Acute Myocardial Infarction with Normal Coronary Arteries

A Possible Manifestation of the Billowing Mitral Leaflet Syndrome

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SUMMARY The findings in four young patients with the billowing mitral leaflet syndrome who presented with evidence of acute myocardial infarction are reported. Because technically adequate coronary arteriograms demonstrated patent vessels and the electrocardiograms initially showed pronounced elevation of the ST segments as occurs in Prinzmetal's angina, it is postulated that spasm of normal coronary arteries was the operative factor. Scrutiny of those cases of clinically apparent ischemic heart disease with normal coronary angiograms is suggested to establish whether there is in fact a causal relationship with the billowing mitral leaflet syndrome.

IN THE DIAGNOSIS of myocardial infarction, selective coronary arteriography almost invariably demonstrates evidence of occlusive atherosclerosis. There have, however, been reports of cases where technically excellent coronary arteriograms have shown normal vessels and a variety of causes other than atherosclerosis have been incriminated.1,4 This problem has not been resolved but some evidence now indicates that spasm of angiographically normal coronary arteries may not only produce angina pectoris but may also lead to myocardial infarction.5,6

This report describes four patients with acute myocardial infarction and the billowing mitral leaflet syndrome (BMLS) and discusses the possibility that the latter might be responsible for inducing reversible reflex spasm of angiographically normal coronary arteries.

Case Reports

Case 1

A 40-year-old white female nurse with a history of chest pain for 18 months was admitted to hospital in February 1975, for assessment as a possible candidate for coronary artery surgery. The pain was usually left sided, but occasionally substernal, and attacks were particularly precipitated by emotional stress or effort and were usually relieved by sublingual nitroglycerin. Alpenrolol (Aptin) and perhexilene maleate (Pexid) reduced the frequency of attacks. She also experienced irregular palpitations, unrelated to the chest pain. She smoked 20–30 cigarettes a day. One year prior to admission she had been treated by her private practitioner for a severe attack of pain and a diagnosis of myocardial infarction had been made on the basis of changes in the electrocardiogram and serum enzymes. Her father and a brother had died suddenly in their thirties, both having complained of chest pain, but neither had been examined.

On physical examination there was no evidence of cardiac enlargement. An intermittent nonejection systolic click was heard at the apex. The chest roentgenogram was normal apart from a narrow antero-posterior chest diameter due to a straight thoracic spine and mild sternal depression. The electrocardiogram showed sinus rhythm and a normal mean frontal plane QRS axis. The T waves, which were flattened in II and inverted in III and aVF, suggested inferior myocardial ischemia but were compatible with the BMLS.7 Fasting cholesterol was 288 mg% and triglycerides 80 mg%.

Cardiac catheterization and cineangiography demonstrated normal intracardiac pressures and left ventricular excursion but definite prolaphe of the posterior leaflet of the mitral valve was present (fig. 1A). Selective coronary arteriography (Judkins technique) revealed normal vessels (fig. 2) apart from mild irregularity of the origin of the right ventricular branch of the right coronary artery (fig. 2B). Thirty hours after the procedure, while ambulant in the ward, the patient suddenly developed severe retrosternal chest pain. She was hypotensive with a sinus bradycardia which responded to intravenous atropine and morphine. The electrocardiogram (fig. 3A & B) showed pronounced elevation of the ST segment in the inferior leads, and depression of the ST segment with flattening of the T wave in leads I, aV5, V6 to V4. During the next three weeks these changes gradually reverted to the findings observed prior to catheterization (fig. 3C). The serum glutamic oxaloacetic transaminase (SGOT), serum lactic dehydrogenase (SLD) and creatinine phosphokinase (CPK) levels were normal prior to cardiac catheterization but rose to 47, 541 and 50 units respectively immediately following the onset of chest pain, were 114, 911 and 501 units on the next day, 76, 904 and 98 units on the third day and thereafter decreased progressively.

Three weeks after the first investigation coronary arteriography was repeated (Sones technique) but no changes were detected. The left ventricular cineangiogram still showed no abnormality of wall movement. Since discharge from hospital she had had intermittent bouts of chest pain and continues to take perhexilene maleate and alpenolol.

