Provocation of Esophageal Pain by Ergonovine or Edrophonium

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Ten patients with anginal symptoms and ergonovine-induced chest pain without coronary artery spasm had esophageal manometry with provocative pharmacologic testing. Increased amplitude of esophageal contractions on baseline manometry (68.2 ± 10.3 mmHg) was the only characteristic discriminating these patients from normals (40.9 ± 6.3 mmHg) and from patients with esophageal motility disorders (39.6 ± 7.5 mmHg). The administration of ergonovine or edrophonium provoked typical chest pain in association with high amplitude, long duration, and repetitive esophageal contractions in all 10 patients. Patients with esophageal motor disorders showed a similar, but less marked esophageal response with pain infrequently produced. Normals showed no response to ergonovine, and a minimal response to edrophonium, but without chest pain. Clinical features of patients with ergonovine-induced chest pain could not distinguish them from patients with coronary artery disease; esophageal symptoms were infrequent and mild. These studies suggest that certain patients with chest pain of esophageal origin may be identified only by provocative testing during esophageal manometry. However, these provocative drugs may also induce coronary artery spasm and should not be used during routine clinical manometry.

The etiology of chest pain can be a major diagnostic problem. Prinzmetal's angina, which presents as anginalike pain often occurring at rest and associated with EKG changes of ST-segment elevation, is associated with coronary artery spasm (1,2). This can be induced at cardiac catheterization by the use of ergonovine maleate. This provocative test is highly specific for coronary artery spasm (3). There still remains a significant group of patients with chest pain having features suggestive of angina who do not have a fixed coronary artery lesion or coronary artery spasm demonstrated at cardiac catheterization. In such a group of patients, as many as a third may develop chest pain when ergonovine maleate is administered without visible coronary artery spasm or electrocardiographic changes (4).

Recent studies indicate that chest pain secondary to esophageal motility disorders may be found in over 30% of patients without evidence of coronary artery disease (5). At our institution a retrospective analysis of the manometric findings in patients with normal coronary angiography referred for esophageal evaluation showed 65% to have esophageal motility disturbances.

The purpose of this study is twofold: first, to establish a possible relationship between disordered esophageal motility and ergonovine-induced pain in patients without Prinzmetal's angina; and second, to determine the clinical features and other provocative tests that may distinguish this group of patients.

Methods
All studies were done in the three groups of patients chosen by the following criteria: Group I — 7 normal volunteers, ages 21-24 yr (mean 23.2 yr) with no history of chest pain or dysphagia. Manometry was required to be free of any spontaneous, simultaneous, and repetitive esophageal contractions. Group II — 9 patients, ages 30-54 yr (mean 47.4 yr), with abnormal esophageal manometry characterized by the presence of simultaneous or repetitive contractions. All patients had esophageal symptoms of either dysphagia or odynophagia. Six of the patients had chest pain attributable to the esophagus. All patients...
were free of cardiac disease, 3 having normal cardiac catheterizations including ergonovine stimulation without induction of pain. Three patients in this group had classical symptomatic diffuse esophageal spasm by clinical and manometric criteria. Patients with achalasia or gastroesophageal reflux were not included. Group III-10 consecutive patients, ages 42-61 yr (mean 54.0 yr) with angiographic chest pain and ergonovine-induced chest pain without coronary artery spasm or fixed coronary artery lesions at coronary angiography. All subjects and patients gave informed consent before the study.

Patients were studied while resting quietly in a supine position after an 8-h fasting period. A belt pneumograph was placed around the larynx to monitor swallowing. Esophageal intraluminal pressures were measured using four polyvinyl catheters (0.8 mm ID), each connected to external transducers, Statham P23 (Statham Instruments, Puerto Rico). The recording catheters were fused into a single unit to preserve the relationship among the four external transducers, Statham P23 (Statham Instruments, Puerto Rico). The recording catheters were fused into a single unit to preserve the relationship among the four side orifices, at 5-cm intervals along the distal part of the recording unit. The catheters were continuously infused with distilled water via a low-compliance capillary tube infusion pump (Arndorfer Medical Specialists, Greendale, Wis.) at a rate of 0.6 ml/min. The outputs from the transducers were recorded on a multichannel rectilinear ink-writing recorder (Beckman Instruments, Inc., Fullerton, Calif.) Upon occlusion of each recording orifice, the rate of rise in pressure exceeded 250 mmHg/s.

The catheter assembly was passed through the nose until all recording orifices were in the stomach and was then withdrawn slowly at 1-cm intervals. The lower esophageal sphincter (LES) pressure was determined using a station pull-through technique. When the most distal orifice was in the LES, the catheter unit was secured with tape at the nose. Intraluminal pressures at 5 cm, 10 cm, and 15 cm above the LES were recorded simultaneously along with the sphincter pressure.

Saline, 1.0 ml; ergonovine maleate, 0.2 mg (Wyeth Laboratories, Inc., Philadelphia, Pa.); and edrophonium chloride, 10.0 mg (Roche Products, Manati, Puerto Rico) were given as intravenous bolus injections, allowing at least 20 min between injections. The order of administration was not known to the patient. After the last injection a Bernstein test was performed. At each stage the presence of chest discomfort or pain was noted and was compared with the patient's usual symptoms.

The records were analyzed in a blinded fashion to determine the LES pressure and the mean amplitude and duration of the esophageal body contractions after the bolus injections of saline, ergonovine maleate, and edrophonium chloride. The physician analyzing the records was not aware of the history or the symptomatic response of the patients.

The mean amplitude and duration of contractions after 25 dry swallows were measured after each injection. The amplitude was expressed in millimeters of mercury with the esophageal pressure between contractions, in the same lead, as zero reference. The duration was measured, in seconds, between the onset of the major upstroke of the wave and the return to baseline. In addition, the presence of spontaneous, simultaneous, and repetitive contractions was noted.

