that the blockade of the renin–angiotensin system by angiotensin-converting enzyme inhibition or AT1 antagonism may yield some differential effects. These are important areas of future investigation.

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Variant angina in patients without obstructive coronary atherosclerosis: a benign form of spasm

See page 1015 for the article to which this Editorial refers

Occlusive coronary spasm in patients with variant angina is caused by local hyper-reactivity of coronary smooth muscle to a variety of constrictor stimuli which operate through various surface receptors. Therefore the condition cannot be prevented by blockade of a specific smooth muscle surface receptor[11]. Local hyper-reactivity which characterizes
coronary spasm is probably related to an intracellular alteration of the mechanisms responsible for smooth muscle contraction. This hypothesis is confirmed by the clinical observation that drugs which reduce intracellular calcium concentration, such as calcium antagonists, or increase the intracellular concentration of cGMP, such as nitrates, efficiently prevent coronary spasm. The degree of this local smooth muscle hyper-reactivity may increase and decrease, thus the intensity of stimuli sufficient to cause spasm may also vary. The variable duration of occlusive spasm may be related to the variable duration of the constrictor stimulus or to variable activation of negative feedback mechanisms. During spontaneous coronary spasm, a generalized mild constriction of non-spastic epicardial coronary artery segments was demonstrated by Kaski et al.[3]. Hence, in patients with the classical syndrome of variant angina, transient coronary spasm is due to a local hyper-reactive response to constrictor stimuli which cause only mild diffuse constriction in non-spastic segments.

Coronary spasm, myocardial infarction and sudden death

Occlusive coronary spasm may cause blood stagnation with platelet aggregation and thrombin and fibrin generation[3]; thus, the longer the duration of coronary spasm, the higher the probability of the formation of an irreversible red thrombus resulting in persisting coronary occlusion and myocardial infarction. Furthermore, in patients with a myocardium vulnerable to ventricular arrhythmias, coronary spasm, even of short duration, can cause sudden death.

Dependent on these potentially devastating consequences, the study of Bory et al.,[4] which shows a rather low incidence of sudden death (3.6%) and myocardial infarction (6.5%) after a median follow-up of 7 years in a large population of 277 patients with vasospastic angina and normal or nearly normal coronary arteries, treated with calcium antagonists. These findings are consistent with previous long-term follow-up studies carried out in Pisa and Montreal. In addition, in 54% of Bory’s patients who developed myocardial infarction and underwent repeat coronary angiography, the infarct-related coronary artery branch showing a critical stenosis was different from the vasospastic branch at the time of the first angiogram, thus confirming that coronary spasm, per se, does not play a key role in the process of plaque formation. These findings also show that in about half of the patients with vasospastic angina treated with calcium antagonists who develop myocardial infarction, the latter may not necessarily be caused by the local smooth muscle hyper-reactivity responsible for coronary spasm.

Not surprisingly, in the study of Bory et al.[4] the response to ergonovine testing performed on treatment at the time of patient enrolment failed to predict the occurrence of myocardial infarction at follow-up. This may be due to three reasons: (1) the low predictive value of a positive test when the pre-test probability of the event is low; (2) a sudden unpredictable increase in local hyper-reactivity or failure of local negative feedback mechanisms; (3) the additional presence of local or systemic thrombogenic stimuli enhancing thrombus formation.

Similarly, the response to ergonovine performed on treatment failed to predict sudden death. Again, this may be due to the low pre-test probability of sudden death and to the fact that sudden death is caused by the vulnerability of myocardial infarction to arrhythmias, which is not directly explored by the ergonovine test. Maseri et al. have previously found that the presence of episodes of ventricular tachycardia, fibrillation or severe arrhythmias during hospitalization are associated with sudden death[5]. Thus, in those patients with vasospastic angina who exhibit syncope, severe ventricular arrhythmias during Holter monitoring and/or a markedly reduced heart rate variability despite maximal treatment with calcium antagonists and nitrates, the addition of an anti-arrhythmic drug, such as amiodarone, to the vasodilators might represent a viable option.

Treatment of vasospastic angina

Angina caused by coronary spasm in the absence of obstructive coronary atherosclerosis responds very well to treatment with calcium antagonists and nitrates. Nevertheless, in the study of Bory et al.[4] about 20% of patients, despite treatment with calcium antagonists, had such severe and persisting anginal symptoms that repeat coronary angiography was carried out. However, in the majority (63%) of patients with refractory angina, coronary angiography confirmed the absence of obstructive coronary atherosclerosis. In this subset of patients a cheaper way to rule out the presence of obstructive atherosclerosis would have been to perform exercise testing after sublingual administration of nitrates in order to eliminate any preventable vasospastic component in the genesis of exercise-induced myocardial ischaemia. Of note, ergonovine test on treatment failed to identify those patients with anginal symptoms refractory to calcium antagonist, thus suggesting that
Symptoms occurring during daily life are caused by vasoconstrictor stimuli stronger than ergonovine.

The 20% of patients refractory to medical treatment in the study of Bory et al. is somewhat higher than the 5–10% reported in previous studies. The reasons for this discrepancy may lie in differences in patient populations or in treatment strategies. Surprisingly, Bory et al. did not treat their patients with intermittent long-acting oral nitrates which prevent smooth muscle contraction through a mechanism different to that of calcium antagonists and which therefore may help prevent coronary spasm in the period of the day in which it most often occurs. Furthermore, the maximal daily doses (360 mg for diltiazem, 480 mg for verapamil, 60 mg for nifedipine) of calcium antagonists given to their patients were lower than the maximal doses (960 mg for diltiazem and verapamil and 100 mg for nifedipine) given in previous studies, which also showed that the addition of guanethidine or clonidine to calcium antagonists and nitrates may offer further symptomatic relief, probably by a reduction of sympathetic vasoconstrictor stimuli.

Conclusions

In patients with coronary spasm and normal or nearly normal coronary arteries, the current treatment offers a relatively good prognosis, although symptom control can occasionally be difficult. Only understanding the causes of local non-specific hyperreactivity in coronary smooth muscle will enable new drugs to be designed specifically to treat coronary spasm. Drugs currently available, which reduce smooth muscle contraction in the whole body, are effective but exhibit frequent side effects; most importantly, in some patients, they may be unable to prevent a fatal episode of coronary spasm.

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