The International Journal of Cardiovascular Imaging (2019) 35:627–632
https://doi.org/10.1007/s10554-018-1501-3

ORIGINAL PAPER

Drop-off in positivity rate of stress echocardiography based on regional wall motion abnormalities over the last three decades

Lauro Cortigiani[1] · Pamela Ramirez[2] · Maico Coltelli[3] · Francesco Bovenzi[1] · Eugenio Picano[4]

Received: 26 June 2018 / Accepted: 13 November 2018 / Published online: 20 November 2018

Abstract

Previous studies have suggested a decline in positivity of stress cardiac imaging based on regional wall motion abnormalities (RWMA). To assess the rate of RWMA positivity of stress echocardiography (SE) over 3 decades in the same primary care SE lab. We retrospectively assessed the rate of SE positivity in 7626 SE tests (dipyridamole in 5053, dobutamine in 2496, exercise in 77) in consecutive patients with known or suspected coronary artery disease and /or heart failure who performed SE in a primary care referral center from April 1991 to May 2018. Starting April 2005, SE based on RWMA was complemented by assessment of coronary flow velocity reserve (CFVR) of the left anterior descending coronary artery. Starting October 2016, we added left ventricular contractile reserve (LVCR). Starting October 2016, we also added B-lines by lung ultrasound. There was a progressive decline over time in the rate of SE positivity based on RWMA from 24% (1991–1999) to 10% (2000–2009) down to 4% (2010–2018) ($p < 0.0001$). Positivity rate was 29% with CFVR, 16% with LVCR, and 12% with B-lines. Over three decades, we observed a dramatic decline in SE positivity rate based on classical RWMA. In the last decade, the positivity rate rose sharply thanks to the stepwise introduction of CFVR, LVCR and B-lines as additional positivity criteria in integrated quadruple SE.

Keywords Echocardiography · Ischemia · Pre-test probability · Stress

Abbreviations

CAD	Coronary artery disease
CFVR	Coronary flow velocity reserve
LVCR	Left ventricular contractile reserve
RWMA	Regional wall motion abnormalities
SE	Stress echocardiography
TTE	Transthoracic echocardiography
WMSI	Wall motion score index

✉ Eugenio Picano
picano@ifc.cnr.it

Lauro Cortigiani
lacortig@tin.it

Pamela Ramirez
pam_r21@hotmail.com

Maico Coltelli
maico.coltelli@estav-nordovest.toscana.it

Francesco Bovenzi
f.bovenzi@tin.it

1 Cardiology Division, San Luca Hospital, Lucca, Italy

2 National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico

3 Department of Computer Science and Technology, ESTAR, Toscana, Pisa, Italy

4 Institute of Clinical Physiology, Biomedicine Department, CNR, CNR Research Campus, Via Moruzzi, 1, 56124 Pisa, Italy

Introduction

Coronary artery disease (CAD) remains the leading cause of death among Europeans and around the world, and despite recent decreases in mortality rates in many countries, it is still responsible for over 1.8 million deaths per year, 20% of all deaths in Europe [1]. Hence, to have precise methods for diagnosis and risk stratification becomes essential. Stress echocardiography (SE) based on the detection of regional wall motion abnormalities (RWMA) is a valuable help for this purpose, being the first line cardiac stress imaging tool for the noninvasive evaluation of CAD recommended by guidelines [2–4].

Nevertheless, a steep decline in rate of positivity rate of SE has been reported in the last 3 decades, likely due to changing referral patterns [5–7]. If this is confirmed under different operating conditions, refined criteria for referral for

testing are needed to optimize the yield of testing. The post-test probability is heavily dependent upon the prevalence of the disease in the studied population according to Bayes theorem. When the prevalence of disease drops-off the false positive paradox occurs, with absence of disease being more likely than presence of disease even after a positive testing [8, 9]. In addition, in the case of SE several new parameters beyond RWMA have recently been proposed to expand the diagnostic and risk stratification potential of the method and currently represent a new standard under large scale validation [10]. These new parameters focus on variables different from epicardial coronary artery stenosis which is the target of RWMA, and allow to gain insight into coronary microvascular function with coronary flow velocity reserve [11–13] (CFVR), extravascular lung water with B-lines [14], and myocardial function with left ventricular contractile reserve (LVCR) through force (also called elastance) assessment [15, 16].

