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Stress Echo 2030: the new ABCDE protocol defining the future of cardiac imaging

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Functional testing with stress echocardiography is based on the detection of regional wall motion abnormality with two-dimensional echocardiography and is embedded in clinical guidelines. Yet, it under-uses the unique versatility of the technique, ideally suited to describe the different functional abnormalities underlying the same wall motion response during stress. Five parameters converge conceptually and methodologically in the state-of-the-art ABCDE protocol, assessing multiple vulnerabilities of the ischemic patient. The five steps of the ABCDE protocol are (1) *step A*: regional wall motion; (2) *step B*: B-lines by lung ultrasound assessing extravascular lung water; (3) *step C*: left ventricular contractile reserve by volumetric two-dimensional echocardiography; (4) *step D*: coronary flow velocity reserve in mid-distal left anterior descending coronary with pulsed-wave Doppler; and (5) *step E*: assessment of heart rate reserve with a one-lead electrocardiogram. ABCDE stress echo offers insight into five functional reserves: epicardial flow (A); diastolic (B), contractile (C), coronary microcirculatory (D), and chronotropic reserve (E). The new format is more comprehensive and allows better functional characterization, risk stratification, and personalized tailoring of therapy. ABCDE protocol is an 'ecumenic' and 'omnivorous' functional test, suitable for all stresses and all patients also beyond coronary artery disease. It fits the need for sustainability of the current era in healthcare, since it requires universally available technology, and is low-cost, radiation-free, and nearly carbon-neutral.

The limitations of regional wall motion abnormality

The rise of stress echocardiography (SE) in the last 40 years has been continuous and remarkable. SE is now widely available, and its use based on stress-induced regional wall motion abnormality (RWMA) is recommended with a class 1 indication for the diagnosis of chronic coronary syndromes in the guidelines of the European Society of Cardiology (ESC) 2019[1] and the American College of Cardiology/American Heart Association (ACC/AHA) 2021.[2] Moreover, the feasibility of diagnostic quality images with selective use of ultrasound-enhancing agents for

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endocardial border enhancement currently exceeds 95% and allows one to obtain diagnostic studies 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 sub-maximal and non-diagnostic 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 RWMA applied in contemporary populations with suspected coronary artery disease showed two major limitations: (1) a decrease in positivity rate (<10% compared with >60% in 1990s) probably due to the current dominant policy of stress testing under full anti-ischemic therapy in patients with atypical symptoms and multiple comorbidities; and (2) the declining prognostic value of the negative test for RWMA when only hard endpoints are considered, likely due to more extensive coronary revascularization. The annual hard event rate (death or myocardial infarction) after a test negative for RWMA was 0.5% in 1980s and 2% in the last decade.[3] The same decline in positivity rate and negative predictive value has been observed with other imaging techniques. This is not surprising and is even expected based on the changed pathophysiological framework and current understanding of coronary artery disease. Older pre-test probability scores, such as the Diamond–Forrester model developed in 1979, estimates the probability of obstructive coronary artery disease, resulting in significant overestimation in contemporary patients referred for non-invasive imaging. 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.[4] Plaque composition is even more important than plaque geometry and severity.[4] Pulmonary congestion and diastolic function, left ventricular structure and contractile reserve, coronary microcirculation, and cardiac autonomic balance are equally important determinants of risk but difficult to assess non-invasively with currently available methods. In this changed operational and conceptual scenario SE has evolved in the last 5 years, taking full advantage of the unsurpassed versatility of the technique. RWMA remains the cornerstone of diagnosis and is the only sign recommended by guidelines based on 40 years of extensive clinical experience. Nevertheless, myocardial ischemia assessment (evaluating RWMA alone with SE) is no longer enough for a comprehensive diagnosis and risk stratification in contemporary patients.

ABCDE protocol: the test of the five reserves

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: epicardial artery reserve with step A[5]; diastolic reserve through pulmonary congestion with step B[6–8]; left ventricular contractile reserve with step C[9]; coronary microcirculatory reserve with step D[10,11]; and cardiac autonomic dysfunction with step E.[12–14] The five parameters converge conceptually and methodologically in the ABCDE protocol which can be applied to all stresses and all patients with symptoms of suspected cardiac origin and allows comprehensive risk stratification of the vulnerable patient beyond coronary artery stenosis.[15] Conceptually, ABCDE-SE targets five different pathophysiological targets each independently contributing to the overall vulnerability profile of the patient.

