Acute coronary insufficiency with normal coronary arteriograms

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Summary
Two patients presenting with apparent symptomatic and electrocardiographic evidence of acute coronary insufficiency and found to have normal coronary arteriograms are documented. The patients remain symptom free at follow-up 9 and 14 months later although one requires 160 mg propranolol daily. The electrocardiographic, myocardial metabolic and haemodynamic data in 413 patients with angina and normal coronary arteriograms are reviewed and the suggested aetiologies documented. Follow-up of patients in these series indicates a good prognosis for symptom-free survival.

Introduction
Although a normal coronary arteriogram may be seen in approximately 10% of patients undergoing coronary arteriography for angina pectoris (Kemp, Elliott and Gorlin, 1967; Kemp et al., 1973) such a finding in the presence of acute coronary insufficiency (pre-infarction, accelerated angina) has been infrequently recorded. This report documents two such cases and briefly reviews the published findings in patients with angina and normal coronary arteriograms.

Case 1
A 53-year-old non-smoking, previously healthy woman presented with a 3½-year history of a squeezing, heavy substernal ache occasionally radiating to the right shoulder and arm and tending to occur with menstruation. The ache always rapidly cleared with glyceryl trinitrate. In the 3 weeks before admission, the pain had become much more frequent and severe, occurred at rest, awakened her from sleep, lasted up to 30 min at a time and was accompanied by nausea and dyspnoea.

On admission, her blood pressure was 150/85 mmHg; clinical examination of cardiovascular and all other symptoms was unremarkable. Results of chest X-ray, haematology, electrolytes, blood urea, and serum enzymes (SGOT, LDH, SBD, and CPK) were all normal. ECG was normal with the patient pain-free, but showed 3 mm ST segment depression during attacks of pain (Fig. 1).

Coronary arteriograms performed for presumed coronary insufficiency were normal (Fig. 1). An exercise stress test performed during a pain-free period was markedly positive (ST depression 3 mm) but did not produce pain. Further investigations including cholecystogram, upper gastro-intestinal barium series and X-rays of cervical spine were also normal. Her pain again settled with glyceryl trinitrate and following reassurance she was discharged to the care of her internist. At follow-up at 9 months, the patient remained symptom free.

Case 2
A 56-year-old man was admitted with almost continual severe retrosternal pain radiating into the left arm of several hours' duration. Chest pain began 3 years earlier and steadily increased in severity and frequency. Two years before admission he was admitted to hospital for a presumed myocardial infarction, although this was not confirmed by ECG or enzyme studies. In the month before admission pain was noted on alternate days, came on with exertion but also at rest, lasted 5–15 min at a time, and was accompanied by dyspnoea. Medications before admission included thiazides for hypertension (2 years) and glyceryl trinitrate to which his chest pain usually responded.

Clinical examination revealed a blood pressure of 120/80 mmHg and a faint systolic murmur at the left sternal margin but was otherwise unremarkable. Results of chest X-ray, haematology, serum electrolytes, urea, enzymes (SGOT, LDH, SBD, CPK), glucose, cholesterol and triglycerides were normal. ECG showed marked ST depression during pain (Fig. 2) with return to a normal pattern after glyceryl trinitrate and analgesics.
Case reports

Figure 1. A normal left coronary arteriogram. The right coronary arteriogram (not shown) was also normal. Marked ST depression is noted during pain.

Figure 2. Normal right and left coronary arteriograms. Marked ST depression occurs with chest pain.
performed for presumed coronary insufficiency were normal (Fig. 2). He was reassured and discharged pain-free on glyceryl trinitrate and propranolol.

In the following 9 months he required two further admissions for recurrent severe chest pain. Further X-rays of cervical spine and barium studies of his upper gastro-intestinal tract were normal; acid stimulation of the distal oesophagus did not provoke pain. An echocardiogram showed asymmetrical septal hypertrophy but right and left heart catheterization revealed normal intracardiac pressures and no gradients at rest or after a Valsalva manoeuvre, amyl nitrate, isoprenaline, exercise, or angiography (Table 1). Left ventricular angiograms showed possible septal hypertrophy and normal LV wall motion, LV volumes, and ejection fraction. His ECG remained normal (when pain-free) but a stress ECG was markedly positive (ST depression of 2 mm) and produced pain.

He is currently, 14 months later, symptom-free and maintained on propranolol 160 mg/day and glyceryl trinitrate. Further tests have confirmed a prediabetic state.

