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

(SZEGED Study)

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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.

Abstracts

I. Balázs E, Csanády M, Forster T, Nemes A. A koronaria áramlási rezerv prognosztikus jelentősége aorta stenosisos betegekben – Eredmények a SZEGED-Tanulmányból. Cardiologia Hungarica 2010; 40 (Suppl G): G5

II. Balázs E, Nemes A, Sepp R, Soliman OI, Csanády M, Forster T. A koronária áramlási rezerv hosszú távú prognosztikus értéke hypertrophiás cardiomyopathiában – Szemelvények a 9 éves továbbkövetéses SZEGED Tanulmány eredményeiből. Cardiologia Hungarica 2009; 39 (Suppl A): A14

III. Nemes A, Balazs E, Pinter KS, Egyed A, Csanady M, Forster T. The independent long-term prognostic value of coronary flow velocity reserve in female patients with chest pain and negative coronary angiograms - Results of a 9-year follow-up. Eur J Echocardiography 2010; 11 (Suppl 2): ii166

IV. Nemes A, Balazs E, Pinter S, Csanady M, Forster T. Long-term prognostic value of coronary flow reserve in patients with significant coronary artery disease not involving left anterior descending coronary artery. Eur J Echocardiography 2009; 10 (Suppl 2): ii 159

V. Nemes A, Balazs E, Csanady M, Forster T. Long-term prognostic significance of coronary flow reserve in patients with aortic valve stenosis. Eur J Echocardiography 2009; 10 (Suppl 2): ii 171

VI. Nemes A, Balazs E, Soliman OI, Csanady M, Forster T. Prognostic value of coronary flow reserve in patients with hypertrophic cardiomyopathy - results of a 9-year follow-up. Eur J Echocardiogr 2008; 9 (Suppl 1): S2-92

Abbreviations

AA	aortic atherosclerosis
AS	aortic valve stenosis
AVR	aortic valve replacement
BP	blood pressure
CAD	coronary artery disease
CFR	coronary flow velocity reserve
DBP	diastolic blood pressure
DM	diabetes mellitus
Dmax	diastolic coronary flow velocity measured at maximal vasodilation
Drest	resting diastolic coronary flow velocity
ECG	electrocardiogram
EDD	enddiastolic diameter
EF	ejection fraction
IVS	interventricular septum
HCM	hypertrophic cardiomyopathy
HR	heart rate
LAD	left anterior descending coronary artery
LM	left main coronary artery
LVM	left ventricular mass
LVMI	left ventricular mass index
CX	left circumflex coronary artery
PTCA	percutaneous transluminal coronary angioplasty
PW	posterior wall
RC	right coronary artery
ROC	receiver operating characteristic
SBP	systolic blood pressure
Smax	systolic coronary flow velocity measured at maximal vasodilation
Srest	resting systolic coronary flow velocity
TEE	transoesophageal echocardiography

Contents

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) (1). Nowadays, CFR can be measured in the posterior descending artery and in the distal LAD, too. 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. Flow within the coronary artery is not calculated by echocardiography because cross-sectional visualisation of the vessel does not allow an accurate measurement of the vessel diameter. 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 (2). Microcirculatory abnormalities may occur in several diseases including hypertension, diabetes mellitus (DM), hypercholesterolaemia, aortic valve stenosis (AS), dilated and hypertrophic cardiomyopathy (HCM) etc. (3). Recently, the independent

prognostic significance of CFR has been demonstrated in a number of diseases (4-21), 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. The day before CFR measurements the consumption of caffeine containing drinks was prohibited. Diabetes mellitus was defined in accordance with the American Diabetes Association (1) and World Health Organization criteria (2). Hypertension was defined as either a systolic or a diastolic elevation of blood pressure (>140/90 mmHg) or ongoing antihypertensive therapy. Hypercholesterolaemia was described as a total cholesterol level >5.0 mmol/l or current treatment with lipid-lowering medications. The study complied with the Declaration of Helsinki. The local ethics committee of the University of Szeged approved the study protocol and all patients gave informed consent.

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 (+ 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%) (Table 1).

Table 1 Clinical and echocardiographic data in all patients

	All patients	CFR >2.2	CFR ≤2.2	No events	Events
No. of patients (%)	45	24 (53)	21 (47)	27 (60)	18 (40)
Age (years)	56.5 ± 9.7	57.5 ± 9.1	55.4 ± 10.5	56.4 ± 8.5	56.7 ± 11.6
Diabetes mellitus (%)	8 (18)	4 (17)	4 (19)	5 (19)	3 (17)
Hypertension (%)	29 (64)	15 (63)	15 (71)	18 (67)	11 (61)
Hypercholesterolaemia (%)	8 (18)	2 (8)	6 (29)	4 (15)	4 (22)
Echocardiography					
LV end-diastolic diameter (mm)	48.2 ± 6.3	47.5 ± 4.9	49.0 ± 7.6	48.9 ± 6.5	47.3 ± 6.1
LV end-systolic diameter (mm)	29.8 ± 7.0	29.3 ± 6.1	30.4 ± 8.0	29.7 ± 8.3	29.9 ± 4.8
Interventricular septum (mm)	10.4 ± 1.5	10.6 ± 1.0	10.1 ± 1.8	10.6 ± 1.4	10.0 ± 1.5
LV posterior wall (mm)	9.9 ± 1.5	10.3 ± 1.3	9.6 ± 1.6	10.2 ± 1.4	9.6 ± 1.5
LV end-diastolic volume (ml)	111.3 ± 37.6	105.7 ± 29.9	115.9 ± 43.3	115.9 ± 39.1	104.9 ± 35.9
LV end-systolic volume (ml)	35.2 ± 22.0	28.8 ± 10.5	40.5 ± 27.4	35.4 ± 26.4	34.9 ± 14.8
LV ejection fraction (%)	67.9 ± 10.2	68.7 ± 9.9	67.0 ± 10.8	69.3 ± 11.8	66.1 ± 7.7
D rest (cm/s)	54.9 ± 29.4	40.3 ± 15.8	70.8 ± 32.8†	50.3 ± 25.2	61.5 ± 34.3
D max (cm/s)	116.9 ± 43.7	120.0 ± 44.2	113.6 ± 43.9	121.8 ± 41.9	109.9 ± 46.4
CFR	2.38 ± 0.85	3.01 ± 0.61	1.67 ± 0.39†	2.67 ± 0.81	1.96 ± 0.73*
Patients with CFR ≤ 2.2 (%)	21 (47)	-	-	8 (30)	13 (72)*
AA mean grade	1.02 ± 0.68	0.95 ± 0.67	1.10 ± 0.70	1.04 ± 0.62	1.00 ± 0.77
Patients with events (%)	18 (40)	5 (21)	13 (62)†	-	-

Abbreviations AA: aortic atherosclerosis, CFR: coronary flow reserve, D rest: resting diastolic coronary flow velocity, D max: diastolic coronary flow velocity at max. hyperaemia, LV: left ventricular

* $p < 0.05$ vs. No events, † $p < 0.05$ vs. CFR >2.2

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%] (Figure 1).

