Infector endocarditis in the billowing mitral leaflet syndrome

A. S. Lachman, D. M. Bramwell-Jones, J. B. Lakier, W. A. Pocock, and J. B. Barlow
From the Cardiovascular Research Unit, Department of Medicine, University of the Witwatersrand; and the Cardiac Clinic, General Hospital, Johannesburg, South Africa

Ten patients with the billowing mitral leaflet syndrome complicated by infective endocarditis are reported. Two patients had a non-ejection systolic click and 8 had both a non-ejection systolic click and a late systolic murmur. These auscultatory features were difficult to detect in 4 instances in that they were intermittent, soft, or brought out only with postural change. Seven patients were unaware of their cardiac lesions. A low grade pyrexia was present in all 10 patients. Four patients presented with clinical features caused by reversible neurological lesions. Blood cultures were positive in all patients, with Staphylococcus albus the infecting organism in 6. Antibiotic therapy was successful with significant mitral regurgitation supervening in only one instance.

The importance of the billowing leaflet as a potential site of infective endocarditis is emphasized. It seems that antibiotic prophylaxis is indicated at times of increased risk of infection in subjects with a non-ejection systolic click or a late systolic murmur.

The auscultatory features denoting billowing of the posterior leaflet of the mitral valve are a late systolic murmur or a non-ejection systolic click, or both (Barlow, 1965; Barlow et al., 1968). It has been postulated (Pocock and Barlow, 1971a) that true or functional lengthening of one or more chordae tendineae of the mitral valve is associated with a variable degree of billowing of the posterior leaflet. Evidence to confirm this postulate has been obtained at surgery (Davis et al., 1971), necropsy (Barlow et al., 1968), by angiocardiographic studies (Criley et al., 1966), and by echocardiography (Kerber, Isaeff, and Hancock, 1971). Other clinical features which may be associated with these auscultatory signs include chest pain (Barlow and Bosman, 1966; Hancock and Cohn, 1966), electrocardiographic manifestations suggestive of postero-inferior myocardial ischaemia (Barlow, 1965; Pocock and Barlow, 1971a), and arrhythmias (Pocock and Barlow, 1970), frequently induced or aggravated by exercise.

Multiple aetiological factors may cause this abnormality of the complex mitral valve mechanism. These include the Marfan syndrome (Criley et al., 1966), rheumatic endocarditis (Barlow, 1965; Pocock and Barlow, 1971a), ischaemic heart disease (Barlow et al., 1968), trauma (Criley et al., 1966), congestive cardiomyopathy (Mercer, Frye, and Giuliani, 1970), and hypertrophic obstructive cardiomyopathy (Barlow et al., 1968). In many patients the underlying aetiology is unknown. In some of these a familial incidence has been established (Barlow, 1965; Stannard et al., 1967; Shell et al., 1969), whereas in others an association with congenital heart disease (Barlow, 1965), particularly secundum atrial septal defect (Pocock and Barlow, 1971b; McDonald et al., 1971), has been observed.

In 1963, when angiocardiographic and other studies indicated that late systolic murmurs and 'mid-late' systolic clicks were not extracardiac in origin, but arose at the mitral valve (Barlow et al., 1963), the possibility was raised that bacterial endocarditis might supervene in some instances. Since that time, however, and excluding our own previous experience (Barlow et al., 1968; Mazansky, Lakier, and Barlow, 1973), we have found only 12 reported cases (Facquet, Alhomme, and Raharison, 1964; Linhart and Taylor, 1966; Stannard and Goble, 1967; Caceres and Perry, 1967; LeBauer, Perloff, and Kelhier, 1967; Shell et al., 1969; Harvey, 1970) of the 'billowing mitral leaflet syndrome' complicated by infective endocarditis. In this paper we describe 10 such patients, 6 of whom have been
briefly mentioned in earlier reports (Barlow et al., 1968; Mazansky et al., 1973) from this laboratory, encountered between 1966 and 1972. It is concluded from this experience that unless the auscultatory signs are carefully sought in patients presenting with the somewhat non-specific clinical picture of infective endocarditis as it not infrequently occurs today (Mazansky et al., 1973; Hamer, 1973; Hayward, 1973), the diagnosis of that condition will be unnecessarily delayed. With the increasing interest in, and awareness of, the billowing mitral leaflet syndrome, it is now apparent that the entity is common (Pocock and Barlow, 1971a; Jeresaty, 1973; Rizzon et al., 1973). The advisability of recommending prophylactic measures against infective endocarditis in patients with a late systolic murmur or non-ejection systolic click is discussed.