Discussion

Electrocardiographic, myocardial metabolic and haemodynamic data on 413 patients collected from nine published series of patients with angina and normal coronary arteriograms are illustrated in Table 2. Whereas angina pectoris secondary to coronary artery disease (CAD) is predominantly a male symptom, all series of patients with angina and normal coronary arteries (NCA) contain disproportionately large numbers of females and some contain females only. These patients are 10–15 years younger than their counterparts with CAD (Anderson et al., 1972) and, although many have atypical angina (Kemp et al., 1973; Bourassa et al., 1973; Bemiller, Pepine and Rogers, 1973; Waxler, Kimbiris and Dreibus, 1971), they frequently cannot be distinguished from patients with angina and CAD (Kemp et al., 1973; Bourassa et al., 1973; Bemiller et al., 1973; Waxler et al., 1971; Dwyer, Wiener and Cox, 1969).

Hyperlipidaemia has been noted in from 8% (Waxler et al., 1971) to 29% (Kemp et al., 1973; Bemiller et al., 1973; Dwyer et al., 1969) of patients with NCA, and glucose intolerance in 14–43% (Kemp et al., 1973; Bemiller et al., 1973; Dwyer et al., 1969; Likoff, Segal and Kasparian, 1967)—incidences approximately half of that seen in CAD (Kemp et al., 1973). Smoking histories, when recorded, occurred in 41–80% of patients but did not significantly affect the ECG response to exercise (Waxler et al., 1971). Family history was unhelpful (Dwyer et al., 1969), no patient was anaemic and all had normal coronary arteriograms.

Abnormalities in the resting ECG were recorded in from 9% (Neill et al., 1972) to 100% (Likoff et al., 1967) of unselected patients. Patients with abnormal resting ECGs were deliberately excluded in one series (Arbogast and Bourassa, 1973).

Objective evidence of myocardial ischaemia has been sought in these patients in an attempt to explain their symptoms. Attention was focused on ECG changes following cardiac stimulation with exercise, hypoxaemia and/or pacing, changes in myocardial lactate metabolism after pacing or isoprenaline infusion, measurements of total and differential coronary flow, and myocardial oxygen uptake and cardiac haemodynamics at rest and after pacing or exercise. Findings have been compared with normal patients and/or with sex-age matched controls with angina and CAD (Bemiller et al., 1973; Dwyer et al., 1969; Neill et al., 1972; Arbogast and Bourassa, 1973; Dwyer, Dell and Cannon, 1972; Eliot and Bratt, 1969). Differences in stimulating modes, rates of pacing and types and degrees of exercise must be remembered when assessing results.

Apparent ischaemic ECG changes have occurred in from 14% (Boudoulas et al., 1974) to 100% (Likoff et al., 1967; Neill et al., 1972; Arbogast and Bourassa, 1973) of patients. However, pacing at over 170 beats/min did not produce any ST changes in twelve of twenty-nine patients in one series (Boudoulas et al., 1974).

Myocardial lactate production or < 10% lactate extraction, as measured across the coronary bed, are

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**Table 1. Cardiac catheterization data (Case 2)**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Valsalva</th>
<th>Amyl nitrate</th>
<th>Isoprenaline</th>
<th>Post-angiography</th>
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<tr>
<td>LV 130/4</td>
<td>155/7</td>
<td>180/82</td>
<td>78/2+</td>
<td>115/10+</td>
<td>137/18</td>
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<tr>
<td>BA 130/70</td>
<td>155/78</td>
<td>180/125</td>
<td>75/35</td>
<td>108/55</td>
<td>142/78</td>
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<td>Cardiac output (resting)</td>
<td>5.1 l/min</td>
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<td>Cardiac index (resting)</td>
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<td>End diastolic volume index</td>
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<td>End systolic volume index</td>
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<td>17 ml/m²</td>
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<td>Stroke volume index</td>
<td></td>
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<td>53 ml/m²</td>
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<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td>0.75</td>
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</table>

