Angina pectoris and normal coronary angiograms

We have read with great interest the paper by Chauhan et al.13. In patients with angina pectoris and normal coronary angiograms they observed an impaired vasodilator response within the coronary microcirculation to both acetylcholine (endothelium-dependent vasodilator) and to papaverine (endothelium-independent vasodilator).

In contrast with the dysfunction at the level of the microcirculation, no impairment of endothelium-dependent vasodilation was observed in the epicardial coronary arteries. Selective dysfunction of the vascular endothelium in the coronary microcirculation without changes in epicardial coronary vascular reactivity in patients with angina and normal coronary angiograms has also been reported by Egashira et al.2.

We were the first to report on impaired endothelium-dependent coronary vasodilation in patients with angina and normal coronary angiograms.9 Our study differs from the studies by Chauhan et al. and Egashira et al. in that endothelium-dependent vasodilation was also severely impaired in the epicardial coronary arteries.

Chauhan et al. attribute the different results in epicardial coronary vascular reactivity to differences in the dose of acetylcholine administered and also to the different populations studied. In our study, graded molar concentrations of acetylcholine ranging from 10^-6 M to 10^-4 M were infused selectively into the left anterior descending artery. At an infusion rate of 2 ml. min^-1, this corresponds to an actual infused dose ranging from 0.36 μg. min^-1 to 362 μg. min^-1, which is almost identical to the doses used by Chauhan et al.

The main explanation for the different study results is therefore only the selection of patients. The authors excluded from their study population patients with an abnormal epicardial coronary vasoconstriction. The advantage of the use of this exclusion criterion is that only patients with a truly 'microvascular' angina were included in the study population. However, an impaired endothelium-dependent coronary vasodilation has a very high prevalence. It can be demonstrated in a large number of patients who have one or more coronary risk factors and/or have early coronary atherosclerosis which is not yet detectable by coronary arteriography. This impairment is frequently not limited to the epicardial coronary arteries but extends to the myocardial microcirculation.

We agree with the authors that the syndrome of angina and with normal coronary angiograms encompasses several subgroups of patients with different pathophysiological mechanisms leading to the development of anginal pain. However, we have the feeling that the subgroup with only selective impairment of the endothelium-dependent vasodilation in the myocardial microcirculation, as in the studies by Egashira et al. and Chauhan et al., represents only a very limited and highly selected group of patients at the extreme end of the spectrum of this syndrome. The majority of patients with this syndrome who come to the cath-lab have both epicardial and microcirculatory endothelial dysfunction related to the presence of coronary risk factors and/or early atherosclerosis. Endothelial dysfunction results in those patients in mild to moderate diffuse coronary vasoconstriction of the epicardial coronary arteries during stress and exercise and also in diminished vasodilator reserve in the myocardial microcirculation, all of which may contribute to the development of myocardial ischaemia and anginal pain symptoms. Although acetylcholine and serotonin (which are very potent coronary vasodilators in the presence of an endothelial dysfunction) can cause severe coronary vasoconstriction in those patients, they do not belong to the subgroup of patients with variant angina since in normal physiological conditions they will not develop occlusive coronary vasospasm.

We believe that it is important that cardiologists should ascertain that the syndrome of angina with normal coronary angiograms is not a rare mysterious and difficult to treat syndrome X, but that there is a large cohort of patients with smooth coronary arteriograms and angina pain symptoms related to the presence of coronary endothelial dysfunction that can easily be treated with nitrates and long-acting calcium antagonists. The endothelial dysfunction in those patients can be reversed by coronary risk factor reduction, lowering of serum LDL-cholesterol by statins2-7 and/or by treatment with ACE-inhibitors8 with a beneficial effect on anginal symptoms.


Lipid-lowering with statins and fibrinolytic parameters

The interrelationship between lipoproteins and the fibrinolytic system is increasingly under scrutiny and it becomes apparent that it is not only the triglyceride-rich lipoproteins that can influence fibrinolysis, but that the apolipoprotein-B-containing very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and possibly also intermediate-density lipoproteins (IDL) can all modulate endothelial synthesis and release of fibrinolytic enzymes. These enzymes are generally thought to be markers for an increased risk of myocardial infarction, but their role in the pathogenesis of atherosclerosis is not clarified yet. A better understanding of the relationship between lipoproteins and fibrinolysis may help us gain insight in the formation and evolution of the atherosclerotic plaque.

In the February issue Mitropoulos et al. reported the results of a substudy of the Oxford Cholesterol Study which sought to elucidate the effect of simvastatin on haemostatic and fibrinolytic variables. A significantly lower LDL-, VLDL- and IDL-cholesterol concentration and a significantly higher plasminogen-activator-inhibitor (PAI-1) activity was found in the patients assigned to simvastatin compared to the patients taking placebo, while other haemostatic parameters were not significantly different.

These results do not contradict the results of previously published studies with lovastatin (a compound related to simvastatin), since the authors of the cited study determined PAI-1 concentration and not activity, two parameters that are not necessarily equivalent. Moreover, in a recently published paper, Bevilacqua et al. reported a significant decrease in LDL cholesterol accompanied by a significant increase of PAI-1 concentration and activity and by a significant decrease in tissue-type plasminogen activator (t-PA) in 24 patients with coronary artery disease treated with fluvastatin, another hydroxy-methyl-glutaryl-coenzyme (HMGCoA) reductase inhibitor. Interestingly, the increase in PAI-1 concentration and activity was also observed in the placebo group, while the decrease in t-PA was not. In a study assessing the relationships between lipid metabolism and fibrinolytic parameters, significant correlations between apolipoprotein B and t-PA antigen as well as PAI-1 activity were found in 191 patients with hyperlipidaemia. Finally, Welty et al. analysed the correlation between LDL-cholesterol and fibrinolytic parameters in 1878 members of the Framingham offspring population. Their data show a significant increase in the levels of t-PA and PAI-1 antigen with increasing LDL-cholesterol concentrations. This relationship was not altered by adjustment for several risk factors associated with coronary atherosclerosis.

The results of these studies indicate that there is an association between the LDL-cholesterol concentration and concentrations of the fibrinolytic enzymes, especially t-PA (which was not determined by Mitropoulos et al.). The somehow conflicting results concerning PAI-1 concentration and activity might be explained by its great variability and by the multitude of factors (such as time of day, activity, body mass index etc.) which influence its level in plasma.

Several large trials have shown that treatment with HMGCoA reductase inhibitors can dramatically reduce the incidence of myocardial infarction and the number of revascularization procedures in patients with hypercholesterolaemia and in patients with a history of coronary artery disease or myocardial infarction. This is thought to be due to the plaque stabilization and the improvement of endothelial dysfunction which accompanies the massive reduction in LDL-cholesterol brought about by these agents. Evidence is accumulating that the LDL-cholesterol reduction also exerts a favourable influence on fibrinolysis which may also contribute to the observed clinical benefits.