The purpose of this study was to assess the rate of positivity of SE based on RWMA over 3 decades in the same primary care SE lab and to evaluate the impact of newly developed parameters (CFVR, LVCR and B-lines) on positivity rate in contemporary patients.

Methods

Using the Lucca Hospital Database, we retrospectively assessed 7626 SE tests (dipyridamole in 5053, dobutamine in 2496, exercise in 77) in consecutive patients with known or suspected coronary artery disease and/or heart failure from April 1991 to May 2018. SE was performed with commercially available instruments according to the well-established protocols [2, 3] using dipyridamole (up to 0.84 mg/kg over 6 min), dobutamine (up 40 mcg/kg/min) or exercise (semi-supine bicycle ergometer with 25W incremental loading every 2 min).

Starting May 2005, SE based on RWMA was complemented by assessment of CFVR during dipyridamole stress, assessed during the standard examination by an intermittent imaging of both wall motion and left anterior descending coronary artery flow [3], with instruments equipped with multifrequency phased-array sector scan probes (S3 to S8) and with second harmonic technology. Coronary flow in the mid-distal portion of the LAD was searched in the low parasternal long axis section under the guidance of color Doppler flow mapping. Flow velocities were measured at least 3 times (at baseline and at peak stress) for each study. We calculated CFVR as the peak stress/rest ratio of diastolic flow velocity, measured by color-Doppler guided pulsed wave Doppler (PWD) of mid-distal left anterior descending artery, defining a positive response like CFVR ≤ 2.0 [16–18]. Starting October 2016, we added LVCR defined as the peak/rest ratio of left ventricular force. The LV force was measured as the ratio of end-systolic pressure by cuff sphygmomanometer/end-systolic volume by 2D (result of a mean between 4 and 2 chambers view). The positivity criterion was ≤ 1.1 for dipyridamole and ≤ 2.0 for dobutamine [19, 20].

Starting October 2016, we also added B-lines by lung ultrasound using a 4-site simplified scan (each site scored from 0 to 10) [21]. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artifact that arises from the pleural line extending to the bottom of the screen without fading and moving synchronously with lung sliding [22–24]. The positivity criterion for B-lines was any appearance or increment in stress score > rest score of ≥ 2 points (for instance: rest score = 0 and stress score = 2 or more; or rest score = 4 and stress score = 6 or more).

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Categorical variables were expressed as percentages. The statistical significance of changes over time in different patients was assessed by the Cochran-Armitage test (for binary variables). Logistic regression analysis was performed to evaluate the risk-adjusted odds ratio of clinical factors predicting abnormal SE results. A two-sided p-values < 0.05 was considered significant. Statistical analysis was performed using SPSS version 16.0.

Results

The characteristics of the study patients in different periods of enrollment are summarized in Table 1. Over 3 decades, there was a progressive decline of patients with known CAD (from 41% in the nineties to 31% in the last decade) and RWMA on resting echocardiogram (from 45 to 19%), with an increase of patients under beta-blocker therapy at the time of testing (from 3 to 33%).

The temporal change in the positivity rate of SE and the increase of beta-blocker therapy are shown in Figs. 1 and 2, respectively.

There was a progressive decline over time in the rate of SE positivity based on RWMA from 24% (1991–1999) to 10% (2000–2009) down to 4% (2010–2018) ($p < 0.0001$) (Table 1). Starting 2005, we included CFVR in dual imaging SE and positivity rate rose to 29% (Table 2) (Fig. 1). Starting October 2016, we included LVCR which added a 16% of positive results, and B-lines in quadruple imaging with 12% of positive results (Table 2) (Fig. 1). Of 342 patients who were consecutively investigated with integrated quadruple imaging (RWMA + CFVR + LVCR + B-lines) from October 2016 to May 2018, 125 (37%) exhibited positivity of at least 1 functional parameter.