Case 2

This 21-year-old white man was well until February 13th, 1972, when he experienced sudden, severe, constricting
retrosternal chest pain at 2:30 a.m. The pain lasted three hours and was associated with sweating, nausea and palpitations. He smoked 15-20 cigarettes a day. Apart from a grandfather who died of a probable myocardial infarction at the age of 60, the family history was noncontributory. Of importance, however, is the fact that his asymptomatic 27-year-old sister has a nonejection click but a normal electrocardiogram.

When admitted to hospital his condition was satisfactory and he was free of pain. His blood pressure was 90/60 mm Hg, a soft nonejection systolic click and a third heart sound were detected at the apex. The chest roentgenogram was normal. Measurement of the enzymes showed peak levels of SLD of 1000 units, CPK 290 units and SGOT of 98 units, all of which returned to normal after five days. A fasting lipogram showed a total lipid content of 501 mg%, cholesterol 153 mg%, triglycerides 99 mg%, and low density lipoprotein of 260 mg%. Serum uric acid and fasting blood sugar levels were normal.

Sequential electrocardiograms (fig. 4) taken from the time of admission were compatible with an evolving anterolateral nontransmural myocardial infarction. Cardiac catheterization 12 weeks after admission demonstrated normal intracardiac pressures. Left ventriculography showed normal contractility. Unfortunately, the mitral valve was outside the field and was not seen. Selective coronary arteriography (Sones technique) showed all the major branches to be widely patent without luminal irregularity and no intercoronary collateral channels were noted.

Since discharge from hospital the patient has remained well and has had no chest pain but the intermittent nonejection click persists. An electrocardiogram on February 27th, 1975 was normal, both before and after strenuous effort.

Case 3

This 23-year-old white dental student was well until March 14th, 1974, when during a soccer match he developed severe retrosternal pain which radiated to the left arm and was associated with nausea, vomiting and sweating. Two days later he was admitted to hospital where a diagnosis of myocardial infarction was made. The only abnormality detected on physical examination was an intermittent nonejection systolic click. The CPK level which was initially 305 units gradually returned to normal. Serum cholesterol was 240 mg% and triglycerides 51 mg%. The electrocardiogram

Figure 1. Left ventricular cineangiograms, right anterior oblique projection. In Case 1 (A) there is billowing (b) of the posterior mitral leaflet. In Case 3 (B) there is scalloping (s) and slight prolapse of the posterior mitral leaflet.

Figure 2. Selective coronary arteriograms (Case 1) taken at 64 frames/sec on 6" tube with overframing lens. A and B) Right coronary artery, left and right anterior oblique views, respectively. There is mild irregularity of the origin of the right ventricular branch. C and D) Left coronary artery, left and right oblique views, respectively. E) Left coronary artery, selective injection into circumflex branch. All show absence of occlusive disease.
showed terminal T wave inversion in V₅₋₆, and on discharge three weeks later, after an uneventful recovery, the tracing was within normal limits. On September 1st, 1974, he was readmitted with another episode of severe chest pain lasting eight hours. Sequential electrocardiograms showed changes compatible with nontransmural anterolateral myocardial infarction (fig. 5). He again made a satisfactory recovery and was discharged from hospital.

On November 27th, 1974, he underwent cardiac catheterization which demonstrated normal hemodynamics. Cineangiography showed a normal left ventricle and interventricular septum but there was scalloping of the posterior leaflet of the mitral valve (fig. 1B). Selective coronary cineangiography was not undertaken at that procedure. Because of recurrent bouts of chest pain he was recatheterized on March 11th, 1975. The only electrocardiographic abnormality at this time was mild terminal dipping of the T waves in leads V₂₋₅. The previous findings were confirmed and coronary arteriography (Sones technique) with multiple injections in various views demonstrated normal vessels (fig. 6). Other investigations showed a normal blood count, serum enzymes, sedimentation rate and negative rheumatoid factor. LE cell preparations and serology for syphilis were negative. He smoked only four cigarettes a day.

The patient has remained well with occasional episodes of chest pain of short duration and the nonejection click persists. His 46-year-old mother has an early nonsystolic murmur of mitral regurgitation* and a brother has a nonejection click; both are asymptomatic and have normal electrocardiograms.

