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Novel insights into the pathophysiology of different forms of stress testing

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ABSTRACT

Background: The impact of different forms of cardiac stress testing (exercise versus pharmacological stress testing) on cardiac wall stress and myocardial ischemia is incompletely understood.

Methods: In a prospective study, 331 consecutive patients with suspected myocardial ischemia referred for nuclear perfusion imaging were enrolled: 266 underwent exercise (bicycle) stress testing and 65 adenosine stress testing. Levels of B-type natriuretic peptide (BNP) measured before and 1 min after stress testing, ischemic ECG changes, and typical angina symptoms were used to compare the 2 testing modalities.

Results: Cardiac wall stress as quantified by changes in BNP levels significantly increased in the exercise stress group, but not in the adenosine group (increase in BNP levels 22 pg/ml (IQR 6–46) versus −3 pg/ml (IQR −3 to 28); $p < 0.001$). In the bicycle exercise stress group, patients with reversible defects on nuclear perfusion imaging more often had angina symptoms (25% vs. 9%, $p = 0.0001$) and ischemic ECG changes (33% vs. 12%, $p = 0.0001$) during the stress test, and a greater increase in BNP levels (28 (IQR 11–58) versus 16 (IQR 3–34) pg/ml, $p = 0.001$) compared to those without reversible defects. Those differences between patients with and without reversible defects were not observed with the adenosine protocol (p-values all >0.05).

Conclusion: Exercise stress testing but not adenosine stress results in an increase of cardiac wall stress, angina symptoms and ECG changes. The absence of these surrogates of myocardial ischemia suggests that adenosine stress does not induce acute myocardial ischemia, but rather displays relative perfusion differences.

Introduction

Coronary artery disease (CAD) is the most common cause of death in the United States and Europe [1,2]. Because coronary events, including death, can be prevented effectively with the use of medical and behavioral therapies in both symptomatic and asymptomatic patients [2], the accurate and early diagnosis of CAD and myocardial ischemia is one of the most important tasks in medicine. The detection of myocardial ischemia is clinically relevant, because there is a fixed therapeutic consequence linked to it: antianginal medication or coronary revascularization.

Myocardial perfusion single-photon emission computed tomography (SPECT) is one of the most accurate non-invasive imaging modalities for the detection of CAD and exercise-induced myocardial ischemia [3]. According to local preference and the physical ability of the patient to undergo bicycle or treadmill testing, cardiac imaging is performed using one of three stress testing modalities: exercise stress testing, pharmacological testing with a vasodilator (e.g. adenosine, regadenoson) alone or combined protocols. Differences of changes in myocardial pathophysiology induced by the three forms of stress testing are incompletely understood.

Using basic hemodynamic variables such as heart rate and blood pressure, clinical surrogates of myocardial ischemia such as characteristic ECG changes and typical angina symptoms, and cardiac wall stress as quantified by levels and changes of B-type natriuretic peptide (BNP), we aimed to describe changes in cardiovascular pathophysiology specific to exercise stress and adenosine stress testing alone [4–6].

Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiography; IQR, interquartile range; CAD, coronary artery disease; SPECT, myocardial perfusion single-photon emission computed tomography; ^{201}Tl, 201 thallium; ^{99m}Tc, metastable nuclear isomer of technetium-99; MBq, megabecquerel; keV, kilo-electronvolt; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.

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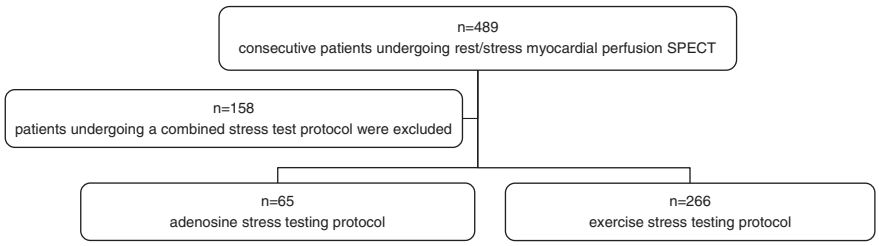

Fig. 1. Patient flow chart.

