 Medicare fee schedule for selected cardiovascular tests, for a cardiac imaging test, compared with the treadmill exercise test considered as equal to 1 (as a cost comparator), the cost of a coronary computed tomography angiography is 2.5x, SE 2.9x, stress scintigraphy 4.8x, stress-cardiac magnetic resonance 5.4x, and a diagnostic catheterization 13x higher [6]. The absolute cost is very difficult to assess, and in the USA the price variation among the top 20 hospitals is substantial. The median prices ranged from $204 to $2588 for an echocardiogram, $463 to $3230 for a nuclear stress test, $2821 to $9382 for a right heart catheterization, $2868 to $9203 for a coronary angiogram, $657 to $25,521 for a percutaneous coronary intervention (PCI), and $506 to $20,002 for pacemaker implantation, the report states. Within-hospital variation also ranged broadly, on average fourfold. The widest interquartile ranges were $3143–$12,926 for a right heart catheterization, $4011–$14,486 for a coronary angiogram, $11,325–$23,392 for a PCI, and $8474–$22,694 for pacemaker implantation [7]. A cardiac stress positron emission tomography (PET) scan has an average national price of *$7900* (ranging from a minimum of $2850 to a maximum of $24,200). A SE has an average cost of $2600, with a range from $200 to $5000 [8]. In other words, the cost of cardiac stress imaging can range anywhere from $200 for the least expensive SE to $24,200 for the most expensive stress PET, which is a 121-fold variation.

After the release of the 2019 European Society of Cardiology guidelines, cardiac imaging has become a first-line diagnostic tool replacing the simple exercise electrocardiography test [9]. Treadmill exercise test-is cardiac imaging more affordable test. The average relative costs of the imaging procedures in Europe show an even steeper cost gradient between SE (relative cost =1) and other noninvasive and invasive imaging techniques [10], with a SE cost three times lower than coronary computed tomography angiography and 18 times lower than a PET (Fig. 40.1)

Costs may vary depending on who pays, the site of service and patterns of downstream costs, costs of environmental impact per procedure, and cost of acute and long-term complications or potential cost savings should be considered implicitly. If we add to the direct costs the downstream and externalized costs, the economic

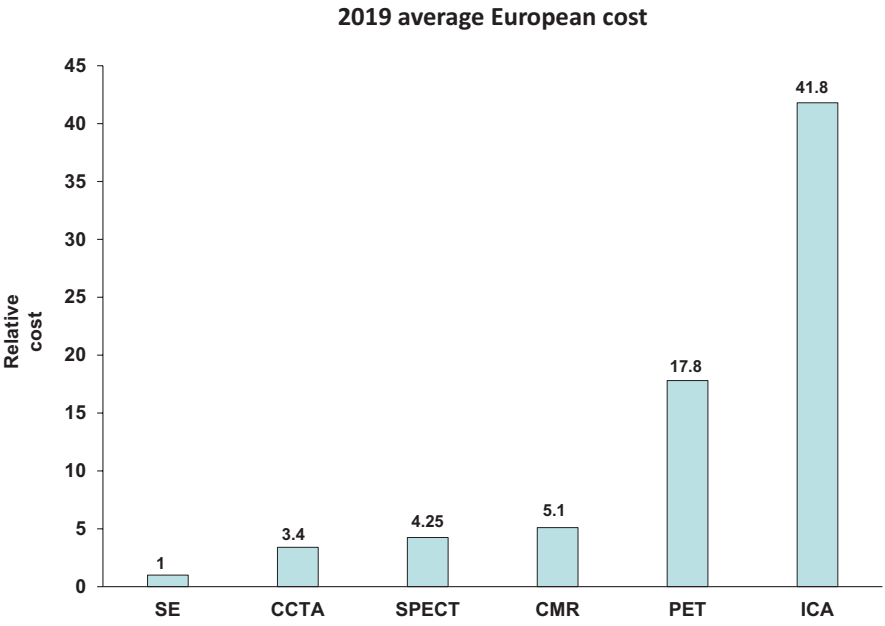

Fig. 40.1 The relative costs of different cardiac imaging techniques. From the average data of the 2019 EVINCI European Consortium fee schedule presented in [10] from Lorenzoni et al. *ICA* invasive coronary angiography

gap in favor of SE further widens. Downstream cost includes the additional cost of extra cancer induced by ionizing radiation [11]. The number of additional downstream examinations is higher with coronary computed tomography angiography or single-photon emission tomography than with SE since anatomic documentation of disease is not enough to justify revascularization and myocardial perfusion imaging is a low specificity technique [12–16].

40.3 The Cost of Inappropriateness

Cardiovascular imaging has become the focus of intensive efforts on the part of public and private payers, since it has substantially increased the escalating healthcare costs in the last 20 years, and payment to cardiologists for imaging services represented 8.7% of total payments for all physician services in 2006 [17]. According to recent estimates, 20–50% of all examinations are uncertain or inappropriate, i.e., risks and costs outweigh benefits [18]. To limit the detrimental consequences of inappropriateness and diagnostic obesity, the European Commission in 2001 [19] and more recently the European Society of Cardiology [20] and the American College of Cardiology Foundation/American Society of Echocardiography [21] have prepared guidelines on the appropriateness of general or specialized imaging testing, including SE [22]. The goal of these documents is to define the appropriate test for the appropriate indication in the appropriate patient: a difficult and elusive

target which is, however, one of the new features, and not the least important, of good-quality medical care. The most frequent appropriate, uncertain, and inappropriate indications encountered in the clinical practice of high-volume laboratories are listed in Table 40.1 [22].

Following these criteria, only two out of three SE tests are appropriate, with similar numbers observed in disparate geographic, cultural, and economic situations—from Europe to Australia to the USA [23–28] (Fig. 40.2).

Of interest, most inappropriate studies were restricted to only a few patient indications, with the three most frequent inappropriate indications accounting for 79% of inappropriate indications in ambulatory patients [26]. These indications included symptomatic patients with a low pretest probability of coronary artery disease having an interpretable exercise electrocardiogram, asymptomatic patients who had undergone angioplasty less than 2 years before, and symptomatic patients with low risk [28].

An inappropriate test also provides negligible prognostic information when compared to an appropriate test and is per se—independent of test positivity or negativity—associated with a lower rate of positive results and better survival as compared with appropriate and uncertain indications [29, 30]. The high rate of inappropriateness is resistant to all efforts to reduce it, including dissemination of appropriateness use criteria by scientific societies [31] and informatic support with computerized

Table 40.1 Most frequent appropriate/uncertain/inappropriate indications in coronary artery disease detection and/or risk stratification

	Appropriate	Uncertain	Inappropriate
ECG uninterpretable or unable to exercise, or prior stress ECG equivocal	√		
Coronary artery stenosis of unclear significance (CT or angiography)	√		
Post-revascularization not in the early post-procedure period, with change in symptoms	√		
Pre-surgery, high-risk non-emergent, poor exercise tolerance <4 METS	√		
Viability (dobutamine) ischemic cardiomyopathy, known CAD, patient eligible for revascularization	√		
Asymptomatic or stable symptoms, repeat SE after >5 years		√	
Asymptomatic <5 years post CABG or < 2 years post-PCI		√	
Asymptomatic, low risk			√
Pre-op, intermediate-risk surgery, good exercise capacity			√
Symptomatic, low pretest probability, interpretable ECG, able to exercise			√
Asymptomatic <1 year after PCI/CABG or stable with recent abnormal stress			√

CABG coronary artery bypass surgery, *CT* computed tomography, *METS* metabolic equivalents, *PCI* percutaneous coronary intervention

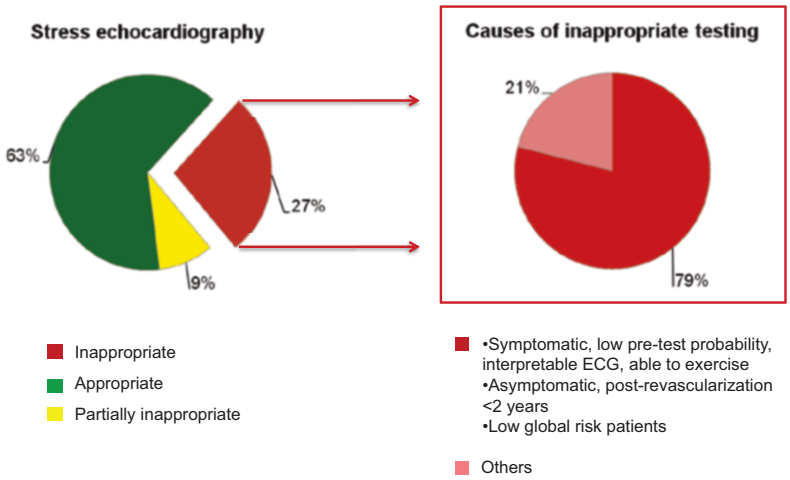

Fig. 40.2 The inappropriateness rate (left) and the main reasons for inappropriate indications. Redrawn from the original data of Picano et al. [23] and Cortigiani et al. [28]

order entry tools [32]. The inappropriateness affects all diagnostic and therapeutic testing, paid by private or public money [33], and any attempt to change this behavior can be a risky business because in many cases health professionals and institutions survive and grow thanks to inappropriateness [34–36].

40.4 Take-Home Message: Our Responsibility to Change

Appropriateness in health care, like quality, can be a moving target and not easy to define. Forty years ago, a *Lancet* editorial complained of the "flooding of laboratory testing" requested by clinicians who believe that "all seem to be for free" and often ask for "diagnostic carpet bombing" instead of carefully targeted, clinically driven testing [37]. The same pattern seems to apply to cardiac stress imaging testing. Several factors may influence the ordering of an inappropriate test such as financial incentives, lack of physician confidence in clinical assessment skills, patient insistence, pro-technology bias, lack of a filtering order system, and knowledge gap of the prescribing physician regarding cost, radiation doses, and environmental impact (Table 40.2).