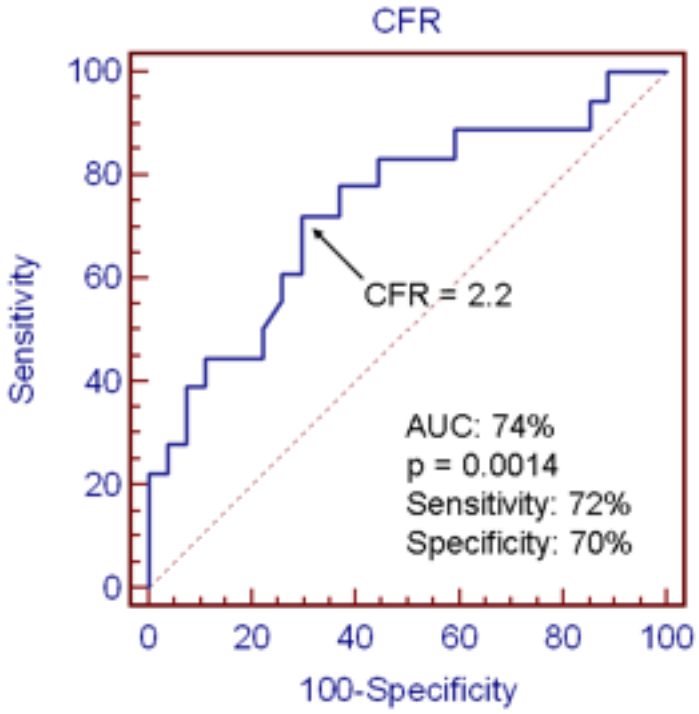

Figure 1. *Receiver operating characteristic (ROC) analysis illustrating the diagnostic accuracy of CFR in predicting cardiovascular outcome in female patients with normal epicardial coronary arteries.*

The Kaplan-Meier cumulative survival curve illustrating the predictive role of CFR is presented in Figure 2.

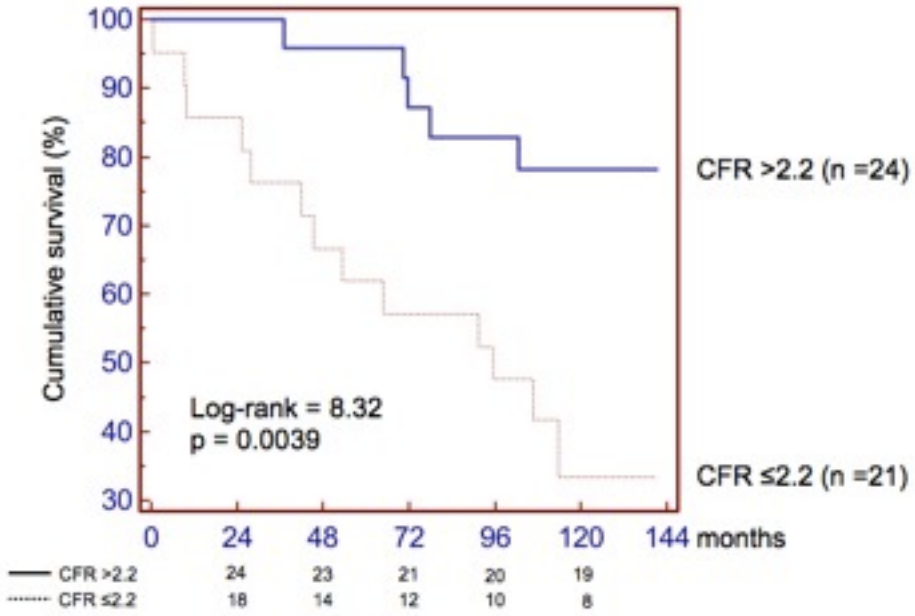

Figure 2. *Kaplan-Meier survival curves illustrating the predictive role of CFR*

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 CAD not involving the LAD

Patient population. total of 49 patients with significant RC and / or 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. Clinical and echocardiographic data of patients with and without events are presented in Table 2. No major complications occurred during vasodilator stress TEE imaging in any of patients.

Table 2 Clinical and echocardiographic data in all patients

	All patients	CFR >2.09	CFR ≤2.09	No events	Events
Clinical data					
No. of patients (%)	43	19 (44)	24 (56)	28 (65)	15 (35)
Males (%)	33 (77)	15 (79)	18 (75)	22 (79)	11 (73)
Age (years)	69 ± 9	68 ± 11	70 ± 8	67 ± 10	71 ± 7
Diabetes mellitus (%)	8 (19)	4 (21)	4 (17)	4 (14)	4 (27)
Hypertension (%)	37 (86)	17 (89)	20 (83)	25 (89)	12 (80)
Hypercholesterolaemia (%)	20 (47)	10 (53)	10 (42)	15 (54)	5 (33)
Echocardiography					
LV end-diastolic diameter (mm)	53.2 ± 5.9	51.8 ± 5.9	54.6 ± 5.8	52.7 ± 7.0	54.2 ± 3.0
LV end-systolic diameter (mm)	34.3 ± 5.3	33.4 ± 5.6	35.1 ± 5.1	33.4 ± 6.2	36.0 ± 2.8
LV end-diastolic volume (ml)	146.8 ± 43.1	132.4 ± 38.4	160.2 ± 44.4	148.1 ± 53.4	144.6 ± 18.8
LV end-systolic volume (ml)	53.4 ± 21.4	48.9 ± 21.9	57.7 ± 20.8	51.4 ± 26.4	56.7 ± 9.0
Interventricular septum (mm)	11.5 ± 2.7	11.0 ± 1.9	11.9 ± 3.2	10.8 ± 2.1	12.7 ± 3.3*
LV posterior wall (mm)	11.1 ± 2.5	10.6 ± 1.8	11.6 ± 3.0	10.5 ± 2.0	12.2 ± 3.0*
LV ejection fraction (%)	63.1 ± 6.3	62.2 ± 6.0	64.0 ± 6.5	64.5 ± 6.7	60.7 ± 4.7
D rest (cm/s)	56.1 ± 21.0	46.0 ± 11.0	64.2 ± 23.7†	50.7 ± 17.9	66.3 ± 23.3*
D max (cm/s)	116.4 ± 40.1	124.1 ± 35.0	110.3 ± 44.8	115.1 ± 40.3	118.8 ± 43.2
CFR	2.15 ± 0.57	2.68 ± 0.35	1.73 ± 0.26†	2.31 ± 0.57	1.85 ± 0.43*
Patients with CFR < 2.09 (%)	24 (56)	-	-	12 (43)	12 (80) *
AA mean grade	1.50 ± 0.67	1.47 ± 0.77	1.52 ± 0.59	1.37 ± 0.69	1.73 ± 0.59
Patients with events (%)	15 (35)	3 (16)	12 (50) †	-	-

Abbreviations AA: aortic atherosclerosis, CFR: coronary flow reserve, Drest: resting diastolic coronary flow velocity, Dmax: maximal hyperaemic diastolic coronary flow velocity, LV: left ventricular

* $p < 0.05$ vs. No events, † $p < 0.05$ vs. CFR >2.09

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) (Figure 3).

