Original Research

Association Between Coronary Flow Reserve and Exercise Capacity

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Introduction: Reduced exercise capacity is of clinical importance. Sometimes no corresponding cardiovascular disease can be found to explain this condition. We hypothesized that coronary microvascular dysfunction may have an effect on exercise capacity in patients without apparent cardiovascular disease.

Methods: Fifty patients (33 female, mean age 46.8 ± 12.4 years) without coronary artery or other cardiac disease were enrolled. Coronary microvascular function was evaluated by measurement of coronary flow reserve (CFR) during transthoracic pulsed-wave Doppler echocardiography with pharmacological stress. CFR was calculated as the ratio of hyperemic to baseline peak diastolic velocities after dipyridamole infusion. Exercise capacity was determined by treadmill exercise testing. Exercise time, metabolic equivalent (MET), and Duke treadmill score (DTS) were recorded and compared with the CFR data.

Results: CFR was correlated with exercise time ($r=0.376$, $p=0.007$), MET ($r=0.435$, $p=0.002$) and DTS ($r=0.458$, $p=0.001$). Exercise time, MET, and DTS were lower in patients with impaired CFR (<2) than in those with normal CFR (≥ 2) (5.3 ± 1.8 min vs. 8.6 ± 2.7 min, $p<0.001$; 7.3 ± 3.1 vs. 11.4 ± 2.8, $p=0.002$; -1.75 (-5.9, 5.0) vs. 7.5 (5.2, 9.41), $p<0.001$; respectively). CFR was lower in patients with MET$\leq$7 as compared to patients with MET>7 (2.0 ± 0.5 vs. 2.6 ±0.6, $p=0.015$).

Conclusions: CFR is associated with exercise capacity. Thus coronary microvascular dysfunction may be a reason for reduced exercise capacity in patients who have no apparent cardiovascular disease.

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Exercise capacity as measured by a treadmill exercise test reflects cardiac functional reserve and future cardiac events.[1,2] Reduced exercise capacity is the most common problem in daily clinical practice. It may be associated with multiple diseases, such as heart failure, coronary artery disease, heart valve disease, pulmonary disease, and immobility; however, not infrequently, no significant cardiac or pulmonary diseases are detected. We hypothesized that coronary microvascular dysfunction may have an effect on exercise capacity without apparent cardiovascular disease. Impaired coronary microvascular function can be evaluated noninvasively by transthoracic Doppler echocardiography with pharmacological stress. This method has been shown to be a reliable and reproducible indicator of coronary microvascular function and has been validated against positron emission tomography and Doppler wire measurements in several studies.[3-5] Accordingly, in this study we aimed to investigate the association between coronary flow reserve (CFR) determined by pharmacological stress transthoracic Doppler echocardiography and cardiac functional capacity and exercise parameters measured by treadmill exercise test.

Methods

Study population

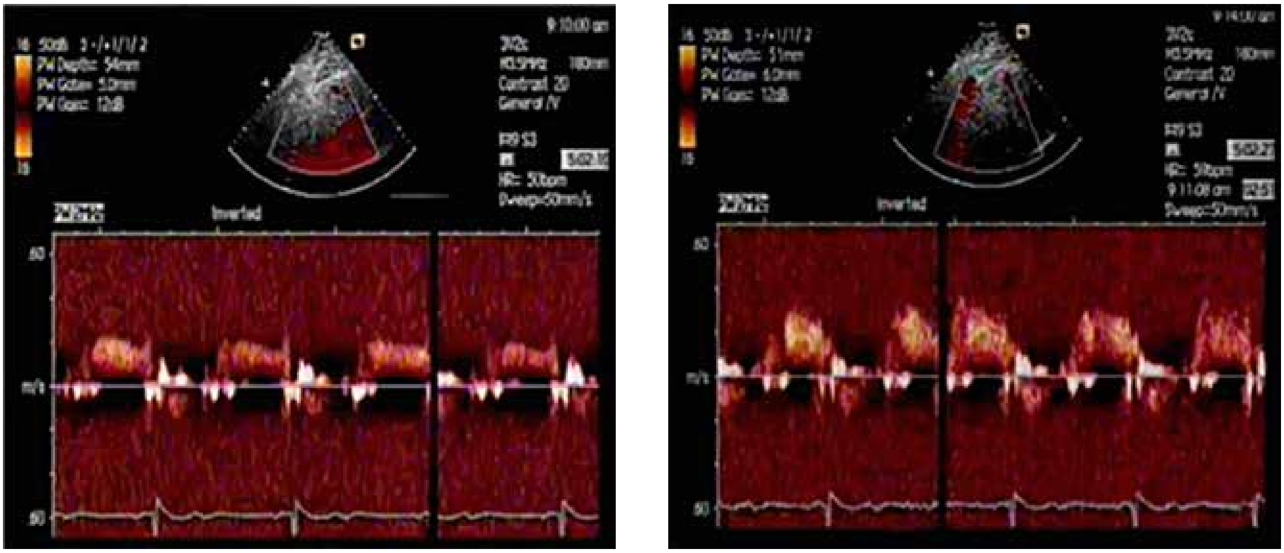
Fifty individuals (33 females and 17 males, mean age 46.8 ± 12.4 years) without coronary artery disease or other cardiac diseases were enrolled in this study. Coronary artery disease was defined as the presence of one of the following: typical angina, ST-segment or T-wave changes specific for myocardial ischemia, Q-waves or incidental left bundle-branch block on the ECG, wall motion abnormalities on echocardiography, a noninvasive stress test revealing ischemia or any perfusion abnormality, or a history of myocardial infarction or revascularization. Patients who had unequivocal symptoms underwent a noninvasive stress test, treadmill exercise or myocardial perfusion scintigraphy, and those demonstrating positive results underwent coronary angiography. Coronary artery disease was defined as stenosis ≥20% in any coronary artery. Coronary angiography was defined as normal when no obstructive lesion (stenosis ≥20% in any coronary artery) was visualized in any projection.

