Medical and surgical treatment of Prinzmetal's angina

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Since the pathophysiologic mechanism inducing coronary artery spasm is poorly understood, both medical and surgical therapy remain empirical. Nitroglycerin remains an extremely effective drug for relief of the anginal chest pain associated with coronary spasm and has been documented to reverse quickly the spasm that occurs spontaneously or in response to ergonovine maleate during coronary arteriography. Long-acting nitrates are also useful, but are usually not complete in their prophylactic effect because a continuous serum level of the drug is needed for it to be effective and because the spasm frequently occurs during the early morning hours. We have found that nitroglycerin paste, applied at bedtime, is frequently effective as a prophylaxis for this problem if the patient can tolerate the side effects. The problem of nitroglycerin tolerance in Prinzmetal's angina has been difficult to document, although a few patients appear to have become nitroglycerin-dependent with an increasing number of pain episodes upon sudden withdrawal of the nitroglycerin, such as at the time of surgery.

One proposed mechanism for the coronary spasm is alpha-receptor mediated coronary artery vasoconstriction, either due to excessive or unbalanced sympathetic tone. Beta blockers have been reported

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by Yasue et al[1] to aggravate Prinzmetal's angina. This observation tends to support the concept of unopposed alpha-mediated spasm occurring when the beta-mediated vasodilation is blocked. For this reason we have used alpha blockers, both phentolamine and phenoxybenzamine, as second line drugs for difficult-to-control symptoms. These agents, in nonrandomized trials, tend to be partially effective but appear to lose their therapeutic efficacy over a short period of time. Additionally, these agents often must be given to the point of orthostatic hypotension to be effective.

Recently, it has become apparent that calcium antagonists are highly effective for the long-term treatment of Prinzmetal's angina. These agents cause marked coronary artery vasodilation by blocking the slow channel transport of calcium during depolarization. This effect appears to be differentially stronger on vascular smooth muscle than on cardiac muscle, thus minimizing negative inotropic effects at therapeutic blood levels of the drug. Three calcium antagonists are currently undergoing evaluation in the United States: verapamil, nifedipine, and diltiazem. There are a number of uncontrolled, unblinded studies reporting dramatic effects of these drugs for Prinzmetal's angina.[2-4]

We are currently carrying out a randomized double-blind trial of diltiazem for patients with documented coronary artery spasm at Stanford University Hospital. Preliminary results are available on nine patients who have completed the study. The protocol involved withdrawal of all prophylactic vasodilators and beta and alpha blockers during the 10-week study (*Table 1*). To be entered in the study documentation of coronary artery spasm was required. During the first 2 weeks, the patient was required to have five or more episodes of pain per week during a single blind placebo period. Patients were then randomized to either 30 mg four times a day of diltiazem or placebo, each taken for a 2-week period, followed by switching to the opposite medication. This was followed by a new randomization to 60 mg four times a day of either placebo or diltiazem, followed by the opposite agent for the last 2-week period. Preliminary results could be analyzed in eight of the nine participants. There were dramatic and highly significant reductions in both pain episodes and nitroglycerin taken (*Table 2*). There were a similar number of pain episodes for the group during all three placebo periods, with a total of 609 pain episodes. There were only 81 total pain episodes on diltiazem at a dose of 120 mg four times a day. There were only 25 episodes on diltiazem at 240 mg four times a day, an 89% reduction in pain frequency. Thus, we believe that the calcium antagonists are highly effective and the drug of choice for the long-term therapy of pa-

Table 1. Protocol design

Single blind			Double blind		
0–14 days	14 days	14 days	14 days	14 days	14 days
Taper and stop other medications	Placebo	D120	Placebo	D240	Placebo
	R_1	Placebo	R_2 D120	Placebo	D240

D120 = diltiazem (30 mg q.i.d.), D240 = diltiazem (60 mg q.i.d.), R_1 = randomization, R_2 = rerandomization.

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Table 2. Efficacy of diltiazem; preliminary results, eight patients

	Placebo	Diltiazem 120 mg/day	Diltiazem 240 mg/day
Patient days	320	127	121
Pain episodes, total	609	81*	25†
Nitroglycerin, total	626	78*	25‡
Pain episodes/day/patient	1.90	0.64	0.21
Nitroglycerin/day/patient	1.96	0.61	0.21

* $p < 0.03$.
† $p < 0.01$.
‡ $p < 0.04$.

tients with coronary artery spasm.

Surgical results have been less predictable or satisfying. Initially, there were a number of attempts at bypassing the area of spasm. However, many of these patients have done poorly, presumably due to spasm involving or moving distal to the grafted area. It is our impression that the more severe the fixed obstruction, the more likely the coronary bypass surgery will be effective, particularly if the occlusion is 80% to 90%.

A few patients have apparently become refractory to medical therapy, including the calcium antagonists. Clark et al,[5] reported on four patients who underwent cardiac denervation, three by stripping of the great vessels and one by autotransplantation. Two patients died in the early postoperative period. The other two had apparent definite reduction, but incomplete relief of the pain episodes. We have denervated one patient at Stanford Medical Center, a 42-year-old woman who had become refractory to vasodilators, including 120 mg of nifedipine daily. After a stormy postoperative course, the patient has done better, with one to two episodes of pain per day. Thus, it would appear that the autonomic nervous system may be permissive, but is not essential to the occurrence of coronary artery spasm. This impression is strengthened by the occurrence of unrelenting coronary spasm in a 45-year-old man 2 years after cardiac transplantation at a time when there was no evidence of reinervation.

In summary, nitroglycerin remains highly effective for the treatment of angina pain related to coronary artery spasm. Surgical therapy is associated with high risks and is usually not curative. Calcium antagonists, such as diltiazem, appear to be highly effective for the long-term medical therapy of this disease.

References

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