Prinzmetal's angina: reflex cardiovascular response during episode of pain

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SUMMARY Previous angiographic studies have shown that coronary spasm occurs in association with the variant angina described by Prinzmetal, confirming his original hypothesis. In this work we recorded the heart rate changes and the incidence of arrhythmias during variant angina. The patients were divided into two groups: anterior, with electrocardiographic signs of anterior ischaemia, and inferior, with changes in the inferior leads. There was a significant increase of heart rate during pain in anterior myocardial ischaemia and a significant decrease when the ischaemia was inferior. The incidence of ectopic arrhythmias during pain was significantly greater in patients with anterior ischaemia, but there was a high incidence of atrioventricular block in patients with inferior ischaemia. We suggest that these findings can be explained by different responses of the autonomic nervous system to anterior and inferior acute myocardial ischaemia.

The angina described by Prinzmetal *et al.* in 1960 is a clinical entity which can be differentiated from classic angina pectoris: (a) *Clinically*: classic angina is regularly preceded by an increase in cardiac work, resulting from an increase in heart rate, peripheral resistances, or ventricular pre-ejection time (Roughgarden, 1966; Robinson, 1967). On the other hand, Prinzmetal angina can appear at rest and is not preceded by changes in these variables (Guazzi *et al.*, 1971b). (b) *Electrocardiographically*: the electrocardiogram during classic angina pectoris is characterised by depression of the ST segment and/or T wave inversion. Prinzmetal angina is accompanied by transient ST segment elevation which returns to normal once the pain has passed off. (c) *Coronary arteriography*: various investigators, the first of whom were Dhurandhar *et al.* (1972) and Oliva *et al.* (1973), have confirmed Prinzmetal's theory that coronary spasm occurred during the episode of variant angina but not during classic angina. This observation shows the similarity between the patients with Prinzmetal's angina and experimental animals subjected to transient coronary ligation. This group of patients are, therefore, ideal for the study of the circulatory changes produced by acute myocardial ischaemia.

In previous studies during coronary arteriography (Perez-Gomez and Garcia-Aguado, 1977), we found a dominant response of the parasympathetic

receptors situated in the inferior wall of the left ventricle. In this investigation we have studied changes in heart rate and rhythm during episodes of pain in patients with Prinzmetal's angina.

Subjects and methods

We made observations on 14 patients with the clinical diagnosis of Prinzmetal's angina who were divided into 2 groups. *Group A* consisted of 7 patients with the typical electrocardiographic changes of Prinzmetal's angina in the anterior precordial leads, and *group I* consisted of 7 patients with these changes in left ventricular inferior wall leads. Coronary arteriography was performed on 12 patients and left ventriculography on 10. The changes in heart rate produced by the pain were recorded in 12 patients.

In order to obtain a large number of patients for statistical purposes, we have reviewed the electrocardiographic tracings in 63 published cases where both the basal electrocardiogram and the electrocardiogram during pain were shown. These cases are those described by Prinzmetal *et al.* (1960), cases 1 and 2; Robinson (1965); Botti (1966); Schwartz *et al.* (1966), case 1; Hilal and Massumi (1967); Dorra *et al.* (1968); Jouve *et al.* (1969), cases 2, 4, 6, 7, and 8; Poggi *et al.* (1969), 2 cases; Whiting *et al.* (1970); Bayes de Luna *et al.* (1971), 2 cases; Casamayor del Cacho *et al.* (1971); Guazzi *et al.* (1971a), cases 1, 3, 4, and 5; Silverman and Flamm

(1971), case 1; Cosby *et al.* (1972), cases 1 and 3; Cheng *et al.* (1973), cases 1, 2, 3, and 4; Cherrier *et al.* (1973), case 7; Ferrer Montagut *et al.* (1973), case 2; MacAlpin *et al.* (1973), cases R.C., C.G., and M.K.; MacMillan *et al.* (1973), case R.W.; Oliva *et al.* (1973); Bodenheimer *et al.* (1974), cases 2, 6, and 7; Gaasch *et al.* (1974), case 3; Kossowsky *et al.* (1974), case 4; Levin *et al.* (1974), 3 cases; Schroeder *et al.* (1974); Vázquez Garcia *et al.* (1974), case 6; Yasue *et al.* (1974), cases M.S., S.S., and H.K.; Donsky *et al.* (1975); Endo *et al.* (1975), cases 2 and 9; Gaasch *et al.* (1975), cases 1 and 2; Smithen *et al.* (1975); Widlansky *et al.* (1975); Marsh *et al.* (1976); Daniel Riesco *et al.* (1976), cases 1 and 2; and Yasue *et al.* (1976), cases 1, 2, 3, and 4. With our 12 cases, there is a total of 75 published cases, of which 38 belong to group A, and 37 to group I. We have excluded those patients who presented with myocardial infarction or severe coronary artery disease in an area other than that which gave rise to the electrocardiographic abnormalities. We also excluded those patients in whom electrocardiograms showed atrioventricular block and those in whom sinus rhythm and ventricular arrhythmias alternated, unless sufficient of the record showed normal sinus rhythm. We compared the basal rate with the rate during pain, measuring average heart rate from all the tracings shown in the publication.