LV, left ventricle; BA, brachial artery; +, overshoot. All pressures simultaneous.
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<tr>
<th>Author</th>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Abnormal resting ECG</th>
<th>Ischaemic ECG with exercise/hypoxia/pacing</th>
<th>Lactate abnormalities with pacing/isoprenaline</th>
<th>Coronary flow/myocardial O₂ uptake</th>
<th>Cardiac haemodynamics</th>
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<tr>
<td>Likoff et al. (1969)</td>
<td>15</td>
<td>F</td>
<td>30–52</td>
<td>15/100</td>
<td>15 (E) 100</td>
<td></td>
<td></td>
<td>Post-exercise pressures: Normal in 8/8</td>
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<td>Eliot et al. (1969)</td>
<td>15</td>
<td>F</td>
<td>18–38</td>
<td>60</td>
<td>2 (E) 20</td>
<td></td>
<td></td>
<td>Post-exercise LV angio-gram: Normal in 6/6</td>
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<tr>
<td>Dwyer et al. (1969)</td>
<td>10</td>
<td>M</td>
<td>34–52</td>
<td>2 (E) 20</td>
<td></td>
<td></td>
<td></td>
<td>Abnormal haemoglobin oxygen dissociation in 14/15</td>
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<tr>
<td>Waxler et al. (1971)</td>
<td>86</td>
<td>F</td>
<td>21–60</td>
<td>49</td>
<td>16/44 (E) 36</td>
<td></td>
<td></td>
<td>↑LVEDP CI LVMWI on exercise</td>
</tr>
<tr>
<td>Neill et al. (1972)</td>
<td>11</td>
<td>M</td>
<td>33–59</td>
<td>9</td>
<td>11/E H 100</td>
<td>1/11 (P 120/min)</td>
<td>O₂ uptake normal pre- and post-pacing in 11/11</td>
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<td>Kemp et al. (1973)</td>
<td>200</td>
<td>F</td>
<td>19–68</td>
<td>103</td>
<td>31/152 (E) 20</td>
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<td></td>
<td>Normal blood O₂ affinity in 10/10</td>
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<td></td>
<td>M</td>
<td>101</td>
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<td>LVEDP LV Volume LV Contractility</td>
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<td></td>
<td>m 47</td>
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<td>Normal blood O₂ affinity in 19/19</td>
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<tr>
<td>Bemiller et al. (1973)</td>
<td>37</td>
<td>F</td>
<td>26–62</td>
<td>20</td>
<td>27/E P 73</td>
<td>10/14 (P)</td>
<td>Normal flow and O₂ uptake in 18/18 at rest</td>
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<td></td>
<td></td>
<td>M</td>
<td>41</td>
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<td>Normal flow in 6/6 &amp; O₂ uptake in 8/8 after isoprenaline</td>
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<td></td>
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<td>m 41</td>
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<tr>
<td>Arbogast and Bourassa (1973)</td>
<td>10</td>
<td>F</td>
<td>6</td>
<td>0</td>
<td>10(P) 100</td>
<td>5/10 (P 140/min)</td>
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<td></td>
<td></td>
<td>M</td>
<td>4</td>
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LVWI, left ventricular work index; LVEDP, left ventricular end diastolic pressure; CI, cardiac index; LVSWI, left ventricular stroke work index; LVMWI, left ventricular minute work index; P, pacing; E, exercise; H, hypoxaemia; EF, ejection fraction; EDV, end diastolic volume.
indices of severe myocardial hypoxia (Shea et al., 1962; Neill and Huckabee, 1966). Atrial pacing (Kemp et al., 1973; Boudoulas et al., 1974; Bemiller et al., 1973; Neill et al., 1972; Arbogast and Bourassa, 1973) or isoprenaline infusions (Kemp et al., 1973) have shown such changes in 9–71% of cases. Pacing rates varied from 120 to 180/min but even at the latter rate, only nine of twenty-nine patients in Boudoulas' series produced lactate. Lactate production was two to three times more common in females (Kemp et al., 1973; Bemiller et al., 1973). Varying methodology in these series made assessment of lactate abnormalities concurrent with ischaemic ECG changes difficult. Only one of Neill's patients (paced at 120/min) produced lactate in the presence of an ischaemic ECG (Neill et al., 1972), as did three of fourteen (Bemiller et al., 1973) but nine of twenty-nine (paced at 180/min) did so (Boudoulas et al., 1974). All patients in the latter series with > 2 mm ST depression produced lactate, whereas those with < 1 mm ST depression did not do so.

