Usefulness of Blunted Heart Rate Reserve as an Imaging-Independent Prognostic Predictor During Dipyridamole Stress Echocardiography

Lauro Cortigiani, MD[a], Clara Carpeggiani, MD[b], Patrizia Landi, IT Tech[b], Mauro Raciti, IT Tech[b], Francesco Bovenzi, MD[a], and Eugenio Picano, MD, PhD[b,*]

A blunted heart rate (HR) response during dipyridamole myocardial perfusion imaging has been associated with a poor outcome. To assess the value of HR response in patients who underwent high-dose dipyridamole stress echocardiography (SE), we retrospectively selected a sample of 3,059 patients (none with pacemakers or atrial fibrillation; mean age 66 ± 11 years). All underwent high-dose (0.84 mg/kg) dipyridamole SE for evaluation of known or suspected coronary artery disease and/or heart failure in 2 laboratories of Pisa-IFC and Lucca. HR (with 12-lead ECG) was obtained each minute and recorded at rest and peak stress. HR reserve (HRR) was calculated as the peak/rest HR ratio. All patients were followed up. Patients were randomly divided into the modeling and validation group of equal size. During a median follow-up time of 1,004 days, 321 hard events occurred: 231 deaths and 90 nonfatal myocardial infarctions. HRR ≤ 1.22 identified by receiver operating characteristic analysis in the modeling group was an independent predictor of infarction-free survival in the modeling (hazard ratio 1.83, 95% confidence interval [CI] 1.30 to 2.60, p = 0.001), in the validation (hazard ratio 1.47, 95% CI 1.08 to 2.01, p = 0.02), and in the overall group (hazard ratio 1.60, 95% CI 1.27 to 2.02, p <0.0001), either off- or on-β blockers. Five-year event rate increased from 8% to 24 % from the highest (≥1.41) to the lowest (≤1.14) HRR quartile. In conclusion, blunted HRR is a useful nonimaging predictor of adverse events during high-dose dipyridamole SE, independent of inducible ischemia, and beta-blocker therapy. **(Am J Cardiol 2019;124:972−977)**

The diagnostic and prognostic information of stress echocardiography (SE) is based on regional wall motion abnormalities (RWMA).[1−6] In principle, also a nonimaging parameter such as the systemic hemodynamic response can help in tailoring the risk profile. During exercise or dobutamine, a worse prognosis is associated with chronotropic incompetence mirrored in a blunted increase in heart rate (HR) at peak stress.[7,8] With vasodilator myocardial perfusion imaging, a blunted increase in HR[9−13] and possibly an excessive systolic blood pressure (SBP) drop[13] have been associated with a higher risk, with independent value over inducible myocardial perfusion abnormalities.[14] Aim of this retrospective analysis of prospectively acquired data in 2 centers was to assess whether HR and SBP responses have prognostic value in patients with known or suspected coronary artery disease (CAD) and/or heart failure (HF) referred to dipyridamole SE.

Methods

Using the cohort data bank of 2 Italian cardiology centers (Pisa-IFC and Lucca), 5,408 patients tested with SE for evaluation of known or suspected CAD and/or HF.[10] The recruitment time window was from 1998 to 2010 for Pisa and from 1998 to 2016 for Lucca. Exclusion criteria at entry were: inadequate acoustic window, severe valvular or congenital heart disease, and significant co-morbidity reducing life expectancy to <12 months (i.e., cancer, end-stage renal disease, and severe obstructive pulmonary disease). Exclusion criteria after test performance and before data analysis were: premature test interruption (n = 67), atropine coadministration by protocol (n = 1,723, in the period 1998 to 2007, afterwards the protocol was abandoned in favor of the accelerated high-dose protocol), atrial fibrillation (n = 324), permanent pacemaker (n = 173), and lost to follow-up (n = 62). The remaining 3,059 patients (1,859 men; age 66 ± 11 years) with a high-dose dipyridamole-SE formed the study group. The study was approved by the institutional ethical committee. All patients accepted by written informed consent to undergo SE.