Methodologically, all five steps are unified under the same ABCDE protocol that uses different imaging modalities: two-dimensional echocardiography for regional wall motion analysis; lung ultrasound for B-lines (with the four-site simplified scan of third intercostal space); volumetric echocardiography for preload and contractile reserve; colour- and pulsed-wave Doppler for coronary flow velocity reserve in the left anterior descending coronary artery; ECG for heart rate reserve. The five steps are used following a strict sequence to optimize the timing of the examination with no loss of information. The protocol can be enriched with the use of ultrasound enhancing agents, which can also provide information on myocardial perfusion or, with a bolus injection, no additional software required, better precision and higher feasibility for detection of left ventricle (LV) regional wall motion, LV volumes, and coronary flow imaging in difficult cases (*Table 1*).

The same transducer is used for cardiac and lung ultrasound scans. Steps A and C use the same set of images (apical 4-, 2- and 3-chamber, the latter useful for strain and perfusion contrast). B-lines are imaged in the early recovery phase (within 1 min after the end of exercise or immediately after antidote administration in pharmacological test) and therefore there is no competition with other parameters. Heart rate reserve is imaging independent and based on a single ECG lead displayed and automatically analysed in the echo monitor. Coronary flow velocity reserve (CFVR) remains a hurdle during exercise, but is still feasible in the intermediate stages of semi-supine exercise, or separately assessed at the end of the standard exercise with a single bolus of vasodilator.[15]

ABCDE+: to each patient the right test

As needed, the core ABCDE protocol is enriched by step G for gradients, step F for regurgitant flows, step L for left atrial volume, step P for pulmonary artery systolic pressure, and E/e' as a proxy of pulmonary artery wedge pressure, and step R for right ventricular function. Each step has its specific application. Transvalvular mean gradients are necessary to assess aortic or mitral stenosis or prostheses. The left ventricular outflow tract peak gradient is significant for decision-making in symptomatic patients with hypertrophic cardiomyopathy and with a resting peak gradient < 50 mmHg. Mitral regurgitation may be assessed in either primary and secondary mitral regurgitation, but also important in other conditions, such as hypertrophic cardiomyopathy or in the screening phase of heart failure with preserved ejection fraction to identify an extra-diastolic cause of dyspnoea. Pulmonary hemodynamic with pulmonary artery systolic pressure from tricuspid regurgitant velocity jet is a part of the functional evaluation in valvular heart disease, heart failure with reduced or preserved ejection fraction, and pulmonary hypertension. E/e' is indicated in heart failure with preserved ejection

Table 1 Imaging and non-imaging parameters for ABCDE SE protocol

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

ANS, autonomic nervous system; CFVR, coronary flow velocity reserve; HRR, heart rate reserve; LUS, lung ultrasound; LVCR, left ventricular contractile reserve; Microcirc, coronary microcirculation; PWD, pulsed-wave Doppler. Modified and adapted from Picano *et al.*[20] http://creativecommons.org/licenses/by/4.0/

fraction to assess diastolic function and filling pressure during stress, and is usually measured in the recovery phase of exercise. The right ventricular contractile reserve can be evaluated with the simplest parameter of tricuspid annulus systolic excursion during stress and is essential to evaluate the right ventricular contractile reserve in patients with congenital heart disease, such as repaired tetralogy of Fallot. This tailored approach allows one to exploit at the fullest the versatility of SE, and to tailor the most appropriate test to the individual patient since all patients share some vulnerabilities. However, each patient may have its own additional specific vulnerability which identifies specific phenotypes and actionable therapeutic targets.[16,17]

Economic, ethical, and environmental sustainability

All five primary imaging techniques (SE, coronary computed tomography angiography, stress-cardiac magnetic resonance, stress-single photon emission computed tomography, stress-positron emission tomography) show similar accuracy and a similar level of recommendations in recent ESC and ACC/AHA guidelines. The choice is left to 'local availability and physician preference'.[1,2] However, health care has transformed in the last 5 years. Three major changes may directly impact the use of cardiac imaging: limited healthcare resources in the pandemic era, increasing evidence of cancer effects of medical diagnostic radiation in the low-dose range < 50 mSv, and climate change emergency emphasizing the environmental impact of our choices. The physician should consider not only the diagnostic accuracy, but the economic, radiologic, and environmental sustainability issues. The different costs can be synthetically expressed as immediate cost (in euros or dollars), radiologic cost (in mSv or chest X-rays equivalents), and carbon cost (carbon dioxide emissions equivalents).