Correlation between the subjective sensation of angina, ischaemic ECG changes and lactate production was also difficult. None of Neill's patients complained of pain despite apparent ischaemic ECG changes in all and lactate production in one (Neill et al., 1972); six of ten, all with ischaemic ECGs and five producing lactate (Arbogast and Bourassa, 1973) complained of pain, as did nine of fourteen lactate producers (two with ischaemic ECGs) (Bemiller et al., 1973) and nine lactate producers all with ischaemic ECGs (Boudoulas et al., 1974).

Myocardial oxygen uptake was normal at rest (Kemp et al., 1973; Neill et al., 1972) and after pacing (Neill et al., 1972) and isoprenaline (Kemp et al., 1973) in all patients examined. Coronary flow was also normal at rest and after isoprenaline when checked in six patients (Kemp et al., 1973). Dwyer, using xenon 133 wash-out techniques, confirmed normal resting mean myocardial blood flows and further demonstrated normal resting mean regional flows in seven patients with angina and NCA (Dwyer et al., 1972).

Left ventricular function (size, contractility and pressures) was normal at rest (Boudoulas et al., 1974; Likoff et al., 1967; Neill et al., 1972) and after exercise (Likoff et al., 1967). Left ventricular ejection fraction, end diastolic volume and contractility were unchanged after pacing; changes in end diastolic pressure were not considered reliable (Boudoulas et al., 1974). Arbogast and Bourassa (1973) noted increases in cardiac index and left ventricular minute work index and falls in end diastolic pressure (LVEDP) and left ventricular stroke work index (LVSWI) after pacing at 140/min. Dwyer, using maximally tolerated work loads, also recorded increases in cardiac index and left ventricular work index but noted an increase in LVEDP (Dwyer et al., 1969).

Bemiller similarly showed increases in LVEDP on exercise accompanied by increases in LVSWI (Bemiller et al., 1973). Left ventricular function as assessed by plotting LVEDP/LVSWI was abnormal at rest and on exercise, but less abnormal than sex-age matched controls with angina and CAD. Left ventricular function was unchanged and coronary arteriograms normal in seven patients when re-examined 4½ years later.

The aetiology remains enigmatic. Changes in coronary flow, apparently mediated by the vagus, have been produced in both anaesthetized and awake animals by gastric, oesophageal and common bile-duct distension (Gilbert, 1942; Cullen and Reese, 1952). ECG changes have been seen following gall-bladder manipulation at surgery and gross ST and T wave changes accompanied by severe retrosternal chest pain noted in a woman with marked oesophageal spasm (corkscrew oesophagus). Forrester, Herman and Gorlin (1970), however, noted no significant increase in the prevalence of gall-bladder disease, hiatus hernia, or cervical root disease in patients with angina and NCA when compared to normals. He concluded that these conditions were not major factors in the aetiology of the syndrome.

Misinterpretation of the coronary arteriograms is unlikely in the presence of widespread reports from excellent centres; the survival characteristics of these patients are not those of patients with CAD. Defects in haemoglobin oxygen dissociation noted in fourteen of fifteen young women (Eliot et al., 1969) have not been confirmed by other workers (Kemp et al., 1973; Neill et al., 1972). Myocardial small vessel disease below the resolution of coronary arteriography is commonly associated with dysrhythmias, cardiomegaly and conduction disturbances (James, 1967), signs which were not especially common in the patients in these series. Furthermore, very few of these patients had conditions associated with small vessel disease. Dwyer et al. (1972) felt that their finding of normal regional myocardial blood flow tended to exclude small vessel disease or non-visualized atheroma, but Wells et al. (1967), noting conjunctival microcirculation abnormalities in eleven of twenty-seven patients with angina and NCA, thought that such abnormalities in the cardiac microcirculation might account for their symptoms. Although coronary artery spasm was not documented in these patients it cannot be excluded as an aetiological possibility and has been associated with variant angina pectoris (Kerin and Macleod, 1974).

Redistribution of blood within the myocardium (Zierler, 1967) in which total coronary flow and oxygen uptake might well remain normal, remains another possible explanation. Although normal
resting regional blood flow has been recorded (Dwyer et al., 1972), similar studies during exercise or pacing have not yet, to the authors' knowledge, been performed in this group of patients.