Table 1 Characteristics of patients in the different periods of enrollment

	1991–1999 (n = 1984)	2000–2009 (n = 3338)	2010–2018 (n = 2304)	p value
Age (years)	63 ± 11	67 ± 11	67 ± 12	< 0.0001
Males	1107 (56%)	1904 (57%)	1347 (58%)	0.21
Clinical history				
Family history of CAD	670 (34%)	998 (30%)	587 (25%)	< 0.0001
Diabetes mellitus	254 (13%)	769 (23%)	622 (27%)	< 0.0001
Arterial hypertension	881 (44%)	2125 (64%)	1531 (66%)	< 0.0001
Hypercholesterolemia	669 (9%)	1451 (43%)	1166 (51%)	< 0.0001
Smoking habit	544 (27%)	719 (21%)	465 (20%)	< 0.0001
Previous myocardial infarction	769 (39%)	951 (28%)	445 (19%)	< 0.0001
Previous PCI	100 (5%)	582 (17%)	530 (23%)	< 0.0001
Previous CABG	56 (3%)	229 (7%)	144 (6%)	< 0.0001
Known CAD	823 (41%)	1323 (40%)	742 (32%)	< 0.0001
Anti-ischemic therapy at the time of test				
β-Blockers	66 (3%)	382 (11%)	757 (33%)	< 0.0001
Calcium antagonists	117 (6%)	160 (5%)	161 (7%)	0.002
Nitrates	516 (26%)	58 (2%)	21 (1%)	< 0.0001
Resting echocardiogram				
WMSI	1.23 ± 0.35	1.18 ± 0.32	1.10 ± 0.26	< 0.0001
WMA	897 (45%)	1165 (35%)	444 (19%)	< 0.0001
Stress echocardiography				
Dipyridamole	1070 (54%)	2040 (61%)	1944 (84%)	< 0.0001
Dobutamine-exercise	914 (46%)	1298 (39%)	360 (16%)	< 0.0001
Ischemic result	483 (24%)	325 (10%)	89 (4%)	< 0.0001

Data presented are mean value ± SD or number (%) of patients

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; WMSI, wall motion score index; WMA, wall motion abnormalities

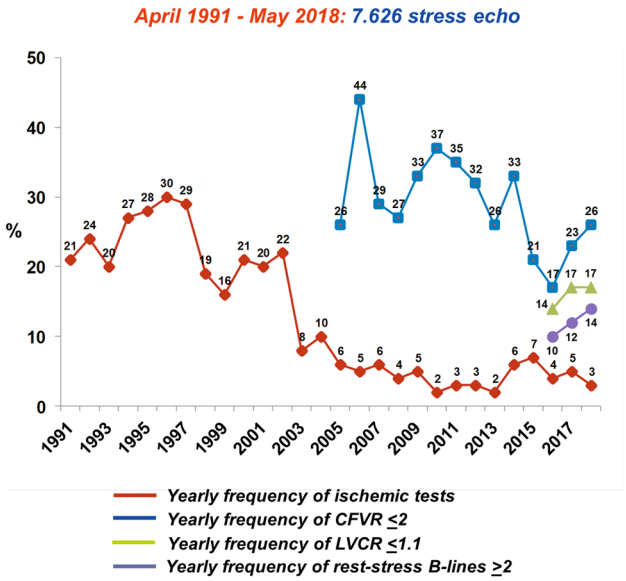

Fig. 1 Decline in positive SE based on RWMA in the last 3 decades. In the last 10 years we observed a rise of SE positivity with the introduction of CFVR (since 2005), LVCR and B-lines (since 2016)

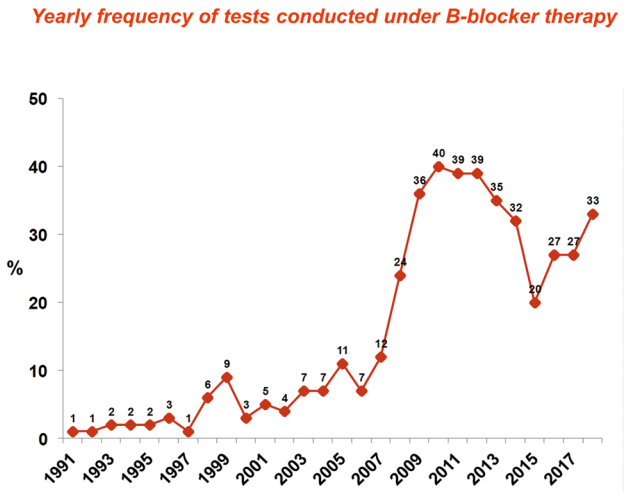

Fig. 2 Yearly frequency of tests conducted under B-blocker therapy

The number of early (< 3 months) stress-echo driven revascularizations remained low and stable in patients with negative SE results for absence of RWMA (4% in the first,