Comparison was made of the mean amplitude and duration of esophageal contractions and the presence of repetitive contractions, in the basal state and after each drug, using the paired t-test with each patient as his own control. Basal parameters and degree of change with each drug were compared between groups, using analysis of variance and unpaired t-tests.

Results

Table 1 shows the baseline manometric parameters in the three groups of patients and subjects. Patients with ergonovine-induced chest pain had only a minor esophageal motility disturbance with 7.0 ± 3.0% of contractions being repetitive and only rare spontaneous or simultaneous contractions as compared with the normals (p > 0.05). The amplitude of the baseline esophageal contractions was significantly greater in the patients with ergonovine-induced chest pain as compared with normals and patients with esophageal motility disturbances. LES pressures were normal in the three groups. Thus, the amplitude of esophageal contractions was the only baseline manometric parameter that distinguished patients with chest pain induced by ergonovine.

Table 2 shows the percentage of patients having
Esophageal contractions in a group III patient after saline, ergonovine, and edrophonium infusion. The normal peristaltic contraction after saline infusion has a single peak, an amplitude of 100 mmHg, and a duration of 4 s. With ergonovine or edrophonium, the peristaltic contraction shows multiple peaks (repetitive contraction), increased amplitude and increased duration.

Figure 1: Esophageal contractions in a group III patient after saline, ergonovine, and edrophonium infusion. The normal peristaltic contraction after saline infusion has a single peak, an amplitude of 100 mmHg, and a duration of 4 s. With ergonovine or edrophonium, the peristaltic contraction shows multiple peaks (repetitive contraction), increased amplitude and increased duration.

The adverse effects of the drugs were minimal and consisted of mild nausea and light-headedness lasting for <2 min with ergonovine. Nausea, light-headedness, salivation, abdominal cramps, and mild slowing of the heart rate lasting for <2 min were noted with edrophonium.

Table 3 shows the clinical features of group III patients. Patients had typical anginalike chest pain with no changes from baseline electrocardiograms. Esophageal symptoms were minimal with dysphagia or odynophagia occurring in 4 patients with 3 of these patients having mild heartburn. Definitive clinical features of chest pain or esophageal symptoms could not distinguish this group, even in retrospect, from patients with coronary artery disease.

Discussion

The results of this study distinguish a specific group of patients who have episodic chest pain characteristic of angina pectoris, but who have normal coronary angiography and chest pain induced by ergonovine. These studies suggest that the chest pain may be related to an esophageal motility disorder characterized by an increased amplitude of baseline esophageal contractions but otherwise minimal dysfunction in peristalsis. With ergonovine or edrophonium these patients have high-amplitude, long-duration, repetitive, peristaltic esophageal contractions which are associated with their typical chest pain.
Motor dysfunction of the esophagus is a recognized cause of chest pain (6). Symptomatic diffuse esophageal spasm is characterized by chest pain and dysphagia with manometric evidence of high-amplitude, simultaneous or repetitive contractions (7). In recent studies in patients with chest pain, high-amplitude, long-duration, but otherwise normal peristaltic contractions were found more commonly than the classical manometric findings of diffuse esophageal spasm (8). The present study using provocative agents further supports these observations that chest pain of esophageal origin may be seen in patients with high-amplitude esophageal contractions but otherwise minimal disturbances in peristalsis.

Our retrospective analysis of 37 patients with chest pain who underwent esophageal manometric studies after normal coronary angiography revealed a 65% incidence of esophageal motor abnormalities. Only 8% of patients had severe motor disorders compatible with symptomatic diffuse esophageal spasm. Our study showed a higher proportion of esophageal motor disorders in patients with anginalike pain and negative cardiac evaluations than did a recent study by Brand where 33% had esophageal motor disorders (5). The higher percentage of motility abnormalities in our review may have reflected a suspicion of esophageal disease by the referring physician but both studies still indicate a high prevalence of esophageal motor disorders in this population. Neither retrospective study utilized provocative tests nor identified patients with only high-amplitude contractions on manometry.

The present study indicates that patients with ergonovine-induced chest pain without coronary artery disease have minimal evidence of a motility disorder on baseline manometric studies, yet show a greater increase in the number of repetitive contractions and the amplitude and duration of contractions with either ergonovine or edrophonium than patients with more marked baseline motility disturbances. The basis of this increased esophageal contractile response to either drug may be due to a denervation supersensitivity as seen in patients with achalasia or diffuse esophageal spasm. Super-sensitivity in these diseases may be nonspecific, and has been noted with cholinergic drugs or pen-
tagastrin (9,10). Ergonovine works via the α-adrenergic receptor or directly on smooth muscle whereas edrophonium is a cholinesterase inhibitor that enhances cholinergic activity at the muscarinic receptor (11). Adrenergic denervation in animals leads to supersensitivity to both α-adrenergic and cholinergic agents (12–14).

We suggest that chest pain may be secondary to an esophageal motor disorder and may account for the symptom complex in this group of patients with ergonovine-induced chest pain without coronary artery spasm. The diagnosis of this condition before coronary artery visualization is difficult, but should be suspected in those patients with esophageal symptoms, high-amplitude esophageal contractions on manometry, and a normal electrocardiogram. Provocative tests with ergonovine and edrophonium allow this diagnosis to be made. Ergonovine is used routinely in the management of obstetric patients, but its safety in the general population is not known. The aim of this study was to determine a source for chest pain in a previously undiagnosed group of patients rather than to describe a new provocative test. The safety of ergonovine and edrophonium in patients with coronary artery disease is not established and we do not advocate the general use of these drugs as provocative agents.

**References**

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