that is innately innocuous or "latent". It may be mainly a function of the large proportion of tumours under 1 ml in volume which would probably remain clinically silent for a very long time. It has been suggested that this unusual volume distribution may simply be the result of a slow growth rate for this tumour in its early phase.[5,6] There is no evidence that carcinoma in the prostate is in any other way substantially different from or less predictable than that of any other organ.

The volume distribution of histological differentiation further supports the concept that progression in the acquisition of malignant characteristics with time and increasing volume is an important feature of the biology of prostate cancer. The only likely explanation for these data is that the great majority of prostate cancers are at least moderately differentiated at first and subsequently lose differentiation. That this phenomenon is similar but not identical for all tumours is implied by the range of differentiation found in even the smallest tumours, as well as the age differences and possibly racial differences found among larger tumours. The reported poor prognosis for prostate cancer among black men[15] may be largely explained by a greater tendency toward loss of differentiation with increasing volume.

Our data indicate that carcinoma of the prostate follows a predictable natural history and that precise determination of volume and capsule invasion should improve the estimation of prognosis in the individual patient. In both our series, the highest category of either volume or capsule penetration identified the cases with metastasis at least as accurately as did the presence of seminal vesicle invasion. Unlike seminal vesicle invasion, volume and capsule invasion are continua, and the division points and ranges of probable greatest significance along these continua have been identified here, though the numerical values we have defined may change as we study more cases and accumulate data from long-term follow-up. The ranges of greatest interest are potentially within reach of measurement by in-vivo imaging techniques. Though the significance of capsule penetration has been debated,[16,17] it has been clarified here by precise determination of both depth and extent of penetration of the capsule.

The predictive value of histological grade was unexpectedly low in both series, even though for all 9 metastatic carcinomas either primary or secondary grade was 4. Poor differentiation became prevalent in a volume range considerably below that at which metastasis was first seen, and in the necropsy series 5% of tumours under 0·46 ml were grade 4. This suggests that grade 4 tumours may be a heterogeneous group in terms of their biological malignant potential; we are currently investigating this possibility. Attempts to improve the predictive value of histological grading should be specifically directed toward finding morphological features of differential prognostic significance within the grade 4 category. Improvements here combined with estimation of cancer volume and extent of complete capsule penetration by in-vivo imaging could achieve a

Correspondence should be addressed to J. E. McN., Department of Urology, Stanford University School of Medicine, Stanford, CA 94305, USA.

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PERCUTANEOUS TRANSLUMINAL VALVULOPLASTY OF ACQUIRED AORTIC STENOSIS IN ELDERLY PATIENTS: AN ALTERNATIVE TO VALVE REPLACEMENT?

ALAIN CRIBIER   THIERRY SAVIN
NADIR SAOUDI   PAULO ROCHA
JACQUES BERLAND   BRICE LETAC

Service des Soins Intensifs Cardiologiques et des Explorations Hémodynamiques Cardiovasculaires, Centre Hospitalier et Universitaire, Hôpital Charles Nicolle, Rouen, France

Summary Percutaneous transluminal balloon catheter aortic valvuloplasty (PTAV) was carried out in three elderly patients with acquired severe aortic valve stenosis. Transvalvular systolic pressure gradient was considerably decreased at the end of the procedure, during which there were no complications. Increased valve opening was confirmed by angiography and echocardiography. Subsequent clinical course showed a pronounced functional improvement. PTAV is recommended as a simple alternative to aortic valve replacement in elderly and/or high-risk patients.

Introduction

PERCUTANEOUS transluminal balloon catheter angioplasty is a recognised treatment for peripheral and coronary artery stenoses. This technique has also been used successfully in certain forms of coarctation of the aorta,[1] pulmonary stenosis,[2–6] congenital aortic valve stenosis,[7,8] and mitral stenosis,[9] but not previously in adults with acquired aortic valve stenosis. It might be thought impossible to dilate such long-standing and usually calcified lesions; if feasible,

We have now carried out PTAV in 3 adults with isolated severe calcific aortic stenosis; in all 3 cases, severity of progression made valve replacement appear both mandatory and urgent. We elected to attempt valvuloplasty, however, because advanced age and poor physical condition made the operative risk very high in 2 patients, while the third refused to contemplate surgery.