Patients were excluded if they had coronary artery disease, heart failure, severe valvular disease, cardiomyopathy, congenital heart disease, arrhythmias, uncontrolled hypertension, diabetes mellitus, systematic disease such as hemolytic, hepatic and renal disease, hypo- or hyperthyroid, chronic obstructive pulmonary disease, *cor pulmonale*, pulmonary hypertension, inadequate transthoracic echocardiographic images, contraindications for or inability to perform a treadmill exercise test.

Coronary microvascular function was assessed noninvasively in all participants by pharmacological stress transthoracic Doppler echocardiography, via measurement of CFR. Exercise capacity was evaluated by treadmill exercise testing. The study complied with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Evaluation of coronary flow reserve

All patients underwent transthoracic echocardiography using an Acuson Sequoia C-256 device (Acuson Corporation, California, USA) with a 3.5 MHz transducer. Echocardiograms were recorded on videotapes. The left anterior descending coronary artery (LAD) was visualized using a modified, foreshortened, 2- chamber view, and an optimal alignment to the interventricular sulcus was obtained. The color gain was adjusted to provide optimal images and coronary flow in the distal LAD, which was examined by color Doppler flow mapping over the epicardial part of the anterior wall. Pulsed-wave Doppler recordings of the mid-to-distal LAD were obtained from each subject. Spectral Doppler of the LAD displayed a characteristic biphasic flow pattern, with a larger diastolic and a smaller systolic component. Hyperemia was induced by infusion of dipyridamole at a rate of 0.56 mg/kg over 4 min. Coronary peak diastolic velocities were measured at baseline and at hyperemia (Figure 1). The highest three Doppler record-



Baseline

Hyperemia

Figure 1. Demonstration of coronary flow velocity at baseline and hyperemia obtained by transthoracic pulsed-wave Doppler echocardiography in the distal left anterior descending coronary artery.

ings were averaged for each measurement. CFR was calculated as the ratio of hyperemic to baseline peak diastolic velocities.[6] A CFR value ≥2 was defined as normal.[7]

Treadmill exercise test

A maximal symptom-limited treadmill exercise test was performed using a Philips StressVue Exercise Testing System (Philips Health Care 3000 Minuteman Rd., Andover MA, USA) according to a modified Bruce protocol. Exercise time and the exercise capacity expressed as metabolic equivalents were measured. The Duke treadmill score was calculated using the formula:[8]

$$\text{exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{exercise angina})$$

where angina was assigned 0 for none, 1 for non-limiting, and 2 for exercise-limiting.

Fatigue, angina, diagnostic ST depression, and persistent arrhythmias were considered as reasons for discontinuing the treadmill exercise test.

Statistical analysis

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test the normality of distribution. Continuous variables are expressed as mean ± SD or median (interquartile range). Categorical variables are given as group percentages. Variables with a normal distribution were compared using unpaired t-tests. Variables that were non-parametrically distributed were compared using the Mann–Whitney U-test. Categorical variables were compared using the chi-square test. Correlations were established by Pearson correlation test. CFR was measured by two experienced observers who were blinded to the exercise test results. In 10 randomly selected patients the interobserver correlation was calculated by Pearson correlation test. In the same group of patients measurements were repeated 2 days later to calculate the intraobserver correlation by Pearson correlation test. A p-value <0.05 was considered statistically significant.

