ORIGINAL ARTICLE

Comparison of coronary flow reserve feasibility in different stress echocardiography protocols: dobutamine, dipyridamole, exercise, and rapid pacing

Karina Wierzbowska-Drabik[1], Eugenio Picano[2], Lauro Cortigiani[3], Jarosław D. Kasprzak[1]; on behalf of the Stress Echo 2020 study group of the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI)

1 1st Department of Cardiology, Medical University of Lodz, Biegański Hospital, Łódź, Poland
2 Institute of Clinical Physiology – CNR, Pisa, Italy
3 Cardiology Department, San Luca Hospital, Lucca, Italy

KEY WORDS

coronary flow velocity reserve, dipyridamole stress echocardiography, dobutamine stress echocardiography, exercise stress echocardiography, pacing stress echocardiography

ABSTRACT

INTRODUCTION The assessment of coronary flow velocity reserve (CFVR) may improve the diagnostic and prognostic value of stress echocardiography (SE).

OBJECTIVES The aim of the study was to compare the feasibility of CFVR assessment in the left anterior descending artery (LAD) in 4 modalities of SE: dobutamine, dipyridamole, rapid cardiac pacing, and exercise using cycle ergometer.

PATIENTS AND METHODS We performed SE in 369 patients (mean [SD] age, 67 [11] years) with dobutamine (n = 230), dipyridamole (n = 73), rapid cardiac pacing (n = 22), or exercise (n = 44) between June 2017 and June 2020. We measured CFVR as the ratio of peak diastolic coronary flow velocity during exercise, pharmacological stress, or pacing to peak diastolic coronary flow velocity at rest in the distal or mid LAD.

RESULTS The feasibility of CFVR was excellent during rapid cardiac pacing (100%), dobutamine (95%), and dipyridamole (95%) and was lower during exercise (73%; $P < 0.01$ vs other groups). In multivariable analysis, the exercise protocol was a predictor of the loss of blood flow in the LAD during SE (odds ratio, 7.89; 95% CI, 2.17–31.33; $P = 0.002$). The median (interquartile range) CFVR was lower with rapid cardiac pacing (1.7 [1.4–2.0]) as compared with dobutamine (2.1 [1.7–2.5]), dipyridamole (2.1 [1.8–2.5]), and exercise (2.0 [1.7–2.3]) ($P < 0.05$ for all).

CONCLUSIONS CFVR in the LAD can be obtained during all forms of SE, but the feasibility is significantly higher with rapid cardiac pacing and pharmacological tests as compared with exercise, which was identified in our study as an independent predictor of the loss of blood flow during a blood flow recording in the LAD at the peak of stress test.

Correspondence to:
Karina Wierzbowska-Drabik, MD, 1st Department of Cardiology, Medical University of Lodz, ul. Kniaziewicza 1/5, 91-347 Łódź, Poland, phone: +48 42 251 62 16, email: wierzbowska@ptkardio.pl
Received: March 31, 2021.
Revision accepted: June 14, 2021.
Published online: June 18, 2021.
Pol Arch Intern Med. 2021; 131 (9): 830-839
doi:10.20452/pamw.16035

INTRODUCTION The assessment of coronary flow velocity reserve (CFVR) in the left anterior descending coronary artery (LAD) combined with regional wall motion abnormalities, expressed semiquantitatively as the wall motion score index (WMSI), is one of the proposed major advancements in stress echocardiography (SE) that may potentially improve its diagnostic and prognostic value.[1-3] Coronary flow velocity reserve increases the detection rates of LAD stenosis and facilitates risk stratification, with a proposed cutoff value of less than 2 indicating lower coronary reserve and worse prognosis.[4,5] However, there is an ongoing debate regarding the feasibility of CFVR in various types of stress tests since

WHAT'S NEW?

Coronary flow velocity reserve (CFVR) in the left anterior descending coronary artery (LAD) may add diagnostic and prognostic value to stress echocardiography (SE). In our group, CFVR was feasible in 100% of pacing and in 95% of pharmacologic SE (dobutamine and dipyridamole) whereas feasibility for exercise test was significantly lower at 73%. Exercise was an independent predictor of the loss of blood flow recording during SE whereas higher resting force predicted higher feasibility of LAD flow at stress. Our study presents an insight into CFVR feasibility and provides data recorded in patients undergoing noninvasive stress pacing, which is so far unique in the literature. Moreover, we compared CFVR feasibility in all 4 most popular protocols of SE in the uniform tertiary single-center conditions, documenting the possibility of a wider application of the LAD-based CFVR assessment beyond vasodilator (dipyridamole and adenosine) settings.

the available data are limited mainly to vasodilator SE. Moreover, success rates largely depend on operator abilities because CFVR assessment seems to be both technically challenging and rarely practiced.[6,7]

We present a prospective single-center study on the assessment of feasibility of blood flow in the LAD and CFVR in contemporary stress test protocols, performed between June 2017 and June 2020, including catecholamines (dobutamine test), vasodilators (dipyridamole test), exercise stress (cycle ergometer), as well as rapid cardiac pacing SE, recommended for the growing population of patients with permanent pacemakers.[8-10]

The primary aim of our study was to compare the feasibility of CFVR in various types of physical, pharmacological, and pacing stress testing performed in the same laboratory. Our secondary aim was to compare the stress-specific CFVR values in relation to the results of SE.

PATIENTS AND METHODS

Study group We included 369 patients (256 women, mean [SD] age, 67 [11] years; age range, 22–92 years) referred for SE as part of the diagnostic workup of coronary artery disease (CAD) at the tertiary Department of Cardiology, Medical University of Lodz, Łódź, Poland.

The choice of SE protocol was based on the physician's evaluation, including indications and contraindications to specific stressors as well as patient preferences. All 22 patients with implanted pacemakers underwent rapid cardiac pacing. Patients able and willing to exercise to an extent likely to provide an appropriate increase in heart rate (without locomotor system diseases, poor hypertension control, or significantly impaired exercise tolerance) exercised on a semi-supine cycle ergometer (44 patients), while others underwent pharmacological SE: a dobutamine (230 patients) or dipyridamole test (73 patients) according to established contraindications (inadequate blood pressure control, high arrhythmic risk, or contraindication to atropine administered in the dobutamine arm to reach the heart limit, as well as asthma, or methylxanthines taken within 24 hours prior to the dipyridamole test).