Case-reports

Case 1

A 77-year-old woman had been treated for 10 years for angina pectoris. In August, 1984 several syncopal attacks on mild exertion led to the discovery of aortic stenosis. Angina and exertional dyspnoea severely limited physical activity. Physical examination showed a mid-systolic grade 3/6 murmur at the aortic area, radiating to the cervical vessels, an absent second heart sound, and a grade 1/6 diastolic murmur. Electrocardiogram (ECG) showed pronounced left ventricular hypertrophy, and the left ventricle was moderately enlarged on the chest radiograph. Two-dimensional (2D) echo-cardiogram showed severe aortic stenosis with calcifications and satisfactory left ventricular function. In view of the severity of symptoms, cardiac catheterisation was proposed for preoperative evaluation, but the patient withheld her consent for a year, during which symptoms steadily worsened, with nocturnal angina and two episodes of syncope at rest.

Left ventricular catheterisation showed left ventricular pressures of 245/28 mm Hg and aortic pressures of 155/70 mm Hg (systolic pressure gradient 90 mm Hg). Aortic valve cusps were moderately calcified. Selective left ventricular angiography showed a normal diastolic volume (73 ml/m^2), with normal left ventricular function (ejection fraction 77%) and clearly thickened walls. Post-stenotic dilatation of the ascending aorta and slight aortic regurgitation were seen on aortic angiography. Selective coronary arteriography did not show any significant coronary lesions. The patient gave informed consent for PTAV as an alternative to surgical valve replacement and this was done three weeks later.

Case 2

A 68-year-old woman had had aortic stenosis diagnosed 15 years previously. Her clinical status deteriorated progressively over the years (New York Heart Association functional class III) and angina appeared and became progressively worse. Admission for further investigation was precipitated by an attack of severe chest pain when walking against the wind, followed by syncope. Physical examination on admission showed a grade 3/6 systolic murmur at the base, absent second heart sound, and a grade 2/6 diastolic murmur. There were clearcut signs of left ventricular hypertrophy on ECG and the chest radiograph showed slight cardiomegaly. 2D echocardiogram showed severe calcific aortic stenosis with normal left ventricular function.

Cardiac catheterisation demonstrated ventricular pressures of 230/22 mm Hg and aortic pressures of 100/50 mm Hg (systolic pressure gradient 130 mm Hg). The aortic valve was massively calcified. Right heart pressures and cardiac index were normal. Left ventricular angiography showed a normal end-diastolic volume (94 ml/m^2) with slightly reduced ejection fraction (54%) and thickened walls. The ascending aorta was moderately dilated, and aortic regurgitation was insignificant. Selective coronary arterio-gram was normal.

Severity of both symptoms and haemodynamic data led us to propose immediate valve replacement, but the patient would not contemplate surgery. However, she accepted PTAV, which was done a month later.

Case 3

A 79-year-old man who had complained of progressive exertional dyspnoea for 10 years was admitted after three syncopal attacks showed severe left ventricular hypertrophy and the chest radiograph mild cardiomegaly and signs of mild pulmonary hypertension. 2D echocardiogram showed severe aortic stenosis with considerable valve calcification and severe left ventricular dilatation with impaired ventricular function. Two days after admission, the patient had an episode of acute, massive pulmonary oedema which was brought under control with difficulty by high doses of frusemide.

At cardiac catheterisation, left ventricular pressure was 140/28 mm Hg (systolic pressure gradient 60 mm Hg) and the aortic valves were massively calcified. Left ventricular angiography confirmed left ventricular dysfunction, with an increased diastolic volume (190 ml/m^2) and greatly decreased ejection fraction (20%). Selective coronary arteriography showed major multiple vessel lesions with proximal left-anterior-descending occlusion. These findings made us reluctant to recommend valve replacement and, with informed consent, we decided to attempt PTAV.

Methods

The same procedure for PTAV was followed in all 3 patients. Premedication consisted of intravenous atropine sulphate 1 mg, clorazepate 50 mg, and heparin 100 u/kg bodyweight. A surgical team was on standby.

