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SummariZation of long-tErm prognostic siGnificance of coronary flow rEserve in special Disorders

(SZEGED Study)

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Summary of PhD thesis

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Relevant publications

Full papers

I. Balázs E, Pintér KS, Egyed Á, Csanády M, Forster T, Nemes A. A koronária áramlási rezerv prognosztikus jelentősége a koronarográfia során a bal koszorúér leszálló szárában szignifikáns szűkületet nem mutató betegekben (Eredmények a SZEGED Tanulmányból). *Orv Hetil* 2010; 151: 338-343.

II. Balázs E, Pintér KS, Egyed A, Csanády M, Forster T, Nemes A. The independent long-term prognostic value of coronary flow velocity reserve in female patients with chest pain and negative coronary angiograms (Results from the SZEGED study). *Int J Cardiol* 2011; 146(2): 259-61.

III. Nemes A, Balazs E, Pinter S, Csanady M, Forster T. Long-term prognostic significance of coronary flow velocity reserve in patients with significant coronary artery disease not involving the left anterior descending coronary artery (Results from the SZEGED Study). *Echocardiography* 2010; 27: 306-310.

IV. Nemes A, Balazs E, Soliman OI, Sepp R, Csanady M, Forster T. Long-term prognostic value of coronary flow velocity reserve in patients with hypertrophic cardiomyopathy – 9-year follow-up results from SZEGED study. *Heart Vessels* 2009; 24: 352-356.

V. Nemes A, Balazs E, Csanady M, Forster T. Long-term prognostic role of coronary flow velocity reserve in patients with aortic valve stenosis – insights from the SZEGED Study. *Clin Physiol Funct Imaging* 2009; 29: 447-452.

1. Introduction

The coronary arterial tree consists of four basic segments: large epicardial coronary arteries, medium-sized and small arteries, arterioles and capillary vessels, directly supplying myocardial cells. Each of these coronary segments creates different level and degree of resistance to coronary blood flow. Normal (non-stenosed) large epicardial coronary arteries play a minor role in the regulation of coronary vascular resistance and act mainly as conductance vessels.

Normally, coronary blood flow can increase approximately three- to sixfold to meet increasing myocardial oxygen demands. This effect is mediated by vasodilation at the arteriolar bed, which reduces vascular resistance, thereby augmenting flow.

The coronary flow velocity reserve (CFR) represents the capacity of coronary circulation to dilate following an increase in myocardial metabolic demands and can be expressed by the ratio between the hyperaemic and resting peak flow velocities. CFR is an important functional parameter in order that we can understand the pathophysiology of coronary circulation and it can be used to examine the integrity of microvascular circulation. CFR could be evaluated invasively in the catheterisation laboratory and in nuclear medicine through perfusion imaging. Besides these both the transoesophageal and transthorasic methods of the vasodilator stress Doppler echocardiography are reliable for the evaluation of coronary flow velocity changes in the left anterior descending coronary artery (LAD). The flow velocity variations are proportional to the blood flow if the vessel lumen is kept constant, so the velocity ratio is used as surrogate of flow reserve. Coronary flow velocity by Doppler assessment appears to be biphasic, with a lower peak during systole and a higher peak during diastole. Myocardial extravascular resistance is higher in systole and lower in diastole due to the effect of myocardial contraction.

Coronary flow velocity reserve assessment on the LAD by echocardiography is an excellent option for the evaluation of coronary microcirculation conditions in the absence of significant LAD stenosis. Microcirculatory abnormalities may occur in several diseases including hypertension, diabetes mellitus (DM), hypercholesterolaemia, aortic valve stenosis (AS), dilated and hypertrophic cardiomyopathy (HCM) etc. Recently, the independent prognostic significance of CFR has been demonstrated in a number of diseases, however its prognostic role remained questioned in some special disorders.

2. Methods

Patient population (general considerations). Hundreds of patients with suspected coronary artery disease, valvular heart disease or cardiomyopathies were selected prospectively starting from 1997 to evaluate the clinical usefulness and prognostic significance of CFR measurements at the 2nd Department of Medicine and Cardiology Center, University of Szeged, Hungary. All patients underwent a standard transthoracic echo-Doppler study to evaluate left ventricular function and a stress vasodilator TEE study to evaluate CFR.