Echocardiography Echocardiography was performed with E9 or VIVID 7 systems (GE Vingmed Ultrasound AS, Horten, Norway) using M4S/M5S probes. Echocardiographic measurements (including Doppler parameters) were taken according to the recommendations.[2,11]

We used 2 views to record the blood flow in the LAD: a modified parasternal long-axis view (the mid part of the LAD, chosen in the majority of cases, approximately 70%) or a modified apical 3-chamber view (distal part of the LAD). The blood flow was mapped by color Doppler at the Nyquist limit of approximately 20 cm/s, and a pulsed wave sample was used to record the coronary flow spectrum. The values from 3 cycles were averaged. During SE, Doppler imaging was repeated to obtain a spectrum of sufficient quality closest to the peak point of the test. CFVR was assessed as the ratio of the highest diastolic blood flow velocity at peak stress to peak diastolic velocity measured in the same part of the LAD at rest.

Stress echocardiography protocols Stress echocardiography was performed using 4 different stressors and respective protocols enabling visual assessment of segmental contractility, detection of B-lines over the pulmonary fields, measurement of the contractile reserve of the left ventricle as well as Doppler assessment of the coronary flow reserve. The ABCD protocol was followed for all the above components. The protocol was introduced in the SE 2020 (Stress Echo 2020) study and is described in detail elsewhere.[1,2] Briefly, A stands for asynchrony, B for B-lines, C for left ventricular contractile reserve, and D for Doppler assessment of blood flow in the LAD and CFVR calculation.[1,2] Left ventricular contractile reserve was defined as the ratio of the left ventricular force (systolic blood pressure divided by left ventricular end-systolic volume) at peak SE to the force at baseline. The heart rate reserve was also assessed as the E step of the ABCDE protocol and defined as the ratio of the peak to the baseline heart rate.[12]

Details of SE protocols are displayed in FIGURE 1. Pacing was performed with an external programming device with the assistance of a physician working in the electrophysiology laboratory, and whenever possible, atrial pacing with physiological conduction to the ventricles was preferred as it renders contraction without septal flash (similar to the left bundle branch block pattern) and potentially preserves better coronary perfusion.[13,14]

Electrocardiogram and blood pressure were monitored and all studies were performed by a cardiologist experienced in various SE modalities (KWD), assisted by a nurse or / and another physician. 12-lead electrocardiogram was recorded before and after the termination of the test.

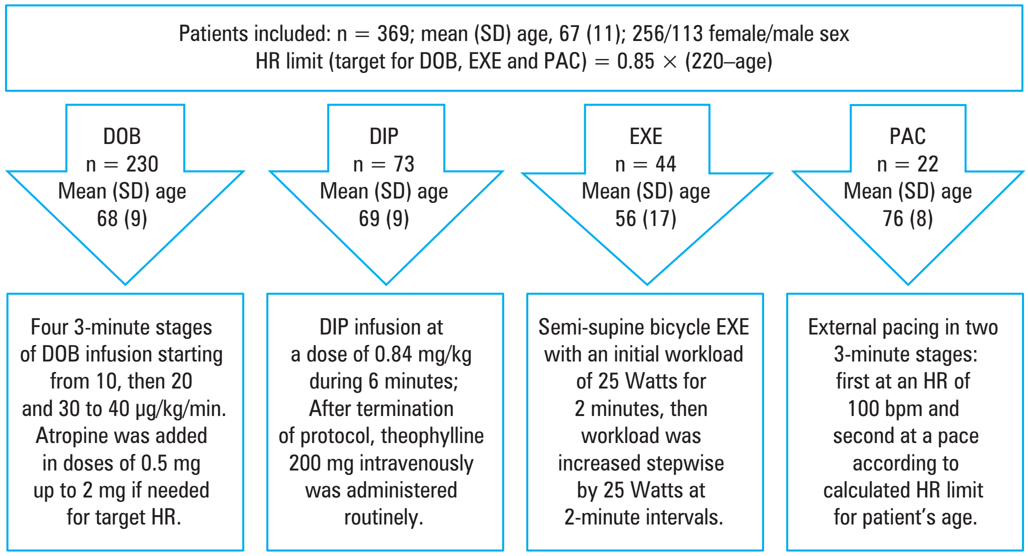

FIGURE 1 Study protocols and flow chart
Abbreviations: DIP, dipyridamole test; DOB, dobutamine test; EXE, exercise stress test; HR, heart rate; PAC, rapid cardiac pacing stress echocardiography

Criteria for interrupting the test were as follows: patient's request, chest pain, induced wall motion abnormalities, significant rhythm disturbances, excessive fatigue, blood pressure increase (systolic >240 mm Hg, diastolic >120 mm Hg), symptomatic hypotension, limiting dyspnea, leg pain, or predicted heart rate.

Reproducibility of Doppler measurements The SE 2020 study provided online training and multicenter reproducibility assessment which included the measurement of the blood flow velocity in the LAD. For all elements of SE protocols, including CFVR evaluation, the training was deemed successful after achieving at least 90% agreement with the core laboratory data.

All examinations and measurements were performed by a single observer (KWD). The second observer (JDK) reviewed and assessed a set of 20 randomly chosen images for interobserver variability evaluation. LAD velocity at rest was feasible in all 20 patients, and at stress in 17 patients.

The intraobserver coefficient of variation for LAD velocity was 5.2% at rest and 2.0% at peak, and for interobserver comparisons it was 13.1% at rest and 11.7% at peak. For intraclass correlation coefficient, the intraobserver values were 0.969 at rest and 0.998 at peak, whereas for the interobserver, 0.726 and 0.909, respectively.

Statistical analysis Data are expressed as mean (SD) for continuous values with normal distribution, as median and interquartile range (IQR) for data with nonnormal distribution, or as a number with percentage for categorical data. The distribution was assessed with the D'Agostino–Pearson test and respective parametric or nonparametric tests were used. Multiple-sample comparison was performed with analysis of variance and the post-hoc Newman–Keuls test for data with normal distribution and with the Kruskal–Wallis test and then the Conover test for data which did not fulfill the normal distribution conditions. Comparison of categorical data frequency was performed with the χ^2 test or the Fisher exact test for groups with 5 or less patients. Statistical significance was set at a P value of less than 0.05 (2-tailed). Correlation was calculated as Pearson coefficient. Predictors of the loss of blood flow in the LAD at peak stress were assessed by stepwise logistic regression analysis with the odds ratio (OR) calculation. For the assessment of intraobserver and interobserver agreement, 2 methods were applied: coefficient of variation as well as the intraclass correlation coefficient calculated separately for rest and stress data. Analyses were conducted with MedCalc, version 12.1.4. (MedCalc Software, Ostend, Belgium).