Table 2 Frequency and abnormal results of stress echocardiography, coronary flow velocity reserve, left ventricular contractility reserve, and stress-rest B-lines

Stress echocardiography	7626
Ischemic result	897 (12%)
CFVR of LAD	2655
CFVR ≤ 2	779 (29%)
LVCR	342
LVCR ≤ 1.1	56 (16%)
Stress-rest B-lines	342
Stress-rest B-lines ≥ 2	42 (12%)

Data presented are number (%) of tests

CFVR, coronary flow velocity reserve; LAD, left anterior descending; LVCR, left ventricular contractile reserve

3% in the second and 5% in the last decade), but increased in patients with positive SE (25% in the first, 22% in the second and 65% in the last decade).

Discussion

Our study documents a marked and progressive decline in the frequency of ischemic SE studies among diagnostic patients over the last 3 decades. Whereas the frequency of abnormal studies was 24% in 1991, by 2018, the frequency of myocardial inducible ischemia decreased to only 3%. This finding reflects the underlying lower prevalence of CAD in the referred population and may profoundly affect the clinical use of SE results. On the other side, the increased use of beta-blocker therapy could protect from stress induced myocardial ischemia and may mask ischemic response, not only for exercise but also for pharmacological stresses [3].

Comparison with previous studies

Our results are consistent with several previous reports on the decline of positivity rate with cardiac stress testing with scintigraphy [5] or SE in the last decades. In particular, as far as SE is concerned, Bouzas-Mousquera et al. evaluated exercise echocardiography from 1997 to 2012 in a cohort of 12,339 patients [5], and observed a decrease from 35.6% in 1997 to 25.4% in 2009 ($p < 0.001$) in frequency of detection of myocardial ischemia. Carpeggiani et al. assessed the rate of SE positivity in a tertiary care referral center from 1983 a 2009 (exercise or pharmacological SE) and observed a steady decline in inducible ischemia from 42 to 22% [6]. Barbieri et al. [7] also evaluated the trends of SE positivity in outpatients and observed a progressive decrease in the frequency of inducible ischemia with pharmacological SE among 1954 patients from 11 to 3% over a 12 years period.

The declining frequency of abnormal SE, in all these studies, was accompanied by a progressive change in SE referral practice, with higher percentage of patients with low pre-test probability of disease with greater percentage of patients studied on therapy which may protect from RWMA [25, 26], and interferes much less with CFVR [27]. Beta-blockers induce a rightward shift in the dose–response curve to dobutamine [28] and also markedly lower the sensitivity of dipyridamole, through a direct anti-steal effect largely independent from the effect on heart rate [28, 29]. Consistently with previous studies, the positivity rate increases with other criteria such as CFVR, B-lines and LVCR [30–32].

Study limitations

Although the study sample was very large, one limitation is that the data reported herein comprise the experience from a single medical center. Also, our study is a retrospective analysis, with the inherent limitations of this study design.

Stress testing involved dipyridamole infusion (for the majority), which is not the principal stressor in many countries. However, dipyridamole was started since the beginning of our activity and has the same accuracy as exercise or dobutamine when the high dose protocol is used [2, 3]. It is by far the easiest stress from the technical viewpoint since the images are not degrade by excessive increase in heart rate or hypercontractility or hyperventilation as happens with exercise and, to a lesser extent, with dobutamine. We employ it routinely with CFVR since 10 years. CFVR is also feasible but with less success rate with dobutamine and exercise [3, 11]. The sensitivity of dipyridamole can be suboptimal in milder form of CAD, i.e. single vessel disease, and with new era of more potent drugs for stable angina, this also could be the reason for frequent test negativity. An alternative approach to overcome the reduction in positivity rate is to use combinations of stresses in the same test, such as dipyridamole immediately followed by exercise [32] or dobutamine [33].

