Role of Autonomic Nervous System in the Pathogenesis of Prinzmetal’s Variant Form of Angina

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SUMMARY

In ten patients with Prinzmetal’s variant form of angina the effects of various drugs were assessed: subcutaneous injection of methacholine (10 mg), atropine (0.7 mg), and epinephrine (0.7 mg); intravenous infusion of isoproterenol (20-25 μg/min); and in the three of the above patients who were having recurrent spontaneous attacks at the time of the examination, oral administration of atropine (0.6-1.2 mg), propranolol (30-90 mg), and phenoxybenzamine (10 mg in one patient). Master’s triple two-step test and selective coronary arteriography were done on all the patients.

In the three patients who were having spontaneous attacks at the time of the examination, the administration of methacholine induced the attacks and that of atropine suppressed the attacks. Epinephrine induced the attacks in two patients and propranolol was without effect in suppressing the attacks. Phenoxybenzamine (in one patient) suppressed the attacks. Neither Master’s triple two-step test nor isoproterenol infusion precipitated the attacks, though heart rate increased to more than 110 beats/min and 160 beats/min respectively in all the patients. Coronary arteriograms were normal in seven of the ten patients.

It is concluded that enhanced activity of the parasympathetic nervous system, which occurs at rest, is involved in the initiation of the attack by stimulating the sympathetic nerve which in turn probably induces coronary arterial spasm by way of activating alpha (vasoconstrictor) receptors present in the large coronary arteries.

Additional Indexing Words:

Parasympathetic nervous system
Methacholine
Coronary arterial spasm
Atropine
Alpha receptors
Propranolol

PRINZMETAL’S VARIANT FORM OF ANGINA

Pectoris is characterized by recurring attacks of chest pain which, in contrast to classical angina, occur at rest and are not precipitated by exercise or emotional stress and are associated with transient ST-segment elevation in the electrocardiogram.1, 2 Prinzmetal and coworkers postulated that coronary arterial spasm was probably the cause of this syndrome and several recent reports3-6 demonstrated arteriographically that severe coronary arterial spasm was indeed associated with the attacks. But the mechanism by which coronary arterial spasm occurs remains unknown.

We examined the relationship between the autonomic nervous system and the attack in this form of angina.

Material and Methods

Ten patients with Prinzmetal’s variant form of angina (table 1) were studied. Three of them (M. S., S. S., and H. K.) were having recurrent attacks at the time of the examination (the attack occurring at 4:00-7:00 a.m. in M. S. and H. K., and at rest during the daytime in S. S.). The other seven patients had been free from the attacks for more than three months at the time of the examination. The subcutaneous administration of methacholine (10 mg), atropine (0.7 mg), and epinephrine (0.7 mg), and the intravenous infusion of isoproterenol (20-25 μg/min), on separate days, were given at 10:00-11:00 a.m. to all the patients. Blood pressure, heart rate, and electrocardiogram were continuously monitored for one hour before and after the administration. M. S. and H. K., who were having recurring attacks in the early morning, received atropine (0.6 mg) and propranolol (20-40 mg) orally at bedtime, and S. S., whose attack occurred at rest during daytime, was given atropine (1.2 mg) and propranolol (30-90 mg) orally in three divided doses, and the effects on the attacks were examined. Phenoxybenzamine (10 mg) was also given orally for H. K. at bedtime. To these three patients, subcutaneous administration of methacholine (10 mg) was repeated 20 minutes after subcutaneous injection of atropine (1.0 mg). Selective coronary arteriography using Judkins’ technique and Master’s triple two-step test were done on all the patients. Daily physical activities of the patients were also examined.