Ethics The study was performed as part of the multicenter SE 2020 project, and its protocol was approved by institutional ethics committees as part of the SE 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; ClinicalTrials.gov identifier, NCT030.49995). All patients gave informed consent to participate in the study.

RESULTS

Characteristics of coronary flow velocity reserve The demographic and clinical characteristics of the study groups are shown in TABLE 1. Resting hemodynamic and echocardiographic data are presented in TABLE 2. In short, patients undergoing rapid cardiac pacing were the oldest with the most prevalent history of myocardial infarction. Patients in the exercise stress group were the youngest and had the lowest rates of cardiovascular risk factors and respective pharmacological treatment.

Consistently with specific stressor profiles, median peak heart rate was the lowest in the dipyridamole test group and the highest blood pressure was observed in the exercise stress group (TABLE 3). The heart rate limit defined as heart rate greater than 85% × (220 – age) was reached by 63% of patients in the dobutamine group, 1% of the dipyridamole group (due to the different mechanism

TABLE 1 Patient demographic and clinical characteristics

Variable		DOB (n = 230)	DIP (n = 73)	EXE (n = 44)	PAC (n = 22)	DOB vs DIP	DOB vs EXE	DOB vs PAC	DIP vs EXE	DIP vs PAC	EXE vs PAC
Age, y		69 (62–73)	69 (64–74)	60 (44–67)	78 (70–83)	0.5	<0.001	<0.001	<0.001	<0.001	<0.001
Sex	Male	57 (24.8)	21 (28.8)	24 (54.5)	11 (50)	0.6	<0.001	0.02	0.01	0.112	0.931
	Female	173 (75.2)	52 (71.2)	20 (45.5)	11 (50)						
BSA, m^2		1.84 (1.71–2)	1.85 (1.67–2.01)	1.91 (1.77–2.09)	1.91 (1.79–2.06)	0.83	0.1	0.16	0.11	0.17	0.93
BMI, kg/m^2		27.7 (24.8–31.2)	28.3 (25.7–31.7)	26.6 (24.1–28.9)	27.7 (25.7–29.7)	0.56	0.03	0.79	0.02	0.43	0.14
MI history		47 (20.4)	14(19.2)	10 (22.7)	10 (45.5)	0.95	0.89	0.02	0.82	0.03	0.11
Hypertension		182 (79.1)	66 (90.4)	24 (54.5)	21 (95.5)	<0.05	0.001	0.09	<0.001	0.68	<0.001
Diabetes		69 (30)	29 (39.7)	4 (9.1)	8(36.4)	0.15	0.003	0.63	<0.001	0.81	0.015
Dyslipidemia		185 (80.4)	62 (84.9)	24 (54.5)	18 (81.8)	0.49	<0.001	0.9	<0.001	0.99	0.03
Smoking		53 (23)	7 (9.6)	7 (15.9)	2 (9.1)	0.02	0.4	0.18	0.07	1.0	0.71
AF		5 (2.2)	4 (5.5)	1 (2.3)	5 (22.7)	0.23	1.0	<0.001	0.65	0.03	0.01
OAC		14 (6.1)	11 (15.1)	2 (4.5)	4 (18)	0.03	1.0	0.06	0.13	0.74	0.09
ACE-I		138 (60)	49 (67.1)	22 (50)	16 (72.7)	0.34	0.29	0.35	0.1	0.81	0.13
β-Blocker		170 (73.9)	54 (74)	22 (50)	20 (90.9)	0.89	0.003	0.12	0.02	0.14	0.001
Diuretic		83 (36.1)	35 (47.9)	8 (18.2)	14 (63.6)	0.09	0.03	0.02	0.002	0.29	<0.001
ASA		121 (52.6)	26 (35.6)	14 (31.8)	14 (63.6)	0.02	0.02	0.44	0.83	0.04	0.03
Statin		183 (79.6)	64 (87.7)	24 (54.5)	19 (86.4)	0.17	<0.001	0.58	<0.001	1.0	0.01

Data are presented as number (percentage) or median (interquartile range).

Abbreviations: ACE-I, angiotensin–converting enzyme inhibitor; AF, atrial fibrillation; ASA, acetylsalicylic acid; BMI, body mass index; BSA, body surface area; MI, myocardial infarction; OAC, oral anticoagulant, others, see FIGURE 1

TABLE 2 Hemodynamic and resting echocardiographic data

Variable	DOB (N = 230)	DIP (N = 73)	EXE (N = 44)	PAC (N = 22)	DOB vs DIP	DOB vs EXE	DOB vs PAC	DIP vs EXE	DIP vs PAC	EXE vs PAC
HR rest, bpm	65 (59–73)	65 (57–72)	64 (5672)	68 (60–76)	0.33	0.27	0.25	0.8	0.11	0.1
DBP rest, mm Hg, mean (SD)	76 (12)	77 (10)	80 (12)	77 (14)	0.37	0.07	0.88	0.28	0.72	0.34
SBP rest, mm Hg	136 (124–150)	146 (135–157)	130 (119–141)	144 (125–157)	<0.001	<0.02	0.41	<0.001	0.36	0.06
EF rest, %	63 (57–68)	65 (59–69)	61 (56–68)	61 (47–66)	0.41	0.31	0.15	0.14	0.07	0.47
WMSI rest[a]	1.0 (1.0–1.0); (1.0–2.18)	1.0 (1.0–1.0); (1.0–2.0)	1.0 (1.0–1.0); (1.0–2.0)	1.0 (1.0–1.0); (1.0–2.65)	0.55	0.4	0.72	0.79	0.96	0.89
B-lines rest[a], n	0 (0–0); (0–9)	0 (0–0); (0–6)	0 (0–0); (0–7)	0 (0–0); (0–11)	0.82	0.76	0.23	0.91	0.38	0.46
LAD rest velocity, cm/s	25 (22–32)	25.5 (22–31)	24 (22–31)	27.5 (23–31)	0.57	0.54	0.95	0.75	0.77	0.65

Data are presented as median (interquartile range) unless otherwise indicated.

a Since median and interquartile range for WMSI at rest equaled 1.0 and B-lines at rest equaled 0 in all subgroups, the minimal and maximal values have been additionally presented.

Abbreviations: DPB, diastolic blood pressure; EF, ejection fraction; LAD, left anterior descending coronary artery; SBP, systolic blood pressure; WMSI, wall motion score index; others, see FIGURE 1

of this SE type), 16% of the exercise group, and 60% of the rapid cardiac pacing group. These results indicate lower efficacy of heart rate measurement during exercise as compared with dobutamine or pacing tests (exercise stress test vs dobutamine test, P <0.001; exercise stress test vs rapid cardiac pacing test, P = 0.001).