We did not use contrast in our tests, due to regulatory and reimbursement reasons.

We pooled results obtained with several generations of instruments, with different operators. However, the techniques of execution, test protocol, criteria of reading and quality control of the operators were remarkably consistent over time and since the beginning- always under the direct responsibility of the same reader (LC). Therefore, the factors modulating the test performance are likely to act outside the SE lab, most probably in the changing referral patterns.

Clinical implications

The positivity rate of SE based on RWMA is unacceptably low in contemporary population of patients referred to a

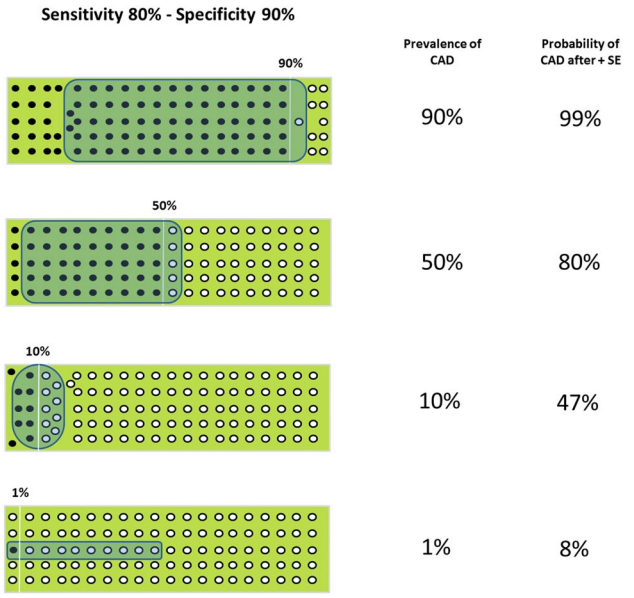

Fig. 3 Visual representation of the declining probability of disease in patients with a positive SE for RWMA due to changing prevalence of disease in the population under study. No CAD, white circles; CAD, dark circles. With a 90% pre-test probability, the post-test probability after a positive SE is 99% (upper panel); with a 50% pre-test probability, the post-test probability after a positive SE is 80% (second panel); with a 10% pre-test probability, the post-test probability after a positive SE is 47% (third panel); with a 1% pre-test probability, the post-test probability after a positive SE is 8% (lowest panel), which leads to a false positive paradox (it is more likely not to have the disease that to have it after a positive test)

primary care lab. In particular this will limit the yield of testing, since the probability of having the disease changes with the incidence of disease in the population under investigation even under the same conditions of test diagnostic performance, assumed for SE to be in the 80% sensitivity and 90% specificity range on the basis of extensive meta-analyses also incorporated into recent guidelines. The concept of declining test performance with changing referral patterns is expected on the basis of Bayes theorem and can be illustrated graphically to display the probability associated with a positive test result (Fig. 3). If the prevalence of CAD is 90% (as it was in the early days of SE), a positive SE for RWMA yields a probability to find CAD at angiographic verification around 99%. If the prevalence of CAD is 50%, the disease probability after the same positive SE decreases to 80%, which is still acceptable. However, if the prevalence of CAD is 10% or even 1%, the probability post-positive test drops-off to 47% and 8% respectively. Therefore, it is important to follow recent ESC and AHA-ACC guidelines suggesting that cardiac stress testing is not indicated in patients with low pre-test probability of disease. This is due not only to very important cost-containment and health care sustainability issues, but also for the inadequate yield of testing in these populations. A better selection of patients and probably an enrichment of the positivity domain with other parameters beyond RWMA are needed to optimize the risk stratification potential of the technique taking advantage of its unsurpassed versatility.

Conclusions

Over three decades, we observed a dramatic decline in SE positivity rate based on classical RWMA.