For continuous aortic pressure monitoring, a 5F catheter was inserted into the descending thoracic aorta. In addition, a Swan-Ganz thermodilution catheter was inserted into the pulmonary artery in patients 2 and 3 for measurement of cardiac output. Left ventricular catheterisation was carried out via the brachial approach which made it easier to cross the stenosed aortic orifice (and was also necessitated by the short length [60 cm] of the dilatation catheters available in our laboratory). A 7F Sones catheter was inserted into the aorta and then in the left ventricle. After simultaneous left ventricular and aortic pressure recording, right-anterior-oblique angiograms of the left ventricle and of the aortic root were done. A Cordis straight guidewire, diameter 0·38 mm, length 270 cm, was inserted into the left ventricle via the Sones catheter to enable its replacement by the dilatation catheter.

We used 9F balloon catheters designed for dilatation of congenital valve stenosis (Meditech, Waterton, Massachusetts). Two radio-opaque markers gave the positions of the distal and proximal ends of the balloon, thus ensuring correct transvalvular positioning which was also confirmed by narrowing of the balloon where it crossed the stenosis during inflation (fig 1). The balloons were 40 mm long. Inflations were carried out by injecting 10 ml of a 50/50 mixture of saline solution and contrast medium, up to pressures of 6−8 atm. Three inflations, lasting 20−60 s, were successively done with three balloons whose maximum inflatable diameters were 8, 10, and 12 mm, respectively. In order to stabilise the balloon in its transvalvular position, the guidewire was left in the ventricular cavity during inflation.

ECG and aortic pressure were continuously recorded during the procedure. Ventricular and aortic pressures were simultaneously measured after each series of inflations. At the end of the procedure, an aortic root angiogram was done to assess valve opening and residual aortic regurgitation.

Results

The haemodynamic and clinical response to the inflations was good. There was no loss of consciousness when the balloon was inflated in transvalvular position. The first patient complained of moderate chest pain after 15−20 s of inflation, at the same time as ST-segment depression was noted in the antero-lateral precordial leads. In patients 2 and 3 the three inflations each lasted 1 min without any ill-effects.

During inflation, the aortic pressure never decreased below 60 mm Hg (fig 2). The obstruction caused by the inflated balloon was therefore incomplete; this was confirmed by manual injection of a few ml of contrast medium into the
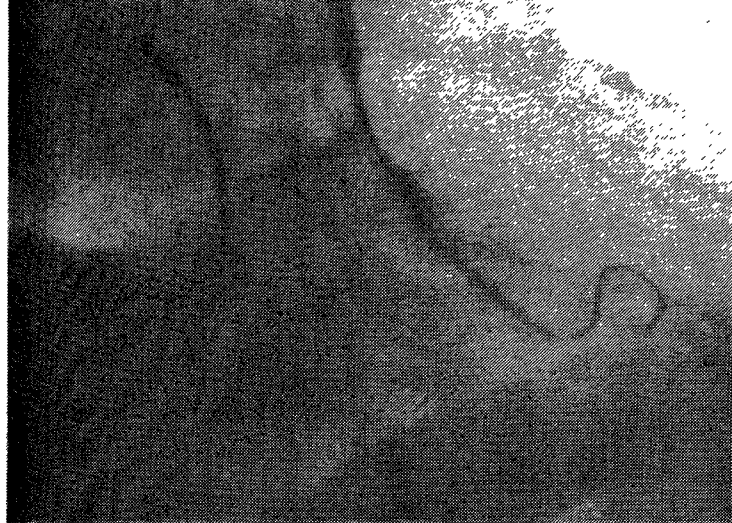
Fig 1—Correct position of the balloon centred across the stenotic aortic valve during early and full balloon inflation to a diameter of 10 mm.

Indentation from the stenotic valve is clearly seen at early inflation and disappears at full inflation. The guidewire is placed in the left ventricle to stabilise the balloon during inflation.

ventricular cavity during one inflation (via the angioplasty catheter with guidewire removed). A few premature ventricular contractions occurred infrequently during the inflations.