Moreover, we observed a correlation between CFVR and WMSI at rest (r = –0.231; P <0.001) and at peak (r = –0.257; P <0.001) in the whole group. CFVR correlated inversely with the number of stenosed coronary arteries (Supplementary material, *Figure S2*).

The percentages of examinations assessed visually as positive for ischemia were similar in all groups (TABLE 3). In the subgroup with positive SE, more patients had coronary angiography performed as compared with the subgroup

TABLE 3 Hemodynamic and echocardiographic data at peak

Variable	DOB (N = 230)	DIP (N = 73)	EXE (N = 44)	PAC (N = 22)	DOB vs DIP	DOB vs EXE	DOB vs PAC	DIP vs EXE	DIP vs PAC	EXE vs PAC
HR peak, bpm	131 (125–138)	80 (70–93)	125 (113–140)	121 (120–130)	<0.001	0.08	<0.001	<0.001	<0.001	0.45
DBP peak, mm Hg	72 (65–82)	75 (68–80)	90 (79–109)	82 (68–88)	0.42	<0.001	0.04	<0.001	0.09	0.03
SBP peak, mm Hg	136 (120–152)	132 (120–158)	186 (155–200)	133 (120–154)	0.57	<0.001	0.76	<0.001	0.94	<0.001
EF at peak, %	68 (63–74)	68 (62–72)	65 (60–71)	62 (47–66)	0.8	0.06	<0.001	0.15	<0.001	0.04
WMSI at peak	1.0 (1.0–1.06)	1.0 (1.0–1.1)	1.0 (1.0–1.06)	1.0 (1.0–1.24)	0.77	0.56	0.3	0.76	0.41	0.62
B-lines peak number[a]	0 (0–0); (0–14)	0 (0–0); (0–9)	0 (0–0.5); (0–9)	0 (0–2.0); (0–11)	0.19	0.35	0.08	0.08	0.02	0.44
LVCR[b]	1.66 (1.32–2.17)	1.09 (0.89–1.32)	1.73 (1.08–2.09)	1.23 (1.0–1.44)	<0.001	0.37	<0.001	<0.001	0.15	0.01
LAD peak velocity, cm/s	55 (45–67)	56 (52–60)	49 (41–62)	46 (35–53)	0.86	0.07	0.002	0.08	0.003	0.18
CFVR	2.1 (1.7–2.5)	2.1 (1.8–2.5)	2.0 (1.7–2.3)	1.7 (1.4–2.0)	0.63	0.26	<0.001	0.18	<0.001	0.03
CFVR in negative SE[c]	2.1 (1.7–2.5)	2.1 (1.8–2.5)	2.0 (1.8–2.3)	1.8 (1.4–2.0)	0.76	0.36	0.003	0.3	0.003	0.041
HRR[d], mean (SD)	1.98 (0.37)	1.28 (0.25)	1.99 (0.48)	1.79 (0.25)	<0.001	0.95	0.02	<0.001	<0.001	0.08
Positive SE, n (%)	16 (7)	5 (6.8)	2 (4.5)	4 (18.2)	0.82	0.8	0.09	0.92	0.37	0.26

Data are presented as median (interquartile range) unless otherwise indicated.

a The minimal and maximal values for B-lines were additionally presented.

b Force at peak/force rest ratio; force was calculated as systolic blood pressure divided by left ventricular end-systolic volume.

c SE was negative in 315 patients with feasible CFVR in 203, 64, 30, and 18 patients from DOB, DIP, EXE, and PAC, respectively.

d HRR was defined as HR peak/HR rest ratio.

Abbreviations: CFVR, coronary flow velocity reserve; HRR, heart rate reserve; LVCR, left ventricular contractile reserve; SE, stress echocardiography; others, see FIGURE 1 and TABLE 2

with negative SE. Respective percentages of coronary angiographies were 66.6% and 32.5% (*P* value <0.001).

Additionally, we compared the group with positive SE (that is, stress-induced ischemia diagnosed as visually worsened contractility) with the group with negative SE (Supplementary material, *Table S1*). CFVR was lower in the group with positive SE (median [IQR], 1.71 [1.47–2.03] vs 2.06 [1.74–2.47]; *P* <0.001). We also observed higher frequency of combined endpoints (deaths, hospitalizations, and need for revascularizations) in the group with positive SE (40.7% vs 7.3%; *P* <0.001).

We also compared subgroups with impaired and preserved CFVR. Patients with impaired CFVR of less than 2 were older, had lower ejection fraction at rest and peak, and higher WMSI at both stages of SE. Moreover, resting LAD velocity was higher in the group with decreased CFVR whereas LAD velocity at SE peak was lower in these patients (Supplementary material, *Table S2*).

Finally, we separately compared patients with LAD stenosis confirmed by angiography with those without LAD stenosis and those after revascularization of the LAD. The patients with LAD stenosis had lower ejection fraction at rest and peak, higher WMSI at rest and peak as well as significantly decreased CFVR (median [IQR], 1.653 [1.36–1.897] vs 2.057 [1.689–2.437]; *P* = 0.02) when compared with patients without significant lesions in the LAD. Moreover, there were no differences in comparisons between patients without LAD lesions and those after LAD revascularization (Supplementary material, *Table S3*).

Feasibility of coronary flow velocity reserve Doppler of blood flow velocity in the LAD could be assessed at rest in 227 out of 230 patients in the dobutamine group (98.7%), 70 out of 73 patients in the dipyridamole group (95.9%), 38 out of 44 patients in the exercise stress group (86.4%), and 22 out of 22 patients in the rapid cardiac pacing group (100%). The measurement of LAD velocity, and thus CFVR, was slightly less feasible at the peak stage of the dobutamine test (218/230, 94.8%) and significantly less feasible at exercise stress (32/44, 72.7%), whereas only one spectrum was lost in the dipyridamole group (69/73, 94.5%) and none in the rapid cardiac pacing group. Therefore, the feasibility of CFVR calculation was significantly lower in exercise stress test as compared with other tests (FIGURE 2). The overall CFVR feasibility in all tests was 92.4% (341/369 examinations).

