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Factors affecting coronary flow velocity reserve and its relations to aortic atherosclerosis

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Relevant publications

Full papers

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IX. 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 2003 (in press)

X. Nemes A, Forster T, Gruber N, Csanády M: Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography. Int J Cardiol 2003 (in press)

XI. Nemes A, Thury A, Forster T, Boda K, Ungi I, Csanády M: Grade of aortic atherosclerosis: a valuable adjunct to coronary flow velocity reserve in the evaluation of coronary artery disease. (submitted)

XII. Nemes A, Forster T, Csanády M, Gruber N: Coronary flow velocity reserve and the indices of aortic distensibility in patients with different grades of aortic atherosclerosis. (submitted)

XIII. Nemes A, Forster T, Csanády M: Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. (submitted)

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Abbreviations

AA	aortic atherosclerosis
ACE	angiotensin converting enzym
ANOVA	analysis of variance
AOS	aortic valve stenosis
ASA	acetyl-salicylic acid
AVR	aortic valve replacement
BSA	body surface area
BP	blood pressure
CAD	coronary artery disease
CFR	coronary flow velocity reserve
DBP	diastolic blood pressure
DD	diastolic diameter
Dmax	diastolic coronary flow velocity measured at maximal vasodilation
Drest	resting diastolic coronary flow velocity
DS	systolic diameter
ECG	electrocardiogram
EDD	enddiastolic diameter
EF	ejection fraction
E(p)	elastic modulus
E(s)	Young's circumferential static elastic modulus
FH	familial hypercholesterolaemia
IVS	interventricular septum
h	diastolic intimomedial thickness
HC	hypercholesterolaemia
HCM	hypertrophic cardiomyopathy
HR	heart rate
LAD	left anterior descending coronary artery
LDL	low density lipoprotein
LLT	lipid-lowering therapy
LM	left main coronary artery
LVM	left ventricular mass
LVMI	left ventricular mass index
MVD	multivessel disease
MRI	magnetic resonance imaging
NC	normocholesterolaemia
NYHA	New York Heart Association
CX	left circumflex coronary artery
PET	positron emission tomography
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

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1. Introduction

In the past decade, an increased understanding can be witnessed about the pathophysiology of coronary artery disease (CAD). The dynamic nature of the disease is defined by the atherosclerotic plaque, endothelial function and an interaction of cellular elements with the vessel wall.

Nowadays, the evaluation of coronary anatomy and function is performed mainly, if not exclusively, during cardiac catheterization using several invasive techniques. Ultrasound exploration of the coronary arteries was first suggested over 15 years ago and has been the object of increasing interest in recent years. Early two-dimensional equipment could not ensure optimal definition of a structure as small as a coronary artery. Transoesophageal echocardiography (TEE) is a relatively new ultrasound imaging modality that makes it possible to obtain high-quality images of the heart and great vessels (1).

The severity of coronary stenosis is usually assessed by coronary angiography. The simple anatomic evaluation of coronary arteries has often a limited value because coronary flow velocity reserve (CFR), the real indicator of the functional importance of the stenosis, only modestly correlates with its anatomic severity.

Numerous methods have been used to assess coronary flow and flow reserve, including nuclear techniques (2), coronary sinus catheterization (3), cineangiography dye washout curves (4), intracoronary Doppler catheters and wires (5), and positron emission tomography (6,7). Each technique has its own considerations of logistics, risk, methodology, and validation and are invasive or require extensive and costly laboratory equipment. In the last few years, several authors have demonstrated the possibility of monitoring the coronary flow velocity response to vasoactive agents in the proximal left anterior descending coronary artery (LAD) by means of transoesophageal Doppler echocardiography (8).

Transoesophageal echocardiography is a widely used semi-invasive method to evaluate the heart structures from a "new window". Heart structures can be visualized as left atrial appendage, regurgitations etc. from another aspects. It has been also used for imaging the coronary arteries and its proximal branches. TEE is an emerging method which even capable of measuring the coronary blood flow velocity in the proximal LAD by Doppler method. The coronary flow velocity reserve of the left anterior descending coronary artery may be determined using TEE Doppler velocimetry at rest and during dipyridamole-induced hyperaemia, as initially described by Iliceto et al. (1). The procedure involves the use of pharmacologic agents such as dipyridamole or adenosine as coronary vasodilators.

Transoesophageal echocardiographic monitoring of flow velocity in the LAD with dipyridamole stress has been validated as an accurate means of estimating LAD flow reserve. The efficacy of systemic infusion of dipyridamole to determine coronary flow velocity reserve and to predict the functional severity of coronary stenoses by TEE Doppler has been recently demonstrated (2). TEE Doppler echocardiography is feasible, relatively inexpensive, safe, and thanks to its limited invasiveness, allows serial assessment of CFR in the same patient and in subjects in whom an invasive procedure is not justified. Measurement of CFR, once used only for research, have gained wide acceptance as an additional diagnostic approach in the decision-making process of diagnostic cardiac catheterisation and coronary interventions.

In 80-85% of patients, angina pectoris and coronary insufficiency are caused by haemodinamically relevant, severe stenosis of one or more coronary arteries. In about 15-20% of patients, however, the coronary angiogram shows no abnormalities, although the patient has significant complaints, abnormal changes in the rest on the course of the attack and exercise electrocardiogram (ECG), and a positive response to nitroglycerin. In patients with angina pectoris and a normal coronary angiogram a disturbance of the coronary microcirculation can be resulted by vascular, extravascular, rheologic and metabolic factors. Previous studies have revealed that the CFR depends not only on the micro- and macrovascular resistance, but also on myocardial resistance (as left ventricular hypertrophy), on endothelial or metabolic factors (hypercholesterolaemia etc), on hyperviscosity etc.

Determinants of CFR are multiple, and the confounding effect of various factors were assessed. The aim of this thesis was to determine the effects of several factors on coronary flow velocities and velocity reserve in patients who underwent coronary angiography. Further aim was to examine the correlations between CFR and aortic atherosclerosis as well as distensibility.

2. Methods

Patient population: From the beginning of the work in december 1997, more than 700 transoesophageal coronary flow velocity reserve examination of 554 patients were performed. The study population for each study will be discussed later in the individual chapters.

Transthoracic echocardiography: Transthoracic echocardiography studies were performed with ATL Ultramark 9 HDI or Toshiba Powervision 8000 echocardiography machine. The left ventricular internal dimensions were measured by 2-dimensionally directed M-mode echocardiography. The left ventricular mass (LVM) was calculated according to the Penn convention (9). Body surface area (BSA) was calculated from height and body mass measurements according to the formula of Du Bois and Du Bois (10). The LVM index (LVMI) was calculated as LVM/BSA. Left ventricular hypertrophy was defined according to the criteria of Devereux (11). The ejection fraction was calculated by using the method of Teichholz et al. (12). The left ventricle-aorta pressure gradient was measured by means of continuous-wave Doppler echocardiography.

Transoesophageal echocardiography: A complete TEE examination was carried out with an ATL® Ultramark 9 HDI echocardiograph using a 5.5 MHz biplane transducer or with a Toshiba Powervision 8000 echocardiograph using a multiplane transducer in all patients.

- During the TEE examination, the grade of aortic atherosclerosis was evaluated using the following five-grade scale list: grade 0: no AA, grade 1: intimal thickening, grade 2: <5 mm plaque, grade 3: >5 mm plaque, grade 4: plaque with mobile parts (13).
- The systolic and diastolic aortic diameters, and the diastolic intimo-medial thickness were also measured in the transversal plane behind the left atrium during the TEE examination. In the case of intimal thickness or aortic plaque, the „worst place" parameters were considered for calculations. Many indices have been derived to describe and quantify the physical behaviour of vessels in response to an intraluminal force. Peterson et al. defined the *Elastic modulus (E(p))* as an index of arterial stiffness, which describes the relationship of strain to intraluminal pressure in an open-ended vessel (14). The original description referred to the change in vessel volume, but since the arterial lumen is generally circular in cross-section, the equation has been modified to E(p) (mm Hg) = (SBP-DBP)/strain, where SBP and DBP are the systolic and diastolic pressures. Strain is the fractional pulsatile diameter change that occurs in an artery exposed to a given change in intraluminal pressure, and is defined as strain = (DS-DD)/DD, where DS is the systolic diameter, while DD is the diastolic diameter. *Young's circumferential static elastic modulus (E(s))* was evaluated via (15) E(s)=E(p)*DD/2

h, where „h" is the diastolic intimo-medial thickness. The blood pressure and heart rate were monitored continuously during the examination.

Dipyridamole stress TEE examinations were carried out according to the standard protocol proposed by Iliceto et al. (8). In all the patients, the aortic root and the proximal portion of the LAD were visualized in the transversal plane. The coronary blood flow was first visualized by colour Doppler flow imaging. A biphasic coronary flow waveform was recorded in the LAD by pulsed Doppler. Flow measurements were made under baseline conditions and after the administration of 0.56 mg/kg dipyridamole during 4 minutes. The peak velocities were measured in the 6^{th} minute at maximal vasodilation. All measurements were recorded on super-VHS videotape. In each case, five consecutive cycles were measured and averaged. The CFR was calculated as the ratio of the hyperaemic to the basal peak (CFR) and those of the mean (mean CFR) diastolic flow velocity.

Coronary angiography: Selective coronary angiography was performed by the Seldinger technique. The stenosis was evaluated qualitatively from multiple projections. Coronary stenosis was assessed with the Siemens HiCor^{TM} biplane angiographic system; a lumen diameter reduction >70% was considered to be significant when the „worst view method" was applied in at least one projection.

Statistical analysis: Data are reported as means±standard deviations; 95% confidence intervals are also given. Analyses were performed with a standard software package (SPSS 9.0, SPSS Inc. Chicago, IL, USA). For group comparisons, Student t test or analysis of variance (ANOVA) were applied. For dichotomous values, Fisher's exact test was used. To establish the prediction power of the variables, receiver operating characteristic (ROC) curves were constructed and the areas under curves are reported, $p<0.05$ was considered statistically significant. Binary logistic regression tests were performed to study the correlation of the variables.

To examine the role of parameters in the evaluation of the severity of coronary artery disease, variables showing significant correlations were entered in a multiple regression analysis; a statistical model was created in order to assess the overall predictive value. A likelihood ratio test was performed to evaluate the difference between the model with or without entering the grade of aortic atherosclerosis (section 4.2.1).