Much imaging practice is driven by habit or anecdote, new methods enter the clinical practice with limited testing of their contribution to improving health, and—most importantly—evidence basis for using imaging is incomplete [38], and we urgently need comparative effectiveness randomized trials of imaging-guided strategies to reliably guide healthcare coverage and medical necessity decisions in the prevalent population [39]. It is also difficult to convince patients with cardiac conditions that routine cardiac imaging is no longer needed and is harmful [40]. The major question that needs to be posed to both the physician and the patient when ordering a test is whether that test is likely to bring about change in management. If not, that test cannot be appropriate under the circumstances [41, 42].

Table 40.2 The road to economic sustainability in the cardiac imaging lab

	What we have	What we need
Philosophy	Moral suasion	"Carrot and stick"
Audit	"Prejudicial to our reputation"	A legal duty
Payment	Pay-per-volume	Pay for appropriateness
Authorization	Specialist self-referral	Radiology manager pass
Indication	Guidelines and "experience"	Decision-support system
Cost and radiation dose	Physician knowledge gap	Embedded in order forms
Induced cancer cost	Ignored	Included
Environmental cost	Ignored	Included
Patient education	Early screening and intensive follow-up	Choosing wisely
Economic climate	Affluent society	Sustainable society
Starting point	High-tech (imaging first)	High touch (patient first)
Industry	Pro-technology bias	Cost-effectiveness
Physician mantra	More is better	Less is more

Although patients, institutions, and physicians all share the goal of delivering effective and high-quality medical care, "in too many instances financial pressures, structural inefficiencies, imperfect information, and irrational patterns of traditional practice, resource allocation and use defeat or deflect the achievement of these ends." The possible countermeasures are a better alignment of payment incentives for physicians and hospitals, transparency of performance measures and cost data, and incentives for promoting more appropriate and responsible delivery of care [43]. Cardiac stress imaging procedures—be it nuclear stress testing or SE—are 2 to 6 times more frequent among patients seen by physicians who provide and bill for these procedures than by those not billing [44], clearly showing the persistence of financial conflicts of interest as a driver of utilization [45]. The quest for appropriateness is a priority for the echocardiography community to improve the quality of our profession, address the legitimate existing concerns of those who pay for these services, and optimize the immense benefits our patients can derive from the appropriate practice of cardiac imaging and SE [26, 46]. When safety issues and economic costs come on stage, they have disruptive effects on prescription patterns [47], with privileged use of less expensive and radiation-free techniques.

Society cannot afford the culture of waste, generating inappropriate and costly examinations. In the USA, the decrease in reimbursements from the Deficit Reduction Acts determined a fall in SPECT and a paradoxical increase in in-office cardiac PET, with the utilization rate tripled from 2010 to 2019 and boosted by financial incentives more than technological advances or interpretation familiarity [48]. When physicians are salaried, without fee-for-service, echocardiography rose by 30% from 2012 to 2017 and the utilization rate is 10 times lower for all imaging techniques, especially for the most expensive ones [49]. The modalities of reimbursement and vested interests are likely more important than scientific evidence, societal costs, climate impact, and long-term risks in determining the utilization rate of different imaging modalities [50]. The direct cost is a key component of the cost-benefit assessment of different cardiac imaging options according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [51].

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Radiologic Sustainability of Cardiac Imaging

41

Maria Grazia Andreassi and Eugenio Picano

Keywords

Atherosclerosis · Cancer · Justification · Optimization · Radiation

41.1 Radiation in Cardiology

The radiation dose and related downstream cancer risk should be included in the risk-benefit balance of any medical diagnostic or therapeutic imaging procedure [1]. Until 2002, radioprotection was missing in cardiology textbook knowledge [2]. The consequence was that both prescribers and practitioners ignored, and sometimes still ignore, the doses and risks of common imaging examinations [3–8]. Yet, ionizing radiation is a proven carcinogen even at low doses [9], the doses of many common tests in cardiology are not so low [10], and the use of radiation is strictly regulated by medical guidelines endorsing a responsible and knowledgeable use of tests based on medical radiation for logical, legal, and ethical reasons [11]. Medical radiation exposure exceeds the dose equivalent of 150 chest X-rays per year per person. One-half of them come from medical radiation performed or prescribed by cardiologists [12–14]. The doses are likely increased in the last 15 years in cardiology due to the proliferation of invasive cardiology and coronary computed tomography angiography, balancing the decline of nuclear cardiology. Cardiologists are also true contemporary radiologists, with a professional exposure per year four to five times higher than diagnostic radiologists [15]. This also means that our

M. G. Andreassi (✉)
Genetics Research Unit, Clinical Physiology Institute, National Research Council of Italy, Pisa, Italy
e-mail: andreassi@ifc.cnr.it

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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cardiology pediatric and adult patients are exposed to increased risks of developing cancer associated with cardiologic procedures and that the cardiologists themselves are at increased risk for developing cancer and noncancer diseases, including coronary artery disease and carotid disease due to unprecedented exposures without adequate protection [16, 17]. In the last decade, the radiation issue was finally embedded in mainstream cardiology and now it is universally accepted that the attention paid to radioprotection is a key aspect of the quality of cardiology practice. A radiation-sensitive practice will protect our patients, our staff, and ourselves, with a deep impact on the overall sustainability of the cardiologic practice. It should be present in every single act of our practice. The risk-benefit assessment of cardiac testing should include acute risk, subacute risk, and long-term risk due to cancer development from radiation exposure [18] (Fig. 41.1).

Following the definition of the American College of Cardiology Foundation, an appropriate imaging study is one in which the expected incremental information, combined with clinical judgment, exceeds any expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication [19].

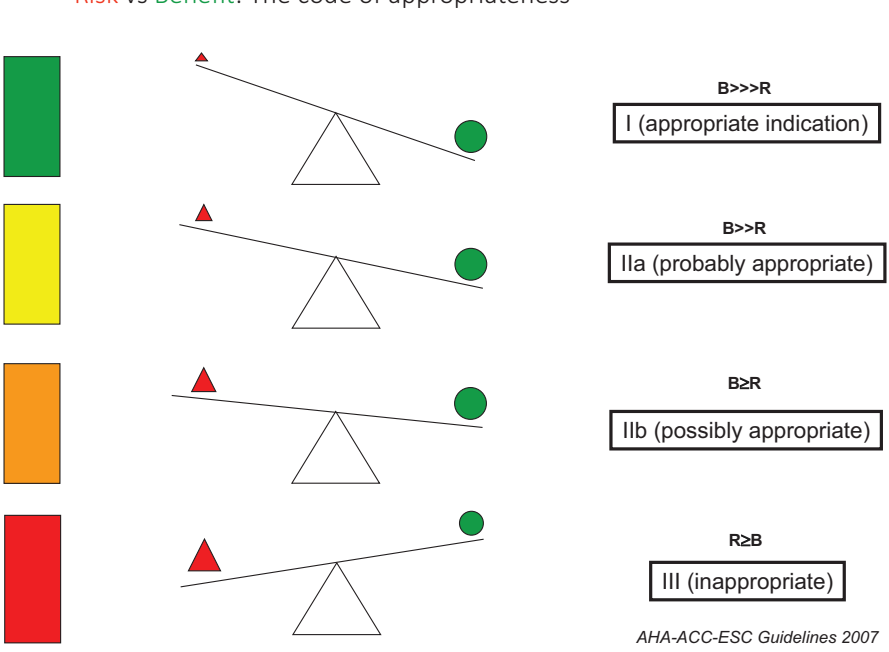

Fig. 41.1 The three angles of risk in risk-benefit balance. The balance between risks (red triangle) and benefits determines the appropriateness score of testing. The three angles of the red triangle represent acute, subacute, and long-term (radiation) risks. Acute risks occur within seconds and minutes (for instance, death or myocardial infarction during a stress test or catheterization); subacute risks within days or weeks (for instance, iodinated contrast-induced nephropathy); and long-term risks (due to cumulative exposure to ionizing radiation) after years or decades

Negative consequences include the risks of the procedure itself (i.e., radiation or contrast exposure) and the downstream impact of poor performance such as delay in diagnosis (false-negative results) or inappropriate diagnosis (false-positive results). This implies potential harm for patients undergoing imaging (who suffer the risks of an imaging study without a commensurate benefit), excessive delay in the waiting lists for other patients needing the test, and an exorbitant cost for society, with no improvement and possibly with a reduction in care quality [19].

An exam can be appropriate if we consider only acute and subacute risks in the risk side of risk-benefit assessment and can become totally unacceptable and even legally liable if we include and spell out the radiation dose and risk. For instance, the images of hybrid imaging with coronary computed tomography angiography-positron emission tomography are of heart-breaking beauty and provide an integrated simultaneous assessment of coronary anatomy and myocardial perfusion. However, the beauty is less attractive if we consider the cost about 30 times that of stress echo, the radiation burden which is at least 1500 chest x-rays, and the environmental footprint which is about 500 times that of stress echo. No surprise that hybrid imaging plays a role in oncology but has no place in cardiology practice since the same information can be obtained with more affordable techniques.

41.2 Radiation in Common Invasive and Noninvasive Procedures in Cardiology Procedures

The largest source of dose exposure in cardiology is invasive fluoroscopy, with diagnostic and therapeutic interventions. The reference doses for common examinations are shown in Table 41.1. Guidelines often propose a wide range of values, due to the many sources of variability [20, 21].

Another important source of dose exposure for patients and doctors is cardiac electrophysiology [20–22]. The reference doses for common examinations are shown in Table 41.2.