Results

The clinical, echocardiographic and treadmill exercise test parameters are presented in Table 1. Coronary artery disease was excluded by a negative treadmill exercise test (n=28), negative nuclear stress test (n=3), or normal coronary angiogram (n=19, after positive stress test) in the study population.

Table 1. Characteristics of the study population

Demographic features	
Age (years)	46.8 ± 12.4
Female/male	33/17
BMI (kg/m^2)	29.2 ± 5.0
Hypertension (%)	30
Diabetes mellitus (%)	0
Dyslipidemia (%)	40
Smoking (%)	32
Exercise parameters:	
Exercise time (min)	8.1 ± 2.9
MET	10.7 ± 3.2
Duke Treadmill Score	7.2 (3.5, 8.8)
Maximum heart rate (pulse/min)	161.9 ± 20.5
% Target heart rate	92.7 ± 10.1
Maximum SBP (mmHg)	161.8 ± 27.2
Maximum DBP (mmHg)	89.7 ± 17.4
Pharmacological stress echocardiography parameters:	
Baseline:	
SBP (mmHg)	123.5 ± 14.4
DBP (mmHg)	76.7 ± 7.3
Heart rate (/min)	72.7 ± 12.8
Baseline diastolic coronary flow (cm/s)	28.2± 5.1
Baseline systolic coronary flow (cm/s)	18.1 ± 4.2
Hyperemia:	
SBP (mmHg)	114.8 ± 16.1
DBP (mmHg)	71.3 ± 11.9
Heart rate (pulse/min)	92.6 ± 12.7
Peak diastolic coronary flow (cm/s)	69.4 ± 15.6
Peak systolic coronary flow (cm/s)	37.4 ± 9.7
Coronary flow reserve	2.5 ± 0.6

Data are expressed as mean ± SD, median (interquartile range), or frequency counts (percentages), as appropriate.
BMI – body mass index; DBP – diastolic blood pressure; EF – ejection fraction; MET – metabolic equivalent; SBP – systolic blood pressure.

The intra- and interobserver correlations of CFR measurements were 97.1% and 98.1%, respectively.

CFR was correlated with exercise time (r=0.376, p=0.007), MET (r=0.435, p=0.002), and DTS (r=0.458, p=0.001) (Figure 2). When the patients were separated into groups according to impaired CFR (CFR<2) and normal CFR (CFR ≥2), exercise time was lower in the impaired CFR group (5.3 ± 1.8 min vs. 8.6 ± 2.7 min, p<0.001). Similarly, MET values were lower in the impaired CFR group than in the normal CFR group (7.3 ± 3.1 vs. 11.4 ± 2.8, p=0.002). Like exercise time and MET, DTS was lower in the impaired CFR group than the normal CFR group (-1.75 (-5.9, 5.0) vs. 7.5 (5.2, 9.41), p<0.001) (Table 2).