Transthoracic SE studies were performed with commercially available ultrasound machines depending on the possibilities and the equipment available in each period. Dipyridamole (up to 0.84 mg/kg over 6 or 10 minutes) SE was performed according to well-established protocol.[3,15] The wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments in a 17-segment model of the left ventricle.[3,15] Ischemia was defined as stress-induced new and/or worsening of preexisting RWMA. HR was recorded from electrocardiogram (ECG) 1 to 5 minutes before (rest HR), each minute during, and 1 to 5 minutes after

[a]Cardiology Division, San Luca Hospital, Lucca, Italy; and [b]CNR Institute of Clinical Physiology, Pisa, Italy. Manuscript received May 3, 2019; revised manuscript received and accepted June 12, 2019.

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*Corresponding author: Tel: +39050 3152246; fax: +390503152374.
E-mail address: picano@ifc.cnr.it (E. Picano).

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dipyridamole infusion. The maximal variation of HR from rest to stress was considered. HR reserve (HRR) was defined as the peak/rest ratio of HR. Blood pressure was simultaneously taken at rest and peak stress. The maximal variation of SBP from rest to stress was considered.

Follow-up data were obtained from review of the patient's hospital record, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient or a patient's close relative conducted by trained personnel, a staff physician visiting the patients at regular intervals in the out-patient clinic. Clinical events were defined as death and nonfatal acute myocardial infarction.[16,17]

Continuous variables are expressed as mean ± SD. Differences in continuous variables were assessed with the unpaired *t* test; the chi-squared test was used for categorical variables. Logistic regression analysis was performed to assess HRR predictors. Linear regression was used to ascertain the correlation between HRR and SBP or stress WMSI. Hard event rates and mortality were estimated with Kaplan-Meier curves and compared by the log-rank test. The association of selected variables with outcome were assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. Hazard ratios) with the corresponding 95% confidence interval (CI) were estimated. Statistical significance was set at $p < 0.05$. Statistical package for the Social Sciences (IBM, SPSS Statistics, version 21) was used for analysis.

Results

The main characteristics of the study patients (modeling and validation groups) are described in Table 1. There were no significant intergroup difference for all main clinical, resting, and SE findings, including WMSI at rest, WMSI during stress, and rest-stress WMSI.

The main rest and SE findings are reported in Table 1. A resting RWMA was present in 1,010 patients (33%). After dipyridamole, an ischemic result with RWMA was observed in 458 patients (15%). The main blood pressure findings are reported in Table 1. The main HR findings are reported in Table 1. In patients on β blockers, resting HR, peak HR, and HRR were lower in comparison to patients studied off β blockers (Table 2). A reduced HRR ≤ 1.22

Table 1
Characteristics of the study population and patients of the modeling and validation group