3.Aims

1. To evaluate the dependence of CFR on the result of coronary angiograms.
2. To determine the diagnostic value of transoesophageal CFR measurement for the identification of significant coronary stenosis in patients with severe aortic stenosis (AOS).
3. To investigate the effect of aortic valve replacement on the diastolic velocities and CFR in patients with a negative coronary angiogram by using stress TEE during an average follow-up of 15 months.
4. To examine whether it is possible to differentiate patients with AOS with or without significant stenosis of the LAD on the basis of the age, gender, hypertension, diabetes mellitus, hypercholesterolaemia, the CFR and the grade of aortic atherosclerosis (AA) evaluated by stress TEE in the course of the same semi-invasive examination.
5. To examine the CFR in patients with hypertrophic cardiomyopathy (HCM) in comparison with normal controls, measured by stress TEE. The effects of obstruction on the CFR were also examined in HCM patients.
6. To evaluate the relationship between the actual cholesterol level, the application or not of lipid-lowering therapy and the CFR measured by stress TEE in patients without major coronary artery disease.
7. To test whether known risk factors, the CFR and the grade of AA detected by stress TEE in the course of the same semi-invasive examination is able to distinguish between patients with significant LAD stenosis or with multivessel disease.
8. To assess the elastic properties of the descending aorta and the CFR evaluated during the same stress TEE examination in patients after coronary angiography.
9. To determine the aortic distensibility indices of the descending aorta and the CFR in the course of the same stress TEE examination in patients with different grades of AA.
10. To test the hypothesis that the elastic properties of the descending aorta of AOS patients reveal early signs of stiffness of the aorta. For this purpose, we compared the CFR and aortic distensibility indices in three different patient populations: control patients without valvular and coronary artery disease, patients with aortic stenosis with normal epicardial coronary arteries, and patients with significant LAD stenosis.

4. Results

4.1. Factors affecting coronary flow velocity reserve

4.1.1. The effect of micro- and macrovascular resistance on CFR – dependence on coronary angiography

Study population: The study comprised 152 patients (109 men, 43 women) who underwent dipyridamole stress transoesophageal echocardiography and coronary angiography. The mean age was 56.4±11.0 years, the youngest patient was a 22 year-old man, while the oldest a 73 year-old woman. The ratio of patients with hypertension and diabetes mellitus did not differ significantly between the groups, and there was no case with significant valvular heart disease.

Results:

The CFR of 152 patients depending on the coronary angiogram are presented in Table 1. A significant difference was observed between groups signed by star and patients with negative coronary angiogram ($p<0.05$). Diastolic coronary flow velocities of patients in different groups are presented in Table 2. The resting diastolic flow velocities of patients with significant LAD disease or with multi-vessel disease and of cases with suspected syndrome X were significantly increased compared to negative patients. The diastolic flow velocities measured at the peak of stress of patients with significant LAD, left circumflex (CX) coronary artery disease and multi-vessel disease and cases with suspected syndrome X were found to be significantly decreased (Table 2).

CFR in patients with negative coronary angiogram: From this patient population nineteen patients showed a negative coronary angiogram. The average CFR was 3.19±1.15. 8 patients were found, who had typical anginal pain, positive treadmill test with significant ST-T changes, but normal epicardial coronary arteries during coronary angiography. The average CFR was 1.24±0.21 (mean CFR:1.23±0.36) which was significantly different compared to not only patients with negative coronary arteries without positive stress test but also cases with LAD single-vessel disease (Table 1).

CFR of patients with non-significant coronary artery disease: No significant difference was found in CFR in patients with different kinds of non-significant coronary artery disease, but it was significantly decreased compared to patients with negative coronary angiogram. There was a significant difference between patients with non-significant CAD and patients with significant LAD disease, patients with multivessel-disease or cases with suspected X syndrome. There was no difference in CFR between patients with non-significant CAD and cases with significant right coronary (RC) or CX single-vessel disease.

CFR of patients with significant single-vessel coronary artery disease: Significant single-vessel coronary artery disease was diagnosed if significant stenosis of a major coronary artery (left anterior descending coronary artery, left circumflex coronary artery, right coronary artery) or its main branch (I. diagonal, obtus marginalis) was found during the coronary angiography. The CFR of patients with LAD single-vessel disease was significantly decreased compared to cases significant CX or RC single-vessel disease (Table 3).

CFR of patients with significant stenosis of the LAD: 34 patients showed a significant stenosis in the LAD during coronary angiography. None of them had undergone percutan transluminal coronary-angioplasty (PTCA) and/or stent-implantation, previously. The CFR of these patients were significantly decreased compared to patients with normal epicardial coronary arteries ($p<10^{-8}$). A non-significant difference was found in the CFR depending on the localisation of the stenosis of the LAD. The CFR of patients with proximal stenosis of the LAD was 1.84, while in cases with distal stenosises was somewhat lower (CFR: 1.75). The CFR of patients with significant LAD stenosis was reduced compared to cases with non-significant stenosis, but the difference did not reached the level of significance (Table 4).

The CFR of patients with different kinds of multivessel-disease (MVD)

There was no difference in the CFR between patients with significant LAD and cases with two- or three-vessel disease. The CFR of patients with CX single-vessel disease was significantly increased compared to two-vessel disease ($p<0.005$) and to three-vessel disease ($p<0.04$). The CFR of cases with RC single-vessel disease was higher, but did not reached the level of significance. The CFR of patients with different kinds of multi-vessel disease are presented in table 5. These values are significantly decreased compared to patients with negative coronary angiogram, non-significant CAD and significant CX single-vessel disease. In patients with multi-vessel disease involving LAD the CFR is decreased. Interestingly, in patients with significant CX and RC disease, the CFR similarly reduced.

Table 1 CFR and mean CFR in patients with different kinds of coronary angiogram

	CFR	Mean CFR	Patient number
Negative	3.19±1.15	3.19±1.17	19
Non-significant coronary artery disease	2.17±0.62*	2.3±0.65*	20
Suspected X syndrome	1.24±0.21**	1.23±0.36**	8
LAD single-vessel disease	1.77±0.47*	1.71±0.51*	34
CX single-vessel disease	2.58±0.87	2.53±1.33	12
RC single-vessel disease	2.13±0.56*	1.97±0.53*	8
Two-vessel disease	1.92±0.62*	1.7±0.47*	43
Three-vessel disease	1.83±0.43*	1.96±0.49*	8

***p<0.05 vs Negative**
****p<0.05 vs LAD single-vessel disease**

Table 2 Diastolic flow velocities at rest and at the peak of stress in different patient populations

	Resting diastolic flow velocities (cm/s)	Diastoles flow velocities at the peak of stress (cm/s)
Negative	49.5±18.6	142.5±29.3
Non-significant coronary artery disease	57.5±25.0	118.9±46.9
Suspected X syndrome	66.3±28.8*	93.8±45.1*
LAD single-vessel disease	65.2±30.7*	108.4±40.1*
CX single-vessel disease	46.1±13.6	114.6±39.7*
RC single-vessel disease	60.0±13.4	123.2±18
Two-vessel disease	61.2±24.5*	106.7±34.1*
Three-vessel disease	76.9±32.3*	134.6±45.2

***p<0.05 vs Negative**

Table 3 CFRs in patients with different kinds of single-vessel disease

	CFR	mean CFR
LAD single-vessel disease	1.77±0.47	1.71±0.51
CX single-vessel disease	2.58±0.87*	2.53±1.33*
RC single-vessel disease	2.13±0.56*	1.97±0.53*

***p<0.05 vs Negative**

Table 4 CFRs of significant and non-significant LAD single-vessel patients

LAD stenosis	CFR	Patient number
>70%	1.71±0.47	34
<70%	1.96±0.65	13

p=NS

Table 5 CFRs of patients with different kinds of multivessel disease

	CFR	Mean CFR	No. of cases
LAD+CX	1.95±0.68	1.71±0.61	12
LAD+RC	1.87±0.49	1.68±0.40	16
CX+RC	2.00±0.81	1.60±0.51	11
LM	1.79±0.39	1.98±0.28	4
Three-vessel disease	1.83±0.43	1.96±0.49	8

p=NS

4.1.2. The effect of left ventricular hypertrophy as an extravascular compressive force on coronary flow velocity reserve

4.1.2.1. Coronary flow velocity reserve is patients with aortic valve stenosis

4.1.2.1.1. How can the CFR be altered by aortic valve stenosis?

Study population: The study population comprised 21 consecutive aortic stenosis patients with normal coronary arteries (group 1), 21 patients with anatomically normal coronary arteries without aortic stenosis (group 2) and 37 patients with significant (visually assessed diameter reduction >75%) left anterior descending coronary artery disease without AOS (group 3). None of the patients with LAD stenosis had undergone previous percutaneous transluminal coronary angioplasty or stent implantation. The demographic and clinical data on the patients are shown in Table 6. Severe aortic stenosis was diagnosed if the mean left ventricle-aorta poststenotic gradient was higher than 50 mm Hg.

Transthoracic echocardiography: The mean left ventricle-aorta pressure gradient of the patients with aortic stenosis was 94±22 mmHg. The left ventricular mass (LVM) and LVM index (LVMI) was significantly higher in group 1 than in groups 2 and 3 ($p<0.05$). There was no significant difference in ejection fraction (EF) between the three groups (Table 7).

Dipyridamole stress transoesophageal echocardiography: During the stress, no patient displayed either significant ST-T changes in the ECG or limiting side-effects. The heart rate was significantly higher, and the diastolic and the systolic blood pressures were lower in all groups after the dipyridamole infusion ($p<0.05$) (Table 8). In patients with aortic stenosis, the systolic blood pressure was lower than in patients with left anterior descending coronary artery disease or in the normal subjects following the dipyridamole infusion. The resting diastolic flow velocity was significantly higher in group 1 and 3 compared to group 3. The post-hyperaemic diastolic flow velocity was significantly lower in group 1 and 3 compared to group 3 (Table 9).

Comparison of CFR in the three 3 groups: The coronary flow velocity reserve and the mean coronary flow velocity reserve were significantly higher in group 2 than in groups 1 and 3 ($p<0.009$) (Table 9).

Table 6 Demographic and clinical data on the patients

	Group 1 (AOS)	Group 2 (Neg)	Group 3 (LAD)
Age (years)	58±10	49±10	56±9
Men/women	11/10	10/11	24/13*§
Hypertension (%)	13/21(62)	8/21(38)@	24/37(65)
Diabetes mellitus (%)	7/21(33)	2/21(10)	10/37(27)
Cholesterol (mmol/l)	4.86±0.44	5.34±0.49	5.57±0.36*
Smoker status (%)	2/21(5)	7/21 (33)@	3/37 (8)
Typical angina (%)	16/21 (76)	17/21 (63)	36/37 (97)*§
Atypical chest pain (%)	2/21 (5)	4/21 (19)	2/37 (5)
Left ventricular hypertrophy in the resting ECG (%)	20/21 (95)§@	8/21 (38)	8/37 (22)
***Medication*: - β-blockers (%)**	8/21 (38)§@	15/21 (71)	27/37 (73)
- ACE inhibitors (%)	15/21 (71)	7/21 (33)*@	27/37 (73)
- Nitrates (%)	10/21 (48)	7/21 (33)	27/37 (73)*§
- Calcium antagonists (%)	4/21 (19)	7/21 (33)	8/37 (22)
- Lipid-lowering therapy (%)	2/21 (5)	4/21 (19)	14/37 (38)*
- Antidiabetics (%)	1/21 (5)	2/21 (10)	4/37 (11)

Values are expressed as number (%) unless otherwise indicated.

