Beneficial effects of atorvastatin on myocardial regions with initially low vasodilatory capacity at various stages of coronary artery disease

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Abstract. *Purpose:* The aim of this study was to analyse non-invasively the regional effect of therapy with an HMG-CoA reductase inhibitor on myocardial blood flow in patients with coronary artery disease (CAD) with special reference to segments with initially substantially impaired vasodilation.
Methods: The study included 26 patients with untreated hypercholesterolaemia. Coronary angiography revealed CAD in nine patients with stenosis >50% and wall irregularities or minimal stenosis <30% in 17 patients. Before and 4.6±1.8 months after atorvastatin therapy, ^{13}N-ammonia positron emission tomography (PET) studies were performed at rest and under pharmacological stress. Minimum coronary vascular resistance (MCR) and coronary flow reserve (CFR) were determined. Segments were divided into those with normal or near-normal (MBF during adenosine ≥2.0 ml/min/g) and those with abnormal (MBF<2.0 ml/min/g) vasodilator flow response. In CAD patients, 156 segments were analysed, 85 of which had abnormal MBF; in the non-obstructive group, 59 of 297 segments had abnormal MBF.
Results: LDL cholesterol decreased after atorvastatin therapy from 186±43 mg/dl to 101±26 mg/dl (p<0.001). In normal segments no significant changes in MBF, CFR and MCR were found. However, initially abnormal segments showed significant improvements in MCR (15%, p<0.0001) and MBF during adenosine (30%, p<0.0001) after therapy.
Conclusion: The improvement in regional coronary vasodilator function after atorvastatin in patients with coronary atherosclerosis may be caused, at least in part, by increased flow-mediated (endothelium-dependent) dilation of the total arteriolar and arterial vascular system. These data further support the concept of non-invasive management of stable CAD by statin therapy and life-style modification guided by PET.

Keywords: Coronary artery disease – Hypercholesterolaemia – Atherosclerosis – Lipid-lowering drugs – Positron emission tomography

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Introduction

Functional vasomotor abnormalities of the coronary arteries are observed in early and advanced coronary atherosclerosis, regardless of the occurrence of haemodynamically significant segmental coronary narrowing. Traditional risk factors such as hypercholesterolaemia, smoking, diabetes, hypertension and coronary atherosclerosis itself impair both vasomotion of epicardial coronary arteries and distal arteriolar vasodilation, mediated at least in part by the endothelium under resting and stress conditions [1–7]. In addition, endothelial dysfunction, in terms of reduced vasodilatory capacity when used as a clinical surrogate for the integrity of vascular function, may be regionally heterogeneous among different coronary arteries, along the lengths of coronary arteries and within the microcirculation [2, 5, 6].

Previous observations using quantitative positron emission tomography (PET) flow measurements in patients with hypercholesterolaemia, normal coronary angiogram or minimal, non-obstructive coronary artery disease (CAD) have revealed a global improvement in coronary vasodilator function after several months of lipid-lowering therapy using different drugs [8–10].

We attempted to test the hypothesis that atorvastatin therapy combined with life-style modification would improve the vasodilator response in myocardial segments with markedly restricted pretreatment vasodilatory capacity. This could be of particular clinical importance, because

these are the regions most vulnerable to developing ischaemia during exercise or other stress conditions. Therefore, we non-invasively investigated the effect of short-term statin therapy in patients with various stages of CAD, previously untreated hypercholesterolaemia and initially substantially impaired vasodilator function. The assessment of whether patients had non-obstructive CAD or obstructive CAD was based on coronary angiography. A 20-segment model was used since this was expected to permit a more precise regional analysis of vasodilator function even in the presence of haemodynamically important coronary stenoses.

Materials and methods

Study population

Our study included 26 patients (16 men, 10 postmenopausal women) with a mean age of 63 years (range 46–75 years) and a baseline low-density lipoprotein (LDL) cholesterol level of >150 mg/dl, who were clinically suspected of having functionally significant CAD. In female patients no hormone replacement therapy was given. Because some patients were pretreated with various anti-anginal and antihypertensive drugs, they were allowed to continue their medication without change during follow-up. In detail, ten patients received β-blocking agents, one was given a calcium antagonist and ten received ACE inhibitors. All vasoactive medications were discontinued ≥12 to 24 h before the patients underwent PET.