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Table 1

ECG, Angiographic Findings and Physical Activities in Ten Patients with Prinzmetal’s Variant Form of Angina

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Resting ECG</th>
<th>ECG during attack</th>
<th>Angiographic findings</th>
<th>Physical activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.S.</td>
<td>64</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Member of soccer club</td>
</tr>
<tr>
<td>S.S.</td>
<td>44</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Teacher of gymnastics</td>
</tr>
<tr>
<td>H.K.</td>
<td>59</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads I, aVL, and V4-6</td>
<td>50% diffuse stenosis in left circumflex artery</td>
<td>Farmer, Champion of high jump</td>
</tr>
<tr>
<td>J.M.</td>
<td>49</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Member of baseball club</td>
</tr>
<tr>
<td>K.N.</td>
<td>63</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Carpenter</td>
</tr>
<tr>
<td>H.Y.</td>
<td>49</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>75% localized stenosis in proximal right coronary artery</td>
<td>Farmer</td>
</tr>
<tr>
<td>K.Y.</td>
<td>61</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Fisherman</td>
</tr>
<tr>
<td>T.O.</td>
<td>60</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads II, III, and aVF</td>
<td>Normal</td>
<td>Railroad laborer, trackman</td>
</tr>
<tr>
<td>T.M.</td>
<td>47</td>
<td>M</td>
<td>Normal</td>
<td>Flattening of T-wave in leads II, III, and aVF</td>
<td>75% localized stenosis in proximal right coronary artery</td>
<td>Member of baseball club</td>
</tr>
<tr>
<td>K.H.</td>
<td>64</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in leads I, aVL, and V4-6</td>
<td>Normal</td>
<td>Carpenter</td>
</tr>
</tbody>
</table>

Results

In M. S., S. S., and H. K., who were having spontaneous attacks at the time of the examination, the administration of methacholine induced the attacks together with ST-segment elevations in the electrocardiogram (in leads II, III and aVF in M. S. and S. S., and in leads I and aVL in H. K.), 11, 14, and 6 min after the injection respectively (figs. 1, 2, and 3). In H. K., ventricular fibrillation followed ST-segment elevation. The injection of methacholine 20 minutes following atropine, however, did not precipitate an attack in the three patients. The administration of epinephrine induced the attack in association with ST-segment elevations in the electrocardiogram in S. S., and H. K. (figs. 4, 5). The administration of atropine consistently suppressed the attacks in all the three patients (figs. 6, 7, and 8) and that of phenoxybenzamine in H. K. (fig. 8). The administration of propranolol, rather than preventing attacks (figs. 6, 7

![Figure 1](http://circ.ahajournals.org/)

The effects of the subcutaneous administration of 10 mg of methacholine on blood pressure, heart rate, and anginal attack. At the arrow, 10 mg of methacholine was given subcutaneously.

![Figure 2](http://circ.ahajournals.org/)

The effects of the subcutaneous administration of 10 mg of methacholine on blood pressure, heart rate and anginal attack. At the arrow, 10 mg of methacholine was given subcutaneously.
Master’s triple two-step test precipitated the attacks, even though heart rate increased to more than 160 beats/min and 110 beats/min respectively. All the patients were either muscular laborers or athletes (table 1). Coronary arteriograms, performed in the absence of the attacks, showed 75% localized stenosis in right proximal coronary artery in two patients (K. Y. and T. M.) and 50% diffuse stenosis in left circumflex coronary artery in one patient (H. K.). In the remaining seven patients, coronary arteries appeared almost normal (table 1).

Discussion

Classical angina pectoris is believed to occur when myocardial oxygen supply-demand relationships are transiently unbalanced by some type of stress in the presence of obstruction of major coronary arteries. The above explanation is not adequate for the manifestations of the variant form of angina. The attacks occurred when the patients were at rest, a time when myocardial oxygen demand is reduced, and were not precipitated by either strenuous exercises or isoproterenol infusion, at which times marked increase in myocardial oxygen demand occurs. The administration of propranolol, which decreases myocardial oxygen consumption, was not effective in suppressing the attacks. The coronary arteriograms done in the absence of the attacks were normal in seven out of ten patients. These findings are in agreement with those of other investigators.

Prinzmetal et al. postulated that coronary arterial spasm was probably the cause of this form of angina.
AUTONOMIC ACTIVITY IN PRINZMETAL'S ANGINA

The effects of the administration of atropine and propranolol on the anginal attacks. Atropine (0.6 mg) and propranolol (20 mg) were given orally at bedtime because the attacks occurred in the early morning. Atropine consistently suppressed the attacks, but propranolol was without effect. The arrow indicates the subcutaneous injection of 10 mg of methacholine.

Figure 6

and several recent reports9-5 demonstrated arteriographically that severe coronary arterial spasm was indeed associated with the attacks of variant form of angina. Our studies support this postulation.