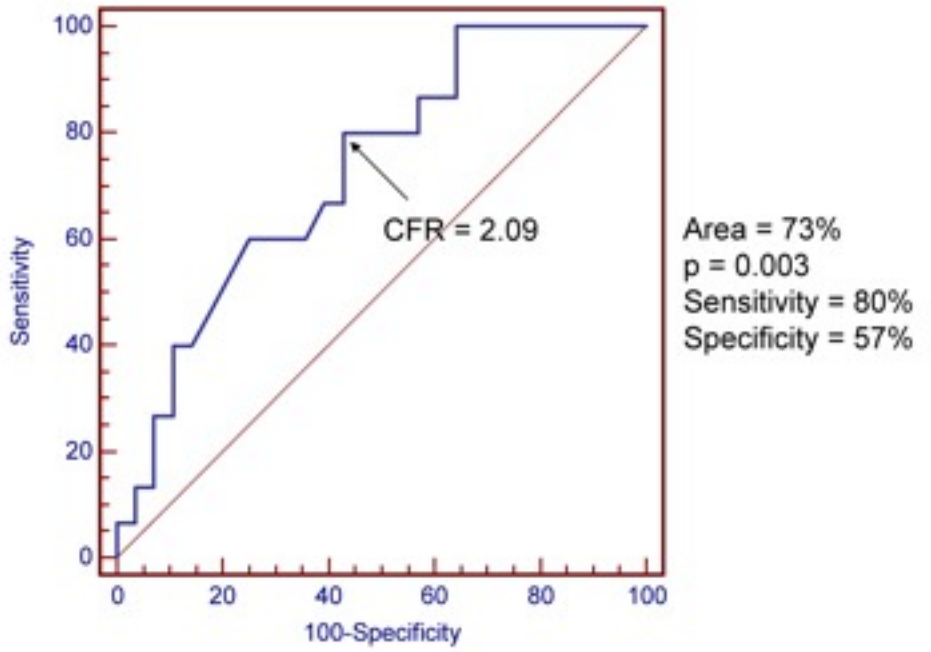

Figure 3. *Receiver operating characteristic (ROC) analysis illustrating the diagnostic accuracy of CFR in predicting cardiovascular morbidity and mortality*

The Kaplan-Meier cumulative survival curve illustrating the predictive role of CFR is presented in Figure 4.

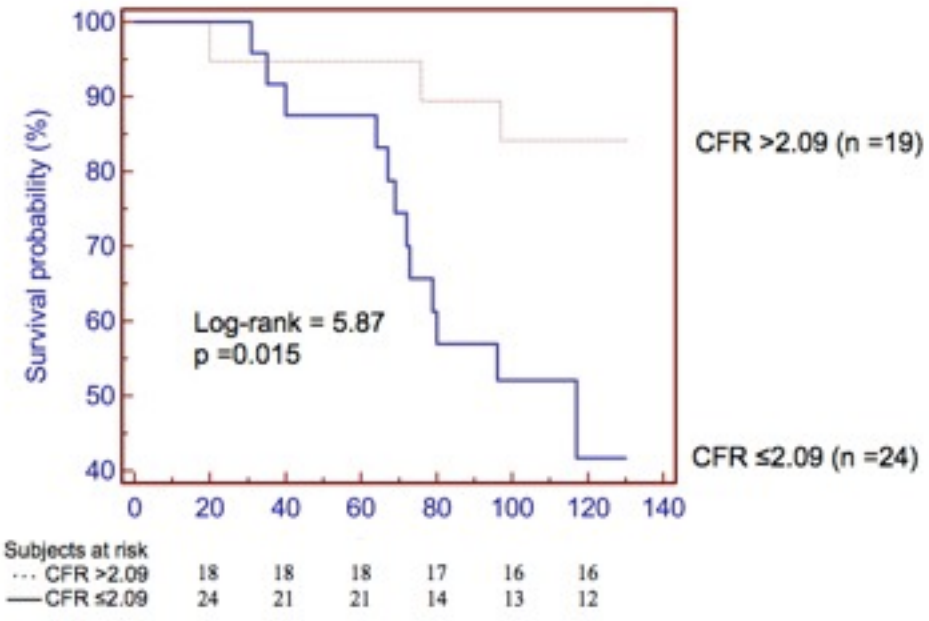

Figure 4. *Kaplan-Meier survival curves illustrating the predictive role of CFR.*

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 (RC) stenosis. Significant left circumflex coronary artery (CX) stenosis were in 9 cases (7%) and combined disease (RC + CX stenosis) in 12 cases (10%). Clinical and echocardiographic data are presented in Table 3.

Table 3 Clinical and echocardiographic data in patients without left anterior descending coronary artery disease

	All patients	CFR >2,13	CFR ≤2,13	No death	Death
Clinical data					
Number of patients (%)	124	67 (54)	57 (46)	97 (78)	27 (22)
Men (%)	69 (56)	36 (54)	34 (60)	48 (49)	21 (78) *
Age (years)	59,6 ± 11,9	57,9 ± 11,8	61,7 ± 11,7	58,7 ± 11,6	57,1 ± 9,0
Diabetes mellitus (%)	26 (21)	15 (22)	11 (19)	18 (19)	8 (30)
Hypertension (%)	86 (69)	46 (69)	40 (70)	66 (68)	20 (74)
Hypercholesterolemia (%)	36 (29)	16 (24)	20 (35)	29 (30)	7 (26)
Echocardiography					
LV end-diastolic diameter (mm)	52,2 ± 7,2	50,7 ± 6,3	53,9 ± 7,9†	51,4 ± 7,5	55,0 ± 5,7*
LV end-systolic diameter (mm)	33,4 ± 8,0	32,2 ± 7,5	34,8 ± 8,5	32,3 ± 8,0	37,3 ± 6,9*
LV end-diastolic volume (ml)	138,2 ± 49,1	127,9 ± 39,4	150,3 ± 56,9†	132,9 ± 51,8	155,8 ± 34,4
LV end-systolic volume (ml)	51,3 ± 35,6	45,4 ± 28,6	58,2 ± 41,8	47,0 ± 36,9	65,8 ± 27,1*
Interventricular septum (mm)	10,9 ± 2,2	10,6 ± 1,8	11,2 ± 2,6	10,6 ± 1,8	11,7 ± 3,0*
LV posterior wall (mm)	10,4 ± 2,0	10,2 ± 1,5	10,7 ± 2,5	10,2 ± 1,7	11,3 ± 2,7*
LV ejection fraction (%)	64,1 ± 10,8	64,6 ± 10,6	63,6 ± 11,1	65,5 ± 10,9	59,1 ± 8,7*
D rest (cm/s)	52,6 ± 24,3	42,9 ± 13,8	63,9 ± 28,7†	52,1 ± 24,2	54,2 ± 25,1
D max (cm/s)	113,9 ± 41,8	122,2 ± 37,1	104,4 ± 45,2†	116,0 ± 40,5	106,4 ± 46,3
CFR	2,32 ± 0,75	2,88 ± 053	1,66 ± 0,30†	2,38 ± 0,47	2,09 ± 0,65‡
Patients with CFR ≤ 2,13 (%)	57 (46)	-	-	39 (40)	18 (67) *
Mean AA stadium	1,20 ± 0,72	1,02 ± 0,76	1,40 ± 0,63†	1,12 ± 0,71	1,46 ± 0,71*
Death (%)	27 (22)	9 (13)	18 (32) †	-	-

