SCIENTIFIC LETTER

Effect of statin treatment on coronary collateral flow in patients with coronary artery disease

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Recent work has suggested an angiogenic,[1] and conversely, an angiostatic[2] or biphasic effect of statins.[3] However, such hypotheses have been tested only in vitro or in animal models. The influence of statins on human arteriogenesis, the formation of collateral arteries, nowadays thought to be necessary to save myocardium from ischaemia, has not been previously investigated.

METHODS

Five hundred patients with stable one to three vessel coronary artery disease (CAD) and without Q wave myocardial infarction underwent quantitative assessment of the coronary collateral circulation during coronary angioplasty. The patients were divided into two different groups according to the use of statins (termed ''statin group'', n = 186) or the absence of statin treatment (termed ''no statin group'', n = 314). All patients underwent left heart catheterisation, including biplane left ventricular angiography and coronary angiography for diagnostic purposes. Aortic pressure was recorded using the angioplasty catheter. Coronary artery stenoses were assessed quantitatively as per cent lumen diameter reduction, using the guiding catheter for calibration. Collateral vessel assessment was performed by three different methods in all patients, whereby the principal end point of the study was the functional measurement obtained by pressure or Doppler guide wires (that is, collateral flow index (CFI) expressing collateral flow as a fraction of normal coronary flow).

Myocardial ischaemia during balloon occlusion was assessed by the occurrence of angina pectoris and also by a simultaneously obtained intracoronary ECG. In the presence of ST segment changes > 0.1 mV during a one minute balloon occlusion, coronary collateral vessels were defined as sufficient.

RESULTS

Patient characteristics are shown in table 1.

Abbreviations: CAD, coronary artery disease; CFI, collateral flow index

Table 1 Clinical characteristics

	Statin group (n = 186)	No statin group (n = 314)	p Value
Men (%)	144 (77%)	243 (77%)	NS
Age (years)	61 (11)	62 (11)	NS
Body mass index (kg/m^2)	27 (3)	27 (4)	NS
Mean blood pressure (mm Hg)	93 (13)	96 (16)	0.04
Heart rate (beats per minute)	69 (11)	73 (12)	0.008
Left ventricular ejection fraction (%)	66 (10)	65 (12)	NS
Left ventricular end diastolic pressure (mm Hg)	13 (6)	14 (6)	NS
Central venous pressure (mm Hg)	6 (3)	5 (2)	NS
Duration of angina pectoris (months)	28 (47)	19 (42)	0.02
Severity of angina pectoris (CCS class)	1.5 (1.2)	1.5 (1.1)	NS
Cardiovascular risk factors			
Diabetes mellitus	26 (14%)	53 (17%)	NS
Systemic hypertension	96 (52%)	159 (51%)	NS
Smoking	78 (42%)	134 (43%)	NS
Obesity	41 (22%)	71 (23%)	NS
Hypercholesterolaemia	156 (84%)	98 (31%)	<0.0001
Family history of coronary artery disease	60 (32%)	112 (36%)	NS
Cardiovascular medication			
Aspirin	159 (85%)	259 (82%)	NS
β Blockers	131 (70%)	179 (57%)	0.003
Nitrates	77 (41%)	119 (38%)	NS
ACE inhibitors	51 (27%)	82 (26%)	NS
Calcium antagonists	36 (19%)	63 (20%)	NS
Diuretics	29 (16%)	36 (12%)	NS
Serum lipids			
Cholesterol (mmol/l)	5.4 (1.3)	5.6 (1.1)	0.01
HDL cholesterol (mmol/l)	1.2 (0.3)	1.2 (0.3)	NS
LDL cholesterol (mmol/l)	3.3 (1.1)	3.5 (1.0)	0.02
Total cholesterol/HDL cholesterol	4.7 (1.6)	5.1 (1.9)	0.02
Triglycerides (mmol/l)	2.3 (1.9)	2.1 (1.5)	NS

Data are presented as the mean value (SD) or number (%) of patients.
ACE, angiotensin converting enzyme; CCS, Canadian Cardiovascular Society; HDL, high density lipoprotein; LDL, low density lipoprotein; NS, not significant

There was no difference between the two groups regarding the number of chronic total occlusions, number of vessels diseased or the number of stenoses, but per cent diameter luminal narrowing of the stenosis of interest was lower in the statin than in the no statin group (mean (SD) 75 (15) *v* 78 (16), p = 0.03). More individuals in the statin group versus the no statin group suffered a previous non-Q wave infarction (40 (22%) *v* 28 (9%), p < 0.0001).

Coronary CFI showed no difference between the statin group and the no statin group (0.201 (0.14) *v* 0.219 (0.15), p = 0.24). Similarly, no difference in sufficient collaterals (that is, a CFI value of ⩾ 0.25 which has been demonstrated to be sufficient to prevent jeopardised myocardium from ischaemia[4]) was observed in the statin versus the no statin group (p = 0.17). Conversely, the number of patients with insufficient collaterals as defined by intracoronary ECG was significantly higher in the statin group (150/186 *v* 222/314, p = 0.01) and there was also a trend to an increased number of patients undergoing statin treatment to suffer angina pectoris during balloon occlusion (129/186 *v* 191/314, p = 0.08).

Mean duration of treatment in the statin group at the time of collateral flow measurement was 9.5 (25) months.

Multiple regression analysis with CFI as the dependent variable revealed that per cent diameter stenosis of the lesion (p < 0.0001), the absence of a previous non-Q wave infarction (p = 0.008), and the use of nitrates (p = 0.04) were the only independent predictors of a high CFI.

DISCUSSION

This is the first large clinical trial in patients with CAD showing that the use of statins has neither a pro-arteriogenic nor anti-arteriogenic effect on quantitatively determined collateral flow.

There are some imbalances in patient characteristics (table 1), which might have biased our results. However, an influence of cholesterol values on human arteriogenesis has not been shown until now and the mean duration of angina pectoris in both groups was so long that no further increase in collateral growth is to be expected. Conversely, an influence of the difference in β blocker treatment is possible.

In agreement with other investigations,[4] we found in a multivariate analysis that stenosis severity is an independent predictor of collateral flow. The reason why the presence of a previous non-Q wave myocardial infarction is a predictor of low collateral flow may be due to a structurally altered microvascular bed as a consequence of scarring following non-Q wave infarction. Another explanation is that patients with high collateral flow suffer less often from cardiac events than those with low collateral flow.[5] The third factor being a predictor for increased collateral flow in multivariate testing was the use of nitrates. This was a statistically false positive result, since univariate analysis did not reveal a significant influence of this medication.

The reason why collateral flow assessment using intracoronary ECG showed a reduced frequency of sufficient collateral flow in the statin group may be explained by the variable severity of CAD among groups. Therefore, we performed a further analysis of the two groups matching them for stenosis severity, use of β blockers, and the presence of an infarction. There was no longer any discrepancy between the different methods to assess collateral flow.

In conclusion, this large clinical study in 500 patients with coronary artery disease reveals no effect of statins on coronary collateral flow.

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