We studied the incidence of arrhythmias during pain in 210 cases, including our 14 cases, cases reported by the authors listed above, and cases reported by Meriel *et al.* (1966), Bouvrain *et al.* (1969), Gillilan *et al.* (1969), Hardel *et al.* (1969), Yeh and Rogers (1970), Gaquière and Quillet (1971), Guazzi *et al.* (1971b), Cheng *et al.* (1972), Dhurandhar *et al.* (1972), Kemp (1972), Fernandez *et al.* (1973), Gonin *et al.* (1973), Hiltgen *et al.* (1973), King

et al. (1973), Levi and Proto (1973), Applefield and Ronan (1974), Auzépy *et al.* (1974), Betriu *et al.* (1974), Hart *et al.* (1974), Kerin and Macleod (1974), Kerin and Schwartz (1974), Nevins (1974), Prchkov *et al.* (1974), Harper *et al.* (1975), Marti Garcia *et al.* (1975), Meller *et al.* (1975), and Shubrooks *et al.* (1975). Cases were included only if the area of ischaemia and the occurrence or absence of arrhythmias was specifically stated.

Applying the same criteria we divided the cases into two groups: group A (anterior) with 104 cases, group I (inferior) with 101 cases, and group I+L (inferior and lateral) with 5 cases. The incidence of ectopic arrhythmias and of second or third degree atrioventricular block was analysed. In each case we only considered the most severe arrhythmia (classifying severity in the following order: ventricular fibrillation, ventricular tachycardia, ventricular ectopic beats, atrial fibrillation, atrial tachycardia, and atrial ectopic beats). However, we have taken into account the association of atrioventricular block and severe ventricular arrhythmias (ventricular fibrillation or tachycardia).

Results

LEFT VENTRICULAR HAEMODYNAMICS (Table 1) Basal left ventricular end-diastolic pressure was normal in all cases, ranging from 5 to 12 mmHg. The ejection fraction was greater than 0.5 in all cases, except for one in which it was 0.41.

CORONARY ARTERIOGRAPHY (Table 1) Obstruction greater than 50 per cent was found in 9 patients, involving 1 artery in 7, and 2 arteries in the remaining 2. The coronary arteries were normal in 2 patients and were slightly abnormal in another.

Table 1 Clinical, haemodynamic, and angiographic data

Case no.	Age	Sex	Sinus rate		Area of ST ↑	Arrhythmias	LVEDP	Ejection fraction	Coronary arteriography		
			Basal	Pain					AD	AD (branches)Cx	RC
1	44	M	115	95	I	—	12	0.66	—	—	25
2	45	M	85	57	I	—	8	0.72	—	—	25(x)
3	51	M	95	62	I	—	—	—	30	—	100
4	46	M	60	130	A	VE	10	0.77	75	—	25
5	50	M	72	90	A	—	—	—	—	—	—
6	65	M	78	100	A	AF	—	—	—	—	—
7	41	F	65	85	A	VE	8	0.41	75	—	50
8	56	M	—	—	—	—	10	0.55	—	75	50
9	51	M	60	45	I	AV block	—	0.85	—	50	—
10	44	M	68	98	A	—	6	0.74	50	—	—
11	44	M	75	63	I	—	10	0.71	50	—	25(x)
12	51	M	60	—	I	—	5	0.76	—	—	90
13	58	M	62	75	A	—	12	0.74	—	—	90
14	68	M	115	95	I	—	—	—	—	—	100(x)

I, inferior ischaemia; A, anterior ischaemia; VE, ventricular ectopics; AF, atrial fibrillation; LVEDP, left ventricular end-diastolic pressure; AD, anterior descending; Cx, circumflex; RC, right coronary.

Data of coronary arteriography expressed in percentage of obstruction. (x), obstruction caused by spasm.

Fig. 1 Right coronary arteriogram in left anterior oblique projection showing severe obstruction.

Fig. 2 Same case as in Fig. 1, after administration of glyceryl trinitrate, showing normal coronary artery.

Distal arteries were normal in all cases. Arteriography showed coronary spasm in 4 cases (Fig. 1 and 2), appearing spontaneously in 3 and after adrenaline injection in the other. In 1 patient the spasm affected the entire length of the anterior descending artery, the contrast medium taking several seconds to reach the peripheral branches. In all cases the spasm passed off after the administration of sublingual glyceryl trinitrate.

CHANGES IN HEART RATE DURING EPISODE OF PAIN

Group A

Mean sinus rate increased with pain from a basal rate of 67.5 beats per minute to 94.6, a change which was statistically significant (Fig. 3). In all published cases, the mean basal rate was 69.3 increasing during pain to 86.3, a highly significant change (Fig. 4).