Abbreviations AA: aortic atherosclerosis, CFR: coronary flow reserve, Drest: resting diastolic coronary flow velocity, Dmax: maximal hyperaemic diastolic coronary flow velocity, LV: left ventricular

† p <0.05 vs. CFR >2,13, * p <0,05 vs. No death, ‡ p =0,066 vs. No death

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) (Figure 5).

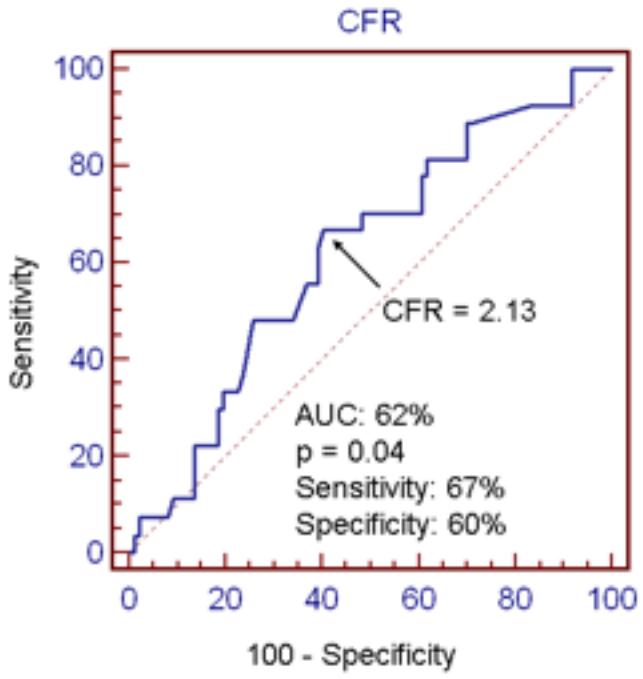

Figure 5. *Receiver operating characteristic (ROC) analysis illustrating the diagnostic accuracy of CFR in predicting cardiovascular morbidity and mortality*

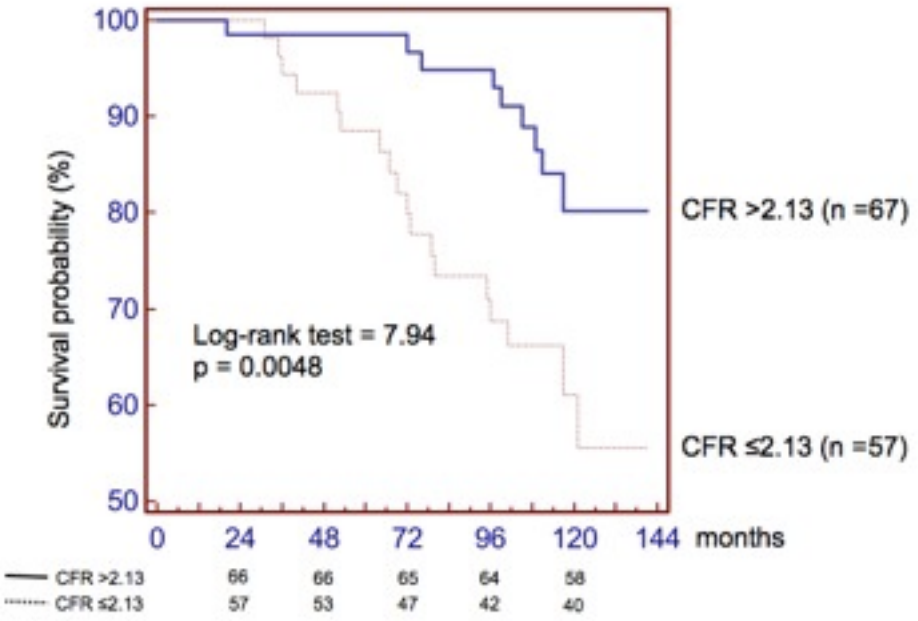

Figure 6. *Kaplan-Meier survival curves illustrating the predictive role of CFR.*

Multivariable analysis. By univariable analysis, grade of AA, 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 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 (AVRs) 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%). Clinical and echocardiographic data of patients with and without events are presented in Table 4. 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.

Table 4 Clinical and echocardiographic data in patients with aortic valve stenosis

	All patients	CFR >2.13	CFR ≤2.13	No events	Events	AVR	No AVR
No. of patients (%)	49	16 (33)	33 (67)	28 (57)	21 (43)	36 (73)	13 (27)
Males (%)	26 (53)	7 (44)	19 (58)	12 (43)	14 (67)	17 (47)	9 (69)
Age (years)	63 ± 9	61 ± 10	63 ± 9	61± 10	65 ± 9	62 ± 10	66 ± 7
Diabetes mellitus (%)	9 (18)	1 (6)	8 (24)	1 (4)	8 (38)*	6 (17)	3 (23)
Hypertension (%)	29 (59)	5 (31)	24 (73)†	13 (46)	16 (76)	19 (53)	10 (77)
Hypercholesterolaemia (%)	12 (24)	3 (19)	9 (27)	8 (29)	4 (19)	8 (22)	4 (31)
Echocardiography							
LV end-diastolic diameter (mm)	53.3 ± 6.7	49.8 ± 5.6	55.1 ± 6.5†	52.1 ± 6.6	55.0 ± 6.6	52.4 ± 6.4	55.8 ± 6.8
LV end-systolic diameter (mm)	34.6 ± 7.0	30.3 ± 5.2	36.8 ± 6.8†	33.7 ± 7.5	35.8 ± 6.4	33.4 ± 6.6	38.0 ± 7.2#
Interventricular septum (mm)	12.7± 3.3	12.6 ± 3.5	12.8 ± 3.2	12.5 ± 3.4	13.0 ± 3.2	12.6 ± 2.9	13.0 ± 4.2
LV posterior wall (mm)	12.1 ± 2.7	11.7 ± 2.1	12.3 ± 2.9	11.8 ± 2.4	12.5 ± 3.1	11.9 ± 2.0	12.8 ± 4.0
LV mass (g)	330 ± 138	289 ± 101	360 ± 136	312 ± 114	368 ± 143	307 ± 116	392 ± 176#
LV ejection fraction (%)	62.4 ± 9.9	67.7 ± 7.3	60.1 ± 10.0†	63.0±10.3	61.7 ± 9.4	63.8 ± 9.4	58.5 ±10.4
D rest (cm/s)	62.6 ± 24.0	48.6 ± 12.8	69.4 ± 25.4†	59.8±24.3	66.4 ±23.7	59.6 ±24.1	70.8 ±22.8
D max (cm/s)	114.9 ± 42.0	122.6 ± 35.6	111.2 ± 44.8	119.8 ± 42.3	108.4 ± 43.0	112.3 ± 41.8	122.0 ± 45.2
CFR	1.95 ± 0.49	2.53 ± 0.30	1.67 ± 0.28†	2.07 ± 0.52	1.79 ± 0.42 *	1.95 ± 0.54	1.96 ± 0.36
Patients with CFR < 2.13 (%)	33 (67)	-	-	15 (54)	18 (86)*	22 (61)	11 (85)
AA mean grade	1.35 ± 0.72	1.13 ± 0.81	1.45 ± 0.67	1.18 ± 0.77	1.57 ± 0.60	1.25 ± 0.77	1.62 ± 0.51
Patients with events (%)	21 (43)	3 (19)	18 (55)†	-	-	12 (33)	9 (69) #
AVR (%)	36 (73)	14 (88)	22 (67)	24 (86)	12 (57) *	-	-
Coronary artery disease (%)	14 (29)	2 (13)	12 (36)†	5 (18)	9 (43)	10 (28)	4 (31)