**Clinical material**

The ages of the 10 patients (Table), 6 of whom were female, ranged from 11 to 59 years. With only 3 exceptions, the mitral valve abnormality was diagnosed for the first time during the current illness. Eight patients had both a late systolic murmur and a non-ejection systolic click, whereas the remaining 2 had an isolated non-ejection systolic click. In 4 patients the auscultatory features were difficult to detect in that they were intermittent, very soft, or brought out only after changes in posture. A 49-year-old man (Case 7, Table) and a 15-year-old girl (Case 3, Table) each had a persistent ductus arteriosus ligated, respectively 5 and 10 years previously, and had been followed at regular intervals in this clinic. A late systolic murmur had been recognized in the man, but the soft isolated non-ejection systolic click in the girl was detected only after repeated auscultation when she presented with a pyrexia caused by the

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Principal clinical features</th>
<th>Auscultatory signs</th>
<th>Blood culture</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>21</td>
<td>F</td>
<td>Pyrexia, anaemia, splenomegaly, sweating</td>
<td>LSM+NESC</td>
<td><em>Staph. albus</em></td>
<td>Post partum</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>'Migrainous paresis', pyrexia, splinter haemorrhages, splenomegaly</td>
<td>LSM+NESC</td>
<td><em>Staph. albus</em></td>
<td>Post dental therapy</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>F</td>
<td>Malaise, pyrexia, splinter haemorrhages, splenomegaly</td>
<td>LSM+NESC</td>
<td>Strep. viridans</td>
<td>Post dental therapy; PDA ligated 10 years previously</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>F</td>
<td>Malaise, pyrexia, clubbing, splenomegaly</td>
<td>LSM+NESC</td>
<td><em>Staph. albus</em></td>
<td>Postuterine curettage; developed severe mitral regurgitation; mitral lesion known</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>M</td>
<td>Malaise, pyrexia</td>
<td>LSM+NESC</td>
<td>Strep. viridans</td>
<td>Post dental therapy; mitral lesion known</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>F</td>
<td>Malaise, pyrexia, pleural effusion</td>
<td>LSM+NESC</td>
<td><em>Staph. aureus</em></td>
<td>Mitral lesion known; PDA ligated 5 years previously; carotid angiogram normal</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>M</td>
<td>Pyrexia, convulsion</td>
<td>LSM+NESC</td>
<td><em>Staph. albus</em></td>
<td></td>
</tr>
<tr>
<td>8*</td>
<td>11</td>
<td>M</td>
<td>Pyrexia, convulsion, left hemiparesis</td>
<td>NESC</td>
<td><em>Staph. albus</em></td>
<td>Carotid angiogram revealed intracranial lesion, ? infarction</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>F</td>
<td>'Migrainous monoparesis', pyrexia, sweating</td>
<td>LSM+NESC</td>
<td><em>Staph. albus</em></td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>59</td>
<td>F</td>
<td>Pyrexia, sweating, malaise, splenomegaly, splinter haemorrhages</td>
<td>LSM+NESC</td>
<td><em>Staph. aureus</em></td>
<td></td>
</tr>
</tbody>
</table>

**Key:**

NESC = Nonejection systolic click.
LSM = Late systolic murmur.
PDA = Persistent ductus arteriosus.
* = On antibiotics at time of presentation.
infective endocarditis. A history of possible source of infection was elicited in 5 patients, none of whom had received prophylaxis against infective endocarditis since there was no prior knowledge of a cardiac abnormality. In 3 of these (Cases 2, 3, and 6, Table) the endocarditis followed dental therapy and in 1 (Case 4) it presented after a curettage for morrhagia after a spontaneous abortion. The remaining patient (Case 1) became ill two weeks after a normal pregnancy and delivery. There was a pyrexia, usually low grade and seldom exceeding 38°C, in all 10 patients. The presenting clinical features in 4 patients resulted from emboli to the central nervous system. Severe headaches were followed by transient pareses and mild paraesthesiae in 2 of these (Cases 2 and 9), one of whom had associated visual disturbances. Both were referred to us with the diagnosis of ‘migrainous paresis’ for elucidation of the auscultatory signs. The other 2 (Cases 7 and 8) presented with convulsions, one of whom (Case 8) developed a left hemiparesis. Carotid angiography was normal in Case 7, but an intracranial lesion, which was subsequently shown to be caused by cerebral infarction, was demonstrated in Case 8. Serological tests for ‘activity’, including the Westergren erythrocyte sedimentation rate, C-reactive protein, and mucoprotein estimations, were abnormal in 7 patients. A positive blood culture was obtained from all the patients. Staphylococcus albus was isolated in 6, Streptococcus viridans in 2, and Staphylococcus aureus in 2. The patients responded to antibiotic therapy and in only one instance (Case 4, Table) was a definite deterioration in the cardiac status detected: significant mitral regurgitation, attributed to ruptured chordae tendineae, developed during therapy in a 35-year-old woman from whom a Staphylococcus albus had been cultured. She has not yet been subjected to surgery.