Follow-up data. During the follow-up, all patients were controlled by phone, mail or other available way. The primary outcome was cardiovascular-related mortality including sudden cardiac death, cardiovascular mortality due to heart failure, cerebro- or cardiovascular thrombosis and hospitalization due to invasive procedures (coronary angiography, percutaneous transluminal myocardial septal alcohol ablation or implantable cardioverter defibrillator implantation). Data on primary outcome were gained from hospital recordings or autopsy reports.

Transthoracic echocardiography. Transthoracic echo-Doppler study was performed in all patients with commercially available echocardiography systems (ATL Ultramark 9 HDI, Seattle, Washington, USA, and Toshiba Powervision 8000, Tokyo, Japan). Left ventricular internal dimensions and wall thickness were measured by M-mode echocardiography and ejection fraction was calculated using the biplane Simpson's or Teichholz's methods, in accordance with guidelines.

Transoesophageal echocardiography. A complete TEE examination was carried out in all patients with an ATL® Ultramark 9 HDI echocardiograph (Seattle, Washington, USA), using a biplane transducer or a Toshiba Powervision 8000 echocardiograph (Tokyo, Japan) with a multiplane transducer. Blood pressure and heart rate were monitored continuously during the examinations. Dipyridamole stress TEE examinations were performed according to the standard protocol proposed by Iliceto *et al.* (3). β-Blockers, nitrates and calcium-antagonists were discontinued two days before the TEE examination. In all patients, the aortic root and the proximal portion of the LAD were visualized in the transversal plane (0 to 120 degrees). Coronary blood flow was visualized by color Doppler flow imaging and the phasic flow

velocity waveform in the LAD was recorded by pulsed-wave Doppler. Care was taken to measure coronary flow velocities at the same angle at rest and at peak stress. Phasic coronary flow velocity patterns were recorded in resting conditions and during hyperaemia. Dipyridamole as a vasodilator agent was infused for 4 min at a dose of 0.56 mg/kg. The peak velocities were measured after 6 min, at maximal vasodilation. CFR was estimated as the ratio of the hyperaemic to the basal peak diastolic coronary flow velocity. All studies were recorded on super-VHS videotape and evaluated by experts in echocardiography who were blinded to the result of coronary angiography. For all patients, five consecutive cycles were measured and averaged.

Statistical analysis. MedCalc (Mariakerke, Belgium) software was used for statistical calculations. Continuous data with normal distribution were presented as mean ± SD, while dichotomous data were presented as number and percentage. All tests were two-sided and a p-value below 0.05 was considered statistically significant. Group comparisons were made with the unpaired Student's *t* test. For the dichotomous variables, chi square analysis and Fisher's exact test were performed. To establish the predictive power of CFR, receiver operator curves (ROCs) were constructed and the area under the curve was reported with sensitivity and specificity values. Kaplan-Meier life table estimates of survival were used to summarize the follow-up. Differences in survival rates between groups were tested by the log-rank test. Variables associated with the study primary outcome were investigated with univariate analysis including age, gender, hypertension, diabetes, hypercholesterolemia, LV end-systolic diameter and volume, LV end-diastolic diameter and volume, LV mass index, LV ejection fraction and CFR (+ aortic atherosclerosis (AA) grade and presence of menopause in female patients with normal epicardial coronary arteries; presence of multivessel disease and AA grade in non-LAD disease patients; AA grade and presence of non-LAD stenosis in patients without LAD stenosis; presence of coronary artrery diseases and mean LV-aortic poststenotic gradient in AS patients). Significant variables on univariable analysis ($p < 0.10$) were integrated into multivariable analysis using Cox-proportional hazard modelling with a forward stepwise model for assessment of independent predictors of the study primary outcome.

3. Aims

To assess whether pulsed-wave Doppler echocardiography-derived CFR has a long-term prognostic value for cardiovascular outcome:

3.1. in female patients with chest pain and normal epicardial coronary arteries

3.2. in patients with right and/or left circumflex coronary artery stenosis without epicardial LAD disease

3.3. in patients without significant epicardial LAD stenosis

3.4. in patients with aortic valve stenosis

3.5. in cases of hypertrophic cardiomyopathy.

4. Results

4.1. Prognostic role of CFR in female patients with normal epicardial coronary arteries

Study population. A total of 68 female patients with chest pain and negative coronary angiograms were enrolled in this prospective follow-up study. Patients with unstable angina, acute myocardial infarction, significant valvular disease or HCM were excluded from the study. No major complications occurred during vasodilator stress TEE imaging. The success rate of follow-up was 45 out of 68 (66%).