All patients were treated with a specific 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (atorvastatin) and received adjuvant dietetic counselling concerning a low-fat, cholesterol-reduced diet.

Exclusion criteria were pretreatment with lipid-lowering drugs, unstable angina, uncontrolled hypertension, current smoking, diabetes mellitus, dilated cardiomyopathy, significant echocardiographic left ventricular hypertrophy and severe concomitant internal diseases. Left ventricular ejection fraction was normal in all patients. Patients continued taking their concomitant medications during the entire study period.

After baseline PET investigation, 10–80 mg of atorvastatin (depending on the baseline LDL cholesterol level) was administered once daily. The individual statin dose was 10 mg atorvastatin in six patients, 20 mg in 18, and 40 mg and 80 mg in two further patients. The mean atorvastatin dose was 20.7±13.5 mg. The dosage of atorvastatin was not changed during follow-up.

Anginal symptoms were reported according to a standardised questionnaire at baseline and before the second PET study according to the Canadian Cardiovascular Society (CCS) classification system [11].

Prior to initiation of the study, the local ethics committee had approved the study protocol. All patients gave their written informed consent.

Measurement of myocardial blood flow with PET

Myocardial perfusion was measured dynamically with ^{13}N-labelled ammonia PET under resting and stress conditions at baseline and at 4.6±1.8 months after the initiation of lipid-lowering therapy. As indicated above, cardiac medications were not changed during follow-up. All patients were asked to abstain from beverages containing caffeine 24 h before the scan.

Dynamic PET with a Siemens ECAT EXACT HR+ scanner was carried out after administration of 370–555 MBq of ^{13}N-ammonia under resting conditions and after adenosine. The adenosine test was applied for pharmacological recruitment of the maximum inducible vasodilatory capacity in the standard dosage of 0.14 mg/min/kg body weight during a 6-min intravenous infusion. ^{13}N-ammonia was injected in the second minute of infusion.

Directly after 10 min of transmission acquisition, the dynamic emission scan was performed with a sequence of 20 frames according to the following frame durations: twelve 10-s frames followed by five 30-s frames, two 120-s frames and one 300-s frame. All emission and transmission data were reconstructed iteratively [ordered subset expectation maximisation (OSEM); 4 subsets, 8 iterations] and by a 128×128 matrix.

Blood pressure was measured automatically and oscillometrically (Boso Oscillomat) during data acquisition at 2-min intervals. ECG and heart rate were registered in parallel. No ECG changes were observed during adenosine infusion.

Quantification of myocardial blood flow

Absolute myocardial perfusion values were determined at rest and under pharmacological stress. The image data were transformed into dynamic area-conserving polar maps, the pixels of which represented equal areas of the myocardial wall. This transformation is achieved with an automatic rendering program, described elsewhere in detail [12–14].

Quantification was performed pixel by pixel in dynamic polar maps using an irreversible two-tissue compartment model described by Hutchins et al. [15]. The polar maps were divided into 20 segments [16] and the average pixel values of each segment were calculated. Sixty-seven segments with a fractional blood volume >50%, indicative of an incorrect wall detection, were excluded from further analysis.

The following parameters of coronary vasodilatory capacity were determined: maximum adenosine-inducible coronary blood flow and minimum coronary vascular resistance (MCR) index, calculated from the ratio of mean arterial perfusion pressure to adenosine flow, measured from the third to the sixth minute of drug infusion.

Mean aortic perfusion pressure was determined non-invasively as the minimum diastolic arterial pressure plus one third of blood pressure amplitude.

Regional analysis of myocardial blood flow

A patient-based analysis of myocardial blood flow (MBF) at rest and in response to adenosine before and after atorvastatin treatment was performed. Segmental analysis was accomplished by evaluating all normal or near-normal segments, defined as having MBF ≥2.0 ml/min/g with adenosine. In the same way, abnormal segments, defined as having MBF <2.0 ml/min/g with adenosine, were evaluated [15, 17–19].

Coronary angiography

High-resolution coronary angiography was performed in all patients before the baseline PET study as described previously [8] and judged by two experienced investigators. Seventeen patients were considered to have non-obstructive CAD as indicated by stenosis ≤30% and/or wall irregularities. Nine patients had CAD with stenosis ≥50% in one or more coronary vessels.