***p<0.05 vs group 1; §p<0.05 vs group 2; @p<0.05 vs group 3**

Table 7 Left ventricular mass, left ventricular mass index and ejection fraction in the three groups

	LVM (g)	LVMI (g/m^2)	EF (%)
Group 1 (AOS)	380.3±119*	185.6±18.1*	63±20
Group 2 (Neg)	234.2±100.2	127.1±20.2	65±11
Group 3 (LAD)	268.2±70.2	130.8±21.3	62±11

***p<0.05 group1 vs groups 2 and 3**

Table 8 Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure in the three groups ('max' means measured at the peak of stress)

	HR rest (1/min)	HR max (1/min)	SBP rest (mm Hg)	SBP max (mm Hg)	DBP rest (mm Hg)	DBP max (mm Hg)
Group 1	77.4±13.3	90.6±12*	137.7±26.4	113.4±27.2*	88±27.2	73.8±21.9*
Group 2	73.5±15.9	92.7±19.1*	139±21.3	123.2±20.4*	88.2±27.2	74.5±17.3*
Group 3	80.1±14.1	94.1±16.4*	149.5±28.3	130.4±22.6*	89.8±18.9	74.8±15.4*

***p<0.05 dip vs rest data**

Table 9 Coronary flow velocities and CFRs in the three groups

	Group 1	Group 2	Group 3
Drest (cm/s)	64.3±24.1*	53.2±19.2	64.8±29.3*
Dmax (cm/s)	123.3±41.6*	147.7±25.5	109.5±41*
CFR	1.98±0.52*	3.13±1.06	1.82±0.46*
Mean CFR	1.91±0.62*	3.19±1.17	1.76±0.5*

***p<0.05 group 2 vs groups 1 and 3**

4.1.2.1.2. The effect of aortic valve replacement on CFR in patients with a normal coronary angiogram

Study population: 30 patients (17 women and 13 men) were enrolled in the follow-up study; they had a normal coronary angiogram and aortic stenosis and underwent dipyridamole stress TEE between Februar 1998 and May 2000. All these patients were recalled for a control examination. One woman died after femur fracture during the follow-up period before AVR. Two patients (1 woman, 1 man) died in cardiac insufficiency before AVR. Three patients (2 women and 1 man) were not operated on because none of them wanted to participate. Three patients (1 woman and 2 men) underwent AVR, but did not participate in this study. Stress TEE was performed 123±137 days before AVR and 497±167 days after AVR. 21 patients remained in this follow-up study. The demographic and clinical data are presented in Table 10. The medication applied pre- and postoperatively are presented on Table 11.

Transthoracic echocardiography: The average gradient of aortic stenosis was 89.5±22.4 mm Hg. After AVR, the average aortic gradient decreased to 26.2±9 mm Hg. The left ventricular dimensions, LVM and LVMI index are presented in Table 12.

Dipyridamole PSTEE: During the stress, no patient displayed either significant ST-T changes on ECG or limiting side-effects. The diastolic blood pressure at rest was significantly higher after AVR. The heart rate was higher, while the blood pressure was lower after dipyridamole infusion in both pre- and post-AVR conditions (Table 13). The average baseline diastolic flow velocity was 62.2±25.5 cm/s before AVR and 40.1±13.6 cm/s after it. The average diastolic velocity measured at maximum stress was 117±42.8 cm/s before AVR, and 91.5±34 cm/s after it (Table 14). Systolic velocities (Srest, Smax) during stress were also examined, and the ratio Smax/Srest was calculated before and after AVR (Table 14).

Comparison of CFR before and after AVR: The calculated CFR was 1.96±0.5 before AVR, and 2.37±0.8 after it.

Table 10 Demographic and clinical data on the patients who underwent the follow-up

	Before AVR	After AVR
No. of patients	21	21
Age (years)	68±8	69±9
Male gender (%)	9 (43)	9 (43)
Hypertension (%)	16 (76)	16 (76)
Diabetes mellitus (%)	5 (24)	5 (24)
Cholesterol (mmol/l)	4.66±0.22	4.63±0.32
Smoker status (%)	2 (10)	0 (0)
Typical angina (%)	9 (43)	1 (5)*
Atypical chest pain (%)	1 (5)	0 (0)
Body weight (kg)	74.3±11.6	75.8±10.7
Body surface area (m^2)	1.88±0.07	1.88±0.06

Values are expressed as number (%) unless otherwise indicated.

*p<0.05 vs before AVR

Table 11 The most important medication applied

	Before AVR	After AVR
β-Blocker (%)	11 (53)	18 (86)*
ACE inhibitor (%)	18 (86)	18 (86)
Nitrate (%)	9 (43)	7 (33)
Ca-antagonist (%)	5 (24)	6 (29)
Diuretics (%)	10 (48)	10 (48)
Coumarin (%)	3 (14)	21 (100)*
ASA (%)	7 (33)	0 (0)*
Lipid-lowering therapy (%)	6 (29)	8 (38)

Values are expressed as number (%) unless otherwise indicated.

*p<0.05 vs before AVR

Table 12 Echocardiographic data before and after AVR

	Before AVR	After AVR	p value
IVS (mm)	13.8±3.4	11±1.7	0.002
PW (mm)	12.7±2.3	10.8±1.6	0.003
EDD (mm)	52.7±6.5	49.7±5.5	0.12
EF (%)	64.1±7.3	65.3±7.7	0.62
LVM (g)	354.9±107.9	223.8±73.6	0.001
LVMI (g/m^2)	189.6±59.7	118.8±37.7	0.001

p=NS

Table 13 Heart rate and blood pressure before and after AVR

	HR rest (1/min)	HR dip (1/min)	SBP rest (mm Hg)	SBP dip (mm Hg)	DBP rest (mm Hg)	DBP dip (mm Hg)
Before AVR	80.1±15.4	94.2±14**	136.5±25	129±26.1	82.2±11.2	76.6±20.5
After AVR	79.5±12.3	89.9±17.5	154.2±26.1	132±22.1@	92.1±10.2*	75.1±18.1&

***p<0.01 vs before AVR; **p<0.01 vs HR rest; @p<0.01 vs SBP rest; &p<0.01 vs DBP rest**

Table 14 Coronary flow velocities and CFR before and after AVR

	Before AVR	After AVR
S rest (cm/s)	27.3±14	21±7.6
S max (cm/s)	43.7±15	42.6±17.6
S max/S rest	1.79±0.69	2.17±1.03
D rest (cm/s)	62.2±25.5	40.1±13.6*
D max (cm/s)	117±42.8	91.5±34**
CFR	1.96±0.5	2.37±0.8***

***p<0.01 vs before AVR; **p<0.05 vs before AVR; ***p<0.05 vs before AVR**

4.1.2.1.3. The comparative value of the aortic atherosclerosis and the CFR in the prediction of patients with aortic stenosis with coronary artery disease

Study population: Consecutive AOS patients who underwent coronary angiography were examined by stress TEE in order to assess the CFR. Investigators were blinded to the result of coronary angiogram. From this patient population, 21 AOS patients with anatomically normal coronary arteries (group 1) and 18 AOS patients with significant (visually assessed diameter reduction >75%) LAD stenosis (group 2) were selected for the present study.

Demographic and clinical data are presented in Table 15. The prevalences of traditional risk factors, typical angina and atypical chest pain were not statistically different in the two patient groups. Only the prevalence of grade 2 or 3 AA was significantly increased in AOS patients with significant LAD stenosis. Average grades of AA are presented in Figure 1.

Transthoracic echocardiography: The mean left ventricle-aorta pressure gradient of the patients with AOS with negative coronary arteries was 81±30 mm Hg, while that of the AOS patients with severe LAD disease was 80±20 mm Hg. There was no significant difference in standard echocardiographic parameters between the two groups (Table 16).

Dipyridamole stress transoesophageal echocardiography: During the stress, no patient displayed either significant ST-T changes in the ECG or limiting side-effects. The coronary flow velocities and CFRs did not differ in the two patient groups (Table 17).

Differentiation of AOS patients with severe LAD disease from AOS patients with a negative coronary angiogram: Binary logistic regression and ROC curves were utilized to establish the prognostic power of the traditional risk factors, the CFR and the grade of AA for the selection of AOS patients with significant stenosis of the LAD from AOS patients with normal coronary arteries (Table 18). Only the grade of AA (ROC area,73%, $p<0.02$) displayed good value for the prediction of AOS with significant LAD stenosis. All the other parameters including hypertension, hypercholesterolaemia, diabetes mellitus, age, gender, and the CFR were without any prognostic power. Only variables with relatively small ($p<0.2$) univariate p-values were included in the multivariate model, namely, the grade of aortic atherosclerosis, the age, the male gender and the CFR also included as possible predictors. As a result, only the grade of aortic atherosclerosis remained as a significant predictor of LAD disease ($\times^2=7.29$, df=1, $p=0.007$).

Table 15 Demographic and clinical data on the patients

	Group 1 (AOS)	Group 2 (AOS-LAD)
No. of patients	21	18
Age (years)	62±11	66±6
Male gender (%)	8 (38)	11 (61)
Hypertension (%)	12 (57)	13 (72)
Diabetes mellitus (%)	2 (10)	4 (22)
Hypercholesterolaemia (%)	5 (24)	3 (17)
Typical angina (%)	10 (48)	9 (50)
Atypical chest pain (%)	1 (5)	1 (6)
Presence of grade 2 or 3 aortic atherosclerosis (%)	7 (33)	14 (78)*

Values are expressed as number (%) unless otherwise indicated.