The clinical presentation, laboratory findings, normal ventricular function (in contrast to that of sex-age matched controls with CAD) and follow-up data have led several workers to doubt the existence of myocardial ischaemia in these patients (Waxler et al., 1971; Neill et al., 1972; Arbogast and Bourassa, 1973). The significance of apparently ischaemic ECGs after pacing or exercise, and raised lactate levels in these anxious patients is questioned (Waxler et al., 1971; Arbogast and Bourassa, 1973). Neill, Kassebaum and Judkins (1968) thought that myocardial hypoxia as shown by lactate production in one of their eleven patients, could reasonably explain that patient's symptoms. Although this patient did not suffer concurrent angina, a similar lack of temporal correlation between bouts of chest pain and chemical signs of myocardial hypoxia was noted in patients with angina and CAD (Neill, 1968).

Boudoulas et al. (1974) felt that the ability to elicit ECG and metabolic changes with pacing suggested that angina in some patients was related to myocardial ischaemia. The significance of their finding that patients paced at 180/min who had at least a 2 mm ST segment depression all secreted lactate is currently unknown. Although exercise produced angina and ECG changes more consistently in their control group with CAD, Dwyer et al. (1969) noted clinical and haemodynamic abnormalities in both groups which were not significantly different.

Bemiller et al. (1973), although finding evidence of abnormal ventricular function in their patients, were sufficiently impressed by the lack of deterioration in ventricular function and coronary arteriograms over 4½ years to suggest a non-progressive disorder.

Although lactate abnormalities and ECG changes seen in many of these patients make a purely functional aetiology unlikely, much of circulatory control and cellular metabolism remains unknown; the disproportionately high female incidence with implied tissue hormonal changes may be significant. Several of the suggested aetiological factors may together be relevant (Kemp et al., 1973).

Normal coronary arteriograms were noted in 19% of a series of seventy-nine patients with acute coronary insufficiency (Scanlon et al., 1973). Both the patients in the present report historically, clinically, and electrocardiographically appeared to present with acute coronary insufficiency. In the presence of normal coronary arteriograms other aetiological possibilities had to be excluded. Although these tests were negative, the dynamic nature of the symptoms suggest that repetition of some examinations during pain might be of interest. The significance of asymmetrical septal hypertrophy in the presence of a normal clinical examination, ECG, LVEDP, and absent outflow gradient is uncertain. Further follow-up may clarify this finding.

Whatever the aetiology, the prognosis appears good for these patients. In 864 patient years of follow-up, seven deaths occurred (Kemp et al., 1973; Bemiller et al., 1973; Waxler et al., 1971; Neill et al., 1972) an annual mortality (0·81%) much below the 2·9% recorded in non-operated patients with at least 50% stenosis in a single coronary artery (Bruschke, Proudfoot and Sones, 1973). Survival is no different from that of the general population (Kemp et al., 1973).

Post-mortem examinations in two of the seven deaths revealed normal hearts and no explanation for demise. The cause of death was unknown in three and non-cardiac in the remaining two. Dwyer et al. (1969) also recorded a sudden death in a young man; a normal heart was found at post-mortem and no cause of death was found.

Eliot et al. (1969) noted sub-endocardial infarctions in the presence of normal coronary arteries and histologically normal small vessels in all three young women dying within a few months of coronary arteriography. The significance of haemoglobin oxygen dissociation abnormalities in their patients remains uncertain. Whether these patients represent a subgroup with a peculiarly critical sub-endocardial oxygen supply/demand balance remains unknown. Symptomatically, 45–80% (Kemp et al., 1973; Bemiller et al., 1973; Waxler et al., 1971; Neill et al., 1972) of patients had a reduction in chest pain, often without therapy. Only 6–19% (Kemp et al., 1973; Waxler et al., 1971; Neill et al., 1972) noted worsening of symptoms and these usually responded to nitrates and/or propranolol, psychotherapy being of very limited value (Kemp et al., 1973).

Conclusions

Angina occurring in the presence of normal coronary arteriograms is predominantly a symptom of women in the age range of 35–45 years. Myocardial oxygen uptake and total coronary flow was normal at rest and after stimulation (pacing/isoprenaline), in all tested patients and regional coronary flow was normal at rest. Varying lactate production occurred and was difficult to correlate with angina and ischaemic ECG changes. Changes in left ventricular function on stimulation depended on the stimulating mode. Abnormalities of LV function on exercise testing in one series were less marked than in sex-age matched controls with coronary artery disease, and were unchanged 4½ years later. Although the aetiology remains uncertain, several workers doubt the
existence of myocardial ischaemia in these patients, whereas others feel that a functional aetiology is unlikely.

Several factors, and perhaps others hitherto unknown, may be relevant. Survival for these patients is no different from that of the general population.

References


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