Case 4

A 32-year-old black construction worker was admitted to a peripheral hospital on July 24th, 1975, with a suspected

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diagnosis of acute myocardial infarction. That morning, while loading bricks, he had experienced severe central chest pain which lasted an hour. After resting he resumed working but the pain recurred and waxed and waned for the following eight hours until he was admitted to hospital and received morphine. The pain was accompanied by nausea and sweating. On admission he was not in cardiac failure. An “extra sound in systole” was heard by the intern and when examined four days later by a more experienced auscultator a soft late systolic murmur was detected. The electrocardiogram recorded on admission showed deep q waves, ST-segment elevation and T wave inversion in II, III, aVF and V₄₋₆ (fig. 7). The SGOT and LDH were 123 and 1950 units, respectively, on admission and two days later had fallen to 24 and 716 units. Chest roentgenography showed a normal cardiac silhouette and evidence of pulmonary tuberculosis at the right apex. Acid fast bacilli were detected in his sputum. Apart from smoking ten cigarettes a day there were no risk factors and a glucose tolerance test, serum lipoproteins and uric acid were within normal limits. Serology for syphilis was negative. His hospital course was uneventful and after 14 days he was discharged on antituberculous therapy.

Because of the extreme rarity of coronary atherosclerosis and myocardial infarction among the South African black population he was admitted two months later for elective investigation. Examination revealed a muscular man with a
normal blood pressure. The only abnormal physical finding was an apical nonejection click followed by a grade III/V1 late systolic murmur. The electrocardiogram showed q waves and T wave inversion compatible with old transmural inferolateral myocardial infarction. Selective coronary arteriography outlined normal vessels. Left ventricular cineangiography demonstrated normal excursion, mild mitral insufficiency and minimal prolapse of the middle scallop of the posterior leaflet of the mitral valve.

Discussion

The clinical, electrocardiographic and angiographic features of the BMLS have been well documented although the pathogenesis and implication of all aspects of the condition have not yet been elucidated. The four patients described in this report are characteristic examples in that they have nonejection systolic clicks and in all but one scalloping or billowing of the posterior leaflet of the mitral valve has been confirmed cineangiographically. The exception, Case 2, has a 27-year-old sister with a nonejection click which suggests that he has the BMLS on a familial basis.

Oclusive coronary artery disease resulting in papillary muscle dysfunction is becoming increasingly well recognized as a cause of a late systolic murmur and nonejection systolic click and, in our view, this association is common. Aranda and co-workers have recently demonstrated mitral valve prolapse by angiography in 30 of 95 patients with extensive coronary artery occlusion although the auscultatory features of a click or late systolic murmur were not detected by them. Although coronary artery disease affecting major vessels was not demonstrated in our patients, Aldridge et al., using a U-arm mounted image intensifier and a table able to be rotated horizontally, have recently unmasked lesions which had been missed with conventional techniques in approximately 20% of patients. They did not comment, however, on the severity or extent of the unmasked lesions and it seems unlikely to us that any of our patients have significant obstructive lesions of the major arteries. Occlusion of the smaller branches not demonstrable on coronary arteriography, which may have caused the myocardial infarction with secondary papillary muscle dysfunction, a nonejection click and billowing of the mitral valve, cannot be entirely excluded. This possibility is unlikely since the click was known to have been present prior to the episode of myocardial infarction in Case 1, and in both Cases 2 and 3 at least one close relative has a nonejection click, making primary involvement of the mitral valve almost certain. In view of the rarity of atherosclerotic coronary artery disease among the black population of South Africa, papillary muscle dysfunction is an improbable cause of the late systolic murmur and click in Case 4.

Although there have been other instances of the BMLS associated with "myocardial infarction," the reports were not based on serial electrocardiograms and enzyme rise following an acute episode of ischemic chest pain. Gulotta and co-workers studied 26 patients with chest pain, systolic clicks, late systolic murmurs and prolapsed mitral leaflets, three of whom were noted to have ECG patterns "compatible with healed transmural myocardial infarction" and in whom coronary angiograms were normal. Tuqan and associates recently reported two young women with electrocardiographic and vectorcardiographic evidence of transmural myocardial infarction in association with the BMLS, but in neither had chest pain been a feature and both had thoracic cage abnormalities which may well have accounted for the electrocardiographic pattern. Serial electrocardiographic evidence of myocardial infarction supported by changes in the serum enzymes are disparate findings not hitherto reported.