Table 41.1 The radiation dose for common invasive fluoroscopy examinations (from [20, 21])

Diagnostic or therapeutic procedures	Effective dose (mSv)	Equivalent CXRs
Diagnostic coronary angiography	7 (2–16)	350
Percutaneous coronary intervention	15 (7–57)	750
Thoracic angiography (pulmonary or aorta)	5 (4–9)	250
Abdominal angiography or aortography	12 (4–48)	600
Pelvic vein embolization	60 (44–78)	3000
TIPS placement	70 (20–180)	3500
Aortic valvuloplasty	39 (12–100)	1950
Dilation chronic coronary occlusion	81 (17–194)	4050
Aortic aneurysm repair procedure	76–119	3800–8950
Renal angioplasty	54	2700
Iliac angioplasty	58	2900

From Picano E et al. 2014 [20] and Hirschfeld et al. 2018 [21]

Table 41.2 The radiation dose for common invasive cardiac electrophysiology examinations (from [25])

Cardiac electrophysiology		
Diagnostic procedures	Effective dose (mSv)	Equivalent CXRs
Diagnostic EP studies	3.2 (1.3–23.9)	160
Ablation procedure:	15.2 (1.6–59.6)	760
Atrial fibrillation	16.6 (6.6–59.2)	830
AT-AVRT	4.4 (1.6–25)	220
Ventricular tachycardia	12.5 (3.0–45)	625
Regular PM or ICD implant	4 (1.4–17)	200
CRT implant	22 (2.2–95)	1100

AT atrial tachycardia, *AVRT* atrioventricular reciprocal tachycardia, *CRT* cardiac resynchronization therapy. From Picano E et al. 2014 [20] and Hirschfeld et al. 2018 [21]

Table 41.3 The radiation dose for common computed tomography and conventional radiology examinations (from [20, 21])

Diagnostic procedures	Effective dose (mSv)	Equivalent CXRs
64-slice coronary CTA	15 (3–32)	750
Calcium score	3 (1–12)	150
Chest x-ray (postero-anterior)	0.02	1

From Picano E et al. 2014 [20] and Hirschfeld et al. 2018 [21]

Table 41.4 The radiation dose for common nuclear cardiology examinations (from [20, 21])

Diagnostic procedures	Effective dose (mSv)	Equivalent CXRs
PET F-18 FDG rest (400 MBq, viability)	8	400
PET Rubidium-82 stress-rest (3700 MBq)	4.6	230
PET N-13 ammonia stress-rest (1100 MBq)	2.4	120
PET ^{15}O-H_2O stress-rest (2200 MBq)	2.5	125
^{99m}Tc-lab erythr (1110 MBq, cardiac function)	7.8	390
SPECT-^{201}Tl stress/redistribution (130 MB)	22	1100
^{201}Tl stress/rest (185 MBq, double injection)	40.7	2035
^{99m}Tc-Sestamibi (1100 MBq, 1 day) stress-rest	9.4	470
^{99m}Tc-Tetrofosmin (1500 MBq, 1 day) stress-rest	11.4	570

From Picano E et al. 2014 [20] and Hirschfeld et al. 2018 [21]

An increasing source of dose exposure for patients is computed tomography [20–22]. The reference doses for common radiological examinations are shown in Table 41.3.

The reference doses for common nuclear cardiology and nuclear medicine examinations are shown in Table 41.4. In 2012 the American Society of Nuclear Cardiology established as the main goal that 50% of exams should reach <10 milliSievert (mSv) of exposure, and since then the reduction of radiation exposure has been a top priority of the nuclear cardiology community and industry [23].

The risk of radiation exposure is four times higher in children than in adults and therefore the exposure of children to radiological interventions is especially relevant (Table 41.5) [20, 21, 24]. Computed tomography has today a central role in

Table 41.5 The radiation dose for common pediatric cardiology examinations (from [25])

Procedure	Effective dose (mSv)	Equivalent CXRs
Diagnostic catheterization	6.0	300
Closure of atrial septal defect	2.8	280
Patent ductus arteriosus occlusion	7.6	360
Balloon valvuloplasty	8.1	410
Right heart and biopsy	4.0	200
Coronary angiography in transplant	9.2	460
Pulmonary hypertension	1.9	95
Aortic coarctation	6.8	340
Right ventricular outflow tract angioplasty/stent	36.4	1765

From Picano E et al. 2014 [20], Hirschfeld et al. 2018 [21], and Glantz et al. 2014 [24]

pediatric cardiac imaging, but according to 2020 American College of Cardiology/American Heart Association guidelines "*its main limitation, especially in patients with congenital heart disease, remains the use of ionizing radiation, which is an important consideration for all congenital heart disease patients requiring serial diagnostic imaging over a lifetime*" [25].

The dose is a moving target and continuous technological implementations are all moving in the direction to abate the dose exposure per exam. Compared to published reference doses, last-generation technology can reduce doses by 95% in coronary computed tomography angiography [26], 50% in nuclear cardiology [27], 100% with near-zero fluoroscopy techniques in cardiac electrophysiology [28], and 40% in invasive cardiology [29], with benefit for patients and operators. The best way to solve or minimize a problem is simply to acknowledge it exists, and this has been the key to dose reduction strategies and technologies in all fields of imaging. Radiological sustainability is now a marketing advantage, and in computed tomography "the slice war" of the industry has been replaced by "the dose war": manufacturers with the least dose have the best chances of winning in the global competition. In addition, much testing with ionizing radiation is progressively replaced by non-ionizing testing as technology and knowledge evolve [30]. For instance, chest CT can be effectively replaced by lung sonography as a first-line technique to monitor pulmonary edema and pulmonary disease during COVID-19 also minimizing the risk of contagion due to patient transportation to the radiology department. Invasive right heart catheterization recommended at rest and during stress for pulmonary hypertension can be replaced by a complete noninvasive study of right heart hemodynamics. Stress cardiac perfusion imaging can be replaced in virtually all patients by stress echo, complemented by stress cardiac magnetic resonance when stress echo is unfeasible or inconclusive [31]. No dose is the best dose, whenever possible (Fig. 41.2).

Reference doses reported in guidelines and recommendations have only indicative values and what counts is the true dose delivered to that individual patient in that particular setting. In Europe the dose must be reported by law starting from February 8th, 2018 (based on Euratom directive 2013/59) [32]. Ignoring the dose opens also a legal vulnerability.

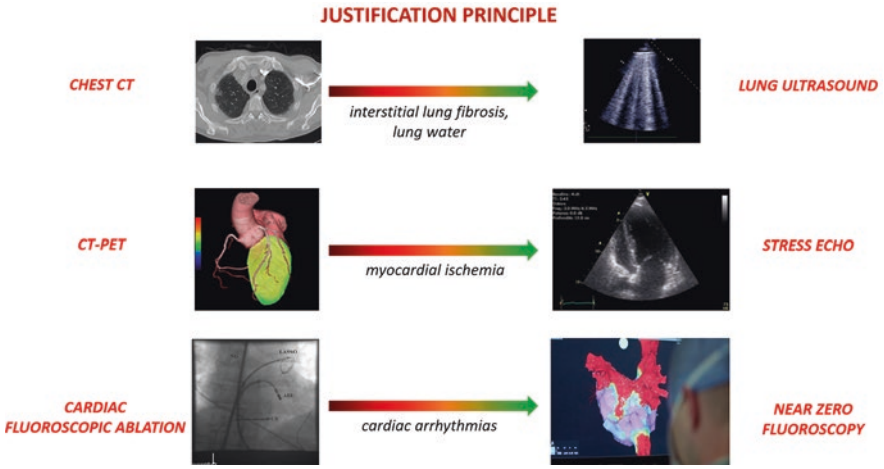

Fig. 41.2 The non-ionizing options in three commonly faced challenges in cardiology patients: pulmonary congestion, myocardial ischemia; ablation of cardiac arrhythmias

41.3 Radiation Cancer and Noncancer Risks

Radiation risk is similar to air pollution risk: cumulative, stochastic, for cancer and noncancer (including atherosclerosis) risks. The risk is variable among groups and, within groups, for individuals, and within each individual, it varies for specific organs.

The risk is cumulative "from womb to tomb" and therefore the radiation dose of each exam should be included in the electronic health record. This aspect is especially important in cardiology patients requiring serial diagnostic imaging over a lifetime, for initial evaluation and diagnosis, monitoring of the natural history of disease progression over time, evaluation of acute and chronic effects of interventions, and risk stratification. The cumulative dose can be significant and on average exceeds 100 mSv in one out of 5 subjects in adult cardiology patients [33–35] and in children with congenital heart disease [36]. This dose is the equivalent of 5000 chest x-rays corresponding to the risk of 1 extra cancer out of 100 exposed subjects. With a molecular epidemiology approach, one can evaluate exposure through the biological biomarker of chromosome aberrations, which are a reliable intermediate biomarker and long-term predictor of cancer. An acute (apparent after 2 h from exposure) and persistent (still evident decades after exposure) increase of chromosome aberrations in circulating lymphocytes are detectable in children after a cardiac invasive fluoroscopy procedure [36, 37] and in interventional cardiologists after 10 years of professional exposure [38].

Cumulative radiation exposure is a known environmental risk factor for cancer and coronary artery disease, independent and additive over traditional risk factors. The level of risk for atherosclerotic disease is likely of the same order of magnitude as cancer [39] and applies not only to high radiotherapy doses [40] but also to low doses due to cumulative diagnostic exposures [41]. Atherosclerosis and cancer may share a common biological mechanism triggered by radiation exposure due to DNA instability, low-grade inflammation, and increased oxyradical stress [41].

The radiation risk for cancer and atherosclerosis is stochastic and applies best to describe the risk of the population rather than individuals. With the increase in dose, there is an increased probability (not an increased severity) of the adverse event (cancer or myocardial infarction). This is not surprising since in medicine every act is probabilistic rather than deterministic. The benefit of aspirin in secondary prevention is proven on a population scale, but we cannot predict in the individual case who will (more likely) prevent myocardial infarction and the patient (less likely) to die from fatal hemorrhage. The aspirin benefit is stochastic and in the same way the radiation risk is stochastic.

The main risk of radiation exposure is cancer. This risk is not negligible for the individual patient and at a population level. The dose from medical radiation sources to the individual patient is relatively high compared to other sources of exposure. The higher the cumulative dose, the higher the risk, since the exam adds to the exam, dose to dose, and risk to risk over a lifetime.

In terms of population burden, the almost ten million scans performed each year in the USA translate into a population risk of about 8000 new cancers per lifetime [42]. In the USA, with 2007 estimates 1.5 to 2% of all cancers are due to CT use [43]. On a global scale, 2% of all cancers are due to medical radiation with old (1996) estimates, and 5 to 10% of all cancers are due to medical radiation exposures with updated estimates of radiation dose [44–46]. Small individual doses multiplied by millions of examinations worldwide become significant population risks [47–50].