***p<0.01 vs group 1**

Table 16. Transthoracic echocardiographic parameters

	Group 1	Group 2
IVS (mm)	13.4±3.5	13.9±2.9
PW (mm)	12.0±2.1	13.6±2.8
EDD (mm)	51.9±6.8	55.2±5.9
EF (%)	62.8±11.2	61.0±8.6
LVM (g)	322±91	408±133
LVMI (g/m^2)	169±48	209±73
Peak aortic gradient (mm Hg)	81±30	80±20

p=NS

Table 17 Coronary flow velocities, ratio Smax/Srest and CFR in patient groups

	Group 1 (AOS)	Group 2 (AOS-LAD)
Srest (cm/s)	26.2±11.0	29.7±17.0
Smax (cm/s)	45.6±15.5	52.6±30.3
Smax/Srest	1.93±0.94	1.88±0.67
Drest (cm/s)	60.8±21.9	68.7±27.7
Dmax (cm/s)	119.9±36.8	117.2±50.6
CFR	2.08±0.56	1.84±0.34

p=NS

Table 18 Differentiation of AOS patients with significant LAD stenosis from AOS patients with normal coronary arteries

Variable	**ROC area (95% CI)**	***P* value Of ROC**	**Binary logistic regression OR (95% CI)**	***P* value**
Hypertension	0.44 (0.25-0.62)	0.52	0.58 (0.15-2.26)	0.43
Diabetes mellitus	0.44 (0.25-0.63)	0.52	0.39 (0.06-2.44)	0.31
Hypercholeste-rolaemia	0.54 (0.36-0.73)	0.66	1.67 (0.34-8.26)	0.53
Age	0.56 (0.38-0.75)	0.50	1.06 (0.98-1.14)	0.16
Male gender	0.62 (0.44-0.79)	0.22	2.55 (0.70-9.31)	0.16
CFR	0.38 (0.20-0.56)	0.21	0.32 (0.07-1.41)	0.13
Grade of aortic atherosclerosis	**0.73 (0.57-0.89)**	**0.02**	**7.00 (1.67-29.38)**	**0.01**

4.1.2.2. Coronary flow velocity reserve in patients with hypertrophic cardiomyopathy

Study population: Nineteen patients (6 women and 13 men) with hypertrophic cardiomyopathy (group 1) and 24 patients (13 women and 11 men) with negative coronary angiograms as controls (group 2) were involved in our study. All patients in group 2 underwent coronary angiography and had a negative stress test (performed because of anginal pain). None of the patients had significant valvular heart disease. The demographic and clinical data on the patients are shown in Table 19.

Transthoracic echocardiography: During the transthoracic echocardiographic examinations, the site of hypertrophy was found to be on the septum; the average thickness was 20.7±3.7 mm. In the control patients, the septal thickness was 10.8±0.18 mm. The difference was mathematically significant ($p<0.05$). There was no difference between the groups examined in the value of the ejection fraction or the EDD. There was a systolic anterior motion (SAM) phenomenon in 6 cases, while a subvalvular gradient was observed in 6 patients in HCM patient group (average value: 38.7±16.3 mm Hg, range: 27-67 mm Hg). The two phenomena were present together in 4 patients. Echocardiographic parameters are presented in Table 21. The LVM was significantly higher in the HCM patients. In HCM patients with an outflow tract obstruction, the PW and LVM were significantly higher than in those without such an obstruction (Table 22).

Stress transoesophageal echocardiography: Coronary flow velocities were measured during stress transoesophageal echocardiography (Tables 23). The resting diastolic flow velocity was higher in the patients with HCM, but the difference was not significant statistically. The diastolic velocity measured at the peak of stress was significantly lower in HCM. The calculated CFR was significantly lower in the patients with HCM (2.14±0.68 vs 3.16±1.1). In 3 HCM patients, we were not able to detect systolic coronary flow velocity at rest, but only at peak stress. In another 3 patients, reverse systolic flow was detected, which remained unchanged during stress. In the HCM patients, both under resting conditions and at peak stress, the systolic velocity and the ratio Smax/Srest were decreased as compared with the controls. The difference between the above parameters were also examined in HCM patients with or without a subvalvular gradient (Table 24). The differences between the parameters were not significant, though the baseline diastolic velocity was higher and the maximal diastolic velocity and the CFR were lower in the presence of a subvalvular gradient.

Table 19 Demographic and clinical data on the patients

	Group 1 (HCM)	Group 2 (controls)
Age (years)	48±9	50±10
Men/women	13/6	12/12
Hypertension (%)	6/19 (32)	10/24 (42)
Diabetes mellitus (%)	0/19 (0)	0/24 (0)
Typical angina (%)	5/19 (26)	18/24 (75)*

Values are expressed as number (%) unless otherwise indicated.

***p<0.05 vs group 1**

Table 20 Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure in the groups

	HRrest (1/min)	HRmax (1/min)	SBPrest (mm Hg)	SBPmax (mm Hg)	DBPrest (mm Hg)	DBPmax (mm Hg)
Group 1	76.5±14.2	93.6±14.8*	151.3±26.7	133.2±23.3*	92±16.3	79.9±20*
Group 2	76.9±11.3	101.5±19.2*	136.6±20	120.4±11.9*	84.5±15.9	71.6±14.4*

***p<0.05 resting vs peak data in group 1**

Table 21 Important echocardiographic parameters and LVM in the groups

	Group 1	Group 2	p value
No	19	21	-
EF (%)	71.6±9.8	64.6±10.3	NS
EDD (mm)	46.9±7.4	52.4±0.6	NS
IVS (mm)	20.7±3.7	10.8±0.18	0.05
PW (mm)	11.4±2.4	10.6±1.5	NS
LVM (g)	410.7±112.8	264.6±79.4	0.0002

Table 22 Echocardiographic parameters in the presence or absence of a subvalvular gradient in HCM patients

Subvalvular gradient	Presence	Absence	p value
No	6	13	-
EF (%)	76.2±7.7	69.5±10.2	NS
EDD (mm)	50.8±11.1	45.2±4.7	NS
IVS (mm)	21.2±4.5	20.5±3.5	NS
PW (mm)	13.4±3.2	10.5±1.2	0.02
LVM (g)	512.0±129.9	364.1±69.0	0.009

Table 23 Coronary flow velocities and CFR in the groups

	Group 1 (HCM)	Group 2 (controls)	p value
D rest (cm/s)	62.1±24.9	52.8±19.7	NS
D max (cm/s)	124.7±40.7	147.8±26.2	0.04
CFR	2.14±0.68	3.08±1.08	0.001
S rest (cm/s)	8.8±29.6	23.2±7.8	0.05
S max (cm/s)	30.6±25.7	65.9±24.1	0.001
Smax/Srest	1.57±0.78	2.98±0.86	0.001

Table 24 Coronary flow velocities and CFRs in patients with HCM in the presence or absence of obstruction

Subvalvular gradient	Presence	Absence	p value
No of cases	6	13	-
D rest (cm/s)	64.2±19.5	61.1±27.8	NS
D max (cm/s)	118.3±44.2	127.7±40.5	NS
CFR	1.90±0.61	2.25±0.70	NS
S rest (cm/s)	21.5±14.3	2.3±32.2	NS
S max (cm/s)	38.0±14.7	26.5±28.5	NS
Smax/Srest	1.71±0.54	1.51±0.89	NS

4.1.3. Relationship between hypercholesterolaemia, lipid-lowering therapy and CFR in patients with a negative coronary angiogram

Study population: 69 patients were enrolled in this study. All the patients underwent coronary angiography, with a negative result. None of the patients had significant valvular heart disease or had had a previous myocardial infarction. The patients were divided into four groups, depending on the cholesterol level and on the performance or not of 25±2 weeks lipid-lowering therapy: normocholesterolaemia (NC) without lipid-lowering therapy (LLT) (Group 1), normocholesterolaemia with lipid-lowering therapy (Group 2), hypercholesterolemia (HC) without lipid-lowering therapy (Group 3) and hypercholesterolaemia with lipid-lowering therapy (Group 4). The cut-off value for hypercholesterolaemia was 5.2 mmol/l and that for the CFR was 2.5. The different effects of different forms of lipid-lowering medication were not examined.

Demographic and clinical data on the patients are presented in Table 25. As concerns the 32 patients who received lipid-lowering medication, the cholesterol level was normal in 16 cases (average cholesterol level: 4.32±0.32 mmol/l), while it remained increased in 16 patients (average cholesterol level: 6.38±0.51 mmol/l) at the time of the PSTEE examination. Among the 37 who did not receive lipid-lowering medication, normocholesterolaemia was observed in 30 cases (average cholesterol level: 4.22±0.41 mmol/l). The cholesterol level was increased in 7 patients who did not participate in lipid-lowering medication (average cholesterol level: 6.44±0.45 mmol/l). Mean age, the ratio of male gender, the prevalence of hypertension, diabetes mellitus, typical angina and atypical chest pain were not different in patient groups. The ratio of abnormal stress test results in the previous 6 months was relatively increased in groups 2, 3 and 4 compared to group 1, but the difference did not reach the level of significance. The effect of cholesterol level on CFR was found to be significant evaluated by two-way ANOVA ($p<0.04$).

The medication administered and the lipid-lowering therapy applied are detailed in Tables 26 and 27. Only the use of ACE inhibitors was significantly decreased in group 3 compared to groups 1 and 2.

Transthoracic echocardiography: There was no significant difference in standard echocardiographic parameters between the groups (Table 28).

Dipyridamole stress transoesophageal echocardiography: During the stress, no patient displayed either significant ST-T changes on ECG or limiting side-effects. Systolic and diastolic flow velocities and CFR are presented in Table 29. In the patients who did not receive lipid-lowering medication and who displayed normocholesterolaemia, the CFR was significantly higher than in the patients who had an increased cholesterol level.

Table 25 Demographic and clinical data on the patients

	Group 1 (NC, no LLT)	Group 2 (NC, with LLT)	Group 3 (HC, no LLT)	Group 4 (HC, with LLT)
Number of cases	30	16	7	16
Cholesterol (mmol/l)	4.22±0.41	4.32±0.32	6.44±0.45*	6.38±0.51*
Age (years)	55.4±11.4	56.8±7.6	52.7±2.9	54.9±8.7
Male gender (%)	16 (53)	4 (25)	2 (29)	7 (44)
Hypertension (%)	20 (67)	12 (75)	3 (43)	12 (75)
Diabetes mellitus (%)	5 (17)	6 (38)	1 (14)	1 (6)
Typical angina (%)	25 (83)	16 (100)	6 (86)	14 (88)
Atypical chest pain (%)	9 (30)	4 (25)	2 (29)	1 (6)
Positive stress test in the anamnesis (%)	10 (33)	8 (50)	4 (57)	8 (50)

Values are expressed as number (%) unless otherwise indicated.

***p<0.05 vs groups 1 and 2**

Table 26 Lipid-lowering medication

	No. in Group 2	No. in Group 4
Fluvastatin	0	1
Simvastatin	12	12
Fenofibrate	1	0
Ciprofibrate	1	0
Combined therapy (fibrate+statin)	2	3

Table 27 Medication applied

	Group 1 (NC, no LLT)	Group 2 (NC, with LLT)	Group 3 (HC, no LLT)	Group 4 (HC, with LLT)
Number of cases	30	16	7	16
ACE inhibitor (%)	20 (67)	11 (69)	1 (14)*	9 (56)
β-Blocker (%)	23 (77)	10 (63)	6 (86)	13 (81)
Ca-antagonist (%)	13 (43)	11 (69)	4 (57)	10 (63)
Nitrate (%)	11 (37)	7 (44)	4 (57)	7 (44)
Diuretics (%)	7 (23)	3 (19)	0 (0)	3 (19)

Values are expressed as number (%) unless otherwise indicated.