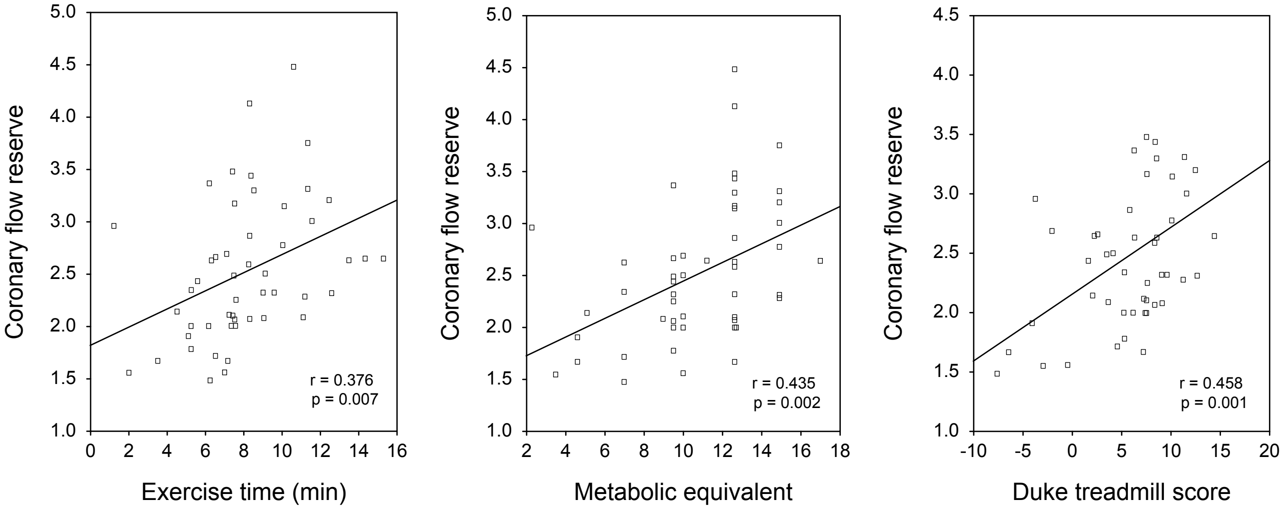


Figure 2. Correlation graphs between coronary flow reserve and exercise time, metabolic equivalents, and Duke treadmill score.

Using 7 METs to separate reduced from normal exercise capacity,[9] baseline diastolic coronary flow velocities did not differ between the 2 groups; however, CFR was lower in patients with MET≤7 than in patients with MET>7 (2.0 ± 0.5 vs. 2.6 ±0.6, p=0.015) (Table 3). Age was higher and female sex was more common in the group with MET≤7 than the group with MET>7.

Baseline and hyperemic diastolic and systolic coronary flow velocities and CFR did not differ between women and men (Table 4). Exercise time, MET value, and DTS were higher in men than in women (Table 4). In both women and men, CFR was correlated with exercise time (r=0.358, p=0.041; r=0.587, p=0.013) and DTS (r=0.432, p=0.011; r=0.555, p=0.026). In addition, CFR was associated with the MET value in women (r=0.454, p=0.008) but not in men (r=0.376, p=0.137).

Discussion

The current study showed that exercise time, MET and DTS were positively correlated with CFR and that CFR was impaired in patients with reduced exercise capacity. These findings suggest that coronary microvascular dysfunction could impact exercise capacity; and that coronary microvascular function may be impaired in patients with reduced exercise capacity.

In a previous study of patients with stable angina pectoris, the degree of stenosis on the coronary arteriogram was not found to be related with exercise capacity.[10] Interestingly, the authors established a good correlation between CFR and exercise capacity on treadmill exercise test in these patients, similarly to our study.[10] The relation between CFR and exercise capacity in the absence of significant epicardial coronary stenosis indicates that microvascular function is likely to be responsible for reduced exercise capacity and performance. Microvascular dysfunction should be considered in patients with reduced exercise capacity in the absence of discernable cardiac disease.

In another study, a relation between exercise capacity and functional stenosis by fractional flow reserve (FFR) was found in patients with stable angi-

Table 2. Comparison of exercise parameters according to coronary flow reserve (CFR).

Value	CFR<2 (n=8)	CFR≥2 (n=42)	p*
Exercise time (min)	5.3 ± 1.8	8.6 ± 2.7	<0.001
MET	7.3 ± 3.1	11.4 ± 2.8	0.002
Duke treadmill score	-1.7 (-5.9, 5.0)	7.5 (5.2, 9.4)	<0.001

Data are expressed as mean ± SD, or median (interquartile range), as appropriate.
*Mann–Whitney U-test.

Table 3. Comparison of coronary flow parameters according to metabolic equivalents (METs).

Value	METs≤7 (n=9)	METs>7 (n=41)	p
Demographic features:			
Age (year)	57.8 ± 10.4	44.4 ± 11.6	0.004*
Female/male	9/0	24/7	0.019†
BMI (kg/m^2)	30.4 ± 5.3	28.9 ± 5.0	0.675*
Hypertension (%)	33.3	66.7	0.065†
Dyslipidemia (%)	15	85	0.613†
Smoking (%)	76.5	23.5	0.138†
Pharmacological stress echocardiography parameters:			
Baseline:			
Diastolic coronary flow (cm/s)	28.3 ± 4.7	28.2 ± 2.7	0.901*
Systolic coronary flow (cm/s)	16.6 ± 4.6	18.5 ±4.0	0.250*
Hyperemia:			
Diastolic coronary flow (cm/s)	57.4.3 ± 15.1	72.1 ± 14.6	0.016*
Systolic coronary flow (cm/s)	33.3 ± 14.3	38.3 ± 8.4	0.039*
Coronary flow reserve	2.0 ± 0.5	2.6 ± 0.6	0.015*

Data are expressed as mean ± SD.
*Mann–Whitney U-test; †chi-square test.