Statistical analysis

All data are reported as mean values±1 standard deviation (SD).

Student's paired *t* test was used for comparison of lipid and coronary parameters before and after study intervention. Unpaired *t* test was used to compare MBF and MCR in patients with CAD and non-obstructive CAD.

Adenosine MBF response to atorvastatin was measured as the ratio of hyperaemic MBF after therapy to baseline hyperaemic MBF. Furthermore, Spearman rank correlation analysis was performed to correlate the hyperaemic MBF response to atorvastatin with baseline hyperaemic MBF and LDL cholesterol response to statin therapy.

All tests were two-tailed and a *p* value of less than 0.05 was considered statistically significant. Statistical analysis was performed with the StatView 5.0 software package (SAS Institute Inc., Cary, NC, USA).

Results

Lipid levels and clinical results

Total cholesterol, LDL cholesterol and triglycerides were markedly lower after atorvastatin therapy, whereas high-density lipoprotein (HDL) cholesterol remained unchanged on average (Table 1). After 4.6 months, atorvastatin had lowered LDL cholesterol by 53%. Atorvastatin therapy was well tolerated by all patients; no adverse events were observed.

CCS score decreased from 2.0±0.6 to 0.6±0.7 after statin therapy ($p<0.001$). Ten patients were free of cardiac symptoms after lipid-lowering therapy. Concomitantly, a decrease in body mass index was measured after about 4 months (26.8±3.1 kg/m^2 versus 26.2±3.0 kg/m^2, $p=0.019$). Body weight decreased from 77.7±12.7 kg to 76.1±11.6 kg ($p=0.019$).

Haemodynamic results

Haemodynamic parameters remained unchanged after atorvastatin therapy on average. There was a slight but non-significant increase in mean arterial pressure after statin therapy. Thus, heart rate and mean arterial pressure were rather comparable before and after atorvastatin therapy (Table 2).

Table 1. Plasma lipid fractions

	Before therapy	After therapy	Paired *t* test
TC (mg/dl)	260±44	169±38	$p<0.001$
LDL (mg/dl)	186±43	101±26	$p<0.001$
HDL (mg/dl)	54±8	50±9	$p=0.16$
TG (mg/dl)	158±98	101±46	$p<0.05$

TC plasma total cholesterol, *LDL* plasma low-density lipoprotein cholesterol, *TG* plasma triglycerides, *HDL* plasma high-density lipoprotein cholesterol

Table 2. Haemodynamic parameters before and after atorvastatin therapy

	Mean arterial blood pressure (mmHg)		Heart rate (beats/min)	
	Rest	Adenosine	Rest	Adenosine
Pre-therapy	93±11	90±11	66±12	84±13
Post-therapy	97±13*	95±13*	63±11*	83±14*

*Paired *t* test: $p\geq0.05$ (PET after atorvastatin vs PET baseline)

Myocardial blood flow and coronary resistance

Global MBF under resting conditions did not change. Under pharmacological stress conditions, MBF increased after therapy (Fig. 1, Table 3). However, coronary flow reserve and minimal coronary resistance index, taking into account arterial perfusion pressure, remained unchanged after atorvastatin therapy.

In normal or near-normal segments MBF at rest and during adenosine showed no significant changes (Table 3). Furthermore, coronary flow reserve and minimal coronary resistance index did not differ significantly after atorvastatin therapy.

In initially abnormal segments MBF at rest increased significantly. Under pharmacological stress conditions, MBF was markedly increased from 1.60±0.28 ml/min/g to 2.11±0.48 ml/min/g ($p<0.0001$). Coronary flow reserve remained without changes after atorvastatin therapy due to increased resting flow. However, minimal coronary resistance index showed a significant decrease from 56±14 to 49±14 mmHg/(ml/min/g) after treatment ($p<0.0001$).

There was a significant inverse correlation between adenosine MBF response to atorvastatin and baseline adenosine MBF ($p<0.0001$; $r=-0.605$).

Three patients (two with CAD and one with non-obstructive CAD) did not show improvement of regional vasodilatory capacity that was substantially impaired at baseline.