*** p<0.01 vs groups 1 and 2**

Table 28 Transthoracic echocardiographic data

	Group 1	Group 2	Group 3	Group 4
EDD (mm)	52.9±7.4	50.2±6.2	52.0±4.4	54.4±10.1
IVS (mm)	10.8±1.5	11.2±1.9	10.7±1.5	11.2±2.8
PW (mm)	10.4±1.4	10.4±1.5	11.3±0.6	10.4±2.6
EF (%)	64.9±12.1	64.9±10.6	61.3±2.1	66.2±14.1

p=NS

Table 29 Systolic and diastolic flow velocities and CFRs in the groups

	Group 1	Group 2	Group 3	Group 4
Number of cases	30	16	7	16
D rest (cm/s)	44.3±18.8	44.9±12.6	54.6±23	53.9±23
D max (cm/s)	112.2±41	108.9±30.1	102.9±43.2	109.1±43.2
CFR	2.65±0.79	2.47±0.88	2.03±0.88*	2.18±0.67*
S rest (cm/s)	20.6±9.5	24.6±8	24.9±10.5	24.3±10.5
S max (cm/s)	49.7±20.4	54.5±20	41.7±20.3	49.7±29
Smax/Srest	2.53±0.87	2.21±1.01	1.80±1.03	2.10±0.94

***p<0.05 vs group 1**

4.2. Relationship between CFR, aortic atherosclerosis and distensibility

4.2.1. Grade of aortic atherosclerosis: a valuable adjunct to CFR in the evaluation of coronary artery disease

Study population: This study involved 125 consecutive patients (mean age: 56±11 years, range: 22-73) with stable angina pectoris without a previous myocardial infarction. AA grade determination and TEE-CFR measurement were undertaken as part of a prospective investigation aimed at establishment of the clinical utility of the TEE-CFR. All 125 patients underwent coronary angiography. Patients with significant right coronary artery or left circumflex coronary artery stenosis were excluded from this study, because CFR measurements were made in the LAD. Coronary stenosis was assessed by a digital caliper method, with the Siemens HiCor™ biplane angiographic system; a diameter reduction >70% was considered to be significant when the „worst view method" was applied. Fourty-seven patients with anatomically non-significant CAD (group 1), 34 patients with significant LAD disease (group 2) and 44 patients with MVD (group 3) were examined. None of the patients had significant valvular heart disease.

Correlation of risk factors and the presence of AA with CAD: The mean age and the incidences of arterial hypertension and diabetes mellitus were not significantly different between patient groups (Table 30). The prevalence of male gender was significantly higher in the patients with MVD. The prevalence of hypercholesterolemia and the prevalence of grade 2 or 3 AA were significantly lower in the patients without major CAD. The CFR was significantly decreased in the patients with significant LAD stenosis or MVD as compared with the patients without major CAD.

Differentiation of patients with MVD from all other patients: Binary logistic regression and ROC curves were utilized to establish the prognostic power of traditional risk factors, aortic grade and the CFR for the to selection of patients with MVD (Table 31). The age (ROC area, 63%, $P < 0.01$), the gender (ROC area, 63%, $P < 0.02$) and the grade of AA (ROC area, 64%, $P < 0.01$) displayed good value for the prediction of MVD. Hypertension, hypercholesterolaemia, diabetes mellitus and CFR failed to distinguish the patients with MVD. By binary logistic regression analysis, the age, the gender and the grade of AA were found to correlate significantly with the prevalence of MVD (Table 31). These variables were entered into multiple logistic regression analysis. In order to differentiate patients with MVD

from all others, the age and gender were entered as the first covariates: the model gave X^2= 15.214 (df=2, p= 0.0005). When the grade of AA was entered, the power of the model increased significantly: X^2= 21.888, df=4, p= 0.0001; assessment by the likelihood ratio test gave X^2= 6.674, df=2, p= 0.036.

Differentiation of patients with MVD from those with LAD disease: Only the grade of AA (ROC area, 63%, $p < 0.05$) was found to exhibit good prognostic value in predicting patients with MVD. All other traditional risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, age, gender and CFR, were without prognostic power (Table 32).

Table 30. Comparison of risk factors and presence of coronary artery disease

	Group 1 (non-significant CAD)	Group 2 (LAD disease)	Group 3 (MVD)
No. of cases	47	34	44
Mean age (yr)	53.7±11	56.1±11.1	59±9
Male gender (%)	28 (60)	24 (71)	40 (91)*
Arterial hypertension (%)	23 (49)	21 (62)	29 (66)
Diabetes mellitus (%)	11 (23)	6 (18)	9 (20)
Hypercholesterolemia (%)	15 (32)	18 (53)*	23 (52)*
Presence of grade 2 or 3 aortic atherosclerosis (%)	6 (13)	30 (88)*	40 (91)*
CFR	2.41±1	1.78±0.48*	1.87±0.58*

Values are expressed as number (%) unless otherwise indicated.

***p<0.05 vs group 1**

Table 31. Differentiation of patients with multivessel disease from all other patients

Variable	ROC area (95% CI)	*P*-value of ROC	Binary logistic regression OR (95% CI)	p-value
Hypertension	0.56 (0.46-0.67)	0.46	1.69 (0.78-3.68)	0.18
Diabetes mellitus	0.49 (0.39-0.61)	0.98	0.98 (0.40-2.44)	0.97
Hypercholeste-rolaemia	0.54 (0.43-0.65)	0.49	1.36 (0.64-2.88)	0.42
Age	**0.63 (0.53-0.73)**	**0.01**	**1.05 (1.00-1.09)**	**0.02**
Male gender	**0.63 (0.53-0.73)**	**0.02**	**4.59 (1.63-12.9)**	**0.01**
Grade of aortic atherosclerosis	**0.64 (0.54-0.74)**	**0.01**	**2.11 (1.22-3.64)**	**0.01**
CFR	0.41 (0.31-0.51)	0.09	0.57 (0.32-1.00)	0.05

ROC = receiver operator characteristic, OR = odds ratio, CI = confidence interval, CFR = coronary flow velocity reserve

Table 32. Differentiation of patients with multivessel disease from those with single-vessel LAD disease

Variable	ROC Area (95% CI)	*P*-value Of ROC	Binary logistic regression OR (95% CI)	p-value
Hypertension	0.52 (0.38-0.65)	0.68	1.14 (0.44-2.97)	0.78
Diabetes mellitus	0.50 (0.37-0.63)	0.98	1.01 (0.33-3.08)	0.98
Hypercholeste-rolaemia	0.48 (0.35-0.61)	0.79	0.87 (0.35-2.17)	0.77
Age	0.60 (0.46-0.73)	0.15	1.05 (0.10-1.10)	0.07
Male gender	0.59 (0.46-0.73)	0.17	3.30 (1.00-10.88)	0.05
Grade of aortic atherosclerosis	**0.63 (0.50-0.76)**	**0.05**	**2.15 (1.02-4.52)**	**0.04**
CFR	0.54 (0.41-0.67)	0.53	1.01 (0.41-2.5)	0.99

ROC = receiver operator characteristic, OR = odds ratio, CI = confidence interval, CFR = coronary flow velocity reserve

4.2.2. Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography

Study population: 112 consecutive patients (36 women and 76 men) with stable angina pectoris without a previous myocardial infarction were enrolled to this study. All of them underwent coronary angiography. None of the patients exhibited significant valvular heart disease. Cases with significant right coronary artery or left circumflex coronary artery stenosis were excluded from the study, because CFR measurements were made in the LAD. The following patient groups were compared: 17 consecutive patients with anatomically normal coronary arteries (group 1), 24 patients with non-significant CAD (group 2), 31 patients with significant stenosis of the LAD (group 3) and 40 patients with multivessel disease (group 4). Transoesophageal CFR measurement and transthoracic echocardiographic examinations were applied on all cases.

The demographic and clinical data on the patients are shown in Table 33. The prevalence of male gender was significantly higher in group 4 as compared with group 1. The average ages of the patients in groups 2, 3 and 4 were significantly higher than that in group 1 ($p<0.03$, $p<0.006$ and $p<0.001$, respectively). Interestingly, the prevalence of hypertension among the group 3 patients was similar to that in group 1. The prevalences of diabetes mellitus and hypercholesterolaemia were similar in the various patient groups.

Transthoracic echocardiography: The thickness of the interventricular septum and the left ventricular mass were higher in groups 2 and 4 as compared to group 1, but the difference was found to be significant between groups 1 and 4 ($p<0.03$ and $p<0.04$, respectively). The thickness of the posterior wall and left ventricular mass index tended to be higher in groups 2 and 4 compared to groups 1 and 3, but did not reach the level of significance. There was no significant difference between the four groups as concerns the ejection fraction and end-diastolic diameter. (Table 34).

Dipyridamole stress TEE: During stress, no patient displayed either significant ST-T changes in the ECG or limiting side-effects. The resting systolic and diastolic velocities were higher in groups 3 and 4 compared to groups 1 and 2, but did not reach the level of significance in these patient populations. The systolic velocities measured at the peak of stress did not differ between the groups. The diastolic velocities measured at the peak of stress were lower in groups 2, 3 and 4. Smax/Srest ratio was non-significantly decreased in groups 2, 3

and 4 compared to group 1. The CFR was significantly lower in groups 3 and 4 as compared with group 1 ($p<0.002$ and $p<0.02$, respectively). The mean CFR was also significantly lower between the same comparisons ($p<0.001$ and $p<0.001$, respectively). E(p) was significantly higher in groups 3 and 4 than in group 1 ($p<0.01$ and $p<0.05$, respectively). E(s) was higher in groups 3 and 4 compared to group 1. No significant relationship was found between group 2 and groups 3 and 4. (Table 35).

Table 33 Demographic and clinical data

	Group 1 (normal coronaries)	Group 2 (non-significant CAD)	Group 3 (LAD disease)	Group 4 (MVD)
No. of cases	17	24	31	40
Male (%)	7 (41)	14 (58)	22 (71)	33 (83)&
Age (years)	47.8±9.9	56.3±10.4*	57.3±9.8**	59.9±7.8***
Hypertension (%)	7 (41)	20 (83)@	18 (58)	31 (78)#
Diabetes mellitus (%)	4 (24)	9 (38)	6 (19)	9 (23)
Hypercholesterolaemia (%)	9 (53)	8 (33)	15 (48)	20 (50)

Values are expressed as number (%) unless otherwise indicated.