This is due to changing referral patterns and will necessarily reduce the diagnostic performance of testing- for unchanged sensitivity/specificity values. Two actions are warranted. First, upstream to the SE lab, a stricter selection of patients, since the test will perform better in patients with intermediate-to-high pre-test probability of disease, as recommended by guidelines—although in clinical practice most inappropriate indications exactly fall in the low-pre-test probability. Second, in the SE lab, a more comprehensive assessment of epicardial coronary, coronary microvascular, extravascular lung water and myocardial function in quadruple imaging will enrich the pathophysiological information and prognostic potential derived from testing in integrated quadruple-SE [34].

Funding This study was supported by Institutional funds of Institute of Clinical Physiology of National Research Council of Pisa.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interests.

References

1. Nichols M, Nick T, Scarborough P et al (2014) Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 35:2950–2959
2. Pellikka PA, Nagueh SF, Elhendy AA, American Society of Echocardiography (2007) et al. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 20:1021–1041
3. Sicari R, Nihoyannopoulos P, Evangelista A (2008) European Association of Echocardiography et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 9:415–437
4. Montalescot G, Sechtem U, Achenbach S et al (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34:2949–3003
5. Bouzas-Mosquera A, Peteiro J, Broullón FJ, Calviño-Santos R, Mosquera VX, Sánchez-Fernández G et al (2015) Temporal changes in the use and results of exercise echocardiography. Eur Heart J Cardiovasc Imaging 16:207–212