Hyperaemic MBF response to atorvastatin therapy at various stages of atherosclerosis in abnormal segments

In patients with CAD, 54% (85 of 156) of segments had abnormal adenosine MBF in comparison to 20% of patients with non-obstructive CAD (59 of 297).

In both patient groups, adenosine MBF and MCR showed significant improvement after atorvastatin therapy (Fig. 2). Under pharmacological stress conditions, MBF was significantly higher in patients with non-obstructive CAD than in patients with obstructive CAD before as well as after therapy. MCR was significantly lower in patients with non-obstructive CAD than in patients with CAD. There was no correlation between the adenosine MBF response to atorvastatin therapy and the LDL changes ($p=0.18$; $r=0.08$).

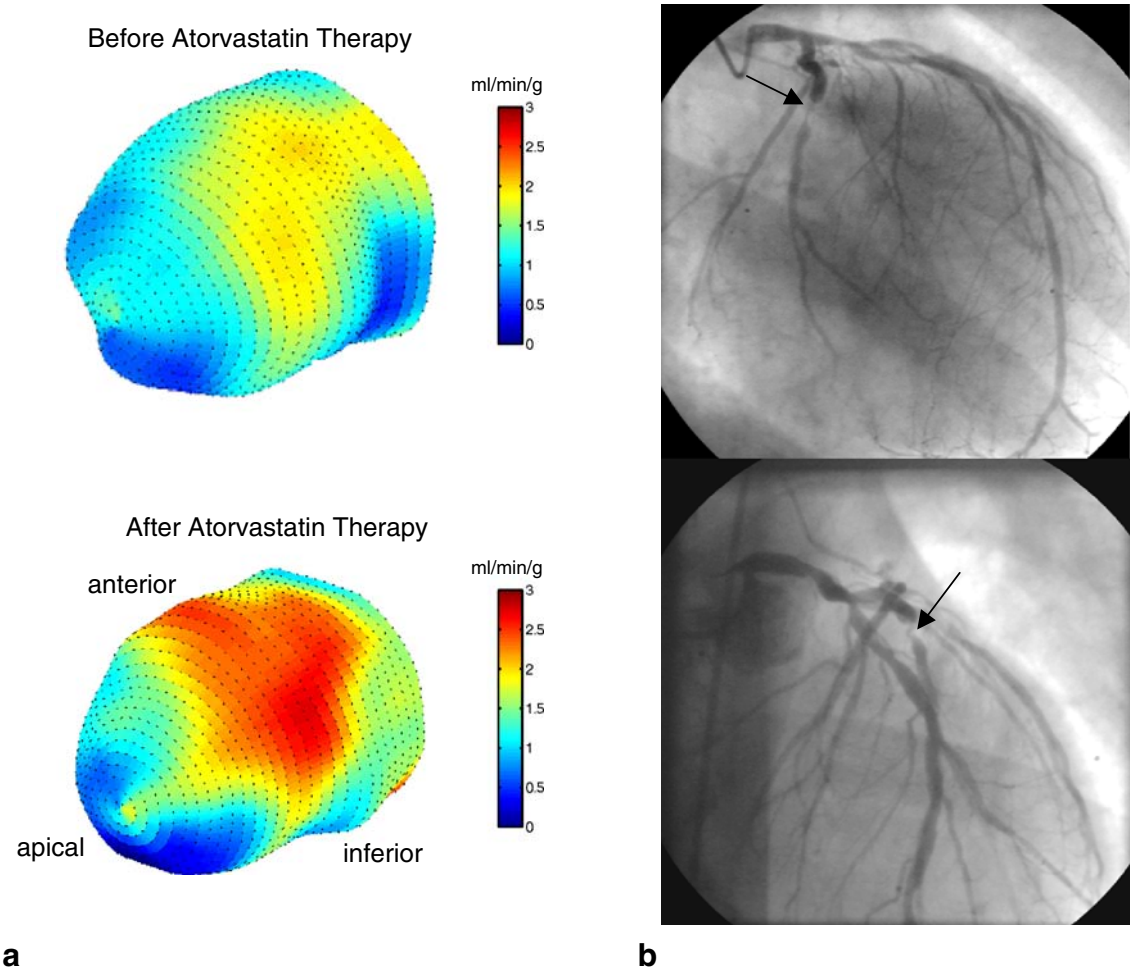

Fig. 1. Improvement of MBF response to adenosine after 3 months of atorvastatin therapy in a patient with advanced CAD. **a** MBF (adenosine) before and after atorvastatin therapy. There was a marked increase in the hyperaemic MBF in both the anterior (from 1.4±0.1 to 1.9±0.3 ml/min/g) and the lateral wall (from 1.2±0.3 to 1.7±0.5 ml/min/g). **b** Coronary angiography showing a high-degree stenosis of the marginal branch of the circumflex coronary artery (CX, *arrow*) and high-degree distal CX stenosis and intermediate stenosis of the left anterior descending coronary artery

Discussion

The major finding of our study is the significant improvement in regional coronary vasodilatory capacity after about 4 months of intensive LDL lowering by atorvastatin in patients with various stages of coronary atherosclerosis presenting substantial restriction of baseline dilator function. Furthermore, the study revealed an improvement in MBF even in patients with more advanced CAD after statin-induced decrease in LDL cholesterol and simultaneous modification of life-style, indicated by a decrease in body mass index. However, we have to concede that this PET-based investigation was not a controlled randomised study despite the relatively large number of patients.

Clinically, the increase in coronary vasodilatory capacity was accompanied by an improvement in symptoms, with a decrease in effort angina and angina-like symptoms. In particular, in myocardial segments with initially depressed vasodilatory capacity, cholesterol-lowering therapy induced a significant improvement in hyperaemic MBF. However, the magnitude of the blood flow response to adenosine-induced vasodilation depends to a large extent on the coronary perfusion pressure [20, 21]. Therefore, we also estimated the minimal coronary resistance index as a more physiological parameter of coronary dilatory capacity to normalise hyperaemic blood flow values for actual mean arterial pressure.