The risk is directly documented even at very low exposure doses as an increased risk of cancer, which means a threefold higher risk of cancer in a child with congenital heart disease that received >6 ionizing test procedures in their early life [51, 52]. Data available in the adult cardiology population [53–56] and interventional cardiologists [57–59] also suggest a detectable increase in risk especially marked in radiosensitive organs receiving the highest radiation dose in a lifetime, and also in highly exposed nominally radio-resistant organs such as the skin and brain. In a subanalysis of the ISCHEMIA trial on over 5000 patients, a higher rate of cancer death was observed in patients enrolled in the invasive compared to those included in the conservative arm. The median time to new malignancy was 3.6 years. An association was detected between the number of cardiovascular procedures involving radiation and risk of malignancy-related death in multivariable analysis, with a twofold higher hazard in participants with two radiation exposures, and a fourfold higher hazard in participants with three radiation exposures compared with those with none or one radiation exposure [56].

The available risk estimates refer to population risk, but the population is heterogeneous in age, sex, genetic factors, and environmental cofactors. As with all fields

of medicine, we are rapidly moving from a population to a tailored and personalized risk. Children are four times more sensitive than adults to a given radiation dose, and every effort should be made by the cardiologist to "image gently" these patients [60, 61]. Women are 38% more vulnerable than males, also for the presence of highly radiosensitive organs such as the female breast and all risk estimates should be not only age-specific but also gender-specific [62]. The additional extra risk of cancer is around 1 in 1000 (for a middle-aged man performing a myocardial perfusion imaging scintigraphy scan) but can be as high as 1 in 300 for a 35-year-old woman undergoing a thallium scan. Women are especially at risk for breast cancer as patients with congenital heart disease and as interventional cardiology doctors. In cardiology patients, the risk of cancer is increased, and the most likely targets for cancer are red bone marrow (leukemia, lymphoma), lung, stomach, and thyroid, which receive the highest organ dose from invasive cardiology examinations. Critical organs for cardiac exams in nuclear medicine irradiation are bone and bladder, which are five times more irradiated than bone marrow, lung, and breast [62].

41.4 Radiation Safety for the Cardiac Sonographer

There are two possible sources of radiation exposure for the cardiac sonographer: patient-emitted radiation in the cardiac imaging lab and external sources in interventional laboratories [63].

Patients who have had a nuclear imaging study with radioactive tracers become radiation emitters ("hot" patients). The dose to surrounding persons can be relevant when patients injected with radiotracers (for cardiology or oncologic studies) are sent to perform other diagnostic examinations. During an echocardiogram, the sonographer/cardiologist has to stay very close to patients for a long time, therefore, increasing health professional exposure to radiation. At 90 min after administration of technetium-99 m, the dose equivalent measured right at the anterior chest wall was 0.37 mSv, while the right chest wall dose equivalent was 0.58 mSv. Sonographers might have a potential dose equivalent as high as 0.16 mSv (lower if the sonographer was left-handed and scanning on the left) during a 24-min echo. A transport worker might face a dose equivalent of 0.02 mSv during a 10-min patient transfer [64]. Cardiac sonographers are frequently asked to perform examinations in patients undergoing multiple procedures in rapid succession, and this setting can lead to considerable radiation exposure for the cardiac sonographer working in close contact with the radioactive patient. In this setting, the radiation protective apparel (such as lead aprons) are of limited value, since high energy photons emitted by radioisotopes are only partially shielded by lead, which blocks 90% of x-rays, but is ineffective against high energy positron-emitting tracers (such as 18F-Fluorodeoxyglucose and ^{13}N-ammonia), modestly effective against intermediate energy ^{99m}Tc-tracers (such as Sestamibi and Tetrofosmin), and effective only against low energy photons of ^{201}Tl. The best protection for the sonographer is increasing the time between isotope administration and the ultrasound procedure,

with the echocardiographic study performed after 1 day in the case of PET or SPECT study with ^{99m}Tc-tracers, and after 1 week in the case of a ^{201}Tl study, characterized by a much longer half-life of a few days.

Cardiac sonographers working in the interventional laboratory receive exposure from external sources. The interventional cardiologist stands closest to the X-ray source and the patient table and therefore receives the highest dose of scatter radiation, but also sonographers can receive the non-negligible amount of irradiation and should be aware, badged with a dosimeter, and shielded to avoid useless damage [65].

As recommended by the American Society of Echocardiography, sonographers should self-educate concerning the basic principles of radiation safety and take personal responsibility to ensure their safety [66].

41.5 Clinical Guidelines

The radiation-wise prescription of cardiac imaging in a responsible way is effective primary prevention of cancer, especially because most chronic coronary artery disease patients are at clear low risk and will eventually die more likely of cancer than of other causes. This is also true for other diseases which changed their prognostic profile in contemporary cardiology, from hypertrophic cardiomyopathy to adult congenital heart disease. The policy to ignore the radiation doses and to neglect the radiation risks with unreadable and obscure informed consent forms is against common sense, good clinical practice, and clearly against the law, rules, regulations [67–70], and clinical wisdom [71, 72].

In the clinical competence statement of the American College of Cardiology-American Heart Association on fluoroscopically guided invasive cardiovascular procedures in 2005, the main recommendation was that "*the responsibility of all physicians is to minimize the radiation injury hazard to their patients, to their professional staff, and themselves*" [9].

In 2009, the American Heart Association position paper listed "Top-10 things to know about ionizing radiation in cardiac imaging." Among the top ten, "*cardiac imaging studies that expose patients to ionizing radiation should be ordered only after thoughtful consideration of the potential benefits to the patient, and in keeping with established appropriateness criteria.*" In addition, "*once it has been established that a cardiac imaging study that uses ionizing radiation is needed, every effort should be made to reduce patient dose*" [73].

In 2014, a scientific statement from the American Heart Association spelled out that "*education, justification, and optimization are the cornerstones to enhance the radiation safety of medical imaging. Limiting the use of imaging to appropriate clinical indications can ensure that the benefits of imaging outweigh any potential risks*" [11].

According to the European Society of Cardiology 2014 position paper on medical radiation, it is not recommended to perform tests involving ionizing radiation when the desired information can be obtained with a non-ionizing test with comparable accuracy. If you perform a test that utilizes ionizing radiation,

choose the one with the lowest dose and be aware of the many factors modulating dose. The actual delivered dose should always be recorded and included in patients' records, as now mandatory by law. Because of the numerous sources of variability, there is no clear threshold between acceptable and unacceptable exposure for any given examination, but the dose that is not even considered is certainly unacceptable. X-rays and gamma rays used in radiology and nuclear medicine are proven (class 1) carcinogens, and cardiologists should make every effort to give "the right imaging exam, with the right dose, to the right patient." "*The priority given to radioprotection in every cardiology department is an effective strategy for primary prevention of cancer, a strong indicator of the quality of the cardiology division, and the most effective shielding to enhance the safety of patients, doctors, and staff. A smart cardiologist cannot be afraid of the essential and often life-saving use of medical radiation but must be very afraid of radiation unawareness"* [20].

In the words of the American College of Cardiology radiation safety position paper in 2018, "*good training should create a culture of respect for radiation hazard and a commitment to minimize exposure and minimize protection*" [21].

In the culture of safety and respect for radiation hazard, there is a downfall (−50% from 2005 to 2015) of myocardial perfusion imaging [74–76] and a parallel rise in the use of stress echocardiography, effective in minimizing radiation exposure at all ages of life and for all forms of cardiovascular disease. Still, in 2020 top cardiac centers offer unproven executive screening including coronary calcium and coronary computed tomography, at a cost ranging from 1000 to 25,000 US dollars [77]. Radiation-optimized practices will protect patients from the risks of cancer, now proven for low doses <50 mSv [78], and physicians from risks of legal vulnerability from radiological inappropriateness [79, 80]. Prescribing medical imaging is a social act, not imply a medical one [81]. The radiation dose is a key component of the risk-benefit assessment of different cardiac imaging options according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [82].

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Environmental Sustainability of Cardiac Imaging

42

Cristina Mangia and Eugenio Picano

Keywords

Carbon · Ecology · Environment · Medical imaging · Planet

42.1 Air Pollution, Climate Changes, and Cardiovascular Health

Air pollution and climate changes are two critical environmental issues both here and now and in the coming years. Although they are phenomena that occur at different spatial and temporal scales, they are closely interconnected: one affects the other and vice versa. Both negatively affect public health [1, 2]. They enter the cost-benefit assessment in all economic fields including energy, transportation, industrial production, and construction. The environmental footprint of medicine and medical imaging is not negligible [3]. Climate change also negatively influences air pollution phenomena which are a chronic risk factor for cardiovascular mortality [4, 5], an acute trigger for coronary syndromes [6], an important co-factor for COVID-19 mortality [7], a modulator of results of cardiac functional stress testing [8], and an actionable therapeutic target at the population, community, and individual level [9]. On the other side, some air pollutants interact with solar and terrestrial radiation by absorbing or reflecting it, perturbing the planetary energy balance with impacts on climate. Mitigation of climate change helps to reduce air pollution phenomena, and clean air reduces global warming. Air pollution and climate change are different

C. Mangia (✉)
CNR, ISAC-Institute of Sciences of Atmosphere and Climate, Lecce, Italy
e-mail: c.mangia@isac.cnr.it

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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phenomena but inexorably linked. Sources of air pollutants can be at the same time sources of climate-altering substances or sources of climate-altering precursors. Pollutants such as ozone (O_3), nitrogen oxides (NO_x), and particulate matter (PM) change the properties of clouds, interact with solar and terrestrial radiation by absorbing or reflecting it, and disrupt the planetary energy balance with implications for climate, either by positive forcing (warming of climate) or negative forcing (cooling of climate) [10–12].

42.2 Environment and Cardiovascular Mortality

Global warming is altering the earth's global land and ocean temperatures. To date, an increase of 1.09 °C is observed in recent years over pre-industrial levels. Each of the last four decades has been progressively warmer than any previous decade since 1850. Consequently, temperature variability, heat, and extreme cold events have become more frequent in many parts of the world [13], with the number of deaths increasing significantly with the repetition of extreme events [14–23]. The Lancet Countdown on Health and Climate Change reported the effects of extreme temperatures on health and disease, including cardiovascular diseases [24], and a 2021 global analysis estimated that more than 5 million deaths per year are associated with nonoptimal temperatures [25]. These trends are expected to worsen in the coming years due to global warming.