Table 4. Comparison of coronary flow and exercise parameters according to sex.

Value	Women (n=33)	Men (n=17)	p
Pharmacological stress echocardiography parameters:			
Baseline:			
Diastolic coronary flow velocity (cm/s)	28.7 ± 5.3	27.2 ± 4.8	NS*
Systolic coronary flow velocity (cm/s)	17.8 ± 4.3	18.7 ± 3.9	NS*
Hyperemia:			
Diastolic coronary flow velocity (cm/s)	68.6 ± 14.6	71.1 ± 17.7	NS*
Systolic coronary flow velocity (cm/s)	36.3 ± 10.4	39.5 ± 8.3	NS*
Coronary flow reserve	2.4 ± 0.6	2.6 ± 0.6	NS*
Exercise test parameters:			
Exercise time (min)	7.4 ± 2.8	9.4 ± 2.6	0.019*
MET	9.4 ± 3.0	13.3 ± 1.9	<0.001*
DTS	5.7 (1.6, 8.2)	9.5 (6.4, 11.5)	<0.001†

Data are expressed as mean ± SD, or median (interquartile range), as appropriate.
*t-test; †Mann–Whitney U-test.
DTS – Duke treadmill score; MET – metabolic equivalent; NS – not significant.

na and intermediate degree coronary stenosis.[11] FFR was significantly correlated with peak oxygen consumption (peak VO_2) and anaerobic threshold measured by a cardiopulmonary exercise test.[11] In our study, we did not measure peak VO_2, but MET values indicate peak oxygen consumption. One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O_2 per kg of body weight per min. We found that MET values were related to CFR. Accordingly, we presume that MET value is associated with coronary microvascular function.

In a new French study, CFR was measured in the acute phase invasively and at follow up (4 ± 1.6 months) noninvasively using stress echocardiography in patients with acute ST-segment elevation anterior myocardial infarction, before and after reperfusion.[12] The investigators found that, in contrast to acute CFR, CFR at follow up was an independent predictor of exercise capacity. They suggested that improvement of the coronary microcirculation is closely linked to physical aptitude after myocardial infarction. In our study we showed that CFR is correlated with exercise time. Like the above authors, we believe that coronary microvascular function can affect exercise capacity.

In patients with cardiomyopathy, no significant relationship between CFR and exercise capacity was found, in contrast to patients with stable angina or intermediate lesions. CFR was found to be weakly and non-significantly related to exercise duration ($r=0.40$, $p>0.05$) and to the MET value ($r=0.32$, $p>0.05$) in patients with hypertrophic cardiomyopathy.[13] Additionally, in patients with dilated cardiomyopathy CFR measured by transesophageal Doppler did not correlate with exercise capacity.[14] Those findings suggest that cardiomyopathy is the main factor affecting cardiac functional capacity, whereas CFR or microvascular function do not contribute to the limitation of exercise capacity in these patients. We excluded cardiomyopathies in the current study.

We found that CFR is correlated with exercise time and DTS in both women and men. However, only in women was there a correlation between CFR and MET values. Microvascular dysfunction and cardiac syndrome X are more common in women than in men.[15] In addition, women suffer more frequently from reduced exercise capacity. Consequently, microvascular dysfunction could have a more significant impact on exercise capacity in women than in men.

Limitations

We evaluated CFR noninvasively by transthoracic Doppler echocardiography instead of using Doppler flow wires. Previous studies showed that assessment of CFR by transthoracic Doppler echocardiography is a reliable and reproducible indicator of coronary microvascular function that has excellent correlations with CFR determined by positron emission tomography[3] and invasive measurements by Doppler wires.[16] We did not perform a cardiopulmonary exercise test and we did not measure peak VO_2 or the anaerobic threshold. However, the treadmill exercise test is widely used in routine clinical practice to determine cardiac functional capacity, is less expensive and easier to perform. Our study population consisted of nearly normal subjects. Therefore, the impaired CFR group and reduced exercise capacity group were small, but we were still able to show the association between CFR and exercise capacity.

In conclusion, CFR is associated with exercise capacity in patients who have no coronary artery disease. Reduced exercise capacity could be related to microvascular dysfunction despite no significant cardiac disease. Notably, women with reduced exercise capacity may require particular attention. Reduced exercise capacity, as a reflector of microvascular function, may potentially be an early finding of ultimate coronary artery disease. Treatments targeted at microvascular dysfunction could contribute to improving exercise capacity.

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