Variable	All patients (n = 3,059)	Patients of the modeling group (n = 1,530)	Patients of the validation group (n = 1,529)	p Value
Age (years)	66 ± 11	66 ± 11	66 ± 11	0.13
Men	1,859 (61%)	929 (61%)	930 (61%)	0.95
Diabetes mellitus	736 (24%)	355 (23%)	381 (25%)	0.27
Arterial hypertension	1,954 (64%)	972 (64%)	982 (64%)	0.69
Hypercholesterolemia	1,756 (57%)	898 (59%)	858 (56%)	0.15
Smoker	1,054 (34%)	537 (35%)	517 (34%)	0.45
Left bundle branch block	181 (6%)	93 (6%)	88 (6%)	0.70
Prior myocardial infarction	1,030 (34%)	510 (33%)	520 (34%)	0.69
Prior coronary bypass	297 (10%)	148 (10%)	149 (10%)	0.95
Prior PCI	775 (25%)	387 (25%)	388 (25%)	0.96
β-Blockers	1,015 (33%)	486 (32%)	529 (35%)	0.10
Calcium antagonists	568 (19%)	274 (18%)	294 (19%)	0.35
Nitrates	539 (18%)	269 (18%)	270 (18%)	0.96
At least one medication	1,534 (50%)	754 (49%)	780 (51%)	0.34
Rest WMA	1,010 (33%)	517 (34%)	493 (32%)	0.36
Rest WMSI	1.17 ± 0.32	1.17 ± 0.32	1.17 ± 0.31	0.58
Stress WMSI	1.21 ± 0.34	1.21 ± 0.34	1.20 ± 0.33	0.29
Ischemic test result	458 (15%)	240 (16%)	218 (14%)	0.27
Rest HR (beats/min)	68 ± 12	69 ± 12	68 ± 12	0.57
Stress HR (beats/min)	88 ± 17	88 ± 17	87 ± 17	0.42
HRR	1.29 ± 0.20	1.29 ± 0.20	1.29 ± 0.20	0.70
HRR ≤ 1.22	1,216 (40%)	606 (40%)	610 (40%)	0.87
Rest SBP (mmHg)	139 ± 20	139 ± 20	140 ± 21	0.16
Stress SBP (mmHg)	138 ± 22	138 ± 22	138 ± 22	0.41
Rest DBP (mmHg)	78 ± 11	77 ± 11	78 ± 11	0.28
Stress DBP (mmHg)	76 ± 13	76 ± 13	76 ± 13	0.59
Duration of follow-up (days)	1,004 (295; 2,353)	1,000 (293; 2,293)	1,011 (299; 2,445)	0.43
Deaths	231 (8%)	117 (8%)	114 (8%)	0.84
Nonfatal myocardial infarctions	90 (3%)	33 (2%)	57 (4%)	0.01
Coronary revascularizations	710 (23%)	369 (24%)	341 (22%)	0.23

Data presented are mean value ± SD, median value with the corresponding first and third quartile, or number (%) of patients.

CAD = coronary artery disease; DBP = diastolic pressure; HR = heart rate; HRR = heart rate reserve; PCI = percutaneous coronary intervention; SBP = systolic pressure; WMA = wall motion abnormality; WMSI = wall motion score index; . Arterial hypertension was present with the patient on antihypertensive therapy or with values ≥140 mm Hg for systolic or ≥90 mm Hg for diastolic blood pressure. Hypercholesterolemia was present with the patient under statin therapy or with total cholesterol >180 mg/dl.

(the best cutoff identified for outcome prediction, see after) was present in 1,177 patients (38%) of the overall population (modeling and validation groups). At multivariate logistic regression analysis, age, diabetes mellitus, arterial hypertension, previous myocardial infarction, previous CABG, β blocker at the time of test, resting WMSI, and resting HR predicted a HRR $\leq$ 1.22 (Table 3).

During a median follow-up of 1,004 days (first quartile 295 and third quartile 2,353), 321 events were recorded: 231 deaths, and 90 nonfatal myocardial infarctions. Follow-up was censored at coronary revascularization in 710 patients (212 surgeries and 498 angioplasties) after a median of 18 days (first quartile 3 and third quartile 229) from SE.

On receiver operating characteristic analysis of the modeling group, HRR $\leq$ 1.22 (area under the curve 0.69 [95% CI 0.67 to 0.71], sensitivity 66%, and specificity 63%) was predictor of either mortality or hard events without significant differences in the modeling and validation groups (Figure 1). HRR $\leq$ 1.22 identified by receiver operating characteristic analysis in the modeling group was an independent predictor of infarction-free survival in the modeling (hazard ratio 1.83, 95% CI 1.30 to 2.60, p = 0.001), in the validation (hazard ratio 1.47, 95% CI 1.08 to 2.01, p = 0.02), and in the overall group (hazard ratio 1.60, 95 % CI 1.27 to 2.02, p <0.0001) (Table 4). In the overall population (modeling and validation groups), the 5-year hard event rate was 10% in patients with preserved and 21% in those with reduced HRR (p <0.0001; Figure 2). The separation between patients with preserved and impaired HRR was similar in 1,015 patients studied off β blockers when compared with 2,044 studied on beta-blocker therapy (Figure 3). Quartile values for HRR were $\leq$1.15, 1.16 to 1.26, 1.27 to 1.40, $\geq$1.41. Hard event rates according to decreasing quartiles were 8% (highest quartile), 12%, 14%, and 24% (lowest quartile) (Figure 4).

