

Prognostic significance of electrocardiographic findings in angina at rest

Therapeutic implications

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SUMMARY Ninety-five patients with angina at rest were observed in the coronary care unit. Eighty-one per cent presented concomitantly or had previously presented some other manifestations of coronary artery disease. These patients were divided into two subgroups. In subgroup 1 (40 patients), episodes of non-exertional angina were associated with a pattern of hyperacute subepicardial injury and, frequently, with ventricular arrhythmias. In subgroup 2 (55 patients), the episodes of angina at rest were attended by horizontal ST depression, isolated T wave inversion, or trivial ST-T changes. Coronary angiographic findings were similar in both subgroups.

Symptoms regressed in only 9% of patients in subgroup 1 while they were receiving beta-receptor antagonists, whereas amiodarone alone or amiodarone with nifedipine was successful in 58%. Of these patients, 25% developed a myocardial infarction shortly after admission.

In subgroup 2 patients, beta-blockers were successful in 61%. Amiodarone isolated or associated with nifedipine was successful in 55% of the patients in whom it was tried. Only 5% of patients in this subgroup developed a myocardial infarction during their hospital stay.

It is concluded that: (1) observation of the electrocardiogram during spontaneous angina in patients with known atherosclerotic coronary heart disease may be of prognostic significance and may influence therapeutic decision. (2) Amiodarone by virtue of its anginal and antiarrhythmic properties may be particularly useful in the treatment of non-exertional angina.

It has long been recognised that angina pectoris can occur spontaneously at rest and that different pathogenetic mechanisms may be involved in the production of this type of myocardial ischaemia.

Recent studies have identified coronary vasospasm as one of the possible causes of the hyperacute attacks of ischaemia which occur at rest.¹⁻⁷ This new concept raises some questions regarding the therapeutic approach for patients with non-exertional angina.⁵

Recently, in our coronary care unit we have observed 95 patients with angina at rest. The present report is concerned with the clinical features and results of treatment in these cases.

Description of patients

All patients in this study group had developed repeated episodes of angina at rest. Their symptoms had lasted for less than three months preceding their

admission to hospital. There were 80 men and 15 women. Fifty-six (59%) of them had a documented history of previous myocardial infarction. Thirty-nine (41%) had antecedents of effort angina. Altogether, 77 patients (81%) presented concomitantly or had previously presented some manifestations of coronary artery disease other than angina at rest.

All patients were carefully monitored in the coronary care unit and their electrocardiograms were scrutinised during episodes of chest pain by recording 12 lead tracings. They were divided into two subgroups depending upon the electrocardiographic pattern observed during angina at rest.

In subgroup 1 (40 patients: 32 male and eight female, ranging in age from 32 to 73 years with an average of 55), the episodes of angina at rest were accompanied by the development of a pattern of hyperacute subepicardial injury with striking slope elevation of the ST segment and, frequently, ventricular arrhythmias (Fig.). Twenty-five (63%) of these patients had known coronary artery disease.



Fig. Example of hyperacute subepicardial injury with rhythm disorders observed during an episode of angina at rest in a group 1 patient.

Seventeen (43%) had antecedents of myocardial infarction, and 12 (30%) had previously suffered from effort angina.

In subgroup 2 (55 patients: 48 male and seven female, ranging in age from 44 to 78 years with an average of 58), the episodes of angina at rest were associated with horizontal ST segment depression, isolated T wave inversion, or trivial ST-T changes; 52 (95%) of these patients had known coronary artery disease, 39 (71%) had antecedents of myocardial infarction, and 27 (49%) a history of effort angina. Altogether, the incidence of previous manifestations of coronary artery disease was higher in subgroup 2 than subgroup 1 ($p < 0.01$).

No instance of so-called transient pseudonormalisation of previously negative T wave was seen.

No data were available on the precise haemodynamic situation of these patients at the onset of non-exertional chest pain.

Coronary angiographic findings

A coronary angiogram was obtained in 65 cases, 36 of group 1 and 29 of group 2. The remaining patients were not submitted to this investigation either because of the early development of a myocardial infarction during hospital stay (13 cases), or because of old age or refusal. The data obtained at coronary angiography are summarised in Table 1. Only lesions producing a greater than 70% narrowing (or 50% for

the left main coronary artery) were taken into consideration. Coronary artery stenosis were depicted in all but six cases. There was no statistically significant difference between the two subgroups as regards the severity or site of stenosis. It is worth noting, however, that no patient in group 1 had left main coronary stenosis whereas four subjects with this type of disease were seen in group 2. But five out of the six patients with normal coronary arteries were classified in group 1. Coronary arterial spasm was observed during arteriography in one of these six patients. No attempt was made, however, to provoke spasm by ergonovine injection during coronary angiography.