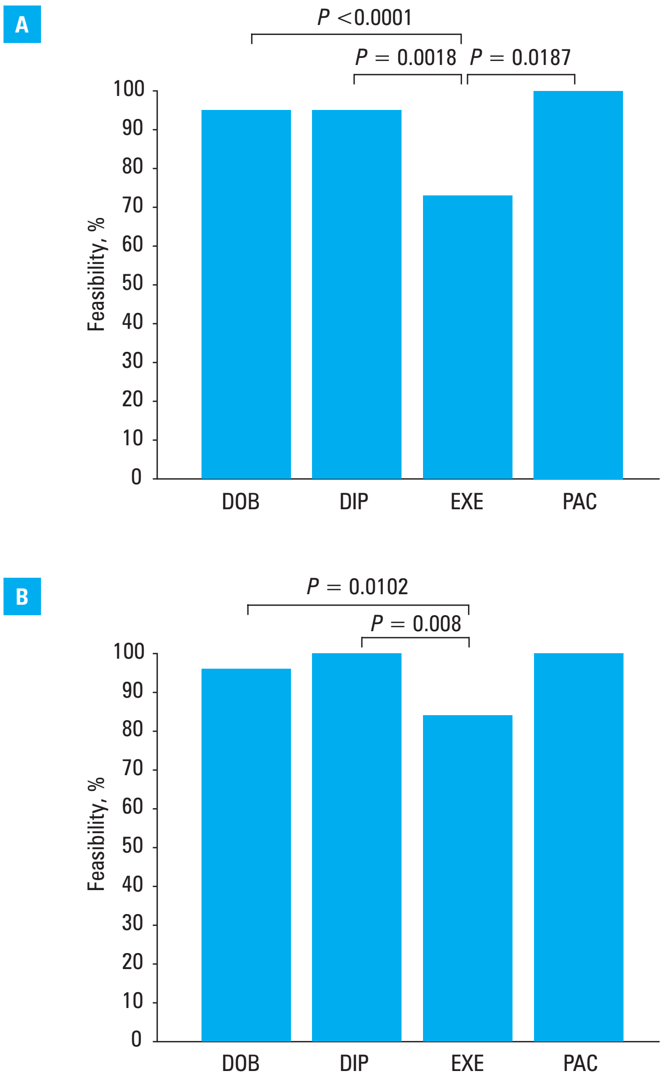

FIGURE 2 Feasibility of coronary flow velocity reserve in 4 stress echocardiography modalities; **A** – comparison of coronary flow velocity reserve feasibility assessment in 4 stress echocardiography tests for all patients; **B** – comparison of coronary flow velocity reserve feasibility assessment in 4 stress echocardiography tests for patients with available resting spectrum in the left descending coronary artery
Abbreviations: see FIGURE 1

With regard to LAD peak velocity, the lowest median (IQR) of 46 (35–53) cm/s was observed in the rapid cardiac pacing group, as compared with the dobutamine group with 55 (45–67) cm/s and dipyridamole with 56 (52–60) cm/s ($P = 0.002$ and $P = 0.003$, respectively). This was reflected by lower median (IQR) CFVR in the rapid cardiac pacing group, 1.7 (1.4–2.0) as compared with 2.1 (1.7–2.5) in the dobutamine group, 2.1 (1.8–2.5) in the dipyridamole group, and 2.0 (1.7–2.3) in the exercise stress group ($P < 0.001$ for dobutamine and dipyridamole and $P = 0.03$ for exercise stress comparison). This relation was generally maintained when the analysis was limited to patients with negative SE (n = 315 tests with feasible CFVR) (TABLE 3). CFVR correlated with peak heart rate in exercise and rapid cardiac pacing groups. The correlation was weak in the dobutamine group, and no correlation was observed in the dipyridamole group (FIGURE 3).

In 16 patients, blood flow in the LAD was lost during SE (dobutamine, 9; exercise, 6; dipyridamole, 1; and rapid cardiac pacing, 0), and the percentage of loss of blood flow in the LAD was significantly higher in exercise (15.4%) than in the dobutamine (4%) and dipyridamole (1.4%) groups ($P = 0.01$ for exercise vs dobutamine and for exercise vs dipyridamole). A comparison between the group with preserved blood flow in the LAD and the group with the loss of blood flow in the LAD during SE showed that in the latter group, there was a higher percentage of patients from the exercise test group (37.5% vs 9.4%; $P = 0.002$); moreover, they had lower rest force (median [IQR], 7.2 [5.1–9.3] mm Hg/ml vs 9.5 [6.8–12.5] mm Hg/ml; $P = 0.01$). (TABLE 4).

Nevertheless, in multivariate logistic analysis, in the model with the area under the curve of 0.833 ($P < 0.001$), exercise protocol of SE strongly predicted the loss of blood flow in the LAD (OR, 7.89; $P = 0.002$), whereas increased force at rest was associated with a preserved blood flow in the LAD (TABLE 5).

DISCUSSION The calculation of CFVR from SE allows to study the coronary circulation with the proven prognostic role in a wide range of patients.[15,16] On the other hand, the practicality of conventional, wall motion–focused SE for detecting high risk groups among those treated with current pharmacotherapy is dropping.[17]

Our study provides evidence for the high feasibility rates of LAD velocity recording in 4 principal tests of SE, probably representing the first such data for rapid cardiac pacing, in which CFVR was feasible in 100% of examined patients, although the group was small (22 patients). Our data also confirmed a very good feasibility of obtaining the blood flow in the LAD at rest and peak stress in both pharmacologic modalities of SE (dipyridamole and dobutamine). The values achieved, 95%, higher than reported in multicenter analyses, may be explained by the long--term experience of our center in different types of SE as well as in coronary morphology, flow, and CVFR assessment.[18-21]

According to Auriti et al,[22] who assessed the feasibility of coronary flow estimation in the posterior descending coronary artery (PDA; originating from the right coronary artery) an important measure allowing improvement in feasibility is the assessment of coronary flow in at least 2 views. Such an approach was also implemented in our study to evaluate the blood flow in the LAD in the apical and modified lower left parasternal view and, similar to the data reported by Rigo[23] and Rigo et al,[24] led to a feasibility exceeding 90%. Moreover, Auriti et al[22] observed for PDA that velocities registered in 2 different views did not differ significantly, and what is more, for CFVR assessment, the observer aims at a repetitive measurement of flow in the same coronary tract both at rest and at peak stress. The same authors maintained