Abbreviations AA: aortic atherosclerosis, AVR: aortic valve replacement has been performed, CAD: coronary artery disease, CFR: coronary flow velocity reserve, LV: left ventricular

* p <0.05 vs. No events, † p <0.05 vs. CFR >2.13, # p <0.05 vs. AVR

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) (Figure 7).

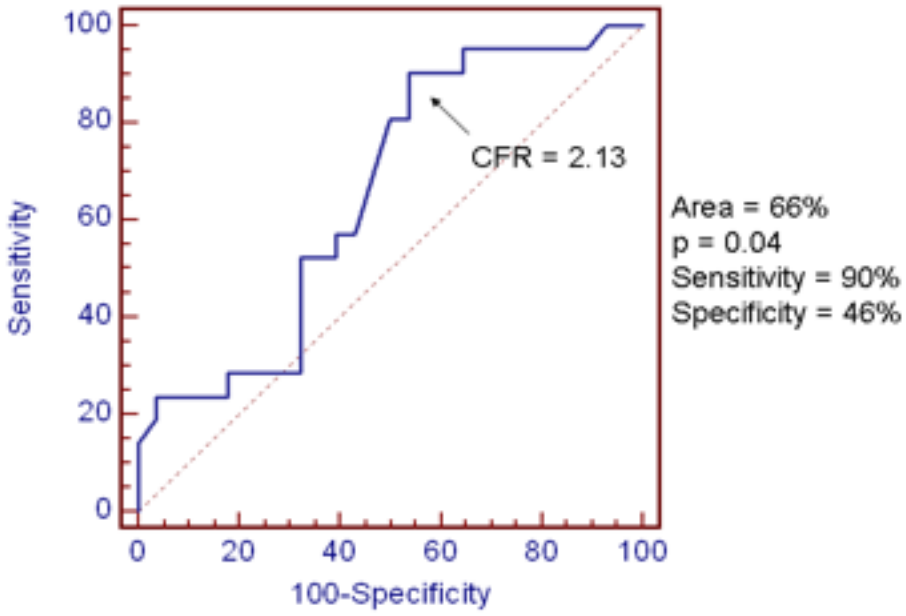

Figure 7. *Receiver operating characteristic (ROC) analysis illustrating the diagnostic accuracy of CFR in predicting cardiovascular morbidity and mortality in patients with significant aortic valve stenosis.*

The Kaplan-Meier cumulative survival curve illustrating the predictive role of CFR is presented in Figure 8.

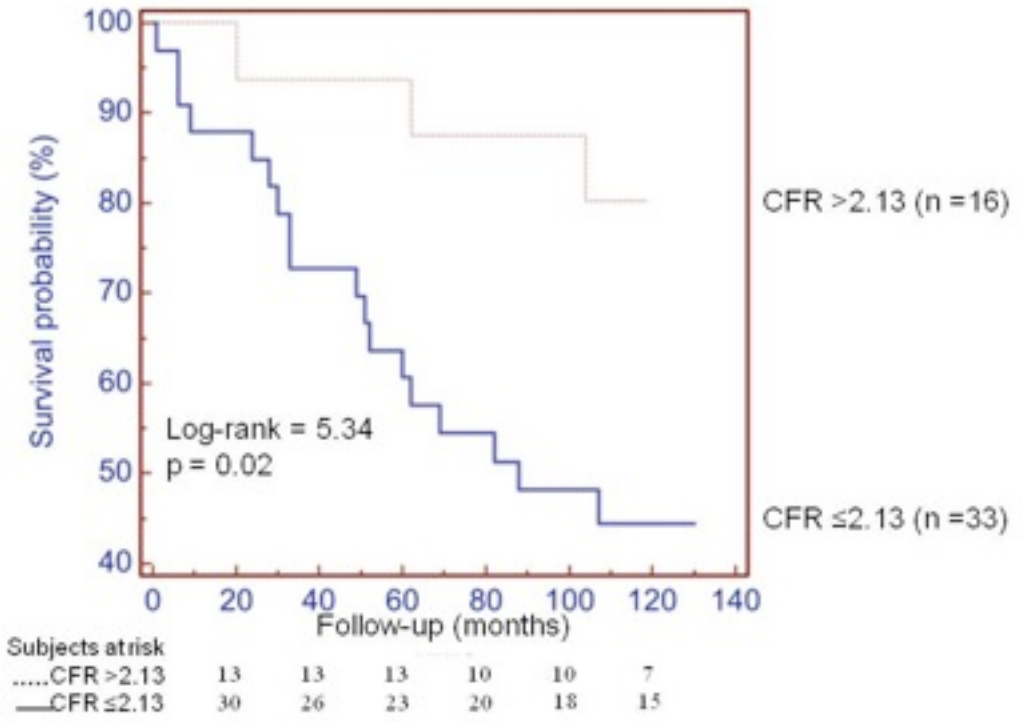

Figure 8. *Kaplan-Meier survival curves illustrating the predictive role of CFR.*

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%). Clinical and echocardiographic data of patients with and without events are presented in Table 5.