The fact that the anginal attack was induced by the administration of the parasympathomimetic drug, methacholine, and was suppressed by the parasympatholytic drug, atropine, strongly suggests that the enhanced activity of the parasympathetic nervous system is involved in the initiation of the attack. The fact that the attacks occur during rest and are not precipitated by strenuous exercises and that the patients are either athletes or muscular laborers are also compatible with this concept, because it is well known12,13 that the activity of the parasympathetic nervous system is increased during rest and is suppressed during exercise. Parasympathetic nervous ac-

Figure 7

The effects of the administration of atropine and propranolol on the anginal attacks. Atropine (1.2 mg daily) and propranolol (30-90 mg daily) were given orally in three divided doses. Atropine consistently suppressed the attacks, but propranolol was without effect.

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tivity increases more at rest in athletes than non-

activities.14 It is then not unreasonable to speculate that the anginal attacks were caused by the transient severe spasm of coronary artery mediated by the enhanced activity of the parasympathetic nervous system.

How can enhanced activity of the parasympathetic nerve cause coronary arterial spasm? The coronary arteries are innervated by both the sympathetic and parasympathetic (vagus) nerves15 and the stimulation of the vagus (parasympathetic) nerve or the intracoronary injection of its neurotransmitter, acetylcholine, causes coronary vasodilatation by direct action.16-21 In association with its direct action, however, acetylcholine is believed to also cause release of norepinephrine from the postganglionic sympathetic nerve terminals in the heart.18, 22-25 In addition, the large coronary arteries are supplied predominantly with alpha (vasoconstrictor) adrenergic receptors.16, 26-32 But coronary blood flow is regulated primarily by the metabolic requirements of the myocardium, increase in myocardial oxygen consumption causing coronary vasodilatation, and neurogenic control of the coronary circulation is of lesser importance.16, 30, 34 When the myocardial effects are eliminated by using either fibrillating or arrested hearts,33 or the intact beating heart after beta receptor blockade,28, 29, 31 however, intracoronary injection of norepinephrine or epinephrine, or stimulation of the sympathetic nerve causes transient coronary vasoconstriction. It is known17-21 that the activity of the parasympathetic nervous system decreases heart rate, blood pressure, and myocardial contractility, all of which lead to reduced myocardial oxygen consumption.

It appears quite probable that excessive activity of the parasympathetic nervous system stimulates the
sympathetic nerve which in turn causes severe vasoconstriction of large coronary arteries by way of activating alpha receptors present in large coronary arteries and that this coronary arterial spasm produces the anginal attack in association with ST-segment elevations in the electrocardiogram. The facts that the administration of propranolol, which decreases myocardial oxygen consumption,6-9 not only was ineffective in suppressing the attack but rather tended to aggravate the attack, and that the administration of phenoxybenzamine, an alpha-adrenergic blocker, suppressed the attack also support this concept, and it is documented that ST-segment elevation in the electrocardiogram without infarction occurs in temporary occlusion of a large coronary artery.1

The injection of epinephrine induced the anginal attack in S. S. and H. K. The attack was severe in S. S. who had spontaneous attacks during rest in the daytime, moderate in H. K., whose spontaneous attacks occurred in the early morning. The attack was not precipitated in M. S. whose spontaneous attacks occurred in the night. These facts can be explained if it is assumed that at the time of injection of epinephrine (10:00-11:00 a.m.), the activity of the parasympathetic nervous system was increased markedly in S. S., moderately in H. K., and little in M. S.

Nowlin et al.36 and Murao et al.36 report that this form of angina is associated with the rapid eye movement (REM) period of sleep, and it is interesting to note in the light of the above facts that the REM period of sleep is triggered by acetylcholine and suppressed by atropine and that procedures which interfere with the action of norepinephrine also suppress the REM period.37

The attacks were precipitated by neither strenuous exercises nor isoproterenol infusion and this is to be expected if it is considered that both strenuous exercises and isoproterenol infusion markedly increase myocardial oxygen consumption which causes coronary vasodilatation and not vasoconstriction.

In seven patients who had been free from the attacks for more than three months at the time of the examination, none of the above drugs induced the attacks. Changes in the activity of the autonomic nervous system over time probably explain this finding.38

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