After short-term cholesterol-lowering therapy, a significant decrease in minimal coronary resistance in involved myocardial segments was observed. These results are in line with Gould et al.'s study of the effect of statin therapy for 3 months combined with life-style modification on relative perfusion in patients with CAD and marked hypercholesterolaemia [22]. In this regard, Guethlin et al. [23] demonstrated that myocardial flow reserve remained unchanged during the first 2 months of fluvastatin treatment, but increased after 6 months in angiographically documented multivessel CAD. Simvastatin has been found to improve regional and/or global vasodilatory capacity after 4–6 months in patients with ischaemic heart disease [17]

Table 3. Effects of atorvastatin therapy on MBF in patients with coronary atherosclerosis

	MBF (rest)	MBF (adenosine)	CFR	MCR
All segments (n=453)				
Pre-therapy	0.9±0.3	2.4±0.8	3.0±1.1	41±14
Post-therapy	0.9±0.2*	2.6±0.7*	3.1±1.0*	39±12*
Normal or near-normal segments[a] (n=309)				
Pre-therapy	0.9±0.4	2.8±0.6	3.3±1.1	34±8
Post-therapy	0.8±0.2*	2.7±0.6*	3.4±1.1*	35±9*
Abnormal segments[a] (n=144)				
Pre-therapy	0.7±0.2	1.6±0.3	2.4±0.9	56±14
Post-therapy	0.8±0.1**	2.1±0.5**	2.5±0.7*	49±14**

MBF myocardial blood flow (ml/min/g), *CFR* coronary flow reserve, *MCR* minimal coronary resistance [mmHg/(ml/min/g)]
*Paired t test: $p \geq 0.05$ (PET after atorvastatin vs PET baseline)
**Paired t test: $p<0.0001$ (PET after atorvastatin vs PET baseline)
[a] Cut-off threshold: initial MBF (adenosine): <2.0 ml/min/g

or without evidence of haemodynamically significant coronary artery stenosis [8]. In a recent study, Yokohama et al. found no changes in myocardial vasodilation after pravastatin therapy for 10 months in patients with hypercholesterolaemia and low probability of CAD, whereas simvastatin significantly improved MBF during hyperaemic stress [9]. Thus, it is suggested that improvement in myocardial vasodilation depends on various mechanisms, such as stage of coronary atherosclerosis or duration and even choice of statin drug. The difference in effect on coronary circulation between various statins is suggestive of variable vascular effects other than the lipid-lowering effect alone [24]. Furthermore, we have demonstrated that in the clinical setting the assessment of instantaneous coronary flow reserve does not necessarily reflect the impact on vasodilatory capacity because changes in myocardial resting blood flow and the specific haemodynamic situation have to be taken into account.