*** p<0.03 vs group 1; ** p<0.006 vs group 1; *** p<0.001 vs group 1; & p<0.004 vs group 1; @ p<0.008 vs group 1; # p<0.01 vs group 1**

Table 34 Transthoracic echocardiographic data

	Group 1	Group 2	Group 3	Group 4
EDD (mm)	50.5±6.6	54.1±7.2	54.6±6.8	53.7±5.9
IVS (mm)	9.5±1.2	11.0±2.4	10.2±1.7	11.5±2.4*
PW (mm)	9.3±1.2	10.9±2.3	10.1±1.6	11.0±2.4
EF (%)	62.0±8.5	63.2±10.5	62.4±10.6	62.2±10.2
LVM (g)	215.9±56.7	307.6±131.7	272.0±72.9	311.2±108.9**
LVMI (g/m^2)	115.4±31.5	162.8±68.4	142.6±39.0	162.0±56.6

*** p<0.03 vs group 1; ** p<0.04 vs group 1**

Table 35 Coronary flow velocities, CFRs and indices of aortic distensibility in the various groups

Coronarogram	Group 1 (normal coronaries)	Group 2 (non-significant CAD)	Group 3 (LAD disease)	Group 4 (MVD)
Srest	26.1±8.5	24.5±9.6	30.0±13.1	32.1±12.3
Smax	56.9±27.2	49.5±29.8	54.3±32.2	65.4±35.0
Smax/Srest	2.31±1.08	2.04±1.02	1.86±0.66	2.19±1.13
Drest	55.1±18.2	54.6±21.0	63.4±27.5	65.4±25.4
Dmax	131.5±42.3	109.3±45.5	103.2±35.4	118.0±39.4
CFR	2.60±1.23	2.06±0.69	1.75±0.45*	1.95±0.73**
Mean CFR	2.73±0.95	2.25±0.65	1.76±0.51#	1.72±0.51##
E(p)	0.45±0.23	0.70±0.39	0.93±0.54@	0.83±0.55@@
E(s)	5.49±4.22	6.75±4.11	9.77±6.67	7.99±6.58

*** p<0.002 vs group 1; ** p<0.02 vs group 1; # p<0.001 vs group 1; ## p<0.001 vs group 1; @ p<0.01 vs group 1; @@ p<0.05 vs group 1**

4.2.3. Coronary flow velocity reserve and aortic distensibility indices in patients with different grades of aortic atherosclerosis

Study population: A total of 113 consecutive patients (77 men and 36 women, aged 31 to 80 years) underwent stress TEE assessment of the CFR. Patients were divided into three groups: cases without AA (group 1), cases with intimal thickening (group 2) and cases with aortic plaque (group 3). All patients had stable angina pectoris without a previous myocardial infarction. All patients underwent coronary angiography for the evaluation of chest pain with the following results: negative, non-significant CAD, significant LAD stenosis or significant multivessel disease. Patients with left circumflex coronary artery and/or right coronary artery stenosis were excluded from the study, because the CFR characterizes the functionality of the LAD and the measurements were made here. MVD was defined as significant stenosis of two or more major coronary arteries or significant left main coronary artery stenosis. Transthoracic echocardiographic examination was performed in all cases, and none of the patients was found to exhibit significant valvular heart disease.

The demographic and clinical data on the patients are shown in Table 37. The average age of the patients with higher grades of AA (groups 2 and 3) was significantly higher than that of the patients without frank AA (group 1). The numbers of patients in the subgroups, depending on the grade of AA and the result of coronary angiography, are presented in Table 38. The prevalence of patients with negative coronary angiograms was significantly less for the higher grades of AA (groups 2 and 3) as compared with the group 1 cases.

TTE: The thickness of the interventricular septum (IVS) and the left ventricular mass (LVM) were significantly increased in group 3 as compared with group 1 ($p<0.04$, in both cases). The thickness of the posterior wall and the LVM index tended to be higher in groups 2 and 3 than in group 1, but the difference did not reach the level of significance. There was no significant difference between the three groups as concerns the ejection fraction or end-diastolic diameter (Table 39).

Dipyridamole stress TEE: During stress, no patient displayed either significant ST-T changes in the ECG or any other procedure's limiting side-effects. The resting systolic velocities increased, while the systolic velocities measured at the peak of stress decreased in parallel with the aortic grade. The diastolic flow velocities behaved similarly. The value of Smax/Srest calculated from the changes in the systolic velocities decreased in parallel with

the grade of AA and a significant difference was found between groups 1 and 3. Finally, the CFR (calculated as Dmax/Drest) and the mean CFR also decreased with the aortic grades, and a significant difference was found between groups 2 and 3 as compared with group 1. Interestingly, there was no difference in CFR or mean CFR between groups 2 and 3. E(p) and E(s) likewise increased with the grade of AA. A significant difference was found when group 3 was compared to groups 1 and 2 (Table 40).

Table 37. Demographic and clinical data on the patients

	Group 1 (no AA)	Group 2 (aortic intimal thickening)	Group 3 (aortic plaque)
n	24	49	40
Age (years)	47.7±8.7	56.8±9.6*	61.7±7.1*/**
Male (%)	17 (71)	38 (78)	22 (55)***
Hypertension (%)	13 (54)	37 (76)	28 (70)
Diabetes mellitus (%)	6 (25)	10 (20)	14 (35)
Hypercholesterolaemia (%)	13 (54)	17 (35)****	24 (60)

Values are expressed as numbers (%) unless otherwise indicated.

***p<0.001 vs group 1; ** p<0.03 vs group 2; ***p<0.05 vs group 2; ****p<0.05 vs group 3**

Table 38. Numbers of patients in the different subgroups

Coronary angiogram	Group 1	Group 2	Group 3
Negative (%)	8 (33)*	5 (10)	3 (8)
Non-significant coronary artery disease (%)	7 (29)	9 (18)	8 (20)
LAD disease (%)	4 (16)	16 (33)	11 (28)
Multivessel disease (%)	5 (21)	19 (39)	18 (45)

Values are expressed as numbers (%) unless otherwise indicated.

***p<0.05 vs groups 2 and 3**

Table 39 Transthoracic echocardiographic data

	Group 1 (no AA)	Group 2 (aortic intimal thickening)	Group 3 (aortic plaque)
EDD (mm)	52.3±7.2	54.3±6.9	53.5±5.7
IVS (mm)	10.0±1.1	10.7±2.0	11.4±2.7*
PW (mm)	9.8±1.1	10.5±1.9	11.1±2.7
EF (%)	63.6±11.9	62.3±8.9	62.1±10.1
LVM (g)	240.1±62.9	291.8±105.5	310.3±119.8*
LVMI (g/m^2)	128.2±33.9	152.3±55.3	162.4±62.3

*** p<0.04 vs group 1**

Table 40 Coronary flow velocities, CFRs and indices of aortic distensibility in the various groups

	Group 1	Group 2	Group 3
Srest	26.5±12.1	27.9±8.8	31.6±14.1
Smax	62.6±33.1	60.3±36.8	51.7±24.8
Smax/Srest	2.46±0.95	2.18±1.10	1.76±0.73**
Drest	53.8±25.5	64.5±24.7	61.5±22.7
Dmax	129.0±43.3	116.7±40.2	103.8±37.7
CFR	2.67±1.09	1.94±0.67*	1.74±0.47*
Mean CFR	2.64±0.89	1.83±0.58*	1.76±0.46*
E(p)	0.53±0.26	0.70±0.45	0.99±0.58@#
E(s)	6.03±3.38	7.37±5.58	9.39±7.16

*** p<0.001 vs group 1; ** p<0.02 vs group 1; @ p<0.002 vs group 1; # p<0.05 vs group 2**

4.2.4. Decreased aortic distensibility and CFR in patients with significant aortic valve stenosis with normal epicardial coronary arteries

Study population: The study population consisted of 71 hospitalized patients (42 men and 29 women; mean age 57.3±11.3 years) with stable angina pectoris. All patients underwent transthoracic echocardiography, stress TEE as CFR measurement and coronary angiography. The following patient populations were compared: patients without valvular heart disease or CAD (group 1), AOS patients with normal epicardial coronary arteries (group 2), and patients with significant stenosis of the LAD (group 3). During stress TEE, the indices of aortic distensibility were also evaluated and calculated from echocardiographic parameters and blood pressure data.

The demographic and clinical data on the patients are shown in Table 41. The prevalence of male gender was significantly higher in group 3 as compared with group 2. The average ages of the patients in groups 2 and 3 were significantly higher than group 1, and significant difference was found also between the values of groups 2 and 3. The prevalences of hypertension, hypercholesterolemia and diabetes mellitus were similar in the various patient groups.

Transthoracic echocardiography: The thickness of the interventricular septum, posterior wall, and the left ventricular mass and LVM index were higher in group 2 as compared to groups 1 and 3. There was no significant difference between the three groups as concerns the ejection fraction and end-diastolic diameter. (Table 42).

Dipyridamole PSTEE: During the stress, no patient displayed either significant ST-T changes on ECG or limiting side-effects. The resting systolic velocities were similar in the patient groups. The systolic velocities measured at the peak of stress were higher in group 1 than in group 2 and 3, but did not reach the level of significance. The resting diastolic velocities were increased in groups 2 and 3 compared to group 1. These differences did not reach the level of significance in this patient population. The diastolic velocities measured at the peak of stress was significantly decreased in group 3 compared to group 1. The Smax/Srest and CFR were significantly lower in groups 2 and 3 as compared with group 1. E(p) and E(s) were increased in groups 2 and 3. (Table 43).

Table 41. Demographic and clinical data of the patients

	Group 1 (Negative coronaries)	Group 2 (AOS)	Group 3 (LAD disease)
No of patients	22	18	31
Age (years)	48.5±8.2*/#	67.8±8.0	57.3±9.8*
Male gender (%)	11 (50)	9 (50)	22 (71)@
Hypertension (%)	12 (55)	14 (78)	18 (58)
Diabetes mellitus (%)	6 (30)	5 (28)	6 (19)
Hypercholesterolaemia (%)	10 (45)	4 (22)	16 (51)

Values are expressed as numbers (%) unless otherwise indicated.