Results of medical treatment

All patients were initially treated medically for one month. Table 2 describes the nature of treatment, and indicates the number of patients who responded by a total suppression of symptoms (without development of myocardial infarction) within four weeks after the start of treatment. This being a retrospective study covering a two year period, various types of treatment were used. They reflect changes in the medical approach to unstable angina over the past few months and were influenced by the recent availability of some drugs, for example nifedipine.

Table 2 Efficacy of medical treatment (number of patients becoming asymptomatic/number of patients in whom treatment was tried)

Table 1 Coronary angiographic findings

	Group 1 (36 cases)	Group 2 (29 cases)
Left main coronary stenosis	0	4
Left anterior descending artery	24	20
Circumflex artery	12	20
Right coronary artery	20	20
Normal coronary arteries	5	1
Single vessel disease	14	10
Double vessel disease	13	10
Triple vessel disease	4	8

Note: No statistically significant difference between the two groups.

Patient group	Drug administered (in addition to isosorbide dinitrate)			
	Beta-blocking agents	Nifedipine (4 × 10 mg/day)	Amiodarone alone (1500 mg IV and 600 mg orally daily during first 3 days; then, 600 mg/day orally)	Amiodarone + nifedipine
Group 1	2/23 (9%)	3/7 (43%)	5/8 (62%)	12/19 (63%)
Group 2	24/39 (62%)	—	2/3 (66%)	4/8 (50%)

Beta-blockers were effective in only two of 23 patients (9%) of group 1 in whom they were tried. They produced a disappearance of symptoms in 24 of 39 patients of group 2 (62%; $p < 0.001$).

Nifedipine (4×10 mg/day), amiodarone (1500 mg intravenously and 600 mg orally daily for the first three days followed by 600 mg orally per day), or a combination of the two were used in 34 patients of group 1 and were successful in 20 (59%). They were, in this group, significantly more effective than beta-blocking agents ($p < 0.001$).

In 12 patients treated with amiodarone, combined in nine instances with nifedipine, an ergonovine test performed according to the procedure proposed by Thérout *et al.*⁸ was carried out to assess the efficacy of treatment. None of these 12 patients developed chest pain but a moderate ST segment elevation was noted in four.

Amiodarone alone (three cases) or combined with nifedipine (eight cases) was also tried in some patients of group 2 and the treatment was successful in six (55%).

Among the whole group, and in spite of treatment, 13 patients developed myocardial infarction early during their hospital stay. Ten were in group 1 (25%) and three in group 2 (5%) ($p < 0.01$). Table 3 indicates which treatment the patients were receiving at the time when their myocardial infarction occurred. None of the subjects with normal coronary angiograms developed this complication.

Operation was undertaken at the end of the first month in 15 patients of group 1 and in eighteen patients of group 2. Thirteen patients in group 1 had cardiac plexectomy⁹ in addition to coronary artery bypass grafting.

Evidence of acute transmural myocardial infarction was observed in the postoperative period in three out of 15 cases of group 1 and in one case of group 2 ($\chi^2 = 1.6$; NS). Two patients, one of each group, died from this complication.

Discussion

The correlation between the electrocardiographic abnormalities occurring during chest pain at rest and the underlying pathogenetic mechanism is still not yet entirely elucidated.⁷ Pronounced ST segment elevation frequently associated with ventricular arrhythmias is characteristic of the now well accepted clinical entity, variant angina. This is believed to be the result of a massive transmural deficit of regional perfusion caused by acute intermittent occlusive vasospasm of a proximal coronary artery. ST segment depression, T wave inversion, or less obvious ST-T changes occurring during angina at rest may be associated either with transient haemodynamic changes increasing myocardial oxygen demand or else also be the consequence of a coronary vasospasm of lesser severity or located more distally than in the first group. The existence or absence of collateral vessels may also influence the direction of the ST segment deviation.

The view most widely held at present indicates that the difference between ischaemic ST segment depression and elevation may be merely one of degree rather than of pathogenetic mechanism.