The improvement in regional vascular resistance during adenosine infusion after about 4 months of atorvastatin therapy is in accordance with the observed beneficial effect of lipid-lowering therapy on stress-induced flow capacity, determined using non-invasive PET, in patients with very early stages of coronary atherosclerosis [8]. The benefit of cholesterol-lowering therapy has also been observed in patients with angina and angiographically normal coronary vessels. Several studies have shown that impaired vascular endothelium-mediated relaxation may play a central role in the pathogenesis of myocardial ischaemia in patients with so-called syndrome X or with coronary risk factors but without angiographic evidence of CAD [25–27]. In this respect, substantial improvement in vasodilatory capacity in patients with normal angiographic appearance or minimally diseased vessels was reported after simvastatin therapy and life-style modification [8]. Further PET studies consistently indicated an improvement in MBF reserve after lipid-lowering therapy in patients with hypercholesterolaemia [8, 10, 17, 23].

Given the short time span of atorvastatin therapy in the present study (about 4 months), the observed improvement in vasodilatory capacity in patients at various stages of atherosclerosis might be primarily attributable not to improvement in coronary anatomy or regression of athero-

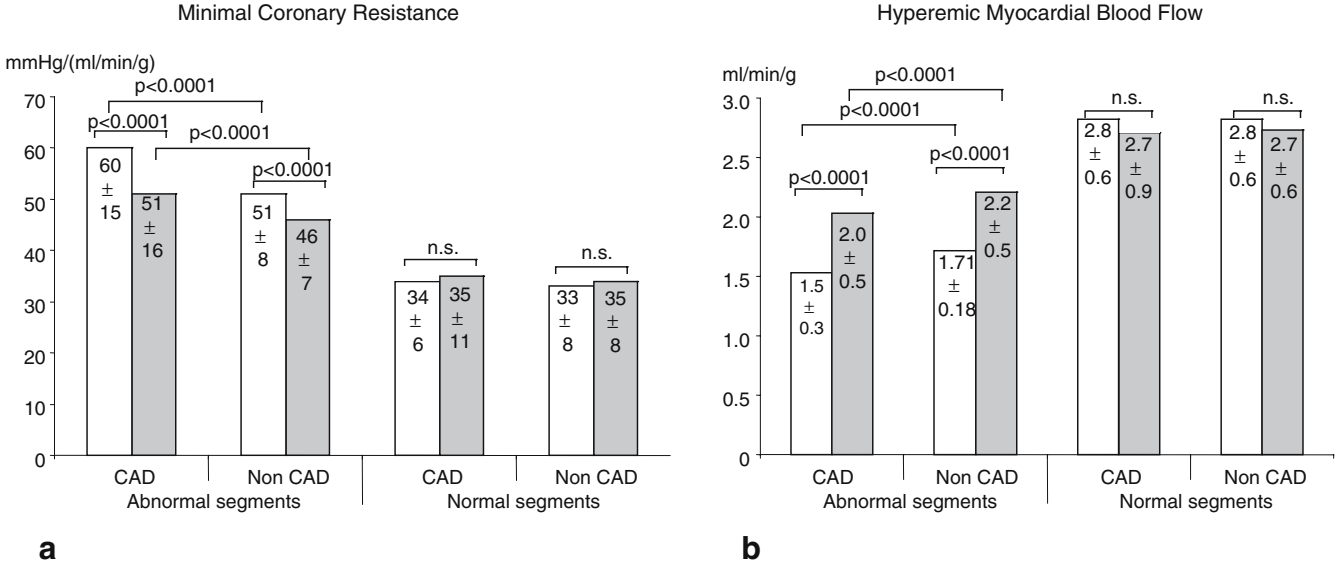

Fig. 2. Minimal coronary resistance (**a**) and hyperaemic MBF (**b**) in abnormal and normal segments before and after statin therapy. There was an improvement in MCR and hyperaemic MBF in initially abnormal segments in patients with CAD and in those with non-obstructive CAD. Normal segments revealed no significant changes in either parameter. *Open bars*, pre-therapy; *grey bars*, post-therapy

matous plaques but rather to functional improvement in stenosis geometry [28] (although coronary angiography was not performed at follow-up) and in flow-dependent dilation [29], as suggested in Fig. 1.