*** p<0.001 vs group 2; # p<0.01 vs group 3; @ p<0.05 vs group 2**

Table 42. Tranthoracic echocardiographic data

	Group 1	Group 2	Group 3
IVS (mm)	9.6±1.3	14.4±3.8*/#	10.2±1.7
PW (mm)	9.5±1.3	13.2±2.4*/#	10.1±1.6
EDD (mm)	49.8±7.2	55.5±7.4	54.6±6.8
EF (%)	64.3±8.3	59.5±10.7	62.4±10.6
LVM (g)	216.9±61.4	421.8±110.3*/#	272.1±72.9
LVMI (g/m^2)	115.7±35.1	220.9±58.3*/#	142.7±39.0

*** p<0.001 vs group 1; # p<0.01 vs group 3**

Table 43. Coronary flow velocities, CFRs and elastic properties of the aorta

	Group 1	Group 2	Group 3
Srest	27.4±8.3	29.1±10.0	30.0±13.1
Smax	64.0±25.6	51.7±25.7	54.3±21.2
Smax/Srest	2.50±1.12	1.87±0.56	1.86±0.66@
Drest	55.3±16.9	68.7±23.7	63.4±27.5
Dmax	138.9±36.0	120.1±43.1	103.2±35.4*
CFR	2.72±1.09	1.89±0.39*	1.75±0.45#
E(p)	0.48±0.25	0.90±0.62@	0.93±0.54*
E(s)	4.97±2.88	9.78±6.89@	9.77±6.67*

*** p<0.01 vs group 1; # p<0.001 vs group 1; @ p<0.05 vs group 1**

5. Discussion

5.1. Factors affecting coronary flow velocity reserve

5.1.1. Coronary flow velocity reserve in patients undergoing coronary angiography (the effect of micro- and macrovascular resistance)

Our results confirm the previous findings that CFR is severly reduced in patients with suspected microvascular disease. There was a good correlation in CFR of patients with suspected X syndrome (negative coronary angiography, positive stress test) with the result of Zehetgruber et al. (1.24±0.21 vs 1.21±0.23) (16). The CFR of patients with non-significant coronary artery disease was significantly decreased compared to cases with normal epicardial coronary arteries. The CFR of cases with LAD disease was 1.77±0.47 which correlated with results of Paraskevaidis et al, who found CFR 1.8 before PTCA. There was no further decrease in LAD-CFR if a significant stenosis of another major coronary artery was associated. The CFR of patients with CX and RC disease was higher compared to LAD disease, the difference reached the level of significance in CX disease. In patients with CX and RC disease the CFR was similar as in patients with significant stenosis of the LAD and CX/RC. The CFR depends on the degree of the LAD stenosis (in case of higher degree of stenosis the CFR is more decreased), the difference was not significant. These results well correlated with results of Stoddard et al. (17). In patients with >70% LAD stenosis the CFR was 1.52 (in our patient population 1.71±0.47), in cases with lower degree of stenosis was 1.93 (in our patient population 1.96±0.65). The CFR depends also on the location of the LAD stenosis. Hutchinson et al. found more decreased CFR in proximal LAD stenosis than distal one (18).

5.1.2. Coronary flow velocity reserve in patients with left ventricular hypertrophy

5.1.2.1. Coronary flow velocity reserve in patients with aortic valve stenosis

Our results confirm the previous findings that transoesophageal Doppler echocardiographic measurement of the LAD velocities is a useful tool for evaluation of the CFR in patients with AOS. In accordance with earlier studies, we have demonstrated that the CFR is decreased in patients with AOS with normal coronary arteries and is reduced to similar extents in patients

with LAD disease (19-22), and it increases after AVR (23,24). However, there is no agreement as to the reason for the improvement of the CFR after a long-term follow-up of AVR. The resting diastolic velocity was significantly decreased after the operation. It was the main reason for the improvement in the CFR. Interestingly, the diastolic velocity measured at the peak of stress decreased after AVR. However, the diastolic velocities decreased to different extents. The improvement in the CFR showed a parallel tendency with the regression of the left ventricular hypertrophy. The CFR was similarly decreased in AOS patients with or without severe LAD disease, and could not be used to distinguish between these patient populations. Neither the age, the gender, the presence of the hypertension, the diabetes mellitus and the hypercholesterolaemia nor the CFR, only the grade of aortic atherosclerosis was suitable for the prediction of AOS patients with significant LAD stenosis from those without it.

Pathophysiological explanation of CFR reduction: The CFR capacity of the coronary arteries depends on at least the following main components: 1. micro- and macrovascular resistance; 2. myocardial resistance; and 3. hyperviscosity and metabolic changes (25,26). In some pathologic conditions; changes in one or other of these factors may lead to an impairment of the CFR capacity. In patients with LAD disease, the key role of the increase in micro- and macrovascular resistance has been demonstrated by a number of authors (8,25,27-30). On the other hand, in the absence of significant CAD, the CFR can be reduced by an increase in myocardial resistance, as revealed in patients with hypertension (31,32) or hypertrophic cardiomyopathy (33,34), but not in physiological left ventricular hypertrophic sportsmen (35).

Comparison with previous studies: Pathological left ventricular hypertrophy is known to impair the coronary flow velocity reserve (21-24,31-34), but in endurance athletes it is supranormal. The reason for that is an enhanced endothelium-independent vasodilatation (35). Our results are in keeping with the data of Julius et al. who demonstrated CFR values in the range 1.5-2 in patients with aortic stenosis and normal coronary arteries, independently of the presence or absence of anginal pain (21). Coronary reserve was examined in patients with aortic valve disease before and after successful aortic valve replacement (23,24). CFR was diminished in preoperative compared with postoperative patients (1.66 ± 0.44 vs 2.22 ± 0.85; $p<0.05$) as well as with controls (vs 2.80 ± 0.84; $p<0.01$). Eberli et al. investigated the CFR of patients with aortic valve disease before and after AVR by the coronary sinus thermodilution technique. Entirely different patient groups were examined before and after AVR. The CFR

was significantly different in the various patient groups (24). They found that the reduced coronary vasodilator capacity was mainly due to an elevated coronary flow at rest, while the maximal coronary blood flow achieved was identical to that in postoperative patients and controls. With the regression of the left ventricular hypertrophy, the flow at rest decreases and this leads to a distinct improvement in the CFR. Hildick-Smith et al. performed an adenosine transthoracic echocardiographic follow-up study in patients with aortic stenosis and normal coronary arteries (23). The resting diastolic velocities were similar under pre- and post-AVR conditions. During hyperaemia, the post-AVR diastolic velocity was significantly higher than the pre-AVR diastolic velocity. The CFR was increased after AVR for aortic stenosis, this increase occurring in tandem with the regression of the left ventricular hypertrophy.

Non-angiographic identification of AOS in patients with CAD: The TEE examination of thoracic atherosclerotic plaque is a powerful predictor of the absence of significant CAD in patients with AOS. Tribouilloy et al. found that the presence of aortic plaque revealed by TEE identified significant CAD with a sensitivity of 90.5%, a specificity of 72.5%, and positive and negative predictive values of 75.0% and 89.3%, respectively. They concluded that TEE can not be regarded as a substitute for coronary arteriography (36). Dipyridamole stress myocardial perfusion tomography is well tolerated, even by patients with severe AOS, and is of high diagnostic value in the assessment of CAD (37). Dobutamine stress echocardiography may be safely performed in patients with AOS. Side-effects are more common than in patients with CAD, but are usually well tolerated without any need for medical treatment (38). SPECT dipyridamole-thallium imaging is a useful noninvasive method to exclude the diagnosis of significant CAD (high specificity) in asymptomatic and symptomatic patients with isolated severe AOS (39). Adenosine stress echocardiography and adenosine stress myocardial perfusion scintigraphy, either separately or in combination, constitute excellent and safe noninvasive diagnostic methods for the detection of CAD in patients with severe AOS (40). Noninvasive pharmacological stress transthoracic echocardiographic examination with dipyridamole is one of the methods of choice for CAD identification in patients with AOS (41).

5.1.2.2. Coronary flow velocity reserve in patients with hypertrophic cardiomyopathy

In the patients with HCM the CFR was decreased. The peak diastolic velocity was significantly lower, while the resting diastolic velocity was slightly increased in the patients with HCM because of the considerably increased LVM. In the presence of obstruction, the CFR was somewhat, but not significantly lower.

Comparison with previous studies on patients with HCM: The decreased CFR in patients with HCM is well documented (42-61). The CFR can be measured during stress transoesophageal echocardiography (33,46-49), by means of intracoronary Doppler-wire (43,54,55), MRI (58), PET (53,57) or chromatography (56). The possibility also exist to measure the CFR with transthoracic echocardiography (52) (Table 44). The CFR was decreased in HCM in all cases. However, in our patients with HCM and in the control subjects the CFR varied in a wide range, which verified the well-known fact that the CFR is highly dependent on the method used and the vasodilator agent (25). Harjai et al. concluded that at this time coronary angiography is the only reliable test for the definitive diagnosis of co-existent coronary artery disease in HCM (48).

The effect of outflow obstruction on the CFR: No relationship found between the outflow gradient and the systolic or diastolic velocities by Crowley et al. (59). An inverse relationship was observed by Memmola et al. between the CFR and the presence of an outflow gradient (33). Our results suggest that the CFR is slightly lower in the presence of obstruction. In these cases, the posterior wall was thicker and the left ventricular mass was significantly higher as compared with the HCM patients without an aortic outflow tract gradient. The baseline diastolic velocity was higher, while the peak diastolic velocity was lower in cases involving obstruction.

Table 44 CFR in patients with HCM in earlier studies

Authors	N	CFR (HCM)	CFR (Control)	P	Method	Vasodilator agent
Nemes et al. (present work)	6 HOCM 13 HCM	1.9±0.61 2.25±0.7	3.16±1.1	0.001	TEE	Dipyridamole (0.56 mg/kg)
Dimitrow et al. (49)	10 HCM	2.37±0.67	-	-	TEE	Dipyridamole (0.56 mg/kg)
Memmola et al. (33)	10 HCM	1.8±0.3	3.1±0.5	0.01	TEE	Dipyridamole
Asami et al. (52)	7 HCM	1.6±0.4	2.7±0.4	0.001	TTE	0.15 mg/kg /min adenosine triphosphate
Schwartzkopff et al. (56)	13 HCM	2.28±0.6	5.34±1.49	0.003	Inert chromatographic argon method	Dipyridamole (0.5 mg/kg)
Kyriakidis et al. (55)	20 HOCM	2.2±0.4	-	-	Intracoronary Doppler catheter	12 mg Papaverine
Negishi et al. (43)	8 HCM	1.7±0.1	2.6±0.1	0.05	Intracoronary Doppler catheter	Vasodilator
Krams et al. (54)	10 HCM	1.8±0.9	2.6±0.8	0.05	Intracoronary Doppler catheter	Adenosine
Lorenzoni et al. (53)	84 HCM	NYHA I=1.93±0.64 NYHA II=1.69±0.54 NYHA III=1.4±0.43	-	-	N13-ammonia or O15-water PET	Dipyridamole
Choudhury et al. (57)	15 HCM	1.45±0.52	-	-	O15-water PET	Dipyridamole
Kawada et al. (58)	29 HCM	1.72±0.49	3.01±0.75	0.01	VEC MR	Dipyridamole (0.56 mg/kg)

5.1.3. Coronary flow velocity reserve and hypercholesterolaemia

CFR evaluated by dipyridamole stress TEE is decreased in patients with a negative coronary angiogram but increased cholesterol level compared to cases with a normal cholesterol level without a history of hypercholesterolaemia and who did not receive lipid-lowering therapy. In patients participating in inadequate lipid-lowering medication the CFR is decreased to a similar extent as in patients not receiving lipid-lowering therapy. In patients who receive lipid-lowering therapy and who exhibit an increased cholesterol level, the CFR is decreased. In patients with a normal cholesterol level in consequence of the lipid-lowering therapy, the CFR is practically normal, but is somewhat lower than in those who have never received anti-lipid medication.