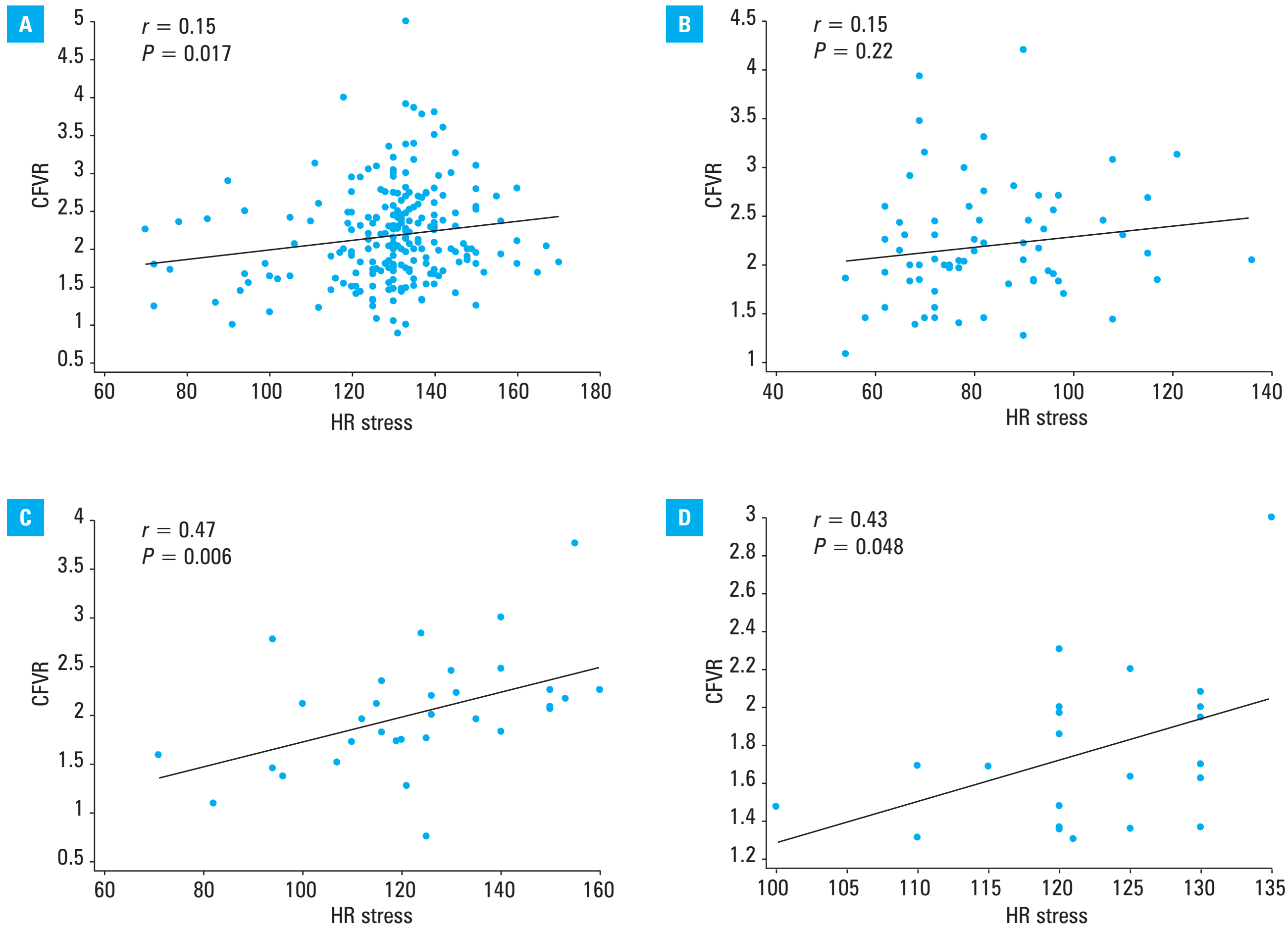

FIGURE 3 Correlation between coronary flow velocity reserve and heart rate at the peak test in dobutamine (**A**), dipyridamole (**B**), exercise (**C**), and pacing (**D**)
Abbreviations: see FIGURE 1 and TABLE 3

that a learning curve of about 100 examinations may be sufficient for effective visualization of coronary flow (in the LAD, grafts, and even in the PDA, although the last seems to be the most difficult) in a time less than 3 minutes to the first recording of a readable spectrum.

On the other hand, we achieved relatively low feasibility for exercise test (73% in our group vs 81% reported by Zagatina and Zhuravskaya[7]), which may reflect hyperventilation and motion of patients during peak exercise. Nevertheless, similar to the mentioned study, we observed a rather low median (IQR) CFVR of 2.0 (1.7–2.3) as compared with mean (SD) value of 1.9 (0.8) in the study cited, which may be related to the difficulty in recording the fastest achievable spectrum. However, the feasibility reported as the percentage of patients for whom the peak velocity was recorded among those with available blood flow in the LAD at rest exceeded 80% in the exercise group (FIGURE 2).

Since the 2008 Stress Echocardiography Expert Consensus Statement,[25] CFVR of the LAD has been recommended as the parameter which increases sensitivity for CAD without losing specificity. Despite its growing role, computed tomography angiography performs best in excluding CAD while having a still poorer impact on the assessment of the significance of coronary stenosis, and therefore should be more often replaced by radiation-free assessment of coronary pathophysiology. Some studies showed that only 49% of cases of coronary stenosis of 50% or greater as observed on computed tomography angiography correlated with invasive fractional flow reserve of less than 0.75 because of visual overestimation of luminal stenosis, especially of lesions with calcifications. That is why patients with suspected stenosis on computed tomography angiography should probably have the evaluation supplemented with noninvasive CFVR quantification.[26,27]

The finding concerning the significant drop-off in the feasibility of CFVR assessment during exercise testing, although intuitive, may prompt the potential modification and standardization of a protocol for the assessment of blood flow in the LAD during exercise testing, for example, testing the possibility, diagnostic value, and threshold of LAD flow registered at early (or immediate) recovery.

Whereas the lowest median value of CFVR (median [IQR], 1.7 [1.4–2.0]) was observed in the rapid cardiac pacing group and reflected more severe coronary lesions, the slightly reduced CFVR value in the exercise group (median [IQR], 2.0 [1.8–2.3]) may be related to the fact that significantly less

TABLE 4 Comparison of clinical and echocardiographic variables between patients with preserved left anterior descending coronary artery flow and loss of blood flow during stress echocardiography

Parameter	LAD flow preserved (n = 341)	LAD flow lost (n = 16)	*P* value
Exercise protocol of SE, n (%)	32 (9.4)	6 (37.5)	0.002
Force at rest, mm Hg/ml	9.5 (6.8–12.5)	7.2 (5.1–9.3)	0.01
BMI, kg/m²	27.6 (24.9–30.9)	26.1 (22.1–28.8)	0.06
LAVI stress[a], ml/m²	25 (20–31)	31 (21.3–40.8)	0.06

Data are presented as median (interquartile range) unless otherwise indicated.

a LAVI was available in 262 patients with LAD flow preserved and in 11 with LAD loss

Abbreviations: LAVI, left atrial volume index; others, see TABLES 1, 2, and 3

TABLE 5 Multivariable logistic analysis for the predictors of the left anterior descending coronary artery flow loss during stress echocardiography

Parameter	Odds ratio (95% CI)	*P* value
Exercise protocol of SE[a]	7.89 (2.14–29.07)	0.002
Force at rest, mm Hg/ml	0.8 (0.67–0.96)	0.02

a All other protocols served as the reference group. All protocols other than exercise did not show significant association with the loss of LAD flow.