In the first patient, transvalvular gradient was 90 mm Hg at the start of the procedure and remained unchanged after the first two series of inflations, with the 8 and 10 mm balloons. After a series of three inflations with the 12 mm balloon, it decreased to 40 mm Hg (fig 3). In the second patient, the initial gradient was found to be 80 mm Hg (rather than the 130 mm Hg measured during the initial catheterisation) and decreased to 70, 60, and finally 30 mm Hg after each series of inflations. In the third patient, improvement of systolic gradient was very similar—from 60 mm Hg to 50, 40, and finally 30 mm Hg. In patients 2 and 3 in whom cardiac output was measured before and after valvuloplasty, valve surface calculated according to Gorlin's formula[10] increased from $0 \cdot 46$ cm^2 to $0 \cdot 96$ cm^2 and from $0 \cdot 50$ cm^2 to $0 \cdot 75$ cm^2, respectively.

Aortic root angiography showed no worsening of the aortic regurgitation. Valve motion, which was considerably impaired before the procedure, was greatly improved, especially in the second patient. These results were supported by the findings of 2D echocardiography done 24 h later: in the parasternal long-axis view, opening of the aortic valve increased from $0 \cdot 45$ to $0 \cdot 77$ cm in the first case; from $0 \cdot 41$ to $0 \cdot 72$ cm in the second (fig 4); and from $0 \cdot 32$ to $0 \cdot 48$ cm in the third. In the cross-sectional view, valve opening was also clearly improved, mainly in the second patient.

Clinical course during the eight days in hospital after the procedure was uneventful in the first two patients, and before discharge both climbed three flights of stairs without any pain or dyspnoea—a striking functional improvement. At four weeks follow-up, the improvement persisted: there had been no syncope, no pain, and very little dyspnoea, even though the patients had by then resumed a normal lifestyle. Follow-up of the third patient has been shorter, but it was uneventful after fifteen days, with no more functional signs, including dyspnoea.

Discussion

To our knowledge, the 3 patients reported here are the first to undergo PTAV of adult acquired aortic stenosis. Immediate results appear very encouraging, since the dilatation resulted in a change from severe to moderate aortic stenosis according to the usual haemodynamic criteria—a pronounced decrease in the ventriculo-aortic systolic pressure gradient, with a residual gradient of 40 mm Hg in one patient, and of 30 mm Hg in the other two.

From the angiographic and echocardiographic data, improvement in the gradient is a consequence of better systolic valve opening. The balloon inflations probably resulted in a partial tear of the stenosed valve. Although the valve orifice is often hard to cross in severe adult calcific aortic stenosis, we experienced no technical difficulty in passing the dilatation catheters via the aortic orifice and in reaching a good transvalvular position. The excellent patient tolerance of the inflations is worth emphasising, since we had feared that inflation of the balloon in a stenosed aortic orifice might lead to syncopal circulatory arrest. During the inflations, the aortic pressure remained satisfactory, suggesting that the
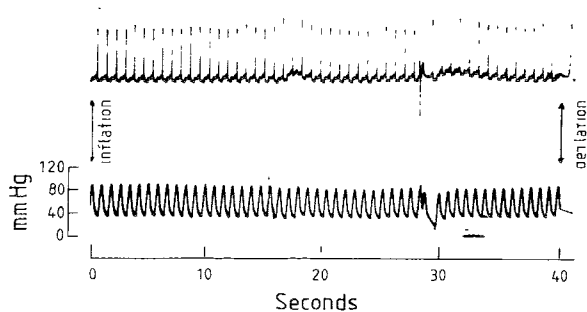

Fig 2—ECG (lead V5) and aortic pressure continuous recording during a 40 s balloon inflation-deflation cycle.

Inflation was associated with a slight decrease in systolic aortic pressure from 85 to 70 mm Hg. There was no change in heart rate and only one premature ventricular contraction.
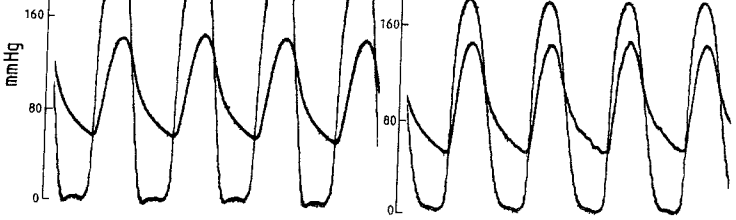
Fig 3—Simultaneous recording of left ventricular and aortic pressures before (left) and at the end of PTAV (right) in case 1.