Cardiovascular events. During the mean follow-up 102 ± 26 months (median value: 113 months), one patient suffered sudden cardiac death and another patient died in gastrointestinal malignancy. During this follow-up period, 16 patients had been hospitalized due to cardiovascular reasons (9 re-coronary angiography with LAD stent-implantation in 2 cases, 3 myocardial infarctions, 3 non-fatal strokes, and 1 cardioversion due to atrial fibrillation).

Coronary flow velocity reserve. Using ROC analysis, CFR <2.2 had the highest accuracy (lowest false negative and positive results) in predicting cardiovascular survival (sensitivity 72% [95% confidence interval (CI) 47-90%], specificity 70% [95% CI 50-86%], area under the curve 74 ± 7 [95% CI 58-86%, p =0.0014], positive predictive value 62% [95% CI 54-75%] and negative predictive value 79% [95% CI 63-91%].

Multivariable analysis. The logistic regression model identified only CFR as an independent predictor of survival (hazard ratio (HR) 2.77, 95% CI of HR: 1.27 to 6.25, p <0.05).

4.2. Prognostic role of CFR in patients with significant coronary artery disease (CAD) not involving the LAD

Patient population. total of 49 patients with significant right coronary artery (RC) and / or circumflex coronary artery (CX) stenosis were enrolled in this prospective follow-up study. All patients had undergone coronary angiography demonstrating significant RC and / or CX disease without LAD stenosis and dipyridamole stress transoesophageal echocardiography (TEE) as CFR measurement. All patients with significant valvular diseases and atrial fibrillation have been excluded from this study. The success rate of follow-up was 43 out of 49 (88%). Coronary angiography showed significant RC disease in 22 patients (51%), CX disease in 9 patients (21%) and combined RC and CX disease in 12 patients (28%). None of patients had significant (>50% stenosis) LAD disease. No major complications occurred during vasodilator stress TEE imaging in any of patients.

Cardiac events. During a mean follow-up of 97 ± 29 months, 14 patients suffered cardiovascular death (12 sudden cardiac deaths and 2 strokes), and one patient died in pulmonal tumor.

Coronary flow reserve. Using ROC analysis, CFR <2.09 had the highest accuracy (lowest false negative and positive results) in predicting cardiovascular survival (sensitivity 80%, specificity 57%, area under the curve 73%, p =0.003).

Multivariable analysis. The logistic regression model identified only CFR as an independent predictor of survival (hazard ratio (HR) 6.26, 95% CI of HR 1.23 to 19.61, p =0.024).

4.3. Prognostic role of CFR in patients without significant LAD stenosis

This study comprised 166 patients without significant LAD stenosis. No major complications occurred during vasodilator stress TEE imaging. The success rate of follow-up was 124 out of 166 (75%). The average time of follow-up was 93 ± 34 months.

Coronary angiography. Coronary angiography showed normal epicardial coronary arteries in 81 patients (65%), while 22 patients (18%) had significant right coronary artery stenosis. Significant left circumflex coronary artery stenosis were in 9 cases (7%) and combined disease (RC + CX stenosis) in 12 cases (10%).

Characteristics of mortality. During follow-up, 7 RC patients (32% of RC patients), 3 CX subjects (33% of CX subjects), and 5 combined RC and CX patients (42% of this patient

group) and 12 cases with negative coronary angiography (15% of this group) died. Casuses of mortality were sudden death in 16 cases (59%), acute heart failure in 3 cases (11%), stroke in 2 cases (7%), and pulmonary or gastrointestinal tumor in 6 cases (22%). Most of death cases (56%) were in patients with non-LAD coronary stenosis, despite they were only 35% of all cases.

Coronary flow reserve. CFR ≤2.13 had the highest accuracy (lowest false negative and positive results) in predicting cardiovascular mortality (sensitivity 67%, specificity 60%, area under the curve 62%, p =0.046).

Multivariable analysis. By univariable analysis, grade of aortic atherosclerosis, CFR and LV end-systolic diameter and volume were significant predictors of cardiovascular morbidity and mortality. Multivariable regression analysis showed that lower CFR (hazard ratio (HR) 2.43, p =0.04) and higher LV end-systolic volume (HR 1.49, p =0.03) were independent predictors of cardiovascular outcome.