6. Carpeggiani C, Landi P, Michelassi C, Sicari R, Picano E (2016) The declining frequency of inducible myocardial ischemia during stress echocardiography over 27 consecutive years (1983–2009). Int J Cardiol 224:57–61
7. Barbieri A, Mantovani F, Bursi F, Bartolacelli Y, Manicardi M, Lauria MG, Boriani G (2018) 12-year Temporal Trend in Referral Pattern and Test Results of Stress Echocardiography in a Tertiary Care Referral Center with Moderate Volume Activities and Cath-lab Facility. J Cardiovasc Echogr 28:32–38
8. Parra-Arnau J, Castelluccia C. Dataveillance and the false positive paradox. HAL Archives Ouvertes. 2018 <hal-011579621v2%3E>.
9. Eddy DM (1992) Probability reasoning in clinical medicine. Problems and opportunities. Cambridge, Cambridge University Press 249–267
10. Picano E, Ciampi Q, Citro R, D'Andrea A, Scali MC, Cortigiani L et al (2017) Stress echo 2020: the international stress echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound 15:3
11. Rigo F (2005) Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. Cardiovasc Ultrasound 3:8
12. Gaibazzi N, Rigo F, Reverberi C (2013) Detection of coronary artery disease by combined assessment of wall motion, myocardial perfusion and coronary flow reserve: a multiparametric contrast stress-echocardiography study. J Am Soc Echocardiogr 23:1242–1250
13. Cortigiani L, Rigo F, Galderisi M, Gherardi S, Bovenzi F, Picano E et al (2012) Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. JACC Cardiovasc Imaging 5:1079–1085
14. Picano E, Frassi F, Agricola E, Gligorova S, Gargani L, Mottola G (2006) Ultrasound lung comets: a clinically useful sign of extravascular lung water. J Am Soc Echocardiogr 19:356–363
15. Bombardini T, Gherardi S, Marraccini P et al (2013) The incremental diagnostic value of coronary flow reserve and left ventricular elastance during high-dose dipyridamole stress echocardiography in patients with normal wall motion at rest. Int J Cardiol 168:1683–1684
16. Rigo F, Sicari R, Gherardi S, Djordjevic-Dikic A, Cortigiani L, Picano E (2008) The additive prognostic value of wall motion abnormalities and coronary flow reserve during dipyridamole stress echo. Eur Heart J 29:79–88
17. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E (2009) Long-term survival of patients with chest pain syndrome and angio-graphically normal or near normal coronary arteries: the additional prognostic value of coronary flow reserve. Am J Cardiol 103:626–631
18. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Picano E, Sicari R (2010) Implication of the continuous prognostic spectrum of Doppler echocardiographic derived coronary flow reserve on left anterior descending artery. Am J Cardiol 105:158–162
19. Bombardini T, Correia MJ, Cicerone C, Agricola E, Ripoli A, Picano E (2003) Force-frequency relationship in the echo lab: a non invasive assessment of Bowditch Treppe? J Am Soc Echocardiogr 17:832–841
20. Grosu A, Bombardini T, Senni M, Duino V, Gori M, Picano E (2005) End-systolic pressure/volume relationship during dobutamine stress echo: a prognos- tically useful non-invasive index of left ventricular contractility. Eur Heart J 26:2404–2412
21. Picano E, Scali MC, Ciampi Q, Lichtenstein D (2018) Lung Ultrasound Ultrasound for the cardiologist. J Am Coll Cardiol Img 11:1692–1705
22. Scali MC, Zagatina A, Simova I, Zhuravskaya N, Ciampi Q, Paterni M, Marzilli M, Carpeggiani C, Picano E (2017) Stress Echo 2020 study group of the Italian Society of Cardiovascular Echography (SIEC), B-lines with Lung Ultrasound: The Optimal Scan Technique at Rest and During Stress. Ultrasound Med Biol 43:2558–2566
23. Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E (2017) Exercise-induced B-lines identify worse functional and prognostic stage in heart failure patients with depressed left ventricular ejection fraction. Eur J Heart Fail 19:1468–1478
24. Scali MC, Zagatina A, Ciampi Q, Cortigiani L, D'Andrea A, Djordjevic-Dikic A, Merlo PM, Lattanzi F, Simova I, Monte I, Dodi C, Kasprzak J, Galderisi M, Boshchenko A, Rigo F, Varga A, Dekleva M, Re F, Pretto JL, Zhuravskaya N, Wierzbovska-Drabik K, Coviello K, Citro R, Colonna P, Carpeggiani C, Picano E (2019) The functional meaning of B-profile during stress lung ultrasound. J Am Coll Cardiol Img 3:169–705
25. Lattanzi F, Picano E, Bolognese L, Piccinino C, Sarasso G, Orlandini A et al (1991) Inhibition of dipyridamole-induced ischemia by antianginal therapy in humans. Correlation with exercise electrocardiography. Circulation 83:1256–1262
26. Sicari R, Cortigiani L, Bigi R, Landi P, Raciti M, Picano E (2004) The prognostic value of pharmacologic stress echo is affected by concomitant anti-ischemic therapy at the time of testing. Circulation 109:1428–1431
27. Sicari R, Rigo F, Gherardi S, Galderisi M, Cortigiani L, Picano E (2008) The prognostic value of Doppler echocardiographic-derived coronary flow reserve is not affected by concomitant antiischemic therapy at the time of testing. Am Heart J 156:573–579
28. Fioretti P, Poldermans D, Salustri A et al (1994) Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. Eur Heart J 15:355–360
29. Ferrara N, Coltorti F, leosco D et al (1995) Protective effect of beta-blockade on dipyridamole-induced myocardial ischemia. Role of heart rate. Eur Heart J 16:903–908
30. Cortigiani L, Huqi A, Ciampi Q, Bombardini T, Bovenzi F, Picano E (2018) Integration of wall motion, coronary flow velocity, and left ventricular contractile reserve in a single test: prognostic value of vasodilator stress echocardiography in patients with diabetes. J Am Soc Echocardiogr 31:692–701
31. Bombardini T, Costantino MF, Sicari R, Ciampi Q, Pratali L, Picano E (2013) End- systolic elastance and ventricular-arterial coupling reserve predict cardiac events in patients with negative stress echocardiography. Biomed Res Int 2013:235194
32. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A (1988) Usefulness of the dipyridamole-exercise echocardiography test for diagnosis of coronary artery disease. Am J Cardiol 62:67–70
33. Ostojic M, Picano E, Beleslin B, Djordjevic-Dikic A, Distante A, Stepanovic J, Reisenhofer B, Babic R, Stojkovic S, Nedeljkovic M, Stankovic G, Simeunovic S, Kanjuh V (1994) Dipyridamole-dobutamine echocardiography: a novel test for the detection of milder forms of coronary artery disease. J Am Coll Cardiol 23:1115–1122
34. Picano E, Morrone D, Scali MC, Huqi A, Coviello K, Ciampi Q (2018) Integrated quadruple stress echocardiography. Minerva Cardioangiol https://doi.org/10.23736/S0026-4725.18.04691-1