Table 2
Rest heart rate, stress heart rate, and heart rate reserve in patients investigated on and off beta-blocker therapy

	Patients on β blockers (n = 1,015)	Patients off β blockers (n = 2,044)	p Value
Rest HR	64 ± 11	71 ± 12	<0.0001
Stress HR	81 ± 14	91 ± 17	<0.0001
HRR	1.27 ± 0.19	1.30 ± 0.21	<0.0001
HRR ≤ 1.22	447 (44%)	769 (38%)	0.0006

Abbreviations as in Table 1.

Discussion

In patients with known or suspected CAD and/or HF, the prognostic value of dipyridamole-induced HRR was present, comparable with and additive over stress WMSI.

Plasma adenosine increases 2- to 3-fold during dipyridamole infusion at the dose employed in SE due to inhibition of cellular reuptake by the drug.[18] Dipyridamole infusion is also accompanied by a 70% increase in plasma noradrenaline of neuronal origin which can be detected even in absence of inducible myocardial ischemia and is not related to blood pressure changes.[19] Adenosine directly stimulates A2A adenosine receptors present on afferent nerve endings in the carotid body, skeletal muscle, heart, and kidney.[20] The increase in noradrenaline determines a rise in HR via stimulation of beta1 receptors present on sinus node.[21] The activation of specific sympatho-excitatory reflexes and simultaneous withdrawal of vagal tone[22] usually override the direct A1-receptor mediated negative chronotropic effect of adenosine on sinus node cells.[23] The blunted increase in HR may reflect that there is a reduced responsiveness to adrenergic stimuli, which can be due to increased baseline activity (mirrored by higher resting HR) or reduced adrenergic responsiveness, both associated to autonomic dysfunction and a higher level of risk. This interpretation is also consistent with previous early experiences with dipyridamole stress, reporting that the HRR (calculated retrospectively from the reported rest and peak values) was 1.20 to 1.50 in patients with or without ischemia[24] and

Table 3
Predictors of heart rate reserve ≤1.22 during dipyridamole stress echocardiography

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.05 (1.04-1.06)	<0.0001	1.06 (1.05-1.07)	<0.0001
Men	0.92 (0.75-1.14)	0.45		
Diabetes mellitus	1.68 (1.33-2.12)	<0.0001	1.44 (1.11-1.86)	0.006
Arterial hypertension	1.57 (1.26-1.95)	<0.0001	1.43 (1.12-1.82)	0.004
Hypercholesterolemia	1.20 (0.98-1.48)	0.08		
Smoker	1.00 (0.81-1.25)	0.94		
Left bundle branch block	1.47 (0.96-2.37)	0.08		
Prior myocardial infarction	1.63 (1.32-2.02)	<0.0001	1.40 (1.07-1.81)	0.01
Prior coronary bypass	1.80 (1.29-2.53)	0.001	1.45 (1.00-2.12)	0.05
Prior PCI	1.08 (0.85-1.36)	0.53		
β-Blocker at the time of test	1.36 (1.10-1.69)	0.004	1.60 (1.24-2.06)	<0.0001
Rest WMA	1.69 (1.36-2.10)	<0.0001		
Rest WMSI	2.63 (1.89-3.65)	<0.0001	1.87 (1.26-2.77)	0.002
Rest HR	1.04 (1.03-1.05)	<0.0001	1.06 (1.05-1.07)	<0.0001
Ischemic test result	1.12 (0.84-1.50)	0.45		

Abbreviations as in Table 1.