Regarding the impact of environmental pollution on health the Global Burden of Disease [23] study estimates that pollution was responsible for an estimated 9 million premature deaths (16% of all deaths worldwide), 61.9% of which were due to cardiovascular disease, including ischemic heart disease (31.7%) and stroke (27.7%). Air pollution remains responsible for the greatest number of deaths, with approximately 6.7 million deaths in 2019 [26].

42.3 Cardiac Imaging Affects the Environment

A simple indicator of environmental impact is needed. The most convenient unit for measuring greenhouse gas footprint corresponding to ecological cost is carbon dioxide (CO_2) equivalent emissions [27]. The environmental impact of medical imaging can vary by a factor of 100 between one test and the other (Fig. 42.1).

One echocardiogram produces 2 kg, and a 3 Tesla magnetic resonance imaging produces 200 to 300 kg of CO_2 equivalent. A cardiac nuclear medicine examination produces 10 times the CO_2 of an ultrasound test [28]. Ultrasound has the least environmental impact, with a CO_2 equivalent per abdominal imaging examination of around 1 kg including production and use phases. Abdominal computed tomography produces 6 kg and abdominal magnetic resonance imaging 20 kg of CO_2 equivalent per examination [29]. Interventional radiology generates substantial greenhouse gas volumes, mostly to maintain climate control in the suites [30]. Imaging with computed tomography and especially magnetic resonance is energy-hungry mostly invested in the cooling process and counteracting heat which arises

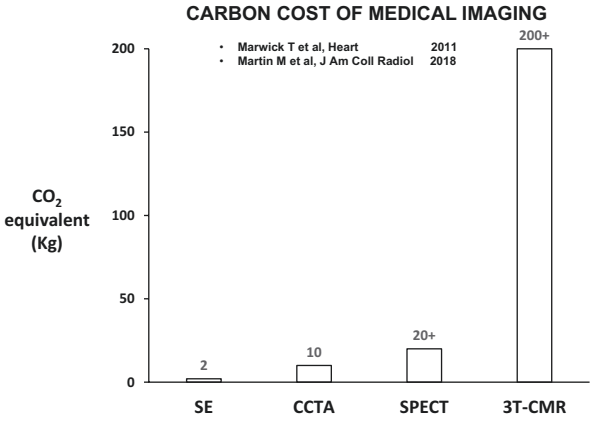

Fig. 42.1 The environmental cost of imaging examinations. Common imaging examinations are ranked on the x-axis and the corresponding production of CO_2 emissions is on the y-axis. From original data of references [28] (Marwick et al.) and [29] (Martin et al.)

Table 42.1 The four dimensions of medical imaging

	Benefit	Cost	Risk	Environment
Years	1980–1990	1990–2000	2000–2020	2020 +
Claim	More is better	Justify	Less is more	Green
Dimension	Benefit	Cost-benefit	Risk-benefit	Climate
Metrics	% Accuracy	€ or $	CXR's equivalent	CO_2 emission
Stakeholders	Physician	Payer	Patient	Planet
Time projection	Days	Months	Years	Decades

CO_2 carbon dioxide, *CXR* chest x-ray

as a side product from operating modalities. The radiology department uses 4% of the total yearly energy consumption at the hospital, equivalent to the usage in a town of 852 people [31].

Overall carbon footprint attributed to health care ranges from 4% in the United Kingdom to 10% in the United States [32]. A conservative estimate of 10 billion medical imaging examinations per year worldwide implies that medical imaging accounts approximately for 1% of the overall carbon footprint and at least 10% of the health care footprint. In 2016, CO_2 emissions from magnetic resonance and computed tomography calculated in 120 countries accounted for 0.77% of global emissions [33]. The small impact of individual imaging test multiplied by billions of tests each year becomes a significant environmental footprint translating into population risks and societal costs [34].

Medical imaging underwent a paradigm shift in the last decades (Table 42.1).

Clinical decision-making in medical imaging is based on diagnostic efficacy, cost-benefit, and risk-benefit assessment including long-term radiation risks. There is increasing awareness of air pollution's impact on public health and resource rationing. The environmental footprint of imaging will also become relevant. We may now add another partner, the planet, to the traditional stakeholders (physician-payer-patient).

The production of CO_2 may not be the only detrimental effect of cardiac imaging on the environment. Most of the gadolinium injected in humans for cardiovascular

magnetic resonance is eliminated in urine into the urban sewer system and transported to urban wastewater treatment plants [35]. The annual discharge of gadolinium is around 3 kg per magnetic resonance machine, with the increased environmental pollution in rivers and seas close to hospitals and toxicity in drinkable water, in absence of any monitoring-quality control measures comparable to those used for radioactive waste or pesticides [36]. The applications of nuclear medicine are associated with the release of radioactivity to the environment from patients and production facilities, radioactive waste generation, increasing costs of disposal, and decreasing availability of disposal options [37].

The environmental footprint adds the fourth dimension in the technology assessment of medical imaging, beyond diagnostic efficacy, cost, and risk. In the presence of comparable diagnostic information, environment-friendly imaging can be preferred over imaging with a significant environmental footprint. This already happens in all aspects of economic life. Countries and transportation modes are ranked as "red" or "green" based on CO_2 production [38], and this can be easily applied to medical imaging or to other medical tests such as pathology testing [39] to integrate ecological issues in medical reasoning. The environmental footprint is also a cost not immediately taken by the payer as a direct cost but covered by society as a long-term, downstream, externalized cost that all citizens will pay collectively.

42.4 Environment Affects Cardiac Imaging Results

The air pollution risk is not conceptually different from other environmental risks more familiar to cardiologists, such as ionizing radiation risk which is now embedded in mainstream cardiology practice. The risk is stochastic, with a probability proportional to the dose and the severity of the effect independent of the dose. The risk of air pollution is chronic and cumulative but also acute for major cardiac events, and air cleaning for lockdown due to the pandemic wave in 2020 was associated with an abrupt fall in hospital admissions for acute myocardial infarction, acute decompensated heart failure, and cardiac arrhythmias largely due to the fall in air pollution [40]. The relationship between the dose of exposure and risk is linear, but the slope can be steep in one patient and flat in another patient, depending on genetic background and other coexistent risk factors [41].

Cardiac functional testing is ideally suited to assess the effects of disparate pollutants on different aspects of cardiac function testing. Two approaches can be adopted: an environmental stress test under controlled laboratory conditions with the administration of a specific pollutant in normal healthy or vulnerable subjects; or an ecologic study observing the changing responses of stress under variable levels of air pollution.

The first approach is more technically complex although feasible. It was pioneered in the early seventies by studies showing a reduction of exercise tolerance in patients with chronic angina pectoris exposed to increased air concentrations of carbon monoxide [42] or fine particulate matter [43]. This approach is well suited to be coupled with imaging techniques. For example, inhalation of diesel exhaust

exposes the patient to a particulate matter concentration of 300 μg/mL, 10 times the acceptable levels in ambient air. In young healthy male volunteers, exposure to diesel exhaust induces an increased pulmonary vasomotor tone by decreasing the distensibility of pulmonary resistive vessels at high cardiac output [44]. This approach has the advantage of studying the subject versus his/her baseline and titrating the environmental stress under controlled conditions. The method has been widely applied so far mostly in animal studies. In rats, chronic exposure for 14 months to traffic air-related pollution (drawing air from a major freeway tunnel in Northern California) increases the expression of genes related to fibrosis, aging, oxidative stress, and inflammation in rats of both sexes, with enhanced collagen accumulation only in female hearts [45].

The observational approach is more ecologic, does not interfere with routine practice, and is more widely utilized. The acute detrimental effects of air pollution are detectable in healthy subjects and diseased patients studied serially with variable levels of air pollution. The increase in air pollution reduces aerobic performance and maximal oxygen uptake in soccer players, especially in the evening and winter seasons [46]. Short-term elevations of fine particulate matter of 10 $\mu g/m^3$ well within current air quality standards are associated with detrimental changes (−15%) in peak oxygen consumption among cardiac rehabilitation patients [47]. Patients with chronic coronary syndromes showed a peculiar sensitivity of coronary flow velocity reserve [48] and especially B-lines [49] to same-day increase in NOx and fine particulate matter. The air cleaning effect had less impact on inducible ischemia, contractile reserve, and cardiac sympathetic reserve. The air quality is a determinant of what happens in the heart during acute cardiovascular events and in a stable chronic phase during functional testing. The definition of the effects of air pollution on cardiac functional testing is especially important since air pollution is an actionable therapeutic target at the population, community, and individual level, for instance with restrictive air pollution limits, air cleaners, and facemasks [9, 50].

42.5 Environmental Sustainability in Clinical Guidelines and Ongoing Studies

Cardiology guidelines were released by the European Society of Cardiology in 2019 and the American College of Cardiology-American Heart Association in 2021 appropriately assigning a class of recommendation 1 (of proven benefit > > risk) for the diagnosis of chest pain to five imaging techniques based on either anatomic (coronary computed tomography angiography) or functional approaches, such as stress SPECT, stress PET, stress cardiovascular magnetic resonance, and SE. The choice is left to the prescribing physician, based on local availability and expertise [51, 52]. However, the five techniques were not created equal for cost, risk, and environmental impact. The environmental footprint ranges from 2 kg of CO_2 emissions equivalent using SE to 200 kg for a stress-magnetic resonance. There is no ethical dilemma in choosing a medical test with less environmental impact when the diagnostic accuracy is similar [52].