Table 5

Clinical and echocardiographic data in patients with hypertrophic cardiomyopathy

	All patients	No events	Events
No. of patients (%)	18	7 (39)	11 (61)
Male gender (%)	12 (67)	4 (57)	8 (72)
Age (years)	48 ± 10	50 ± 12	47 ± 8
Diabetes mellitus (%)	1 (6)	0 (0)	1 (9)
Hypertension (%)	12 (67)	4 (57)	8 (73)
Hypercholesterolemia (%)	13 (72)	6 (86)	7 (100)
Beta-blockers (%)	17 (94)	7 (100)	10 (91)
Calcium channel blockers (%)	4 (22)	2 (29)	2 (18)
Echocardiography			
LV end-diastolic diameter (mm)	48 ± 11	50 ± 17	48 ± 9
LV end-systolic diameter (mm)	30 ± 12	34 ± 20	27 ± 5
LV end-diastolic volume (ml)	131 ± 91	135 ± 133	129 ± 79
LV end-systolic volume (ml)	46 ± 58	75 ± 110	36 ± 25
Inter-ventricular septum (mm)	21 ± 5	22 ± 7	22 ± 3
LV posterior wall thickness (mm)	12 ± 3	12 ± 4	11 ± 2
LV mass index (g/m^2)	236 ± 57	217 ± 134	238 ± 39
LV ejection fraction (%)	65 ± 19	62 ± 22	66 ± 19
CFR	2.32 ± 0.93	2.88 ± 1.25	1.96 ± 0.42*
resting diastolic coronary flow velocity (cm/s)	60 ± 27	47 ± 17	68 ± 29
diastolic coronary flow velocity at peak stress (cm/s)	126 ± 41	123 ± 39	128 ± 44
Patients with CFR ≤ 2.35 (%)	11 (61)	2 (29)	9 (82)*
Follow-up			
Hospitalizations (%)	11 (61)	-	11 (100)
Death (%)	4 (22)	-	4 (36)

Abbreviations: CFR: coronary flow reserve, LV: left ventricular;

* $p < 0.05$ vs. No events

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 (Table 5). 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) (Figure 9).

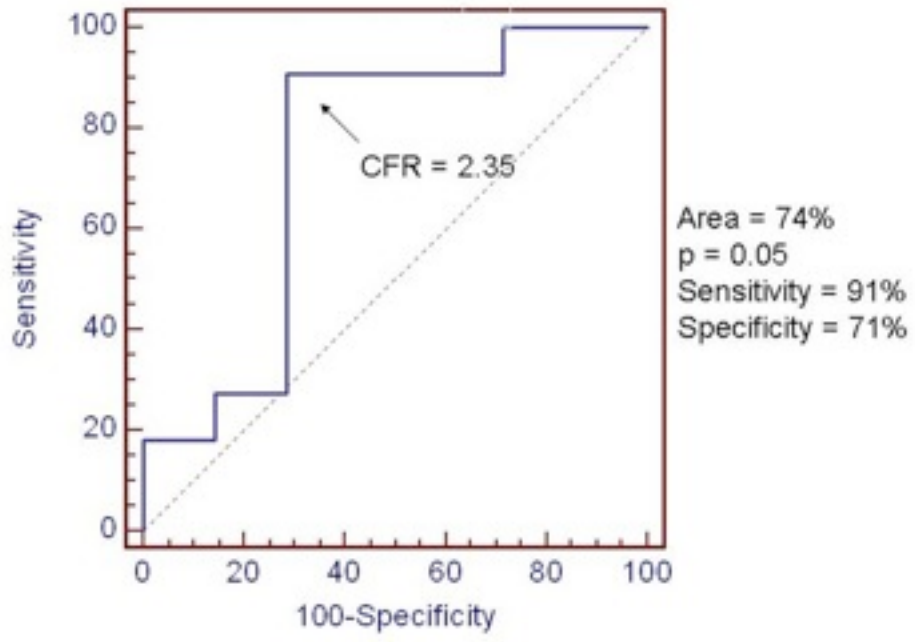

Figure 9. *Receiver operating characteristic analysis illustrating the diagnostic accuracy of CFR in predicting cardiovascular morbidity and mortality.*

The Kaplan-Meier cumulative survival curve illustrating the predictive role of CFR is presented in Figure 10.

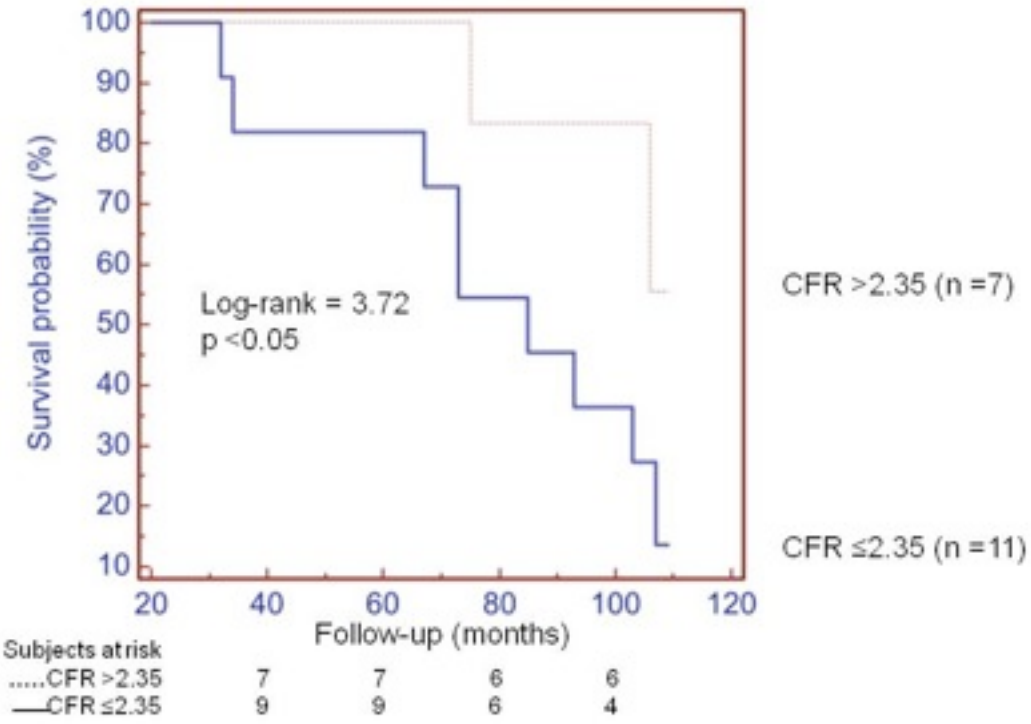

Figure 10. *Kaplan-Meier survival curves illustrating the predictive role of CFR.*

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 (3). 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. (4-8). 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) (5,6,9). 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 (40,41) and hypertrophic cardiomyopathy (42,43), diabetes mellitus (44,45), and after heart transplantation (46).