It must be pointed out that in parallel with the marked drug-induced reduction in LDL cholesterol, all patients attempted to change their life-style, as indicated by a decrease in BMI in the majority of the patients. All patients were recommended to adhere to a low-fat diet and were encouraged to increase their physical activity by regular exercise. In this regard, beneficial effects of intensive lifestyle modification, including unconventional exercise regimens, on MBF and endothelium-dependent coronary vasodilator reserve have been reported in patients with ischaemic heart disease [30, 31].

In our study, the substantial improvement in perfusion abnormalities in patients with localised coronary artery stenosis or wall irregularities probably documents the functional significance of relatively small changes in atherosclerotic coronary stenosis resistance for myocardial perfusion under vasodilator stress. Relaxation of arterial vasomotor tone, caused by improvement in local and/or general endothelial function, and subsequently increased perfusion, physiologically related to lumen radius and raised approximately to the fourth power, are most likely to be responsible for early improvement in vasodilatory capacity. In particular, this effect has been observed (including in the present study) in the most impaired segments in patients with stenotic CAD or with wall irregularities, suggesting that functional stenosis flow reserve and segmental vasodilatory capacity depend considerably on regionally endothelium-mediated mechanisms [2, 7, 22, 28–30, 32].

Methodological aspects

In this PET-based study, exclusion of a placebo group has to be recognised as a limitation. However, PET flow measurements show high measurement accuracy and reproducibility [15, 33]. In addition, current knowledge of the atherogenic and vasoconstrictive effects of LDL hypercholesterolaemia, as well as the beneficial effects of statin therapy on cardiovascular events, means that inclusion of a sufficiently large placebo group of patients could hardly be justified, even if those patients were to be at a very early stage of coronary atherosclerosis; this conclusion is reinforced if one considers also the repeated delivery of nuclear radiation within a short time frame. Instead, each patient in this study served as his or her own control before and after the treatment period. In this regard, our study patients were characterised by a reduced coronary vasodilatory capacity compared with an internal reference group of normolipidaemic controls [34].

It should also be pointed out that the absence of significant changes in both MBF and minimal coronary resistance index in normal or near-normal segments may be regarded as arguing against a regression to the mean (placebo) effect being responsible for the improvement in MBF response in initially abnormal segments [35]. Moreover, a non-specific improvement confined to markedly abnormal regions seems most unlikely since an elegant study by Gould et al. [22] again indicated a decrease in abnormal regional myocardial perfusion following short-term (3 months) cholesterol-lowering therapy in patients with ischaemic heart disease who had high LDL cholesterol levels at baseline, with a return to pretreatment levels 2 months after withdrawal.

Until several years ago, the vasodilator effect of adenosine was considered to be attributable solely to direct stimulation of A2-adenosine receptors on vascular smooth muscle cells (so-called endothelium-independent vasodilation). However, in the past decade it has been recognised that adenosine also acts as an important endothelium-dependent vasodilator [32, 36–38], and that this mechanism of action accounts for at least 20–40% of the overall effect of adenosine on coronary vasodilatory capacity. Consequently, adenosine vasodilator response may be used as a non-invasive measure of total arterial/arteriolar vasodilatory capacity, integrating both endothelial function and smooth muscle relaxation [39].

Clinical implications

This study underlines the conclusion that PET constitutes a powerful non-invasive tool for the identification of patients with altered functional vascular reactivity under the impact of risk factors such as elevated LDL cholesterol. Schächinger et al. [4] have recently shown that coronary vasodilator function independently predicts the long-term risk of spontaneous cardiovascular events. Consequently, non-invasive imaging of regional and overall coronary vasodilatory capacity may be an appropriate approach to the evaluation of dietary and/or pharmacological interventions for primary or secondary prevention with the aim of reversing or delaying the progression of CAD and thereby ultimately reducing cardiovascular events.

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