Chest pain is a frequent presenting symptom of the BMLS and usually is not typical of angina pectoris or myocardial infarction, in that it is sharp, transitory, inconsistently related to effort, often left-sided and has a tendency to disappear for long periods without treatment. Occasionally, however, the pain may resemble that of ischemic heart disease and patients have been admitted to hospital with a suspected but unsupported diagnosis of myocardial infarction.

Electrocardiographic abnormalities are also a common component of the syndrome and are sufficiently characteristic to arouse suspicion of the BMLS even prior to clinical examination. The commonest findings are flattening or inversion of the T waves in leads II, III and aVF; the ST segments are usually normal, slightly elevated or mildly depressed with an upward convexity. These changes may vary greatly over time, may normalize spontaneously or after exercise and become more pronounced after inhalation of amyl nitrite and on adoption of the erect posture.

In the typical BMLS, coronary arteriograms have invariably been normal. The most acceptable explanation for the usual type of chest pain and the abnormal electrocardiogram is that undue tension of the chordae tendineae from the prolapsing mitral leaflet compromises the blood supply to the relevant papillary muscle. This suggestion would be compatible with the retraction of the left ventricular wall observed angiographically and of the apical impulse on apex cardiography. These observations do not supply a satisfactory explanation for the acute episodes of prolonged chest pain in our patients in whom the electrocardiograms in the early phase showed pronounced ST-segment elevation followed by an injury pattern compatible with transmural infarction in one, nontransmural necrosis in three and elevation of the serum enzymes in all four. Despite this undoubted evidence of myocardial infarction, selective coronary arteriography showed patent vessels.

The large majority of patients with clinically apparent ischemic heart disease have oclusive atherosclerosis of the major coronary arteries and their epicardial branches. It is unusual for such lesions not to be found at coronary angiography. Indeed, James has suggested that normal coronary arteriograms under such circumstances are the result of inadequate technique or misinterpretation. Nevertheless, there are increasing numbers of reports showing technically excellent arteriograms, supported by occasional necropsy findings, which lend credence to existence of the entity of myocardial infarction with normal coronary arteries. A variety of hypotheses has been advanced to explain this phenomenon. "Small vessel" disease as a result of arteritis or transient occlusion by thrombi or platelets is an unsatisfactory explanation when a large discrete area of myocardium is infarcted. Furthermore, endomyocardial biopsy, albeit in a
very limited number of subjects, has been unrewarding in the
demonstration of small vessel disease in patients with angina
pectoris and normal coronary arteriograms. Similarly,
evidence28 incriminating hypoxia resulting from shift of the
oxyhemoglobin dissociation curve to the left has not been
confirmed by subsequent investigation.29

Because Prinzmetal's variant angina is attributed to cor-
nary arterial spasm with or without atherosclerotic lesions,28-29
some authors have considered the possibility that
sustained coronary artery spasm could cause myocardial in-
farction.3 6 29-36 It is certainly tempting to implicate this
cause since diffuse spasm has been observed at the time of
surgery, occurs with coronary artery catheterization and is
also the probable cause of angina pectoris and sudden death
in workers in nitrate plants after their exposure is discon-
tinued.40 The pathophysiology of coronary artery spasm is
not understood. The true incidence of spasm induced
mechanically during coronary arteriography appears to be
rare (less than 1%) but the exact frequency is difficult to
determine because of the common practice of routinely ad-
ministering nitrates prior to that procedure. In Prinzmetal's
angina it has been postulated that spontaneous spasm could
result from excessive catecholamine release stimulating
smooth muscle in the coronary arteries41 or by reflex
vasomotor impulses,42 the source of which is unknown.
Cheng et al.4 described the case of a 52-year-old woman who
developed acute inferior myocardial infarction shortly after
coronary angiography which had demonstrated severe spasm
of the left circumflex artery; three months later her coronary
angiograms were normal. It is noteworthy that left ven-
tricular contractility was initially normal but that there was
mild mitral insufficiency; subsequently the diaphragmatic
wall was hypokinetic. MacAlpin et al.43 performed cardiac
catheterization and coronary angiography in 19 patients
with Prinzmetal's angina. Although the coronary angi-
ograms were abnormal in all but one patient, left ventricular cineangiography revealed no abnormalities in nine of the 11
patients who had that procedure; in one patient who had
only 57% occlusion of the right coronary artery there was
mild systolic prolapse of the posterior mitral leaflet with
minimal mitral regurgitation. Sasse et al.44 described two
young pregnant women with acute transmural myocardial
infarction in whom coronary arteriograms were normal 3½
and 4 months later. In one of them, the left ventricular angiogram (fig. 4, p. 450),4 in our opinion, definite prolapse of the posterior leaflet of the mitral valve as well as
the so-called ballerina foot29 deformity of the left ventricle
which may be associated with the BMLS. Sasse et al.44 speculated that prolonged but reversible coronary arterial
spasm caused the myocardial infarction and that the spasm
in their patients was related to renin release from transiently ischemic chorion. Possibly, however, the mitral valve may
be involved in this process.