Transvalvular systolic gradient decreased from 90 to 40 mm Hg.

complications during or after the procedure, although calcium embolism could be considered a risk.[11]

It is too early to predict the possible place of PTAV in the treatment of severe adult acquired aortic stenosis from so few patients. Nevertheless, our 3 cases illustrate the feasibility of the procedure, its good patient tolerance, and the resulting haemodynamic and clinical improvement. Although the results are unlikely to compare in quality with those of valve replacement, PTAV can offer a simple therapeutic alternative to patients, mostly elderly, in whom surgery would be too risky or impossible.
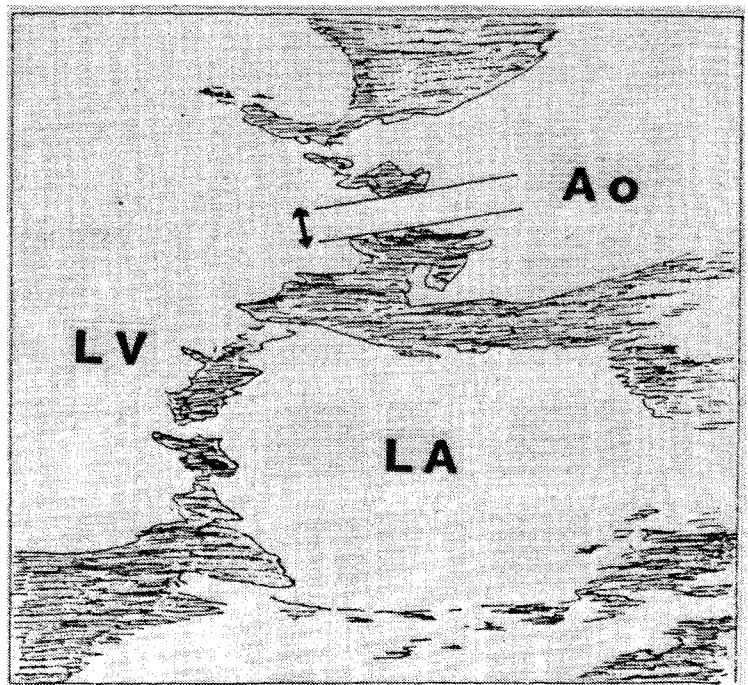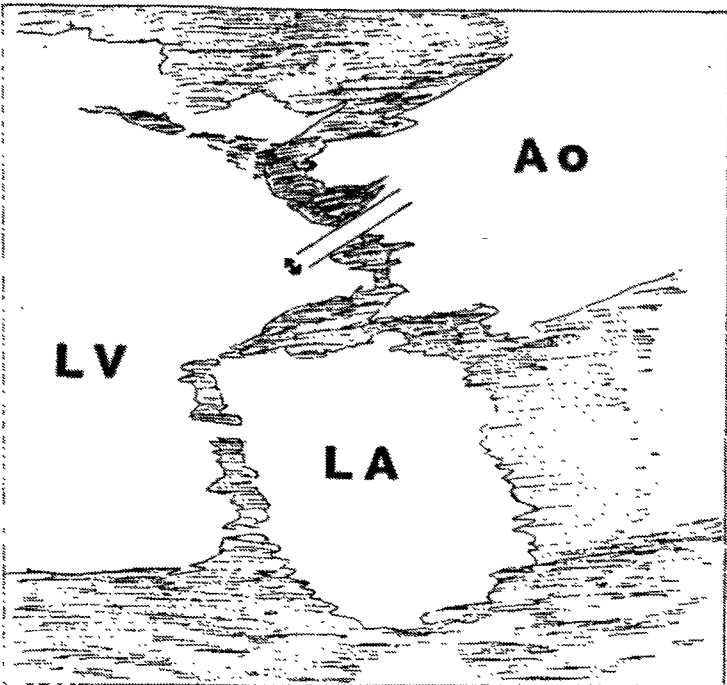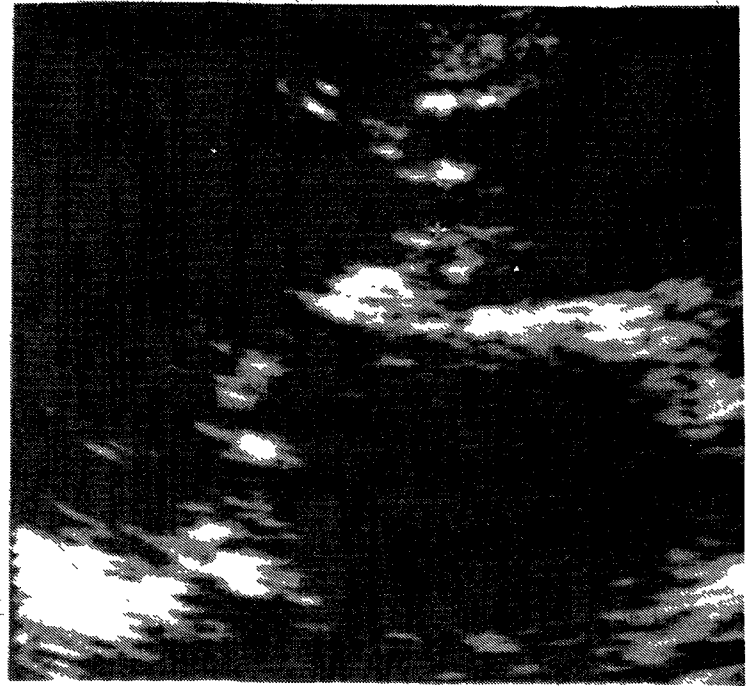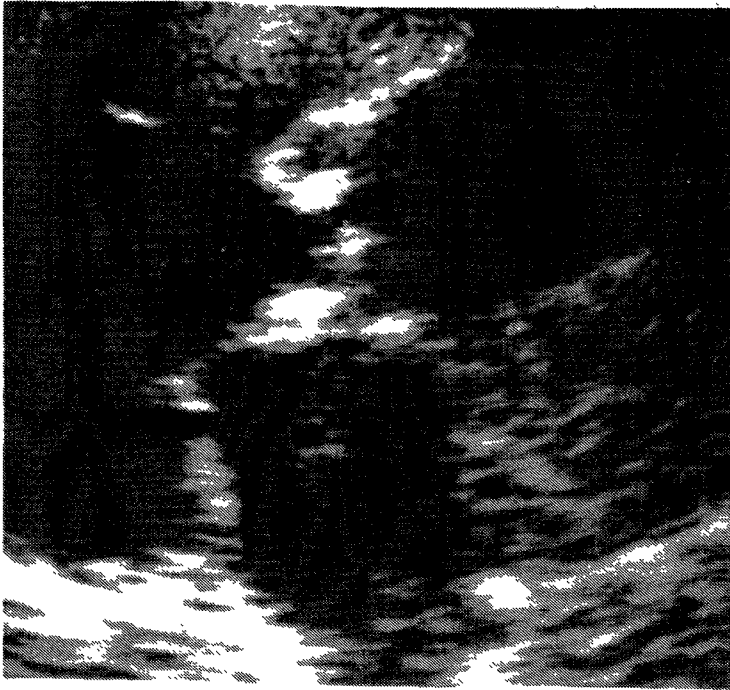
Fig 4—2D echocardiogram (parasternal long axis view) in case 2 before (left) and 24 h after (right) PTAV.