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 (35-39, 49). CFR provides independent prognostic information also in diabetic and non-diabetic patients with known or suspected CAD (45). 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%) (36). 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 (48). Moreover, the relative prognostic value of CFR and simultaneously evaluated wall motion (38,39), aortic distensibility indices (49) or grade of aortic atherosclerosis (50) were demonstrated**.** Theoretically microvascular disease may 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 (5,10-16). 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 (16). CFR was found to be similarly decreased in

AS patients with and without severe left anterior descending coronary artery (LAD) disease (17). Moreover, CFR was not found to be suitable for the differentiation or prediction of AS patients with and without significant LAD disease (17). An improvement in CFR was found 6-12 months after aortic valve replacement (AVR) in prospective follow-up studies (18,19). 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 (20). 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 (21). 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 (22-24). HCM patients commonly have evidence of myocardial ischaemia and perfusion impairment despite angiographically normal epicardial coronary arteries (25). 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 (26). Both vasodilator stress TEE (27) and TTE (28) 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 (29). Dimitrow *et al.* demonstrated that dipyridamole-assessed CFR was weakly related to parameters of exercise capacity (30). Moreover, impaired coronary circulation with impaired CFR and higher resting diastolic velocity were found in apical hypertrophic cardiomyopathy as well (31,32). Soliman *et al.* confirmed that microvascular dysfunction in HCM improves after percutaneous transluminal septal myocardial ablation due to relief of extravascular compression forces (33). 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 (34).

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.

5.1. 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 (51).

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 (52).

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.

7. References

1. American Diabetes Association. All about diabetes. <www.diabetes.org/about-diabetes.jsp> (Version current at July 2, 2010)
2. World Health Organization. Diabetes programme: What is diabetes? <who.int/diabetes/BOOKLET_HTML/en/index4.html> > (Version current at July 2, 2010)
3. Iliceto S, Marangelli V, Memmola C, Rizzon P. Transesophageal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation. Circulation 1991; 83:61-69.
4. Rigo F. Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. Cardiovasc Ultrasound.2005; 3:8.
5. Nemes A, Forster T, Varga A, Vass A, Borthaiser A, Pálinkás A, Csanády M. How can coronary flow reserve be altered by severe aortic stenosis? Echocardiography 2002; 19:655-659.
6. Nemes A, Neu K, Forster T, Gruber N, Csanády M. Relationship between hypercholesterolemia, lipid-lowering therapy and coronary flow velocity reserve evaluated by stress transesophageal echocardiography in patients with a negative coronary angiogram. Echocardiography 2004; 21:37-41.
7. Nemes A, Lengyel C, Forster T, Várkonyi TT, Takács R, Nagy I, Kempler P, Lonovics J, Csanády M. Coronary flow reserve, insulin resistance and blood pressure response to standing in patients with normoglycaemia: is there a relationship? Diabet Med 2005; 22:1614-1618.
8. Nemes A, Forster T, Csanády M. Reduction of coronary flow reserve in patients with increased aortic stiffness. Can J Physiol Pharmacol 2007; 85:818-822.
9. Dimitrow PP, Galderisi M, Rigo F. The non-invasive documentation of coronary microcirculation impairment: role of transthoracic echocardiography. Cardiovasc Ultrasound. 2005;3:18.
10. Fallen EL, Elliott WC, Gorlin R. Mechanisms of angina in aortic stenosis. Circulation 1967; 36: 480-488.

11. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. A mechanism for angina pectoris with aortic stenosis in patients and normal coronary arteries. N Eng J Med 1982; 307: 1362-1366.
12. Kawamoto R, Imamura T, Kawabata K, Date H, Ishikawa T, Maeno M, Nagoshi T, Fujiura Y, Matsuyama A, Matsuo T, Koiwaya Y, Eto T. Microvascular angina in a patient with angina pectoris. Jpn Circ J 2001; 65: 839-841.
13. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, Camici PG. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. Circulation 2002; 105: 470-476.
14. Kume T, Akasaka T, Kawamoto T, Watanabe N, Yoshitani H, Akiyama M, Koyama Y, Neishi Y, Wada N, Yoshida K. Mechanism of impaired coronary flow reserve in patients with aortic stenosis: transthoracic Doppler echocardiographic study. J Cardiol 2004; 43: 173-178.
15. Carpeggiani C, Neglia D, Paradossi U, Pratali L, Glauber M, L'Abbate A. Coronary flow reserve in severe aortic valve stenosis: a positron emission tomography study. J Cardiovasc Med (Hagerstown) 2008; 9: 893-898.
16. Garcia D, Camici PG, Durand LG, Rajappan K, Gaillard E, Rimoldi OE, Pibarot P. Impairment of coronary flow reserve in aortic stenosis. J Appl Physiol 2009; 106: 113-121.
17. Nemes A, Forster T, Thury A, Kovács Z, Boda K, Csanády M. The comparative value of the aortic atherosclerosis and the coronary flow velocity reserve evaluated by stress transesophageal echocardiography in the prediction of patients with aortic stenosis with coronary artery disease. Int J Cardiovasc Imaging 2003; 19: 371-376.
18. Hildick-Smith DJ, Shapiro LM. Coronary flow reserve improves after aortic valve replacement for aortic stenosis: an adenosine transthoracic echocardiography study. J Am Coll Cardiol 2000; 36: 1889–1896.
19. Nemes A, Forster T, Kovacs Z, Thury A, Ungi I, Csanady M. The effect of aortic valve replacement on coronary flow reserve in patients with a normal coronary angiogram. Herz 2002b; 27: 780–784.
20. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. Circulation 2003; 107: 3170–3175.

21. Nemes A, Forster T, Kovacs Z, Csanady M. Is the coronary flow reserve improvement after aortic valve replacement for aortic stenosis transient? – Results of a 3-year follow-up. Heart Vessels 2006; 21: 157-161.
22. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED. Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003; 2:1687-713.
23. Fujii N, Tsuchihashi K, Sasao H, Fujii N, Tsuchihashi K, Sasao H, Eguchi M, Miurakami H, Hase M, Higashiura K, Yuda S, Hashimoto A, Miura T, Ura N, Shimamoto K. Insulin resistance functionally limits endothelium-dependent coronary vasodilation in nondiabetic patients. Heart Vessels 2008; 23:9-15
24. Suzuki K, Tsurumi Y, Fuda Y, Ishii Y, Takagi A, Hagiwara N, Kasanuki H. Postprocedural resistance of the target lesion is a strong predictor of subsequent revascularization: assessment by a novel lesion-specific physiological parameter, the epicardial resistance index. Heart Vessels 2007; 22:139-145.
25. Soliman OI, Knaapen P, Geleijnse ML, Dijkmans PA, Anwar AM, Nemes A, Michels M, Vletter WB, Lammertsma AA, ten Cate FJ. Assessment of intravascular and extravascular mechanisms of myocardial perfusion abnormalities in obstructive hypertrophic cardiomyopathy by myocardial contrast echocardiography. Heart 2007; 93;1204-1212.
26. Kofflard MJ, Michels M, Krams R, Kliffen M, Geleijnse ML, ten Cate FJ, Serruys PW. Coronary flow reservein hypertrophic cardiomyopathy: relation with microvascular dysfunction and pathophysiological characteristics. Neth Heart J 2007; 15:209-215.
27. Nemes A, Forster T, Pálinkás A, Hőgye M, Csanády M. Coronary flow reserve measured by stress transesophageal echocardiography in hypertrophic cardiomyopathy patients with subvalvular gradient. Kardiol Pol 2002; 57 (8): 96-100