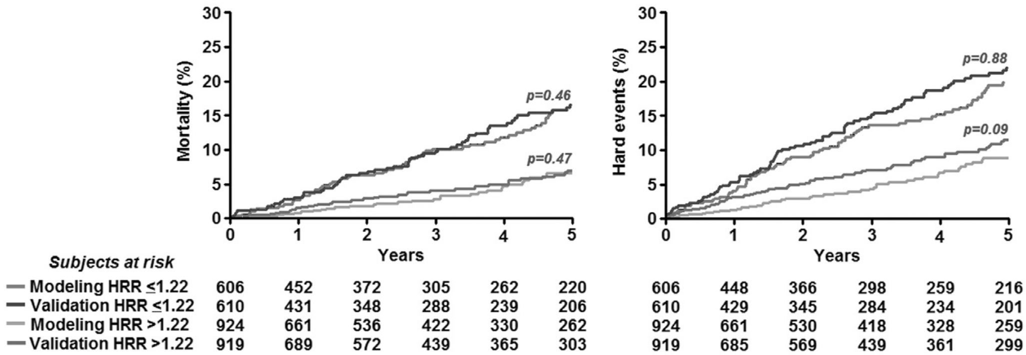

Figure 1. Receiver operating characteristic analysis for best cut-off value of HRR to predict future hard events.

Table 4
Univariate and multivariate predictors of mortality and hard events (death and myocardial infarction) in the entire study population

	Mortality				Hard events			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.09 (1.07-1.11)	<0.0001	1.08 (1.06-1.10)	<0.0001	1.07 (1.06-1.08)	<0.0001	1.06 (1.05-1.07)	<0.0001
Men	1.13 (0.86-1.47)	0.38			1.12 (0.89-1.41)	0.32		
Diabetes mellitus	1.42 (1.07-1.88)	0.02			1.41 (1.11-1.79)	0.005		
Arterial hypertension	1.00 (0.77-1.31)	0.98			0.96 (0.76-1.20)	0.72		
Hypercholesterolemia	0.80 (0.61-1.03)	0.09			0.76 (0.61-0.95)	0.01		
Smoker	0.95 (0.73-1.24)	0.71			1.01 (0.81-1.27)	0.93		
Left bundle branch block	0.96 (0.55-1.67)	0.87			0.90 (0.55-1.46)	0.66		
Prior myocardial infarction	1.65 (1.27-2.13)	<0.0001			1.85 (1.49-2.31)	<0.0001		
Prior coronary bypass	1.71 (1.23-2.37)	0.001			1.42 (1.06-1.91)	0.02		
Prior PCI	0.80 (0.58-1.09)	0.15			1.05 (0.82-1.34)	0.72		
β-blocker at the time of test	1.36 (1.04-1.77)	0.02			1.28 (1.02-1.60)	0.03		
Rest WMA	2.00 (1.55-2.60)	<0.0001			1.76 (1.42-2.20)	<0.0001		
Rest WMSI	3.17 (2.38-4.23)	<0.0001			2.46 (1.90-3.19)	<0.0001		
Ischemic test result	1.04 (0.68-1.60)	0.86			1.42 (1.03-1.97)	0.03		
Stress WMSI	3.14 (2.35-4.20)	<0.0001	2.52 (1.86-3.41)	<0.0001	2.61 (2.02-3.38)	<0.0001	2.19 (1.67-2.86)	<0.0001
HRR $\leq$ 1.22	2.62 (2.00-3.43)	<0.0001	1.70 (1.29-2.25)	<0.0001	2.31 (1.85-2.89)	<0.0001	1.60 (1.27-2.02)	<0.0001
Stress/rest SBP $\leq$ 5 mmHg	1.30 (1.00-1.68)	0.05			1.22 (0.98-1.52)	0.08		

Abbreviations as in Table 1.

almost abolished in patients with transplanted and denervated hearts.[25]