Abbreviations: see TABLES 2 and 3

patients (16%) achieved hear rate limit as compared with the dobutamine group (63%; $P < 0.01$) and the rapid cardiac pacing group (60%; $P = 0.001$) which could hamper the achievement of maximal blood flow in the LAD in this cohort.

The significant positive correlation of CFVR values with peak heart rates observed in exercise testing and rapid cardiac pacing testing is a crucial difference when compared with the more widely applied dobutamine and dipyridamole testing, in which this correlation was far weaker or completely absent.

The significant positive correlation between CFVR and heart rate may become clinically important when assessing data of patients whose heart limits (calculated for stress test) or exercise capacity vary markedly and may indicate that these potential differences in the achieved maximal LAD flow velocity needs to be accounted for. Based on these observations, we believe that in the future, the indexing of CFVR for heart rate for a particular test should be considered for easier and more informative assessment of CFVR values.

In the search for the predictors of the loss of blood flow in the LAD during SE, we found that in the univariable analysis, exercise SE and decreased left ventricular force were related to difficulties in LAD recording at peak stress. In multivariable analysis, exercise SE was an independent predictor of the loss of blood flow in the LAD (OR, 7.89) and increased resting force (OR, 0.8). Whereas the role of exercise in the hampering of LAD recording seems to be obvious taking into account the vigorous motion of cycling patients together with tachycardia and tachypnoea, the role of increased left ventricular force seems to be related to the increased diameter of coronaries in patients with a more hypertrophic heart. The imaging of coronaries and coronary flow was reported to be easier in patients with hypertrophic cardiomyopathy.[28]

The positive correlation of CFVR values with peak heart rates was significant in all SE tests except dipyridamole, but showed moderate strength only in exercise and rapid cardiac pacing groups (FIGURE 3). This is consistent with the established underlying mechanism, since vasodilation with rapid cardiac pacing and exercise is secondary to the increase in myocardial demand largely due to the increased heart rate, while vasodilation during dipyridamole testing is the result of the primary effect of endogenous adenosine accumulation and is largely independent of heart rate increase.[29,30]

Literature search did not reveal any data on the CFVR in rapid cardiac pacing, and in our experience, 100% feasibility reflects the facile recording of the blood flow in the LAD in this protocol in which the patients are not only immobile during the test but also free of the side effects of catecholaminergic response or dipyridamole-related dyspnea. This value, however, must be interpreted with caution as the rapid cardiac pacing group was the smallest subset in our study since it was limited to those with implanted pacemakers.

Limitations Our study presents feasibility data from a single center with a long-standing interest in the echocardiographic assessment of coronary flow in transthoracic echocardiography which may be important for extrapolation. Studies were performed with equipment from a single manufacturer. The quality of Doppler images varies considerably between echocardiography systems, but our results were obtained with high-end machines.

Notably, within our study cohort, exercise and especially rapid cardiac pacing subgroups were small. All groups differed in terms of numbers of patients, mean age, and sex distribution, which warrants a cautious interpretation of the results, such as the 100% feasibility in rapid cardiac pacing. Moreover, in our study, there was a predominance of women (69%), which might reflect an observed tendency to first refer women to noninvasive functional tests rather than invasive coronary angiography.

Despite analyzing 369 stress examinations in total, we were still limited by the small number of specific tests in subgroups. This especially hampered a more in-depth analysis of positive and negative studies in subsequent modalities of SE. On the other hand, in recent years, a decreasing rate of positive stress examinations assessed visually has also been observed in larger studies and seems to go beyond the field of echocardiography, and has also been reported in scintigraphy and perfusion analysis.[31-33]

Of note, we do not have coronary angiographic data for most of our patients since the present guidelines discourage invasive testing for CAD after achieving a negative SE test. Moreover, the anatomic evaluation of a coronary lesion would still be insufficient to assess CFVR unless fractional flow reserve was performed.

Additionally, although feasible, safe, and promising, Doppler assessment of coronary reserve is prone to many potential pitfalls, including the misinterpretation of coronary arteries as diagonal or intermediate in place of the LAD or prolonged apical part of the LAD in place of the distal PDA as well as the misinterpretation of wall noise, epicardial space, atrioventricular, or right ventricular flow with coronary flow. Moreover, stenosis in epicardial coronary arteries cannot be differentiated from microvascular disease based on decreased CFVR.

Finally, the assessment was limited to the LAD only, without attempting to register flow in the right coronary artery or marginal branches.

Conclusions CFVR in the LAD can be obtained with a high success rate in all protocols of SE, but feasibility is higher with rapid cardiac pacing and pharmacological tests (dobutamine, dipyridamole) as compared with exercise. The choice of exercise protocol was related to the 8-fold risk increase in the loss of blood flow in the LAD recorded during peak stress.

The results of our study encourage a broader assessment of CFVR in various SE beyond vasodilators, providing evidence of the possible excellent feasibility in pacing as well as pharmacological tests and predictable lower feasibility in exercise examinations. Our analysis also provided lacking pilot data on CFVR values in the paced group consistent with typical patients with pacemakers encountered in clinical practice.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The study was partially supported by a travel grant of Erasmus plus staff training mobility from Poland to Pisa (to KW-D).

CONTRIBUTION STATEMENT KW-D and JDK planned the study. KW-D was responsible for data acquisition. All authors analyzed and interpreted the data, and contributed to manuscript preparation.

CONFLICT OF INTEREST None declared.

HOW TO CITE Wierzbowska-Drabik K, Picano E, Cortigiani L, Kasprzak JD; on behalf of the Stress Echo 2020 study group of the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI). Comparison of coronary flow reserve feasibility in different stress echocardiography protocols: dobutamine, dipyridamole, exercise, and rapid pacing. Pol Arch Intern Med. 2021; 131: 830-839. doi:10.20452/pamw.16035

REFERENCES

1 Picano E, Ciampi Q, Citro R, et al. Stress echo 2020: the international stress echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound. 2017; 15: 3.