Maximum aortic valve opening (arrows) increased from 0·41 to 0·72 cm. Ao = aorta; LA = left atrium; LV = left ventricle.

addition, PTAV has been carried out in another eleven patients with similar results.

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COMPARISON OF TWO METHODS OF PREDICTING OUTCOME IN PERINATAL ASPHYXIA

M. I. Levene   Caroline Sands
Helen Grindulis   J. R. Moore

Department of Child Health, University of Leicester School of Medicine, and Leicester Royal Infirmary

Summary   In a follow-up study of 122 full-term infants in whom postasphyxial encephalopathy occurred the incidence of death or severe handicap was 1 in 1000 deliveries. The abilities of two methods of diagnosing intrapartum asphyxia to predict outcome at a median age of 2·5 years were compared. A decision matrix calculation was undertaken to assess the sensitivity and specificity of low Apgar score and postasphyxial encephalopathy. A 10 min Apgar score $\leqslant 5$ was the most sensitive of six different Apgar ratings in predicting adverse outcome (sensitivity 43%, specificity 95%) but even this was much less sensitive than the presence of moderate or severe encephalopathy in predicting death or severe handicap (sensitivity 96%).

Introduction

Asphyxia is the most common cause of major cerebral birth injury in the perinatal period; its incidence in full-term infants varies between 2·9 and 9·0 cases per thousand.[1-6] There have been several attempts to relate either low Apgar scores[4] or abnormal neurological findings after asphyxia[3,7-9] to outcome. If we are to use an assessment of asphyxia at birth to predict neurological sequelae, the ability of the method to evaluate prognosis should be tested.

We have assessed two methods of diagnosing intrapartum asphyxia (low Apgar score and postasphyxial encephalopathy) for their ability to identify infants with a poor prognosis as well as those likely to have a good prognosis. We have used a decision matrix[10] to assess the sensitivity and specificity of both methods in predicting outcome. Sensitivity measures the proportion of infants with adverse

We have previously reported the incidence of encephalopathy after intrapartum asphyxia in our university obstetric department.[6] Encephalopathy was graded as: mild (minor disturbances of tone, hyperalertness, and slight feeding difficulties, recovering by 48 h after birth); moderate (lethargy, more pronounced abnormalities of tone, poor feeding, and convulsions, with signs of recovery by 7 days); and severe (coma, failure to maintain adequate ventilation, profound hypotonia, and seizures). The infants previously reported represent the population of full-term infants born in a teaching hospital maternity unit in the 4 years from 1980. Leicestershire Health District provides both obstetric and paediatric care for almost all the families living in the geographical area. Leicester Royal Infirmary undertakes care of high-risk pregnancies and at-risk infants, and severely handicapped children born anywhere in Leicestershire are subsequently assessed at the child development centre attached to the main hospital.

Children surviving postasphyxial encephalopathy were regularly assessed. We were unable to trace 4 children (3%) for follow-up. 6 others had moved out of Leicestershire and information on their developmental achievements and neurological function was obtained from general practitioners and health visitors. All 6 children were reported to be functioning normally. The age at follow-up of the 122 children was between 1 and 5 years (median 2·5 years). Any child with equivocal neurodevelopmental assessment or neurological signs was assessed by one of us. Children with developmental delay were further assessed by an educational psychologist using the Bayley scales. Severe neurological abnormality was defined as cerebral palsy sufficient to impair independent locomotion, developmental delay probably severe enough to warrant special education, sensorineural hearing loss, visual impairment, or epileptic seizures (not associated with fever) requiring medication. Adverse outcome was defined as one or more of these severe neurological deficits and/or death.

Since the index cases for follow-up consisted of children who had had postasphyxial encephalopathy, we made a thorough search for children who might have had brain damage as the result of asphyxia defined on the basis of low Apgar scores but who had shown no evidence of encephalopathy. We examined the notes of all children referred to the child development centre from January, 1981, to June, 1985 who had been born at full-term in Leicester Royal Infirmary. No handicapped children were found who had had low Apgar scores alone without encephalopathy.

We first attempted to correlate the duration and severity of Apgar score depression defined in six different ways with outcome. For the main analysis two hypotheses were tested: that adverse outcome was predicted either by moderate and severe encephalopathy or by a low Apgar score (the sensitivity). This can be conversely stated as a favourable outcome predicted by mild postasphyxial encephalopathy or a normal Apgar score (the specificity). The sensitivity is calculated as the proportion of infants with adverse outcome predicted by the method (true-positives divided by true-positives plus false-negatives). Specificity is the proportion of infants with favourable outcome predicted by the method (true-negatives divided by true-negatives plus false-positives).[9]

Results

During the study period there were 20 975 full-term, live births; postasphyxial encephalopathy developed in 126 infants—an incidence of 6·0 per 1000.[6] Follow-up information was obtained for 122 of the 126. 14 children died: 7 during the first week of life from the effects of severe cerebral asphyxia; 6 between 8 days and 9 months, all showing grossly abnormal neurological behaviour before death; and 1 aged 1 year after cardiac surgery (she had severe oculomotor apraxia).