4.4. Prognostic role of CFR in patients with aortic valve stenosis

Patient population. A total of 49 patients with moderate, severe or critical AS (mean age: 63 ± 9 years, 26 men) were enrolled in this prospective follow-up study. AS was considered according to the current guidelines: if the mean transvalvular left ventricular (LV)-aortic gradient is <25 mm Hg, the stenosis is mild; if the mean gradient is between 25 mm Hg and 50 mm Hg, the stenosis is moderate; if the mean gradient is >50 mm Hg the stenosis is severe; and when the gradient is greater than 70 mm Hg, the stenosis is critical. If the aortic valve area is between 1.3 and 2.0 cm^2, the stenosis is mild; if the valve area is between 1.0 and 1.3 cm^2, the stenosis is moderate; if the valve area is between 0.7 and 1.0 cm^2, the stenosis is moderate-severe; areas of less than 0.7 cm^2 constitute severe AS. Patients with unstable angina, acute myocardial infarction, other significant valvular disease than AS or HCM were excluded from the study. The day before CFR measurements the consumption of caffeine containing drinks was prohibited. Prosthetic aortic valve replacements have been performed 20 ± 31 weeks after stress TEE measurements in 36 patients.

CFR measurement. No major complications occurred during vasodilator stress TEE imaging. The success rate of follow-up was 49 out of 49 (100%). The peak and mean

transvalvular gradients were 85 ± 22 and 54 ± 9 mm Hg, respectively. The mean resting aortic valve area was 0.81 ± 0.21 cm^2.

Aortic valve replacements. AVR has not been performed in 13 patients if the patient did not agree to the operation or conservative therapy was suggested. Patients who did not undergo AVR had larger baseline LV mass and more events but similar baseline CFR compared to cases who underwent AVR.

Cardiovascular events. During a mean follow-up of 82 ± 38 months (median value of follow-up: 104 months), 18 patients suffered cardiovascular death (12 sudden cardiac deaths, 3 heart failures, 1 stroke, 1 anticoagulant-related bleeding and 1 exsiccosis), one patient had non-fatal stroke and two patients underwent reoperation of dysfunctional prosthetic aortic valve.

Coronary flow velocity reserve. CFR in patients with critical, severe and moderate AS was 1.89 ± 0.50, 2.00 ± 0.51 and 2.23 ± 0.45, respectively. Using ROC analysis, CFR ≤2.13 had the highest accuracy (lowest false negative and positive results) in predicting cardiovascular survival (sensitivity 90%, specificity 46%, area under the curve 66%, p =0.02).

Multivariable analysis. By univariable analysis, diabetes mellitus, hypertension, presence of coronary artery disease and lower CFR were significant predictors of cardiovascular morbidity and mortality. Multivariable regression analysis showed that only lower CFR (hazard ratio (HR) 1.67, 95% CI of HR: 1.05 to 4.29, p <0.05) was independent predictor of cardiovascular outcome.

4.5. Prognostic role of CFR in patients with hypertrophic cardiomyopathy

Patient population. We prospectively studied 20 patients with typical features of HCM who were enrolled in 1999. The diagnosis of HCM was made according to guidelines. Seven patients had undergone coronary angiography with a negative result.

CFR measurement. No major complications occurred during vasodilator stress TEE imaging. The success rate of follow-up was 18 out of 20 (90%).

Cardiac events. During a mean follow-up of 90 ± 24 months, four patients suffered cardiovascular death (2 sudden cardiac deaths and 2 strokes). Other seven patients underwent invasive procedures (coronary angiography, implantable cardioverter defibrillator

implantation, percutaneous transluminal septal myocardial ablation) or showed cerebrovascular events.

Coronary flow velocities and reserve. Resting diastolic coronary flow velocities were somewhat higher, while diastolic coronary flow velocities measured at peak stress were similar in HCM patients with events. Using ROC analysis, CFR <2.35 was a significant predictor for cardiovascular survival (sensitivity 91%, specificity 71%, area under the curve 74%, p =0.05).

Multivariable analysis. By univariable analysis, increased left ventricular (LV) end-systolic diameter, increased LV mass index, and lower CFR were significant predictors of cardiovascular outcome. Multivariable regression analysis showed that only CFR (hazard ratio (HR) 4.21, 95% CI of HR: 1.01 to 19.22, p <0.05) was independent predictor of cardiovascular outcome.