Comparison with previous studies: The CFR evaluated by means of PET is decreased even in anatomically normal coronary arteries in hypercholesterolaemic patients (62). Yokoyama et al. reported that the CFR is reduced in patients with familial hypercholesterolaemia (FH) (63). Pitkanen et al. found a reduced CFR in young men with FH. The results demonstrate a very early coronary vasomotion impairment in hypercholesterolaemic patients (64), and also abnormalities in coronary flow regulation in young asymptomatic familial combined

hyperlipidemia patients expressing phenotype IIB (65). The results of Baller et al. suggest that cholesterol-lowering therapy with simvastatin may improve the overall coronary vasodilator capacity assessed noninvasively by PET in patients with mild to moderate hypercholesterolemia. Consequently, intensive lipid-lowering therapy is recommended as a vasoprotective treatment for selected patients in very early stages of coronary atherosclerosis with the aim of preventing further disease progression (66). Mellwig et al. found that a 30% improvement in coronary vasodilatation capacity could be demonstrated quantitatively and noninvasively by PET within 24 h after a single LDL apheresis (67). The low-density lipoprotein cholesterol level but not the total cholesterol level, correlated inversely with the CFR in hypercholesterolaemic subjects (68). The improvements in stress blood flow and CFR are delayed as compared with the lipid-lowering effect of fluvastatin, suggesting a slow recovery of the vasodilatory response to adenosine (69). All of these results were examined by means of PET.

5.2. Coronary flow velocity reserve and aortic atherosclerosis and distensibility

5.2.1. Coronary flow velocity reserve and the grade of aortic atherosclerosis in the prediction of severe coronary artery disease

Our results confirm that the age, the gender and the grade of aortic atherosclerosis were suitable for the prediction of patients with multivessel disease from all other cases. Moreover, a new prediction model was created which verified that the grade of AA exhibits an important additional value for predicting MVD. Additionally, the grade of AA exhibits good prognostic power for the differentiation of LAD disease patients from those with MVD. The CFR was significantly decreased in patients with vs. without CAD, but it was unable to distinguish patients with significant stenosis of the LAD from those with MVD, and had no predictive value in the evaluation of MVD.

Previous studies found, that the detection of AA by TEE may be a marker for CAD in different patient populations (13,70-77). Acarturk et al. reported that the sensitivity and specificity of AA in the detection of CAD were 75.9% and 67.7% (70). The presence of atherosclerotic lesions in the thoracic aorta is a strong predictor of CAD only in patients <70 years old (72,73). In elderly patients, the detection of atherosclerotic aortic plaque by TEE is not useful in predicting significant CAD. The detection of atherosclerotic plaque by TEE in

the thoracic aorta is useful in the noninvasive prediction of the presence and severity of CAD in patients with valvular heart disease (74), even in the elderly (75). Multiplane TEE examination of thoracic atherosclerotic plaque is a marker for CAD in women and is an especially powerful predictor of the absence of significant CAD (76). Multivariate logistic regression analysis showed that aortic plaques were a stronger predictor of CAD than were conventional risk factors (77). Khoury et al. observed a strong correlation between the presence of significant CAD and aortic, femoral and carotid atherosclerosis (78). The sensitivity and specificity of the presence of AA for the detection of CAD were the highest from among all the sites measured. The AA "score" (the sum of the plaque thickness in millimetres at distinct locations in the descending aorta) was significantly higher in patients with CAD than without it, though this variable did not distinguish patients with one-, two- or three-vessel disease. In contrast, we used a five-scale system (13) to characterize AA during TEE in our study, which differentiated the groups of patients with single-vessel LAD disease vs. MVD. The presence of significant obstruction in other vessels than the LAD impair the estimation of LAD stenosis and is also influenced by a microvascular dysfunction (79). The invasive assessment of the relative CFR overcomes this problem, but necessitates placement of a Doppler wire in two coronary arteries (80). However, the TEE-CFR is similarly decreased in patients with significant LAD stenosis and in cases with MVD, but it is unable to differentiate them.

5.2.2. Coronary flow velocity reserve and indices of aortic distensibility in patients after coronary angiography

Vascular properties of the aorta and CFR evaluated by stress TEE have been assessed simultaneously in patients after coronary angiography. The results demonstrate decreased CFR (and mean CFR) and increased indices of aortic distensibility in patients with LAD disease as compared to patients with normal epicardial coronary arteries. There were no further changes in these values in cases with MVD. In patients with non-significant coronary artery stenosis, the CFRs and stiffness moduli fall between those for the negative cases and patients with LAD disease/MVD.

Comparison with previous studies: Bogren et al. used magnetic resonance imaging and suggested that there was a reduction in coronary flow in patients with a decreased aortic distensibility (81). The effect of a decreased aortic distensibility on myocardial perfusion has been investigated; an additive effect on myocardial ischaemia was revealed in the presence of

coronary artery stenosis (82,83). Previously mainly the relationship between hypertension, antihypertensive therapy and vascular properties was investigated, but the E(p) and E(s) in patients with different kinds of coronary angiogram were never have been assessed (84-89). The effect of hypertension on the CFR is also well-known. The 41-83% of the patients in the different groups had hypertension, which is one of the limitations of this study. Ivanovic-Krstic et al. reported that in elderly persons with isolated systolic hypertension the aortic distensibility was significantly lower in comparison to normotensive subjects of the same age. They also found inverse correlation between the aortic distensibility and the mean systolic blood pressure (85). According to their findings, patients with non-significant CAD is a good example for the influence of hypertension on CFR as well as indices of aortic distensibility. However, where significant CAD was accompanied with hypertension, CFR and E(p) showed significant difference. E(s) in patients with LAD disease/MVD was also higher, but these values because of the high standard deviation and relatively low patient number showed no mathematical significance. These data underlines the fact, that vascular atherosclerosis has a higher influence on CFR and indices of aortic distensibility than hypertension. Previous studies also found that nifedipine administration increases the aortic distensibility in both normal subjects and patients with CAD (84).

5.2.3 Coronary flow velocity reserve and indices of aortic distensibility in patients with different grades of aortic atherosclerosis

Transoesophageal Doppler echocardiography can be used for the parallel evaluation of the grade of AA, the indices of aortic distensibility and the CFR. The CFR was reduced in patients with even minimal grade of AA in case of aortic intimal thickening relative to cases without relevant aortic atherosclerosis. Interestingly no further decrease was observed in patients with frank higher grades of AA (in the presence of different grades of aortic plaque). The indices of aortic distensibility increased continuously in parallel with the aortic grade, and significant differences were found between patients with grade 2-3 or with grade 0 or 1 AA.

Previous studies showed a strong correlation between aortic plaque and CAD. In the present study, an appreciable relationship has been found between CFR as a functional marker of the LAD stenosis as well as the presence of AA. This association has even been observed in the

occurance of intimal thickening as the minimal grade of AA. Increased aortic stiffness was incident to echocardiographically evaluated higher grade of AA.

Comparison with previous studies: Thoracic aortic atherosclerosis determined by TEE in autopsy studies is associated with increasing age and the evidence of significant CAD was found earlier as in the present study (77,90-93). Aortic plaque is useful in the noninvasive prediction of the presence and severity of CAD as earlier discussed (70-77). Other authors found also good correlations between the atherosclerosis of periferial vessels and aorta as well as CAD (78).

5.2.4. Coronary flow velocity reserve and indices of aortic distensibility in aortic stenosis patients with a negative coronary angiogram

We have demonstrated a reduced CFR, characterizing the diminished reserve capacity of the LAD, and altered aortic distensibility (increased E(p) and E(s), as functional markers of the descending aorta) in AOS patients with normal epicardial coronary arteries and in cases with significant stenosis of the LAD as compared to patients without valvular heart disease or significant CAD.

Previous studies demonstrated an impaired CFR in the presence of left ventricular hypertrophy as in aortic stenosis discussed earlier. The measurement of aortic wall thickness and stiffness is highly attractive measures of the structural and functional alterations caused by atherosclerosis, hypertension and other degenerative process (94). An increased aortic distensibility indices as functional markers of the descending aorta was found in AOS patients without epicardial CAD. As revealed by previous studies, the CFR is decreased in AOS, and increases during the long-term follow-up of AVR in parallel with the regression of left ventricular hypertrophy. Nevertheless, the CFR does not reached the level in patients without valvular heart disease or significant epicardial CAD, suggesting that other factors may also play a role in the pathogenesis of the impairment of the CFR in AOS. The present study has demonstrated a decreased aortic distensiblity and an appreciable stiffness of the descending aorta in AOS patients with normal epicardial coronary arteries. This result can be explained as an early manifestation of the atherosclerotic process, decreased perfusion of the aorta etc., and it requires further investigation.

6. Conclusions (new observations)

1. There is a considerable benefit of prosthetic aortic valve replacement as concerns the coronary flow velocity reserve in patients with a normal coronary angiogram after a long-time follow-up in parallel with the regression of left ventricular hypertrophy.
2. Our results confirm that the grade of aortic atherosclerosis can be utilized to differentiate patients with aortic stenosis with severe LAD disease from AOS patients with a negative coronary angiogram. The CFR is unsuitable for the prediction and differentiation of these patient populations, cannot be regarded as a substitute for coronary angiography and from a practical point of view is useless. If grade 2-3 AA is found, the coronary angiography is advisable.
3. There is a considerable stiffness of descending aorta in patients with AOS but with normal epicardial coronary arteries. The indices of aortic distensibility are similarly increased as to cases with significant LAD stenosis.
4. The grade of AA furnishes additional help in the prediction of patients with severe coronary artery disease. The grade of AA can differentiate patients with multivessel disease (MVD) from those with significant LAD stenosis. CFR has no any predictive power in this evaluation.
5. There is a decreased aortic distensibility (increased E(p) and E(s)) and also decreased CFR in patients with significant LAD stenosis and MVD as compared to patients with negative coronary angiogram. In patients with non-significant coronary artery stenosis, the CFR, mean CFR and stiffness moduli lie between those for negative cases and those for patients with LAD disease/MVD. Not only the CFRs, but also E(p) and E(s) displayed no further changes in cases with MVD as compared with LAD disease.
6. The CFR is decreased in patients with aortic intimal thickening, but no further decrease was observed in the event of aortic plaque. The indices of aortic distensibility increased continuously in parallel with grade of AA.

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Photocopies of essential publications