Methods

Patient population

From January 2010 to August 2010, 489 consecutive patients with suspected CAD referred to the University Hospital Basel for rest/stress myocardial perfusion SPECT were prospectively recruited for the BNP for Ischemia Evaluation (BASEL VIII) study. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

Two different testing protocols

Two different stress testing protocols were used: exercise stress and adenosine stress. Since it was the aim of our study to examine the differences in the pathophysiology between exercise and pharmacological stress testing, patients undergoing a combined protocol, e.g. those who didn't reach submaximal heart rate with exercise stress testing and consequently switched to the combined protocol, were excluded (n = 158), leaving 331 patients for this analysis (Fig. 1).

In the bicycle stress test protocol, a symptom-limited bicycle exercise test according to current guidelines was performed. Reasons for test termination were physical exhaustion, severe angina, sustained ventricular arrhythmia or exertional hypotension. At near-maximal exercise, the stress tracer as described below was injected and exercise was continued for 2 additional minutes. If submaximal heart rate was not reached by the patient testing, modality was switched to the adenosine-protocol as described below.

In the adenosine stress test protocol, pharmacological vasodilator stress was performed by infusion of adenosine (140 μg/kg per min). After 3 min, the stress tracer as described below was injected and the adenosine infusion was continued for another 3 min at the same rate.

Whenever possible, β-blocking medications as well as negative chronotropic calcium antagonist were withheld for 48 h and long-acting nitrates for 24 h before exercise testing. Coffee intake was withheld for 24 h before stress testing. If coffee was consumed nevertheless, the adenosine dose was doubled [7].

SPECT acquisition protocol

All patients underwent a routine rest/stress dual isotope (^{201}Tl for rest, ^{99m}Tc sestamibi for stress) myocardial perfusion SPECT protocol as previously described [8,9]. Rest–SPECT was obtained 30 min after administration of 111 MBq ^{201}Tl. Post-stress gated SPECT was acquired in average 95 to 100 min after the stress injection of 740-MBq ^{99m}Tc sestamibi in all three stress protocols. SPECT imaging was performed following standard protocols. No attenuation or scatter correction was used. SPECT images were acquired and processed with a circular 180° acquisition. For ^{201}Tl imaging (rest), two energy windows were used, including a 30% window centered on the 70-keV peak and a 20% window centered on the 167-keV peak. For ^{99m}Tc sestamibi imaging (stress), a 15% window centered on the 140-keV peak was used. Finally, the post-stress left ventricular ejection fraction (LVEF), the end-diastolic volume, and the end-systolic volume were calculated by automated gated measurements (QGS, Cedars Sinai Medical Center, Los Angeles, CA).

ECG monitoring and interpretation

The ECG monitoring of the patients was the same in the two stress protocols: 12-lead ECG monitoring was recorded continuously and stored electronically during the test. Printouts were done every minute. Maximal degree of ST-segment change at 60 ms after the J point of the

Table 1
Baseline characteristics of all patients in the different stress test protocols.

	All patients	Bicycle	Adenosine	p-Value bicycle vs. adenosine
	N = 331	N = 266	N = 65	
Age	64 (±11.8)	62.2 (±11.3)	71.5 (±10.9)	<0.001
Male gender (%)	227 (69)	179 (67)	48 (74)	0.308
Risk factors				
Hypertension (%)	234 (71)	183 (69)	51 (79)	0.125
Hypercholesterolemia (%)	181 (55)	146 (55)	35 (54)	0.880
Diabetes (%)	70 (21)	46 (17)	24 (37)	<0.001
Current smoking (%)	53 (16)	44 (17)	9 (14)	0.595
History of smoking (%)	136 (41)	108 (41)	28 (43)	0.716
History of				
Coronary artery disease (%)	139 (42)	102 (38)	37 (57)	0.007
Previous myocardial infarction (%)	90 (27)	64 (24)	26 (40)	0.01
Previous PTCA (%)	104 (31)	79 (30)	25 (39)	0.172
Peripheral artery disease (%)	32 (10)	23 (9)	9 (14)	0.203
Previous stroke (%)	22 (7)	16 (6)	6 (9)	0.351
CABG (%)	34 (10)	23 (7)	11 (17)	0.049

Data are presented as mean ± SD or number (percentage).
P values were based on t-tests, Wilcoxon rank sum tests or Chi-square tests.
PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass graft surgery.