The electrocardiograms in our patients were characterized
initially by pronounced elevation of the ST segments as oc-
curs in Prinzmetal's variant angina; subsequently this was
followed by a pattern of injury. It is tempting to invoke cor-
nary artery spasm as the cause and to consider the possibility that the BMLS might be responsible. The BMLS
is frequently complicated by arrhythmias of which ven-
tricular ectopic beats are the most common.1 12 14 15 Sudden
death has been reported11 14 15 but is rare3 and the
mechanism has not been established with certainty. Wit et al.45 have demonstrated diastolic depolarization of muscle
fibers in the anterior mitral leaflet of the dog in response to
stretch as well as catecholamines and suggested that the
mitral valve could be the site of ectopic impulse formation.
The latter mechanism, or stimuli arising from injured papillary muscles, may be factors responsible for a reflex
vasomotor response operative in inducing coronary artery
spasm in the BMLS, especially during exertion or emotion.

The usual type of chest pain and electrocardiographic ab-
normality in the BMLS probably result from traction of
stretched chordae tendineae on the involved papillary
muscle. In some instances, however, it has been postulated47
that the occurrence of sudden death, myocardial infarction
and arrhythmias may result from spasm of a normal coronary
artery in reflex response to billowing of the posterior mitral
leaflet. The clinical detection of a nonejection systolic click, which is often intermittent, may be difficult, and the frequency
definitely varies with observer experience. Furthermore, mild billowing or scalloping of the posterior mitral leaflet may
cause escape detection in laboratories processing large
numbers of coronary arteriograms. We suggest that an
examination of this hypothesis is warranted and may well
provide a clue to the etiology and pathogenesis of some in-
stances of angina pectoris or myocardial infarction in which
the coronary arteriograms are normal.

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EXERCISE-INDUCED ST ELEVATION/Chahine, Raizner, Ishimori 209


The Clinical Significance of Exercise-induced ST-segment Elevation

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SUMMARY The significance of exercise-induced ST-segment elevation remains unsettled. We reviewed the treadmill tests of 840 consecutive patients and exercise-induced ST-segment elevation was noted in 29 (3.5%). Only eight of these (28%) stopped because of angina. Anterior myocardial infarction (AMI) was found on the resting electrocardiogram in 25 (85%). Angiographic studies performed on 21 showed critical lesions of the left anterior descending (LAD) in 19 (90%) and left ventricular aneurysm in 18 (86%). When all the patients who had AMI or critical LAD obstruction during the study period were reviewed, only 22% and 18% respectively showed exercise-induced ST-segment elevation, while 64% of the cases with left ventricular aneurysm displayed this phenomenon.

Thus, exercise-induced ST elevation seems to reflect the presence of severe coronary artery disease most commonly with an associated left ventricular aneurysm and may relate more to the abnormal wall motion than to the myocardial ischemia per se.

INVESTIGATORS have yet to agree on the significance of exercise-induced ST-segment elevation. This phenomenon has been described in association with: 1) severe ischemic heart disease and usually during an unstable phase,1 2) Prinzmetal's variant angina,3 3) left ventricular aneurysm,4 4) abnormal cardiac hemodynamics with elevated left ventricular end-diastolic pressure and poor ejection fraction,5 5) asymptomatic healthy individuals studied in the Seattle Heart Watch.4 There seems to be no readily available information as to the relative frequency of these associations. The present study was undertaken in order to determine the incidence of exercise-induced ST-segment elevation in a population of male patients being evaluated for cardiovascular disease and to assess the diagnostic value of this phenomenon with regard to the various possible underlying conditions.

Methods

The experience in our exercise laboratory during 18 consecutive months was reviewed. The exercise tests were performed on a motor driven treadmill according to the Bruce
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