28. Kim HK, Kim YJ, Sohn DW, Park YB, Choi YS. Transthoracic echocardiographic evaluation of coronary flow reserve in patients with hypertrophic cardiomyopathy. Int J Cardiol 2004; 94:167-171.
29. Memmola C, Iliceto S, Napoli VF, Cavallari D, Santoro G, Rizzon P. Coronary flow dynamics and reserve assessed by transesophageal echocardiography in obstructive hypertrophic cardiomyopathy. Am J Cardiol 1994; 74:1147-1151.
30. Dimitrow PP, Krzanowski M, Bodzoń W, Szczeklik A, Dubiel JS. Coronary flow reserve and exercise capacity in hypertrophic cardiomyopathy. Heart Vessels 1996; 11:160-164.
31. Yoshida K, Hozumi T, Takemoto Y, Sugioka K, Watanabe H, Muro T, Yoshiyama M, Takeuchi K, Yoshikawa J. Impaired coronary circulation in patients with apical hypertrophic cardiomyopathy: noninvasive analysis by transthoracic Doppler echocardiography. Echocardiography 2005; 22:723-729.
32. Youn HJ, Lee JM, Park CS, Ihm SH, Cho EJ, Jung HO, Jeon HK, Oh YS, Chung WS, Kim JH, Choi KB, Hong SJ. The impaired flow reserve capacity of penetrating intramyocardial coronary arteries in apical hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2005; 18:128-132.
33. Soliman OI, Geleijnse ML, Michels M, Dijkmans PA, Nemes A, van Dalen BM, Vletter WB, Serruys PW, ten Cate FJ. Effect of Successful Alcohol Septal Ablation on Microvascular Function in Patients with Obstructive Hypertrophic Cardiomyopathy. Am J Cardiol 2008; 101:1321-1327.
34. Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriatti G, Girolami F, Torricelli F, Camici PG. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006; 47:1043-1048.
35. Nemes A, Forster T, Ungi I, Nagy V, Vass A, Palinkas A, Varga A, Csanady M. The coronary flow velocity reserve measured by stress transoesophageal echocardiography evaluates the success of coronary interventions--results of a 5-year follow-up. Scand Cardiovasc J 2005;39:286-92.
36. Rigo F, Sicari R, Gherardi S, Djordjevic-Dikic A, Cortigiani L, Picano E. Prognostic value of coronary flow reserve in medically treated patients with left anterior

descending coronary disease with stenosis 51% to 75% in diameter. Am J Cardiol 2007;100:1527-31.

37. Meimoun P, Benali T, Elmkies F, Sayah S, Luycx-Bore A, Doutrelan L, Hamdane Z, Boulanger J, Tribouilloy C. Prognostic value of transthoracic coronary flow reserve in medically treated patients with proximal left anterior descending artery stenosis of intermediate severity. Eur J Echocardiogr 2009;10:127-32.
38. Rigo F, Cortigiani L, Pasanisi E, Richieri M, Cutaia V, Celestre M, Raviele A, Picano E. The additional prognostic value of coronary flow reserve on left anterior descending artery in patients with negative stress echo by wall motion criteria. A Transthoracic Vasodilator Stress Echocardiography Study. Am Heart J 2006;151:124-30.
39. Rigo F, Sicari R, Gherardi S,. Djordjevic-Dikic A, Cortigiani L, Picano E. The additive prognostic value of wall motion abnormalities and coronary flow reserve during dipyridamole stress echo. Eur Heart J 2008;29:79-88.
40. Rigo F, Gherardi S, Galderisi M, Pratali L, Cortigiani L, Sicari R, Picano E. The prognostic impact of coronary flow-reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy. Eur Heart J 2006;27:1319-23.
41. Rigo F, Gherardi S, Galderisi M, Sicari R, Picano E. The independent prognostic value of contractile and coronary flow reserve determined by dipyridamole stress echocardiography in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2007;99:1154-8.
42. Cortigiani L, Rigo F, Gherardi S, Galderisi M, Sicari R, Picano E. Prognostic implications of coronary flow reserve on left anterior descending coronary artery in hypertrophic cardiomyopathy. Am J Cardiol 2008;102:1718-23.
43. Nemes A, Balazs E, Sepp R, Csanady M, Forster T. Long-term prognostic value of coronary flow reserve in patients with hypertrophic cardiomyopathy – 9-year follow-up results from SZEGED study. Heart Vessels 2009; 24(5):352-6.
44. Nemes A, Forster T, Geleijnse ML, Kutyifa V, Neu K, Soliman OI, Ten Cate FJ, Csanády M. The additional prognostic power of diabetes mellitus on coronary flow reserve in patients with suspecte coronary artery disease. Diabetes Res Clin Pract 2007;78:126-31.

45. Cortigiani L, Rigo F, Gherardi S, Sicari R, Galderisi M, Bovenzi F, Picano E. Additional Prognostic Value of Coronary Flow Reserve in Diabetic and Nondiabetic Patients With Negative Dipyridamole Stress Echocardiography by Wall Motion Criteria. J Am Coll Cardiol 2007;50:1354-61
46. Tona F, Caforio AL, Montisci R, Gambino A, Angelini A, Ruscazio M, Toscano G, Feltrin G, Ramondo A, Gerosa G, Iliceto S. Coronary flow velocity pattern and coronary flow reserve by contrast-enhanced transthoracic echocardiography predict long-term outcome in heart transplantation. Circulation 2006;114:I49-55.
47. Sicari R, Rigo F, Gherardi S, Galderisi M, Cortigiani L, Picano E. The prognostic value of Doppler echocardiographic-derived coronary flow reserve is not affected by concomitant antiischemic therapy at the time of testing. Am Heart J 2008; 156:573–579.
48. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. Am J Cardiol 2009; 103:626–631.
49. Nemes A, Forster T, Geleijnse ML, Soliman OI, Ten Cate FJ, Csanády M. Prognostic value of coronary flow reserve and aortic distensibility indices in patients with suspected coronary artery disease. Heart Vessels 2008;23:167-73.
50. Nemes A, Forster T, Geleijnse ML, Soliman OI, Cate FJ, Csanady M. Prognostic role of aortic atherosclerosis and coronary flow reserve in patients with suspected coronary artery disease. Int J Cardiol 2008;131:45-50.
51. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL; European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2008;9:415-37.
52. Lim HE, Shim WJ, Rhee H, Kim SM, Hwang GS, Kim YH, Seo HS, Oh DJ, Ro YM . Assessment of coronary flow reserve with transthoracic Doppler echocardiography: comparison among adenosine, standard-dose dipyridamole, and high-dose dipyridamole. J Am Soc Echocardiogr 2000; 13:264–270

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Photocopies of essential publications