2 Picano E, Ciampi Q, Wierzbowska-Drabik K, et al. The new clinical standard of integrated quadruple stress echocardiography with ABCD protocol. Cardiovasc Ultrasound. 2018; 16: 22.

3 Pellikka PA, Arruda-Olson A, Chaudhry FA, 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.e8.

4 Ciampi Q, Zagatina A, Cortigiani L, et al. Functional, anatomical, and prognostic correlates of coronary flow velocity reserve during stress echocardiography. J Am Coll Cardiol. 2019; 74: 2278-2291.

5 Djordjevic Dikic A, Tesic M, Boskovic N, et al. Prognostic value of preserved coronary flow velocity reserve by noninvasive transthoracic doppler echocardiography in patients with angiographically intermediate left main stenosis. J Am Soc Echocardiogr. 2019; 32: 74-80.

6 Blomster JI, Svedlund S, Westergren HU, Gan LM. Coronary flow reserve as a link between exercise capacity, cardiac systolic and diastolic function. Int J Cardiol. 2016; 217: 161-166.

7 Zagatina A, Zhuravskaya N. The additive prognostic value of coronary flow velocity reserve during exercise echocardiography. Eur Heart J Cardiovasc Imaging. 2017; 18: 1179-1184.

8 Picano E, Alaimo A, Chubuchny V, et al. Noninvasive pacemaker stress echocardiography for diagnosis of coronary artery disease. A multicenter study. J Am Coll Cardiol. 2002; 40: 1305-1310.

9 Płońska-Gościniak E, Kleinrok A, Gackowski A, et al. Diagnostic and prognostic value of rapid pacing stress echocardiography for the detection of coronary artery disease: influence of pacing mode and concomitant antiischemic therapy (final results of multicenter study Pol-RAPSE). Echocardiography. 2008; 25: 827-834.

10 Płońska-Gościniak E, Lancellotti P, Kleinrok A, et al. Influence of gender on diagnostic accuracy of rapid atrial and ventricular pacing stress echocardiography for the detection of coronary artery disease: a multicenter study (Pol-RAPSE final results). J Am Soc Echocardiogr. 2008; 21: 1116-1120.

11 Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16: 233-270.

12 Zagatina A, Zhuravskaya N, Shmatov D, et al. Exercise stress echocardiography with ABCDE protocol in unexplained dyspnoea. Int J Cardiovasc Imaging. 2020; 36: 823-831.

13 Gligorova S, Argusta M. Pacing stress echocardiography. Cardiovasc Ultrasound. 2005; 3: 36.

14 Zanon F, Bacchiega E, Rampin L, et al. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. Europace. 2008; 10: 580-587.

15 Cortigiani L, Rigo F, Gherardi S, et al. Prognostic implication of Doppler echocardiography derived coronary flow reserve in patients with left bundle branch block. Eur Heart J. 2013; 343: 64-73.

16 Cortigiani L, Rigo F, Gherardi S, et al. Prognostic value of Doppler echocardiographic-derived coronary flow velocity reserve of left anterior descending artery in octogenarians with stress echocardiography negative for wall motion criteria. Eur Heart J Cardiovasc Imaging. 2015; 16: 653-660.

17 Cortigiani L, Urluescu ML, Coltelli M, et al. 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; 12: e008564.

18 Kasprzak J, Drozdz J, Peruga Z, et al. Definition of flow parameters in proximal nonstenotic coronary arteries using transesophageal Doppler echocardiography. Echocardiography. 2000; 17: 141-150.

19 Wierzbowska-Drabik K, Hamala P, Kasprzak JD. Delayed longitudinal myocardial function recovery after dobutamine challenge as a novel presentation of myocardial dysfunction in type 2 diabetic patients without angiographic coronary artery disease. Eur Heart J Cardiovasc Imaging. 2015; 16: 676-683.

20 Wierzbowska-Drabik K, Picano E, Bossone E, et al. The feasibility and clinical implication of tricuspid regurgitant velocity and pulmonary flow acceleration time evaluation for pulmonary pressure assessment during exercise stress echocardiography Eur Heart J Cardiovasc Imaging. 2019; 20: 1027-1034.

21 Wierzbowska-Drabik K, Picano E, Simiera M, et al. Wall motion index, force, strain, and ejection fraction for the prediction of SYNTAX/GENSINI coronary scores by dobutamine stress echocardiography: head-to-head comparison of different indices. Kardiol Pol. 2020; 78: 715-724.

22 Auriti A, Cianfrocca C, Pristipino C, et al. Improving feasibility of posterior descending coronary artery flow recording by transthoracic Doppler echocardiography. Eur J Echocardiography. 2003; 4: 214-220.

23 Rigo F. Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. Cardiovasc Ultrasound. 2005; 3: 8.

24 Rigo F, Murer B, Ossena G, Favaretto E. Transthoracic echocardiographic imaging of coronary arteries: tips, traps, and pitfalls. Cardiovasc Ultrasound. 2008; 6: 7.

25 Sicari R, Nihoyannopoulos P, Evangelista A, et al; European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008; 9: 415-437.

26 Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol. 2008; 52: 636-643.

27 Tanabe Y, Kurata A, Matsuda T, et al. Computed tomographic evaluation of myocardial ischemia. Jpn J Radiol. 2020; 38: 411-433.

28 Ferreiro DE, Cianciulli TF, Saccheri MC, et al. Assessment of coronary flow with transthoracic color Doppler echocardiography in patients with hypertrophic cardiomyopathy. Echocardiography. 2013; 30: 1156-1163.

29 Picano E. Dipyridamole-echocardiography test: historical background and physiologic basis. Eur Heart J. 1989; 10: 365-376.

30 Lucarini AR, Picano E, Marini C, et al. Activation of sympathetic tone during dipyridamole test. Chest. 1992; 102: 444-447.

31 Cortigiani L, Ramirez P, Coltelli M, et al. Drop-off in positivity rate of stress echocardiography based on regional wall motion abnormalities over the last three decades. Int J Cardiovasc Imaging. 2019; 35: 627-632.

32 Jouni H, Askew JW, Crusan DJ, et al. Temporal trends of single-photon emission computed tomography myocardial perfusion imaging in patients without prior coronary artery disease: a 22-year experience at a tertiary academic medical center. Am Heart J. 2016; 176: 127-133.

33 Duvall WL, Rai M, Ahlberg AW, et al. A multi-center assessment of the temporal trends in myocardial perfusion imaging. J Nucl Cardiol. 2015; 22: 539-551.