Discussion
A diagnosis of infective endocarditis based on typical physical signs, abnormal ‘activity’ tests and positive blood cultures is easily made in patients with overt heart disease. A satisfactory therapeutic result can then usually be achieved (Mazansky et al., 1973). However, the presentation is not infrequently less clear. The onset is often insidious with vague general symptoms such as malaise and sweating. Pyrexia invariably occurs but this is frequently low grade and there may be afebrile periods. Recognition of infective endocarditis in such instances will be unduly delayed unless the pathological significance of relatively unimpressive auscultatory features, such as a soft aortic ejection systolic murmum (Barlow and Pocock, 1962; Hayward, 1973), late systolic murmum or isolated non-ejection systolic click are fully appreciated. A high index of suspicion of infective endocarditis is mandatory for early diagnosis and the fact that a non-ejection systolic click or late systolic murmum may be soft, intermittent, or audible only after alterations in posture (Barlow et al., 1968), deserves emphasis.

We submit that patients should be auscultated in the supine, left lateral, standing, and squatting positions before the billowing mitral leaflet syndrome can, in all probability, be excluded.

Although neurological presentations of infective endocarditis have been well documented (Ziment, 1969), Hayward (1973) has recently pointed out that many patients are still primarily admitted under neurologists, neurosurgeons, and psychiatrists. Four of our patients presented with neurological signs and symptoms. In 2 of these, and despite the absence of a previous history of migraine, the rather unlikely diagnosis of ‘migrainous paresis’ had been postulated. In another (Case 8, Table) cerebral angiography, air encephalography, and craniotomy were carried out for a suspected cerebral lesion.

Hayward’s important statement (Hayward, 1973) that ‘organisms of low virulence and identical in the laboratory may in one case cause valve rupture and heart failure within 6 to 8 weeks from the onset of symptoms, whereas in another the disease is a true ‘endocarditis lente’, with febrile symptoms often for over a year without embolism or progressive valve damage...’ is in accord with our own experience of infective endocarditis in this institution. Though deterioration in the mitral valve lesion was detected in only one patient (Case 4, Table) in this series, it is clearly desirable to make a diagnosis of infective endocarditis as early as possible. The 35-year-old woman who developed moderately severe mitral incompetence while still in hospital receiving antibiotic therapy for Staphylococcus albus endocarditis had had symptoms for at least 5 months before treatment was begun. LeBauer and co-workers (1967) were the first to report a case of infective endocarditis in a patient with an isolated non-ejection systolic click. Their 58-year-old male patient had had symptoms for one month but during antibiotic therapy developed a late systolic murmum which they believed was a consequence of the infection of the valve. Shell and associates (1969) quoted a patient with a late systolic murmum in whom a pansystolic murmum and congestive heart failure supervened during the course of the infection. Unfortunately, neither the length of the illness nor the organism involved was stated.