Chronotropic incompetence is considered a marker of autonomic dysfunction.[7] This finding has been consistently observed with adenosine,[9] dipyridamole,[10] and A2A receptor adenosine agonist regadenoson.[26] The present study is the first one with echocardiography, which is different from perfusion scintigraphy (SPECT) since ischemia is the required end point, and is the first one with the high dose, which is the standard for echocardiography imaging.[5,6] Association of

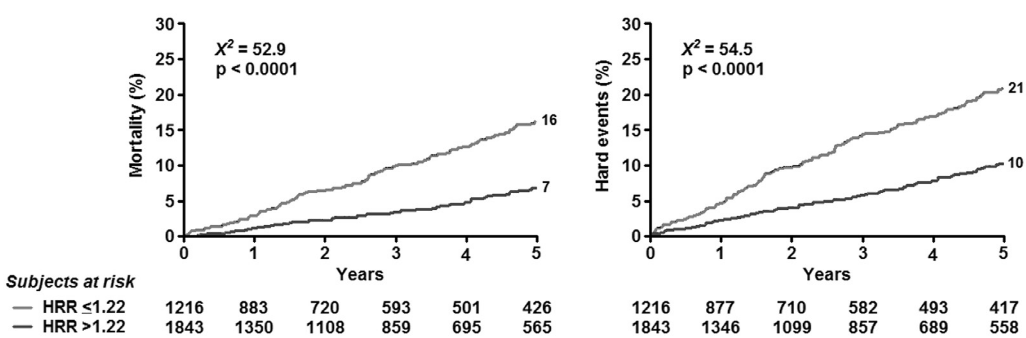

Figure 2. Kaplan-Meier survival (left panel) and hard event-free (right panel) curves in patients with normal and abnormal HRR. Number of patients per year is shown.

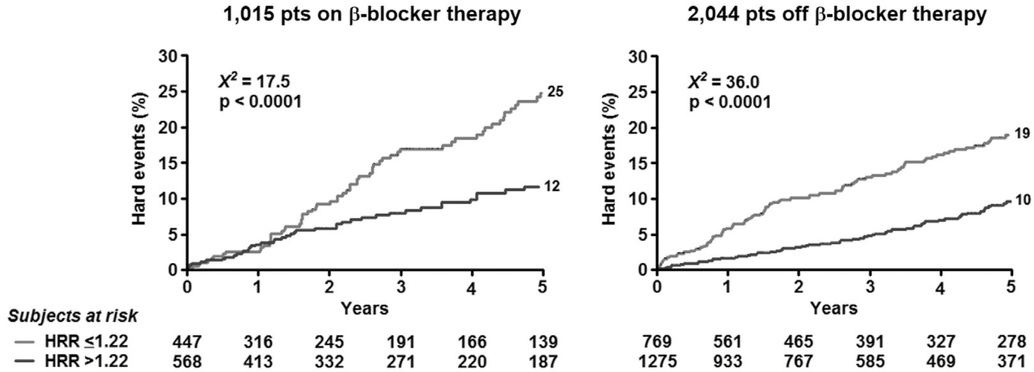

Figure 3. Kaplan-Meier hard event-free survival curves in patients with normal and abnormal HRR in populations on (left panel) and off (right panel) β blockers at the time of testing. Number of patients per year is shown.

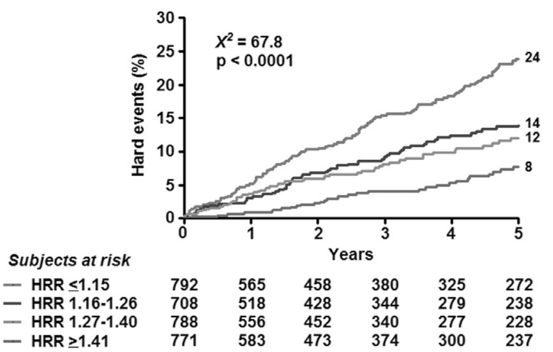

Figure 4. Kaplan-Meier hard event-free survival curves according to quartiles of HRR. Number of patients per year is shown.