Economic sustainability

The average relative costs of the imaging procedures in Europe show a cost gradient between SE (relative cost = 1) and other non-invasive and invasive imaging techniques. SE costs three times less than coronary computed tomography angiography and 24-times less than stress-positron emission tomography. In the United States, the cost of cardiac stress imaging can range anywhere from 200 dollars for the least expensive SE (median cost of 2,600, range 200–5000) to $24 200 for the most expensive cardiac stress-positron emission tomography (median cost $7900). Worldwide, diagnostic information of similar value according to guidelines can be bought with a 400-fold difference in cost between the least expensive SE in Europe and the most expensive cardiac stress-positron emission tomography in the United States. In the United States, there is a six-fold variation for all cardiovascular tests across top-ranked hospitals and four-fold variations within the same institution, now exposed by the enactment of the 2021 Hospital Price Transparency Final Rule. It is challenging to propose any cost-effectiveness analysis when the cost varies within this enormous range, probably unique to the healthcare market compared to all other markets. It is also an easy guess that the private or public payer will take countermeasures to avoid waste of health care money that our system cannot afford.

Radiologic sustainability

The radiologic cost of cardiac imaging is expressed in effective dose in millisievert (mSv) or chest X-rays equivalents (1 mSv = 50 chest X-rays, posteroanterior projection).[18] Radiologic exposure is zero for radiation-free SE or stress-cardiac magnetic resonance, 150 chest X-rays (3 mSv) for a cardiac stress-positron emission tomography, 200 chest X-rays (4 mSv) for a coronary computed tomography angiography, and 500 chest X-rays (10 mSv) for a stress-single photon emission computed tomography.[2] Radiation exposure is especially important in children (four times more sensitive than adults to radiation) and women (38% more sensitive than males), and when the patient is exposed to cumulative damage from serial radiation exposures.[18]

Environmental sustainability

Carbon dioxide emissions are linked to climate change and it is a healthcare priority to minimize carbon emissions for all medical activities. The carbon cost of cardiac imaging varies with a factor of >100 from SE (2 kg of carbon dioxide emissions per test) to 10-fold higher values for coronary computed tomography angiography (20 kg) and 100-fold higher values (200–300 kg) for cardiac magnetic resonance.[19]

The issue of sustainability is increasingly important in our society. In this perspective of sustainability for payers, patients, and the planet, SE is fit for the role of first-line

Figure 1 SE2030. 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. Stress echocardiography protocols are indicated from 1 to 12 clockwise and cover a wide spectrum of clinical conditions extending beyond coronary artery disease. *Source:* Picano *et al.*[20] http://creativecommons.org/licenses/by/4.0/.

test of functional imaging for its feature of low cost, zero radiation, and near-zero carbon footprint. The awareness of the integrated economic, radiologic, and environmental costs of testing will hopefully drive the change towards more sustainable models of health care delivery. In medical imaging, less is more, zero radiation is better, and near-zero carbon is best. More sustainable cardiac imaging with affordable, radiation-optimized, and carbon-neutral practices will benefit all stakeholders: patients, payers, and the planet. Prescribing medical imaging is a social—not simply a medical—act.[19]

SE2030

The shift from the time-honoured SE based on RWMA to a more comprehensive protocol (ABCDE+) also implied the transition from an evidence-rich to an evidence-poor scientific environment. Clinical decisions are better supported by studies on thousands of patients than by a few hundred collected in specialized centres. Therefore, the obligatory pathway was to start again a new wave of multicentre studies helping to collect the evidence required to change the clinical practice in a relatively short time. This was possible with the SE2020 study started in 2016 and now expanded in the SE2030 study projected to 2030.[20]

With the SE2020 study, a new standard of practice in stress imaging was developed and disseminated: the ABCDE protocol for functional testing within and beyond coronary artery disease. The unsurpassed versatility of echocardiography allows for studying virtually all patients, and each one differently. The comprehensive protocol was the fruit of SE2020 and is the seed of SE2030, which is based on the ABCDE+ protocol and is articulated in 12 projects covering a broad spectrum of disease: from coronary artery disease to coronary vasospasm, from hypertrophic cardiomyopathy to heart failure with preserved ejection fraction, from chest radiotherapy to COVID-19, from valvular to congenital heart disease, from strain to contrast, from air pollution modulation of SE results to cumulative medical imaging radiation load

as a determinant of long-term outcome. Image analysis and data mining are supported by artificial intelligence. The study aims to recruit in 5 years (2021–2025) ≥ 10 000 patients followed for ≥5 years (up to 2030) from ≥50 quality-controlled laboratories from ≥20 countries. (*Figure 1*). As of 1 November 2022, the SE2020–2030 network has collected 9000 studies, one-half with the complete ABCDE protocol. Step D is incorporated in the standard protocol either with a single test (dipyridamole, dobutamine, or semi-supine exercise) or with hybrid physical-pharmacological testing (treadmill followed at the end of the recovery phase by single bolus adenosine for CFVR assessment).