As already happened with radiological sustainability, also in this case the radiology community will lead the change. The radiology and medical imaging field made great strides in patient and doctor safety by decreasing radiation doses in cardiac radiology, interventional cardiology, and nuclear cardiology once the problem was understood by physicians and a culture of respect towards radiation hazards was built. In the words of the President of the American College of Radiology in 2021 "*Similarly, through our technological expertise and awareness, we can decrease our carbon footprint, with the ultimate goal of mitigating climate change and preventing a looming public health crisis*" [53]. According to the latest 2021 release of the ethical code of the World Medical Association, "*physicians should strive always to practice medicine in ways that are environmentally sustainable to minimize environmental health risks to current and future generations*" [54]. The environmental footprint also increases long-term detrimental effects on human health and therefore externalized costs. Same-day, same-hour air pollution levels may be included in medical records since they can affect admission rates for severe acute cardiovascular disease and may significantly modulate several aspects of cardiovascular function at rest and during stress. Cumulative radiation exposure from medical testing can be a significant environmental risk factor for atherosclerotic events and cancer. In a subset of patients of the prospective SE 2030 study, both air pollution levels and lifetime medical radiation exposure are collected to assess the effects of air pollution in modulating acute stress test results and chronically the risk of cancer and atherosclerotic events (Fig. 42.2) [55]. The environmental footprint is a key component of the cost-benefit assessment of different cardiac imaging options according to the 2023 clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology [56].

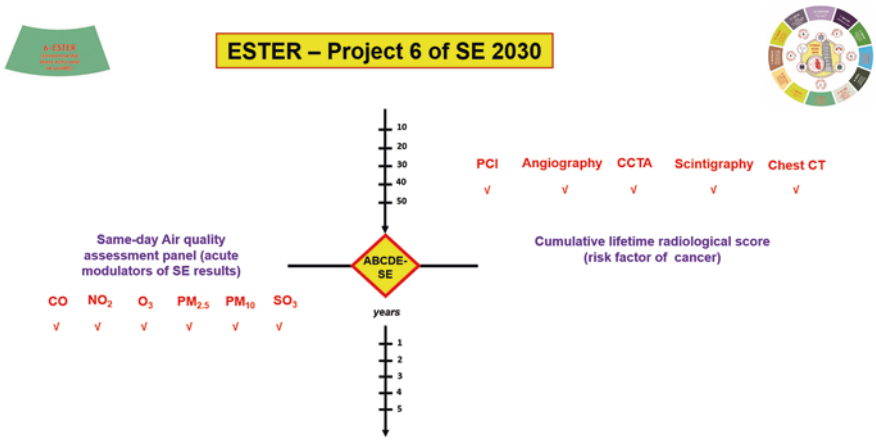

Fig. 42.2 The ESTER project of SE 2030. Same-day air pollution as a modulator of stress results, and cumulative medical radiation exposure as a potential determinant of cancer and atherosclerotic events. From original data of reference [55] (Picano et al.)

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The Road to Stress Echo 2030

43

Patricia A. Pellikka and Eugenio Picano

Keywords

Functional testing · Sustainability · Stress echo 2030 · Versatility

43.1 Stress Echo Evolution

Stress echocardiography (SE) provides a dynamic evaluation of myocardial structure and function under conditions of physiologic or pharmacologic stress [1, 2]. Both specialty recommendations [3, 4] and general cardiology guidelines [5, 6] recommend SE as a primary tool for evaluating patients with established or suspected coronary artery disease. The diagnostic cornerstone is the detection of stress-induced regional wall motion abnormality. This key diagnostic sign has remained unchanged in the last 40 years.

However, the ultrasound images obtained during conventional SE provide more information than segmental wall motion abnormality. From a SE era with a one-size-fits-all approach (wall motion by 2-dimensional echo in the patient with known or suspected coronary artery disease) we have now progressed to a highly diverse, next-generation laboratory employing a variety of technologies: M-mode echocardiography, 2-dimensional and real-time 3-dimensional echo; pulsed,

P. A. Pellikka (✉)
Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: pellikka.patricia@mayo.edu

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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continuous, color and tissue Doppler; lung ultrasound; deformation imaging with speckle tracking; contrast echocardiography with ultrasound-enhancing agents. Patients assessed with SE cover the entire spectrum of wellness and disease severity (from elite athletes to patients with end-stage heart failure) and ages (from children with congenital heart disease to the elderly with low-flow, low-gradient aortic stenosis) (Fig. 43.1) [7].

The long history of the technique laid the solid experimental, pathophysiological, technological, and clinical foundations of SE. Current state-of-the-art applications with leading-edge expertise and technology rely on an integrated, simultaneous assessment of left ventricular wall motion, B-lines, left ventricular contractile reserve, and coronary flow velocity reserve. The echocardiographic information is integrated with symptoms, electrocardiogram, and blood pressure. The new developments currently in progress are better understood from the historical perspective, with the 50-year-long attempt to minimize the pitfalls (dependence on the acoustic window and operator expertise) and exploit to the fullest the intrinsic advantages of this technique, i.e., versatility and sustainability.

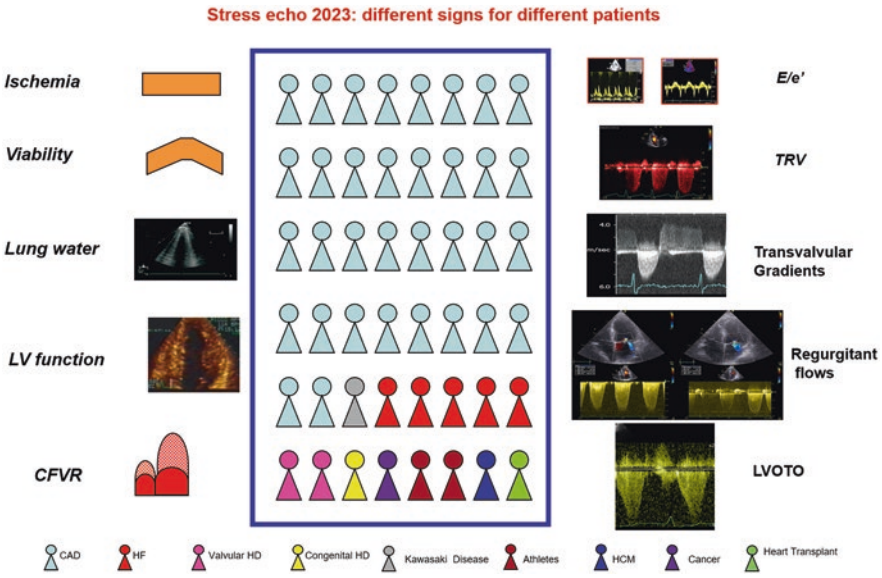

Fig. 43.1 SE as it is today (2023): many different technologies (from 2-dimensional echocardiography to Doppler to lung ultrasound), many signs (from wall motion abnormalities to B lines, from left ventricular contractile reserve to coronary flow velocity reserve), all patients (from cardiomyopathies to valvular and congenital heart disease). *CAD* coronary artery disease, *HCM* hypertrophic cardiomyopathy, *HD* heart disease, *HF* heart failure

43.2 The Past: From Experimental Studies to the 2-Dimensional Approach

In 1935, Tennant and Wiggers showed that coronary occlusion resulted in almost instantaneous abnormality of wall motion [8]. Experimental studies performed some 40 years later with ultrasonic crystals during acute ischemia [9] and 2-dimensional echocardiography on a canine model of myocardial infarction [10] showed that reductions in regional flow are closely mirrored by reductions in regional contractile function, setting the stage for the clinical use of ultrasonic methods in ischemic heart disease. The feasibility of using echocardiography to identify stress-induced wall motion abnormalities in the clinical arena was first demonstrated with M-mode recordings during exercise-induced [11] or ergonovine-induced ischemia [12]. The M-mode technique was the only method available to cardiologists in the 1970s and nowadays appears largely inadequate for providing quality information when diagnosing myocardial ischemia. The time-motion technique sampling, according to an "ice-pick" view, greatly limited exploration to a small region on the left ventricle. Although this feature could hardly be reconciled with the strict regional nature of acute and chronic manifestations of ischemic heart disease, for the first time the M-mode technique outlined echocardiography's potential in detecting ischemia, clearly showing that a reversible segmental wall motion abnormality is an early, sensitive, specific marker of transient ischemia, much more accurate than electrocardiogram changes and chest pain.

The practical impact of these observations had to await the development of 2-dimensional echocardiography, which allowed exploration of more segments of the left ventricle with an excellent spatial and temporal resolution and was thus ideally suited for detecting the regional and transient manifestations of myocardial ischemia. In addition, the technical difficulties and degraded quality of echocardiographic imaging during exercise—due to excessive chest wall movement, hyperventilation, and tachycardia—were minimized with two different approaches. Post-treadmill imaging, pioneered by Feigenbaum's group in Indianapolis, is still the standard modality in the USA [13], based on the realization that stress-induced wall motion abnormalities produce stunned myocardium permitting immediate post-treadmill echoes to be clinically useful.

An alternative approach, more popular in Europe, was the introduction of pharmacological SE as an exercise-independent approach for detecting myocardial ischemia with vasodilators (introduced by the Pisa group in 1985) [14] or dobutamine (first proposed by the Liege group in 1986) [15].

The method's clinical relevance was increased by the introduction of digital recording techniques and split-screen displays so that the same views on rest and stress images could be acquired and viewed synchronously side-by-side [16]; this initially required stand-alone computers, but ultrasound systems now have a direct digital output and quad screen display is standard on most systems. The advent of new technologies such as harmonic imaging of tissue [17] or the use of

ultrasound-enhancing agents for endocardial border recognition and left ventricular cavity opacification improved image resolution [18]. The introduction of native tissue harmonic imaging, which increases lateral resolution and signal-to-noise ratio, clearly improved endocardial border detection. Intravenous contrast echocardiography with second-generation lung-crossing agents for endocardial border recognition allowed cardiologists to study otherwise difficult patients and segments.

The validation of SE involved the demonstration of its accuracy for the detection of coronary artery disease and its prognostic value. The sensitivity and specificity of SE to detect angiographic coronary artery disease were documented by multiple groups of investigators [19]. Such evidence already existed for the earlier established nuclear perfusion techniques. Meta-analyses, as well as a direct comparison with tomographic nuclear perfusion imaging, demonstrated a comparable accuracy of SE and SPECT perfusion imaging. The next step was to establish evidence of the prognostic utility of SE. This evidence was collected by multiple investigators studying large consecutive series of patients, including men and women [20], the elderly [21], patients with diabetes mellitus [22], chronic kidney disease [23], and peripheral vascular disease [24]. The safety of SE, even when supervised by registered nurses rather than physicians [25], was also documented. SE was then accepted as a valid tool that could be used to study the safety of drugs and devices [26] and is appropriate for the assessment of many types of patients [27]. The technique was upgraded from a research toy to a clinical tool, receiving wide-scale support and credibility from prospective multicenter studies and international registries providing effectiveness [28, 29] and safety [30] data in the real world—beyond the experience of a few research-oriented centers. At the beginning of the new millennium, and after some 20 years of experience, the technique was finally ready for widespread clinical use [31].