Group I

The mean basal rate in our cases was 90.9 beats per minute which decreased during pain to 69.5, a change which was not statistically significant (Fig. 3). In all published cases, the mean basal rate was 76.5

Fig. 3 Change in heart rate during pain in our cases. There is an increase of rate in patients with anterior ischaemia and decrease in those with inferior ischaemia.

Fig. 4 Change in heart rate during pain in all published cases.

which fell during pain to 64.6, a highly significant change (Fig. 4).

ARRHYTHMIAS DURING EPISODE OF PAIN

Group A

One of our patients developed atrial fibrillation and 2 ventricular ectopic beats. Of the 104 published cases (Table 2), 30 developed severe ventricular arrhythmias (tachycardia or fibrillation) during pain, 22 had ventricular ectopic beats, and 5 had atrial arrhythmias. Three cases (Table 3) had atrioventricular block, which in 2 was accompanied by a severe ventricular arrhythmia. One of these

cases had had previous inferior myocardial infarction, one other had severe right coronary artery disease, and the other slight narrowing of the anterior descending coronary artery.

Group I

One of our cases developed atrioventricular block but none developed ectopic arrhythmias. Of the 101 published cases, however, 4 had severe ventricular arrhythmias, and 6 ventricular ectopic beats. Severe ventricular arrhythmias associated with atrioventricular block were reported in 8 cases (Table 3) and isolated atrioventricular block in 17. Statistical analysis showed that ectopic arrhythmias occurred more commonly in group A than in group I, both when these arrhythmias were seen in isolation ($P < 0.001$), and when those associated with atrioventricular block were included ($P < 0.005$).

Discussion

Coronary arteriography during the episode of Prinzmetal's angina, first performed by Dhurandhar *et al.* (1972) and Oliva *et al.* (1973), and subsequently by others, has confirmed the occurrence of the transient coronary spasm which was postulated by Prinzmetal *et al.* (1960) as the cause of this syndrome. Recent studies have shown that coronary spasm accompanied by the classical symptoms can be reproduced by the injection of methacholine (Yasue *et al.*, 1974), ergometrine (Gaasch *et al.*, 1975), or adrenaline in the presence of beta-adrenergic blockade (Yasue *et al.*, 1976). For this reason, the patient with Prinzmetal's angina is an ideal subject for the study of the circulatory and central nervous system responses to transient acute myocardial ischaemia. During the episode of pain the characteristic haemodynamic change is a conspicuous rise in left ventricular end-diastolic pressure reflecting left ventricular dysfunction. In the cases published by Guazzi *et al.* (1971b), Cheng *et al.* (1973), Kerin and Macleod (1974), Levin *et al.* (1974), Gaasch *et al.* (1975), and Smithen *et al.* (1975), there was no difference in haemodynamic behaviour between patients with anterior and those with inferior ischaemia. We believe, therefore, that the dependence of heart rate response on the site of coronary spasm

Table 2 Arrhythmias during pain

	Ventricular tachycardia	Ventricular fibrillation	Ventricular ectopic beats	Atrial fibrillation	Atrial ectopic beats	Supraventricular tachycardia
Anterior	16	14	22	1	1	3
Inferior	3	1	6	1	—	—
Inferior + lateral	—	1	1	—	—	—

Table 3 Atrioventricular block during pain

	Isolated AV block	Atrioventricular block	
		+ Ventricular tachycardia	+ Ventricular fibrillation
Anterior	1	1	1
Inferior	17	6	2
Inferior + lateral	—	—	2

implies a difference in the response of the autonomic nervous system to anterior and inferior ischaemia, with a predominant sympathetic response to anterior ischaemia, and a predominant parasympathetic response to inferior ischaemia. This difference has not been recognised in the past because there have been few published cases and because they have not been divided into those with anterior and those with inferior ischaemia.

The appearance of ectopic arrhythmias is facilitated by a slow heart rate, because of the longer non-refractory diastolic period. Whiting *et al.* (1970) have shown that severe ventricular arrhythmias accompanying atrioventricular block ceased after the implantation of a demand pacemaker, even when episodes of pain continued. However, we have found that the incidence of ectopic arrhythmias is greater in the patients with a faster sinus rate (that is, those with anterior ischaemia). This may result from sympathetic stimulation, as suggested by Daggett and Wallace (1966), increased myocardial oxygen consumption resulting from tachycardia, or the greater extent of myocardial damage which follows the obstruction of the anterior descending artery. Nevertheless, this greater damage can be partly caused by increased heart work because of tachycardia and a high degree of catecholamine release.

There are cases which cannot be included in either of the two principal groups, in whom ST elevation occurs during pain in I, aVL, V5 to V6, and inferior leads; Wiener *et al.* (1976) have shown simultaneous spasm of the three main coronary arteries in one of these cases.

Dr P. Zarco performed most of the angiographic studies. Drs C. Benito and J. Dominguez sent us patients for investigation, and Drs W. Brigden and A. Bayes de Luna gave us their help and criticism. We also thank Mr R. Carrera for his help.

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