Of our 10 patients, 8 had positive staphylococcal blood cultures and in 6 of these the organism was Staphylococcus albus. It is readily accepted that Staphylococcus albus is not infrequently responsible for infective endocarditis after cardiac surgery (Cerubin and Neu, 1971; Hayward, 1973), but many physicians are reluctant to accept this organism as significant in non-surgical patients. While ceding that Staphylococcus albus is one of the most common contaminants of bacterial cultures, its
isolation from a specimen cannot automatically be regarded as evidence of contamination (Smith et al., 1958; Brandt and Swahn, 1960). On the contrary, previous work in this laboratory suggests (Mazansky et al., 1973) that this organism is often responsible for infective endocarditis, especially in subjects exposed to a hospital environment, many of whom are on long-term penicillin as prophylaxis against rheumatic activity. Staphylococcus albus was the only organism cultured from a 26-year-old man (Case 2, Table) with a non-ejection systolic click and a late systolic murmur who had undergone dental therapy 2 weeks before the onset of his symptoms. The possibility that the mouth, even in edentulous subjects, may serve as a portal of entry for the Staphylococcus albus has recently been discussed (Croxford, Altmann, and O'Brien, 1971).

Although Hayward (1973) emphasized that the value of antibiotic prophylaxis against infective endocarditis has yet to be confirmed, he commented that, 'In our present state of knowledge it seems obligatory to use prophylactic antibiotics for those at risk'. The overall incidence of infective endocarditis in subjects with established cardiac lesions is probably low. From the limited data currently available, it would be difficult indeed to assess the significance of the risk of infective endocarditis supervening in subjects with a late systolic murmur or non-ejection systolic click. If the 10 patients in this series are included, the total number of reported cases of infective endocarditis is still less than 25. It is uncertain at present whether a late systolic murmur and a non-ejection systolic click represent an equal risk of infective endocarditis, and it is unknown whether the pathological process involving the mitral valve mechanism is important in relation to the incidence of infection.

In our experience, non-ejection systolic clicks and late systolic murmurs are heard very frequently during routine cardiological practice. Subsequent to the 220 subjects with these auscultatory features and multiple aetiological factors involving the mitral valve mechanism whom we have already reported (Barlow et al., 1968; Pocock and Barlow, 1971a), we have encountered more than 200 similar patients in this clinic, the majority of whom were referred either for elucidation of the auscultatory signs or because of symptoms. These numbers do not provide data from which the prevalence of the billowing mitral leaflet syndrome in the general population can be estimated, and this figure is at present uncertain. Rizzon and co-workers (1973) auscultated 1009 young adult female students in Bari, Italy, and detected a non-ejection systolic click or late systolic murmur in 0.33 per cent. In a recent survey, primarily undertaken to assess the prevalence of established rheumatic heart disease, of 12 050 South African Negro schoolchildren by workers from this laboratory (M. J. McLaren et al., unpublished data), a late systolic murmur, non-ejection systolic click, or both, was the commonest abnormal cardiac finding and was detected in 1.4 per cent of all the children examined. However, rheumatic heart disease is prevalent (Chesler et al., 1966) in the South African Negro population, and it is possible that a rheumatic process is responsible for the abnormal mitral valve in many of these children. For this reason similar surveys elsewhere, in which the observers must necessarily be experienced in, and orientated towards, the detection of soft or intermittent non-ejection clicks and late systolic murmurs, may well reveal a significantly lower prevalence.

We are uncertain whether all patients with these auscultatory features, whether intermittent or not, and irrespective of the pathology of the mitral valve, should be advised to take prophylactic measures against infective endocarditis. Harvey (1970), who emphasizes that infection may supervene in patients with an isolated click, states that they should. Stannard and associates (1967) originally regarded the risk of infective endocarditis as minimal and considered that prophylaxis was unnecessary. Shortly thereafter, however, they modified this opinion (Stannard and Goble, 1967) after they had encountered a case of streptococcal viridans endocarditis in a 35-year-old man with a non-ejection systolic click and late systolic murmur. Though our current policy is to advise prophylaxis against infective endocarditis in all patients with a late systolic murmur or non-ejection systolic click even when these findings are only intermittently present, this approach may well be modified in the future.

Addendum

Since this paper was submitted for publication, the recent study by Allen, Harris, and Leatham (1974) has come to our attention. These authors followed 62 patients with a late systolic murmur, 33 of whom had an associated non-ejection click, for a period ranging from 9 to 22 years (mean 13.8 years). Five of the 62 patients developed infective endocarditis, one of whom died and another developed severe mitral regurgitation. Allen et al. emphasized the importance of the risk of bacterial endocarditis in patients with an isolated late systolic murmur.

References

Lachman, Bramwell-Jones, Lakier, Pocock, and Barlow


Requests for reprints to Professor J. B. Barlow, Cardiac Clinic, General Hospital, Johannesburg 2001, South Africa.