43.3 State-of-the-Art Stress Echocardiography

The rise of SE in the last 40 years has been continuous and remarkable. SE is now widely available. Moreover, the feasibility of diagnostic quality images with selective use of ultrasound-enhancing agents for endocardial border enhancement currently exceeds 95% and allows one to obtain diagnostic images even in acoustically difficult patients (such as those with morbid obesity and severe lung disease). In addition, flexible use of exercise, vasodilators, and dobutamine stress in every echo lab maximizes the feasibility of performing a stress test, avoids specific contraindications of each, provides a second choice when the preferred test has produced submaximal (and therefore rarely useful) results, and makes it possible to tailor the most appropriate stress for the individual patient (for instance, exercise for evaluating hemodynamic changes in heart failure, vasodilators to assess coronary flow reserve, and dobutamine for contractile reserve).

However, SE based on regional wall motion abnormality applied in contemporary populations with suspected coronary artery disease showed two major limitations: (1) a decrease in positivity rate (< 10% compared to >60% in the 1990s) probably due to the current dominant policy of stress testing under full anti-ischemic therapy in patients with atypical symptoms and multiple comorbidities [32–35]; and (2) the declining prognostic value of the negative test for regional wall motion abnormality (from 99% in the 1980s to 85% in the last decade), when only hard endpoints are considered [36, 37]. The same decline in positivity rate has been observed with other imaging techniques [38]. This is not surprising and is even expected based on the changed pathophysiological framework and current understanding of coronary artery disease. It is now accepted that coronary artery stenosis is not the only, and probably not even the most important, prognostic vulnerability of the patient, within and beyond coronary artery disease. Plaque composition is even more important than plaque geometry and severity [39]. Pulmonary congestion and diastolic function [40], left ventricular structure and contractile reserve [41], coronary microcirculation [42], and cardiac autonomic balance [43] are equally important determinants of risk but difficult to assess noninvasively with currently available methods. In this changed operational and conceptual scenario, a mutation of SE took place in the last 5 years, taking full advantage of the unsurpassed versatility of the technique [44, 45]. Five parameters now converge conceptually, logistically, and methodologically in the ABCDE protocol. They are (1) regional wall motion abnormalities; (2) B-lines measured by lung ultrasound; (3) left ventricular contractile reserve assessed as the stress/rest ratio of force (systolic arterial pressure by cuff sphygmomanometer/end-systolic volume from 2D); (4) coronary flow velocity reserve in the left anterior descending coronary artery (with color-Doppler-guided pulsed wave Doppler) or coronary perfusion assessed with ultrasound-enhancing agents; (5) ECG-based heart rate reserve. ABCDE protocol allows a synoptic functional assessment of epicardial coronary artery stenosis (wall motion), lung water (B-lines), myocardial function (left ventricular contractile reserve), coronary small vessels (coronary flow velocity reserve in mid or distal left anterior descending artery), and cardiac autonomic function. Step A stands for Asynergy; B for B-lines; C for Contractile reserve; D for Doppler flowmetry; E for EKG [46, 47].

The normal response is characterized by the absence of inducible wall motion abnormalities (nonischemic heart), with normal A-lines at lung ultrasound ("dry lung") [48], small end-systolic volume with normal force reserve ("strong heart") [49], > twofold increase in coronary flow ("warm heart") [50], and normal heart rate response ("fast heart") [51].

On the opposite side of the spectrum, a fully abnormal response is characterized by the presence of inducible wall motion abnormalities (ischemic heart), abnormal B-lines at lung ultrasound ("wet lung"), larger end-systolic volume during stress with reduced force reserve ("weak heart"), blunted increase in warm coronary flow ("cold heart"), and low heart rate increase ("slow heart") [48–51].

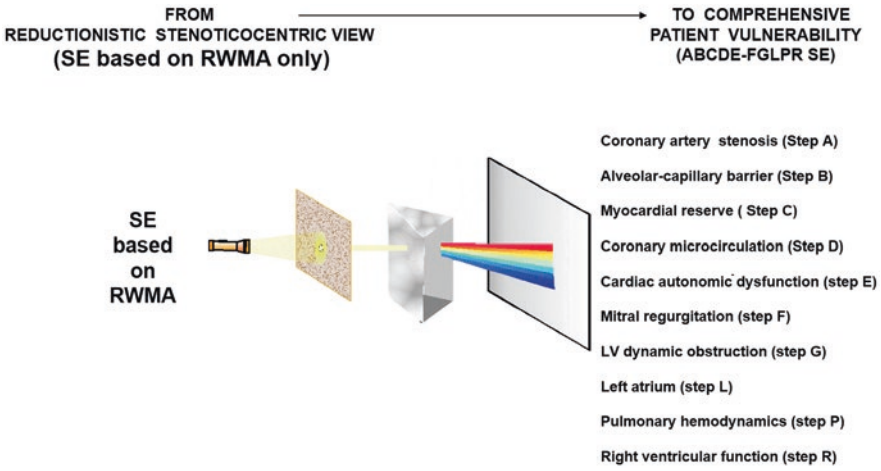

Fig. 43.2 The prism of functional responses with SE ABCDE+

The integration of five different variables into a single one-stop-shop expands the risk stratification potential of SE in patients with dyspnea or chest pain [52, 53]. The current approach to risk stratification is based on the presence or absence of regional wall motion abnormality. This approach is the only possible evidence-based strategy today but under-uses the unique versatility of SE when comprehensive imaging is applied [49]. The annual hard event rate of 1.6% of a patient with negative SE by wall motion criteria falls to a fourfold lower rate with ABCDE score = 0 (all parameters normal) and increases fivefold higher with ABCDE score = 5 (all parameters abnormal). The black-and-white risk stratification becomes color-coded with a spectrum of responses (from benign all-negative green code to malignant all-positive red code) (Fig. 43.2) [53].

43.4 The Next Step

The three next major challenges and opportunities for SE are removing operator dependence on image quantification, expanding awareness of sustainability needs for effective healthcare delivery in the present era, and rapid building of scientific evidence with the new comprehensive protocols.

43.4.1 Objective Reading

SE is relatively simple and widely available, but training recommendations should be followed [7, 8]. In general, many parameters used in SE applications beyond CAD can be more difficult to acquire but are easier to measure and more

amenable to quantification than regional wall motion assessment; therefore, these applications may be less dependent upon the subjectivity of interpretation and experience. Speckle tracking echocardiography—once the limiting problem of inter-vendor comparability of strain values is settled—is especially attractive for the detection of subtle global and regional abnormalities in LV longitudinal strain, not otherwise detectable with regional wall motion analysis and linked to minor degrees of subendocardial ischemia [4]. Real-time 3-dimensional echocardiography also has proven benefits in accuracy and reproducibility, but its methodology is time-consuming, and frame rates are at times still too low for optimal transthoracic imaging during the high heart rates achieved with stress [4]. Artificial intelligence is the most immediate solution for operator-independent assessment of regional wall motion and left ventricular volumes at baseline and during stress, with the promise of less time, training, and variability for SE finally at hand [54].

43.4.2 Sustainability

The optimized use of SE will contribute to the primary prevention of cancer through the reduction of inappropriate and unjustified use of ionizing radiation during testing [55]. We should always minimize the avoidable long-term damage of tomorrow when treating the cardiac patient today [56], exactly as the oncologists should minimize the prognosis-limiting future cardiac damage when treating cancer with radiotherapy and chemotherapy. In addition to radiologic sustainability, the advantages of affordable cost and minimal environmental impact are increasingly relevant in the current era of cost containment and respect for the environment. Carbon dioxide emission per exam is 10 to 100 times lower for echocardiography compared to other energy-hungry techniques, such as computed tomography and cardiovascular magnetic resonance [57]. The reduction of radiation, cost, and carbon dioxide emissions in cardiology may contribute substantially to the overall increased sustainability of medical imaging in cardiology [58, 59] (Table 43.1).

Table 43.1 Sustainability of cardiac imaging

	Cardiac imaging	Stress echo
Cardiologic	Focus on coronary stenosis	Focus on patient vulnerability
Logistic	The patient goes to the imaging	Imaging may go bedside
Cultural	Imaging specialist the driver	Cardiologist the driver
Economic	Intermediate to high cost	Low cost
Radiologic	Absent to moderate radiation	Non-ionizing radiation
Environmental	Moderate to high CO_2 emission	Minimal CO_2 emission

43.4.3 Evidence-Building

The shift from the time-honored SE based on regional wall motion abnormalities to a more comprehensive protocol (ABCDE+) also implied the shift from an evidence-rich to an evidence-poor scientific environment. Our clinical decisions are better supported by studies on thousands of patients than by a few hundred collected in specialized centers. Therefore, the obligatory pathway was to start again a new wave of multicenter studies helping to collect in a relatively short time the evidence required to change the clinical practice. This was possible with the SE2020 study started in 2016 [60] and now expanded in the SE2030 study started in 2021 and projected to 2030 [61].

43.5 Stress Echo 2030: Building a Worldwide Network

With the SE 2020 study, a new standard of practice in stress imaging was developed and disseminated: the ABCDE-FGLPR protocol for functional testing within and beyond coronary artery disease. The comprehensive protocol was the fruit of SE 2020 and is the seed of SE 2030, which is articulated in 12 projects. Image analysis and data mining are supported by artificial intelligence. The study aims to recruit in 5 years (2021–2025) ≥10,000 patients followed by ≥5 years (up to 2030) from ≥40 quality-controlled laboratories from ≥20 countries (Fig. 43.3).