chronotropic incompetence with events was present also in patients on β blockers,[27] as previously reported with exercise[28] and dipyridamole perfusion imaging stress.[11] Clinical physiology studies demonstrate that β blockers do not abolish the increase in HR elicited by adenosine, suggesting that vagal withdrawal (enhanced by β blockers) is also important in determining the increase in HR during dipyridamole.[23] With stress imaging, the prognostic dimension of electrical instability possibly linked to cardiac autonomic unbalance is missed. Yet, we know that cardiac autonomic dysregulation is pivotal to the development and progression of most cardiovascular diseases, from hypertension to HF and CAD, characterized by the negative prognostic implications of enhanced-sympathetic activity and impaired parasympathetic responsiveness.[14] The possibility to gain this elusive dimension of cardiac autonomic function and sympatho-vagal balance with a new parameter of striking simplicity such as HRR is appealing. HRR during vasodilator test is, at least in principle, also a simple cardiac autonomic function test.

The present study was a retrospective analysis of prospectively acquired patients, with the inherent limitations of this study design not allowing to control all variables. The positivity rate of SE was 15%, but the revascularization rate was 23%, possibly for symptoms or anatomy-driven indication to revascularization. We did not separately analyze cardiac death for statistical and methodological reasons, since the number of events would have been too small and it is not always so easy to identify the cause of death, or even more the subtype of cardiac death.[7] Whether HRR is good at discriminating not only groups but also individual patients remains unclear. The fact that β blockers were associated with blunted HRR but not with increase of hard events suggests a complex relation of blunted HRR with prognosis in the individual patient. We observed an almost trivial effect of an ischemic response on mortality and hard events, which may appear in contradiction with extensive previous literature from our group and many other groups using pharmacological or exercise SE.[3−6] However, over the last 2 decades SE changed its status from promising innovation to established technique embedded in guidelines. This led to proliferation of ischemia-driven myocardial revascularizations changing the natural history of the test and blunting the prognostic impact of a positive test. In addition, the referral pattern of patients referred to SE lab changed with the dissemination of the test, and patients with negative result had a 3-year hard event rate of 2.5% in the years 1983 to 1989 and 7.2% in the years 2010 to 2016.[2] This further emphasizes the need of a more comprehensive assessment of SE response, including parameters (such as HRR) capable to unmask vulnerabilities outside and beyond coronary artery stenosis when the end point is risk stratification, and not only CAD diagnosis. We pooled data of patients receiving the high dose of dipyridamole over 10′ (standard protocol) or 6’ (accelerated protocol) since these doses have comparable effects on HR, and their different ischemic effect (higher for accelerated protocol) is due to the stronger proischemic effect of faster coronary arteriolar dilation, rather than to different systemic hemodynamic effects.[3] Mean HR increases of 20 beats with standard high dose[5] or accelerated high dose,[6] and of 40 beats after addition of atropine.[24] Retrospectively analyzed data were derived from the documentation from the 18-year period from 2 centers. During this period the diagnostic criteria, imaging methodology and the drug infusion protocol remained the same.[3,6] We restricted our analysis of ECG to the simplest HRR, but in theory the entire rest and stress ECG information might be more easily combined with imaging data with the now emerging artificial intelligence approach.[29]

We did not assess the newer parameters now present in the state-of-the art protocol of SE, including coronary flow velocity reserve assessment on left anterior descending coronary artery, B-lines, and force-based left ventricular contractile reserve. Their relative value in risk stratification compared with HRR is currently under investigation in the prospective stress echo 2020 large scale multicenter study.[30]

In conclusion, patients with known or suspected CAD and/or HF are at increased risk of events in presence of a reduced HRR during dipyridamole SE.

Disclosures

The authors have no conflict of interest to disclose.

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