It has been indicated that patients with variant angina and normal coronary arteries usually have a favourable outcome.¹⁰ The present study, however, addresses itself to a different group of patients. The great majority of our subjects had previously suffered from other manifestations of coronary artery disease (81%) and when coronary angiography was performed most had evidence of severe coronary atherosclerotic lesions (90%). The prognosis of angina at rest may of course be different in these conditions.

We classified our patients into two subgroups depending on the nature of the ST-T changes developing during the episodes of spontaneous chest pain.

In this series, subjects developing ST segment elevation, in spite of the presence of severe coronary lesions, had less frequent antecedents of ischaemic pain on effort or myocardial infarction than the others. They appeared, however, to have a less good prognosis since they had a higher incidence of acute myocardial infarction while in hospital. In addition, their response to beta-blockers was, on the whole, poor. This is in keeping with the popular belief that beta-blockers are not the treatment of choice in variant angina. They may be useful in rare and

Table 3 Treatment received by the patients who developed a myocardial infarction

Sex	Age (y)	Treatment
<i>Patients of group 1</i>		
M	53	Amiodarone and nifedipine
F	60	Nifedipine
M	66	Nifedipine
M	54	Propranolol
M	55	Propranolol
M	71	Amiodarone for seven days, subsequently discontinued by practitioner
M	73	Propranolol
M	54	Propranolol
M	57	Propranolol
M	60	Nifedipine + amiodarone infusion
<i>Patients of group 2</i>		
M	62	Glyceryl trinitrate only
M	55	Propranolol
M	51	Propranolol

isolated cases by driving the blood from regions with normal arteries towards regions with stenotic arteries.¹¹ In other cases, they might produce a deleterious effect and enhance the tendency to vasospasm by exacerbation of the alpha effect of catecholamines.¹²⁻¹⁴

Patients in subgroup 2 had a more favourable outcome in terms of development of myocardial infarction. Their response to beta-blockers was also better than in subgroup 1. The reason for this remains unknown.

The beneficial effects of calcium antagonists in vasospastic angina have been well established and prompted our use of nifedipine¹⁵ in some of our cases. We were, however, tempted to try amiodarone also.¹⁶ Amiodarone, a benzofurane derivative, was initially introduced as an antianginal agent and is now largely used as an antiarrhythmic drug. The initial pharmacological studies^{17 18} of this substance showed that it was a powerful coronary vasodilator. Amiodarone also reduces responses to sympathetic stimulation and to injected catecholamines. Effects mediated by alpha- and beta-adrenoreceptors are both reduced, though never abolished. Amiodarone also induces a pronounced bradycardia unaffected by atropine. On theoretical grounds, these properties make amiodarone a promising drug for the treatment of vasospastic angina as well as of angina related to increased myocardial oxygen demand.

Brochier *et al.*¹⁹ were the first to use it in 12 patients suffering from severe variant angina. In 10 of their patients chest pain and syncopal attacks disappeared completely in two days. Our results indicate that amiodarone, either alone or in combination with nifedipine, can be effective both in patients with pronounced ST segment elevation and in patients showing less spectacular ST-T changes during the episodes of spontaneous chest pain. In both groups, 50 to 60% of patients became asymptomatic after treatment was started. With these drugs, coronary arteriography can be performed in more satisfactory conditions and the preparation for coronary bypass surgery is more comfortable.

The present paper suffers from limitations of which the authors are well aware. It is retrospective and therefore only contains clinical reports in which there was no attempt to standardise the investigations or the treatment. Its conclusions can therefore only serve as working hypotheses for future controlled studies. Two messages can be derived from the observations.

First, our patients with angina at rest could be divided into two subgroups. Those who showed pronounced ST segment elevation during episodes of chest pain at rest appeared at greater risk of developing an acute myocardial infarction, thus confirming the statement of Prinzmetal *et al.*²⁰ in their

initial description of the syndrome. In addition, these patients failed to respond to beta-blockade. Those who showed ST segments depression, T wave inversion, or minimal ST-T changes seemed at lesser risk and their response to beta-blockers was favourable in some 60% of cases. During episodes of spontaneous angina at rest in patients with known atherosclerotic coronary heart disease the electrocardiogram can be of prognostic significance and could influence therapeutic decisions.

Secondly, amiodarone which has gained increasing acceptance throughout the world as a powerful antiarrhythmic agent is well tolerated and might be of great value for non-exertional angina by virtue of both its antianginal and antiarrhythmic effects.

We believe that new investigations should be implemented to study further these two preliminary conclusions.

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