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Data availability

No new data were generated or analysed in support of this research.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C *et al*. The task force for the diagnosis and management of chronic coronary syndromes of the European society of cardiology. *Eur Heart J* 2020;**41**:407–477.
2. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK *et al*. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: A report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol* 2021;**78**:e187–e285.
3. Cortigiani L, Urluescu ML, Coltelli M, Carpeggiani C, Bovenzi F, Picano E. Apparent declining prognostic value of a negative stress echocardiography based on regional wall motion abnormalities in patients with normal resting left ventricular function due to the changing referral profile of the population under study. *Circ Cardiovasc Imaging* 2019; **35**:627–632.
4. Marzilli M, Merz CN, Boden WE, Bonow RO, Capozza PG, Chilian WM *et al*. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link!. *J Am Coll Cardiol* 2012;**60**:951–956.
5. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR *et al*. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American society of echocardiography. *J Am Soc Echocardiogr* 2020; **33**:1–41.
6. Scali MC, Ciampi Q, Zagatina A, Cortigiani L, D'Andrea A, Borguezan Daros C *et al*. On behalf of the stress Echo 2020 study group of the Italian society of echocardiography and cardiovascular imaging. Lung ultrasound and pulmonary congestion during stress echocardiography. *JACC Cardiov Imaging* 2020;**19**:2085–2095.
7. Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E. The added value of exercise-echocardiography in heart failure patients: assessing dynamic changes in extravascular lung water. *Eur J Heart Failure* 2017;**19**:1468–1478.
8. Merli E, Ciampi Q, Scali MC, Zagatina A, Merlo PM, Arbucci R *et al*. Pulmonary congestion during exercise stress echocardiography in ischemic and heart failure patients. *Circ Cvimaging* 2022;**15**:e013558.
9. Cortigiani L, Ciampi Q, Carpeggiani C, Lisi C, Bovenzi F, Picano E. Additional prognostic value of heart rate reserve over left ventricular contractile reserve and coronary flow velocity reserve in diabetic patients with negative vasodilator stress echocardiography by regional wall motion criteria. *Eur Heart J Cardiovasc Imaging* 2022;**23**:209–216.
10. Ciampi Q, Zagatina A, Cortigiani L, Gaibazzi N, Borguezan Daros C, Nadezhda Zhuravskaya N *et al*. Functional, coronary anatomic and prognostic correlates of coronary flow velocity reserve during stress echocardiography. *J Am Coll Cardiol* 2019;**74**:2280–2293.
11. Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN *et al*. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J* 2022;**43**:1582–1593.
12. Elhendy A, Mahoney DW, Khanderia BK, Burger K, Pellikka PA. Prognostic significance of impairment of heart rate response to exercise. Impact of left ventricular function and myocardial ischemia. *J Am Coll Cardiol* 2003;**42**:823–830.
13. Chaowalit N, Mc Cully RB, Callahan MJ, Mookadam F, Bailey KM, Pellikka PA. Outcomes after normal dobutamine stress echocardiography and predictors of adverse events: long-term follow-up of 3014 patients. *Eur Heart J* 2006;**27**:3039–3044.
14. Cortigiani L, Carpeggiani C, Landi P, Raciti M, Bovenzi F, Picano E. Usefulness of blunted heart rate reserve as an imaging-independent prognostic predictor during dipyridamole-echocardiography test. *Am J Cardiol* 2019;**124**:972–977.
15. Ciampi Q, Zagatina A, Cortigiani L, Wierzbowska-Drabik K, Kasprzak JD, Haberka M *et al*. Prognostic value of stress echocardiography assessed by the ABCDE protocol. *Eur Heart J* 2021;**42**:3869–3878.
16. Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. *Eur Heart J* 2014;**35**:1033–1040.
17. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R *et al*. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European association of cardiovascular imaging and the American society of echocardiography. *J Am Soc Echocardiogr* 2017;**17**:1191–1229.
18. Picano E, Vano E, Rehani M, Cuocolo A, Lont L, Bodi V *et al*. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC associations of cardiovascular imaging, percutaneous cardiovascular interventions, and electrophysiology. *Eur Heart J* 2014;**35**:665–672.
19. Picano E. Economic, ethical, and environmental sustainability of cardiac imaging. *Eur Heart J* 2022:ehac716. doi:10.1093/eurheartj/ehac716.
20. Picano E, Ciampi Q, Cortigiani L, Arruda-Olson AM, Borguezan-Daros C, de Castro e Silva Pretto JL *et al*. Stress Echo 2030: the novel ABCDE-(FGLPR) protocol to define the future of imaging. *J Clin Med* 2021;**10**:3641.