5. Discussion

The long-term prognostic significance of CFR for prediction of cardiovascular outcome was demonstrated in the SZEGED study during a 9 to 10-year follow-up in patients with significant CAD not involving LAD, in an extended patient group without significant LAD stenosis, in female patients with chest pain and negative coronary angiograms, in a patient group of aortic stenosis, and hypertrophic cardiomyopathy. To my best knowledge, there are the first studies in which prognostic significance of CFR for the prediction of cardiovascular morbidity and mortality has been demonstrated in these patient groups during a 9-10-year follow-up.

CFR could be calculated by means of invasive techniques (thermodilution, Doppler catheters), measuring blood flow (or blood flow velocity) in baseline conditions and during maximal or submaximal vasodilatation induced pharmacologically. The results of these invasive methods have good correlation with the findings measured by transoesophageal echocardiography. TEE provides high-quality images of the heart, and blood flow in the LAD can be adequately recorded in the majority of cases. The advancement of technology does not stop, in recent studies transthoracic Doppler echocardiography has been confirmed to be a more suitable technique for the assessment of CFR in the daily practice than stress TEE. The

transthoracic method is more patient-friendly and could be combined with wall motion analysis.

CFR represents the capacity of coronary artery to dilate following an increase in myocardial metabolic demands. It is an important functional parameter to understand the pathophysiology of coronary circulation and can be used to examine the integrity of microvasculature in patients with normal epicardial coronary arteries. Isolated coronary microvascular abnormalities are overt due to reduced CFR despite normal epicardial coronary arteries. In the absence of macrovascular disease, reduction of CFR may be associated with the following abnormalities: microvascular resistance, myocardial resistance (left ventricular hypertrophy), hyperviscosity, metabolic factors, smoking exposure, vegetative neuropathy, insuline resistance, aortic stiffness etc. In some pathologic conditions, changes in one or other of these factors may lead to an impairment of CFR capacity. These abnormalities may occur in several diseases (arterial hypertension, diabetes mellitus, syndrome X, aortic stenosis, HCM and idiopathic dilated cardiomyopathy). Coronary microvascular dysfunction may represent a common pathway leading to a disease progression in these disorders, as well.

It is known, that men are several times more likely to die from cardiovascular disease than women, and male gender is considered as one of the most important cardiovascular risk factors. However, the prognostic significance of CFR has never been assessed in a selected female population.

In recent studies, the prognostic impact of CFR by echocardiography has been demonstrated in different patient populations: dilated and hypertrophic cardiomyopathy, diabetes mellitus, and after heart transplantation.

The independent prognostic value of pulsed Doppler-derived CFR during dipyridamol stress echocardiography has been already demonstarted in patients with known or suspected coronary artery disease. CFR provides independent prognostic information also in diabetic and non-diabetic patients with known or suspected CAD. Decreased (<2) CFR was found to be associated with a worse outcome in medically treated patients with single-vessel LAD disease of intermediate severity (50 to 75%). Moreover, in a general patient population with angiographically normal or near-normal coronary arteries (<50% quantitatively assessed stenosis in any major vessel) and preserved at-rest regional and global left ventricular function at baseline and during stress, CFR adds incremental value to the prognostic stratification. Moreover, the relative prognostic value of CFR and simultaneously evaluated

wall motion, aortic distensibility indices or grade of aortic atherosclerosis were demonstrated. Theoretically microvascular disease may be present in LAD in patients with significant epicardial coronary artery diseases not involving LAD (in RC and/or CX disease) and it might represent the triggering event leading to CFR impairment, which is independently associated with a less benign long-term clinical outcome. However, in the present study the independent prognostic value of CFR by Doppler echocardiography has been confirmed in patients with significant CAD not involving LAD.

It is known that angina pectoris, myocardial ischaemia, inadequate left ventricular hypertrophy, smaller coronary artery dimensions and reduced coronary flow reserve occur in most of AS patients. The reduction of coronary flow reserve that is associated with AS can be explained by the concomitant presence of reduced myocardial supply as a result of decreased coronary perfusion pressure, and increased myocardial metabolic demand as a result of increased left ventricular workload. CFR was found to be similarly decreased in AS patients with and without severe left anterior descending coronary artery disease. Moreover, CFR was not found to be suitable for the differentiation or prediction of AS patients with and without significant LAD disease. An improvement in CFR was found 6-12 months after aortic valve replacement (AVR) in prospective follow-up studies. Rajappan *et al.* proposed reduced extravascular compression and increased diastolic pressure time as the main mechanisms for the improvements in myocardial blood flow and CFR after AVR, which are not directly dependent on regression of the left ventricle mass. Recently, in a long-term follow-up study it has been confirmed, that despite a small initial improvement of CFR after AVR, CFR deteriorates further at 1 to 3 years of follow up. This phenomenon could not be explained by extravascular compressive forces; vascular factors or the progression of the atherosclerotic disease could play a role in this CFR impairment.