The various projects will include patients with coronary artery disease (project 1) or suspected coronary vasospasm (project 12), heart failure with preserved ejection fraction (project 2), hypertrophic cardiomyopathy (project 3), status post-chest radiotherapy (project 4), repaired tetralogy of Fallot (project 6), cardiopulmonary involvement post-COVID 19 (project 8), identification of hearts appropriate or unfit for heart donation (project 9), ischemic secondary mitral regurgitation (project 10), and valvular heart disease (project 11). The study will exploit and possibly contribute to upgrading the leading-edge quantitative and operator-independent technology of artificial intelligence (project 5) for image interpretation and data analysis. The study will also evaluate the results of SE parameters in the context of powerful environmental modulators of stress results and/or long-term outcomes such as air pollutants and medical radiation exposure analyzed through big data mining (project 6).

Five important aspects will be shared by SE2030 in full continuity with SE2020, with minor adaptations and implementations.

43.5.1 Upstream Quality Control

The study is a prospective registry, but it is necessary to have an upstream quality control with a certified reader from each center. Peripheral reading from each center is necessary to have a snapshot of the real world. On the other side, a multicenter study is like a fish soup. The more the fish or contributing centers, the tastier is the soup, but it is enough to have a rotten fish and the entire soup is uneatable. Therefore, mandatory quality control is necessary for conventional and innovative parameters, since the volume of activity is necessary but not sufficient to ensure the quality of reading.

Fig. 43.3 Stress echo 2030. The core protocol of SE2030 is the same as in SE2020 with ABCDE: epicardial coronary artery stenosis (with regional wall motion abnormality), step A; lung water (with B-lines), step B; myocardial function (with left ventricular end-systolic volume for contractile reserve and end-diastolic volume for preload reserve), step C; coronary microvascular dysfunction (with coronary flow velocity reserve or myocardial perfusion with an ultrasound-enhancing agent), step D; cardiac autonomic balance (with heart rate reserve), step E. Ancillary steps (necessary in some but not all patients) are step F (regurgitant flows), step L (left atrial volume and function), step P (pulmonary and left ventricular pressures), and step R (right ventricular function). The study is endorsed by the Italian Society of Echocardiography and Cardiovascular Imaging and initiated in Pisa, Italy, as shown by the Leaning Tower present in the logo. SE protocols are indicated from 1 to 12 clockwise and cover a wide spectrum of clinical conditions including but extending beyond coronary artery disease. (From Picano E 2021 [61])

43.5.2 Peripheral Reading and Inclusivity

Once the reader has been certified, the peripheral reading will be directly entered into the data bank with the redcap program property of the Italian Society of Echocardiography and Cardiovascular Imaging. This will allow a more flexible and rapid platform compared to the standard excel approach which required greater human resources and greater chances of error in data inputting and better compliance with new regulations strictly protecting privacy in clinical studies. Another

feature of SE2030 is inclusivity, so that any center meeting the selection criteria can be enrolled, allowing centers traditionally outside the editorial stage but producing high-quality clinical activity relevant to the scientific community.

43.5.3 Uniform Methodology

Each laboratory will adopt the preferred choice of stress among physical, pharmacologic, or pacing stress according to a standardized protocol in line with guidelines and recommendations. Physical includes semi-supine bike exercise, peak or post-treadmill, or upright bicycle. Pharmacologic testing will be done with dobutamine or vasodilators (dipyridamole, adenosine, or regadenoson) according to physician preferences, patients' contraindications, local availability, and cost. Independently from the chosen stress, execution, performance, archiving, and interpretation of testing will follow a standardized format with the ABCDE protocol. All laboratories will be granted free artificial intelligence software and, if possible, a free supply of ultrasound contrast to help leading-edge technology upgrade and encourage uniformity of methods across all study laboratories.

43.5.4 The Full Spectrum of Enrolled Patients Is Evaluated for Clinically Relevant Endpoints

The overarching aim of the study is to make SE practice more uniform, versatile, standardized, quantitative, and evidence-rich, producing data potentially relevant to changing clinical practice.

43.5.5 Sponsored by a Professional Scientific Society

The study is investigator-driven and not industry-driven. It is endorsed by an independent professional society (Italian Society of Echocardiography and Cardiovascular Imaging) and not sponsored by industry, although some materials useful for project completion such as artificial intelligence software and ultrasound-enhancing agents will be supplied in kind by industrial partners for recruiting centers.

The working hypothesis is that the white light of identical symptoms and signs can now be deconstructed with a prism assessing the different phenotypes and the different levels of risk. The number of abnormal biomarkers determines the overall prognosis of the patient if left untreated, from the excellent prognosis associated with a low SE score to the poor prognosis of a high SE score. Each marker identifies a specific phenotype, a selective pathophysiological vulnerability, and a potential therapeutic target. Some key phenotypes such as diastolic dysfunction can only be identified with the help of an integrated approach, at first excluding inducible ischemia, blunted systolic function with global longitudinal strain, chronotropic incompetence, stress-induced mitral regurgitation, and dynamic

intraventricular obstructive gradients in the screening phase, and later positively identifying diastolic dysfunction as a combination of pulmonary congestion (B-lines), limited preload reserve and left ventricular end-diastolic volume increase at intermediate stages of exercise, increased E/e′ and pulmonary artery systolic pressure, and dilated left atrium [62]. We do not know exactly the most useful combination of parameters for every individual patient, but we are aware that the one-size-fits-all approach is over in the era of personalized medicine. Applications of a stress test should always start from the clinical question or suspicion. Whether each letter offers essential or ancillary information may well depend on the type of patient and scope of testing, which may be very different: primary diagnosis of coronary artery disease, identification of functional mechanisms of disease and symptoms, risk stratification, guide to therapy, or objective assessment of therapy efficacy. The identification of phenotypes is correlated to other clusters of symptoms, clinical signs, clinical chemistry, and imaging data to focus on potential therapeutic targets (Fig. 43.4).

The old landline telephone with a single sign of regional wall motion abnormality for one patient with known or suspected coronary artery disease is now a versatile smartphone with multiple applications and can be tailored to the individual patient according to clinical needs. The letters of the comprehensive protocol will not all be used in all patients, exactly as we do need all the letters of the alphabet for writing a letter. The letter, and the functional test, must be personalized, and with

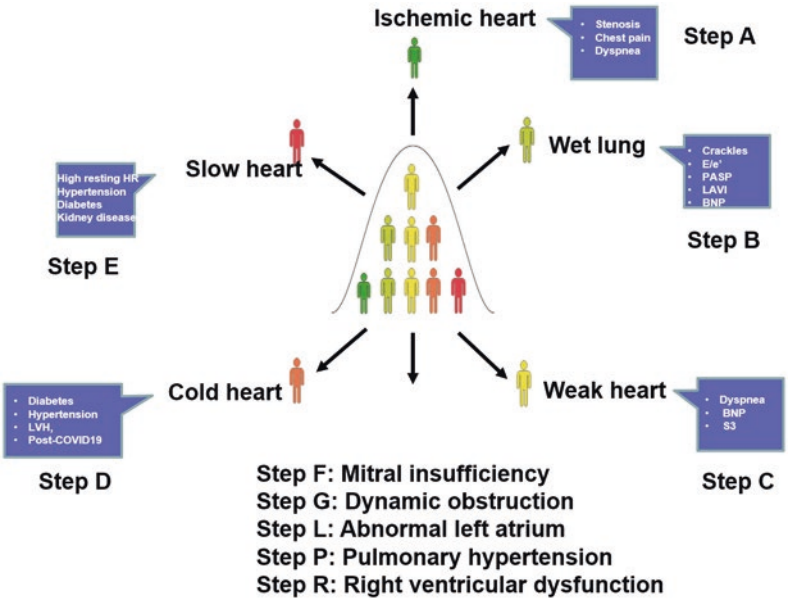

Fig. 43.4 Comprehensive echocardiography as a roadmap to therapy. The combination of clinical data with imaging data allows the identification of specific phenotypes which represent actionable therapeutic targets

multiple available letters, it is easier to better write the more appropriate letter to a given person. All proposed parameters have already been extensively used outside coronary artery disease to allow a flexible approach to different clinical scenarios [7, 62], but probably a more systematic and comprehensive approach can now be proposed.

At rest or during stress, with exercise or drugs, comprehensive echocardiography will play an essential, ubiquitous, and versatile role on the road to personalized medicine with a low-cost, universally available, and ionizing radiation-free approach. We are still far from this ideal test, but in the last 50 years we have come a very long way, and hopefully, we are still moving in the right direction, at a faster pace in the last 5 years (Fig. 43.5). The inclusion of centers from many sites contains the potential to recognize similarities and differences between countries, continents, cultures, and ethnicities. Inclusivity will also allow assessment of how the proposed protocol will materialize in different scenarios (private practice settings, public hospitals, academic institutions) with different reimbursement policies and variable direct costs and commercial availability for drugs (such as dipyridamole and adenosine) and ultrasound-enhancing agents.

These features are completely different from efficacy studies, as when highly specialized centers recruit highly selected patients, the resulting data may be difficult to translate into clinical practice. For these reasons, in 2013, the American Society of Echocardiography identified as top research need "*the development of a registry of echocardiographic information (and eventually images) that can serve as a platform for quality improvement and clinical research. Such registry data would be accessible to the research community facilitating a broad range of clinical research on the effectiveness of echocardiography for the improvement of patient management and outcome*" [63]. SE2030 will establish the platform of evidence to

Fig. 43.5 Cielo di Pisa, the flagship slide of stress echo 2030. The consortium of 40 centers from 20 countries and 4 continents is recruiting 10,000 patients in 12 different protocols with the support and endorsement of SIECVI Italian Society of Echocardiography and Cardiovascular Imaging. (Pictures of contributors as of June 30, 2023, are shown)

build the modern SE test, suitable for all patients, anywhere, anytime, and also quantitative and operator-independent. The need for such an ideal test is especially vital in our times, when the economic crisis, the COVID pandemic, the increased awareness of cancer and noncancer radiation damage, and the pressing need for climate-neutral choices in health care are potent propelling forces for the diffusion of a low-cost, radiation-free, climate-friendly, and portable technique such as cardiovascular ultrasound [64].

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