HCM is a genetic cardiac disease characterized by left ventricular hypertrophy in the absence of another cause of increased cardiac mass. HCM patients commonly have evidence of myocardial ischaemia and perfusion impairment despite angiographically normal epicardial coronary arteries. Kofflard *et al.* found that in HCM patients haemodynamic (LV enddiastolic pressure, LV outflow tract gradient), echocardiographic (indexed LV mass) and histological (% luminal area of the arterioles) changes are responsible for a decrease in CFR. Both vasodilator stress TEE and TTE have been demonstrated capable of assessing CFR in HCM. Memmola *et al.* found an inverse relationship between CFR and the presence of an outflow

gradient. Dimitrow *et al.* demonstrated that dipyridamole-assessed CFR was weakly related to parameters of exercise capacity. Moreover, impaired coronary circulation with impaired CFR and higher resting diastolic velocity were found in apical hypertrophic cardiomyopathy as well. Soliman *et al.* confirmed that microvascular dysfunction in HCM improves after percutaneous transluminal septal myocardial ablation due to relief of extravascular compression forces. Moreover, Olivetti *et al.* suggested in a PET study that severe microvascular dysfunction is a potent long-term predictor of LV adverse remodeling and systolic dysfunction in HCM, which can be identified well before irreversible morphologic and functional changes occur.

Despite a relatively small number of patients investigated by our working group abnormal LAD-CFR was found to be a strong and independent predictor of long term outcome in every studied population.

5. Study limitations.

1. Only a limited number of patients in different subgroups were involved in the study. Further studies are warranted to examine whether prognostic differences of CFR for cardiovascular outcome exist between pre- and postmenopausal female patients with chest pain with normal epicardial coronary arteries in a larger population. Although AS patients were regularly seen by their own cardiologist, only mortality and hospitalisation due to cardiovascular reasons were considered as cardiovascular events. In the present study, it has not been examined if regular cardiological examination has a role in survival in AS patients.

2. 'Old fashioned' stress TEE was used for evaluation of CFR. The authors know that transthoracic Doppler echocardiography is a more suitable, patient-friendly and less invasive technique for assessment of CFR, but only data with the transoesophageal method have 10-year follow-up.

3. Blood flow velocities, but not blood flow itself, were measured by TEE. The measurement of coronary blood flow requires an evaluation of the luminal cross-sectional area. Furthermore, there is an angle between the ultrasound beam and the vessel direction, as a result of which blood flow velocities measured with this approach can be lower than the real values. However, both the numerator and the denominator in the formula for the CFR are measured at the same angle, and the ratio is not appreciably influenced by the angle or the vessel direction.

4. In a stress echocardiography consensus statement it has been concluded that the evaluation of LAD-CFR by echocardiography is feasible but the use of CFR as a "stand alone" diagnostic criterion suffers from several structural limitations.

5. "Low dose" dipyridamole was used for CFR evaluations, which is unable to grant maximal vasodilation. The vasodilators most commonly used are adenosine (in a dose of 140 μg/kg/min) and dipyridamole (in a dose of 0.56 mg/kg or 0.84 mg/kg). In a recent transthoracic echocardiographic study, it has been demonstrated that the vasodilator effects of 0.84 mg/kg of dipyridamole and 140 μg/kg/min of adenosine are comparable and superior to 0.56 mg/kg dipyridamole.

6. Conclusions (new observations)

1. CFR has a long-term prognostic value for the prediction of cardiovascular outcome during a 10-year follow-up in female patients with negative coronary angiograms.

2. Long-term prognostic significance of LAD-CFR for the prediction of mortality can be demonstrated during a 9-year follow-up in patients with significant coronary artery disease not involving LAD.

3. Prognostic value of CFR for the prediction of mortality has been demonstrated during a long-term follow-up in patients without significant LAD stenosis.

4. Long-term prognostic significance of CFR for the prediction of cardiovascular morbidity and mortality can be demonstrated during a 9-year follow-up in patients with AS. CFR was found to be an independent predictor for future cardiovascular events in AS patients.

5. CFR should be considered as an independent predictor for future cardiovascular events in HCM patients.

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