Factors affecting left ventricular function after correction of tetralogy of Fallot

MICHEL DE LORGERIL, BEAT FRIEDLI, ANDRÉ ASSIMACOPOULOS

From the Pediatric Cardiology Unit, Cardiology Center, and Division d'Informatique Médicale, University of Geneva Medical School, Geneva, Switzerland

SUMMARY To investigate the possible causes of left ventricular dysfunction after total correction of tetralogy of Fallot, 84 patients, aged 1½ to 16 years, were studied by left ventricular cineangiography both before and a mean of 4·6 months after operation. Left ventricular ejection fraction and mean velocity of circumferential fibre shortening were calculated; using multivariate analysis the results were correlated with age at operation, the degree of hypoxia and polycythaemia before operation, occurrence of hypoxic spells, and the duration of operative procedures (cardiopulmonary bypass and aortic cross clamping). The postoperative left ventricular ejection fraction was decreased slightly or moderately in 46% of patients. The variable most significantly associated with altered left ventricular function was a history of hypoxic spells. Age, the degree of chronic hypoxia, and polycythaemia did not correlate significantly with left ventricular function indices. Although no correlation was found between the duration of cardiopulmonary bypass and left ventricular ejection fraction, bypass times exceeding 120 minutes were associated with decreased ejection fractions; this was statistically significant and independent of the variable "hypoxic spells".

Thus repeated episodes of acute hypoxia and long operative procedures appear to have a deleterious effect on left ventricular function in tetralogy of Fallot.

Surgical correction of tetralogy of Fallot results in considerable symptomatic and haemodynamic improvement in most patients. Persistence of heart failure or decreased exercise tolerance late after surgery is usually due to residual abnormalities—for example, residual ventricular septal defect or right ventricular outflow obstruction. In some cases, however, it may be due to left ventricular dysfunction.

Indeed, several postoperative studies have found left ventricular dysfunction in the absence of other haemodynamic abnormalities.[1-5] This is most likely to be due to changes in the myocardium, but its cause is presently unknown; hypoxia, abnormal left ventricular development,[5] or the operative procedure are possible factors. It is important to identify risk factors of myocardial damage, since this will allow a strategy to be developed to prevent it.

The purpose of this study was to assess left ventricular function during cardiac catheterisation both before and after complete surgical correction and to determine factors which correlate with left ventricular performance or dysfunction.

Patients and methods

Eighty four patients (59 boys and 25 girls) who had complete correction of tetralogy of Fallot and underwent both preoperative and postoperative catheterisation were studied. Postoperative catheterisation is carried out routinely after correction of tetralogy of Fallot in this hospital whether residual defects are suspected or not. We included in the present study only the 84 patients who had a left ventricular angiogram of good enough quality after operation to allow accurate volume measurement. This was the only criterion for selection. Seventy eight patients had also had a left ventricular angiogram performed preoperatively. The age of the patients at operation ranged from 18 months to 16 years (mean 6·6 years). Only four patients were <2 years old.

Thirteen patients had undergone previous palliative shunts (Waterston anastomosis in six and Blalock Taussig in seven). Two patients had undergone palliative enlargement of the right ventricular outflow tract before complete correction.

The patients' haematocrit before operation ranged from 35% to 75% (mean 54%). Preoperative arterial oxygen saturation ranged from 45% to 94% (mean 78%). Forty patients had hypoxic spells; these received propranolol (1 to 3 mg/kg/day).

Cardiac catheterisation was performed percutaneously via the femoral vein and artery under light sedation (a mixture of pethidine, promethazine, and chlorpromazine). The preoperative catheterisation was carried out 2–4 weeks before operation. The postoperative study took place generally between two and six months (mean 4·6 months) after it. At postoperative catheterisation, no patient had a residual shunt of haemodynamic importance. Three had a significant residual pulmonary stenosis (gradients of 65, 80, and 90 mm Hg); all the others had gradients <30 mm Hg.

INDICES OF LEFT VENTRICULAR FUNCTION
Left ventricular volumes and ejection fractions were obtained from left ventricular angiograms. Images were recorded either in biplane left and right anterior oblique (52 angiograms in both preoperative and postoperative studies) or single plane right anterior oblique projections (108 angiograms).

Left ventricular volumes were calculated according to the area length method described by Dodge *et al*[6] at end diastole and end systole. Care was taken to avoid extrasystoles or postextrasystoles. Either a grid system or a sphere of 6 cm diameter was used to correct for magnification. "True" volumes were obtained from corrected volumes by applying the formula of Graham *et al*[7] for the biplane angiograms and the regression equation of Hermann and Bartle[8] for single plane angiograms. Finally, the absolute value for volume was indexed (divided by the body surface area) and expressed in ml/m² (normal values 73(11) ml/m²).[7]

Left ventricular ejection fraction was calculated by the formula: $[(EDV-ESV)/EDV] \times 100\%$ where EDV is the end diastolic volume and ESV the end systolic volume.

Comparison of single plane and biplane measurements—To assess whether patients investigated with single plane cineangiography only could be included in the study, left ventricular volumes and ejection fractions of the 26 patients who had biplane angiograms were calculated twice, first using both planes and then from the right anterior oblique projection only. When both the preoperative and postoperative cineangiograms were included this yielded

52 pairs of values for comparison. For left ventricular volumes the correlation was good (r=0·82), but the single plane method overestimated the volume and there was a large standard error of the estimate (11·2 ml/m²). For ejection fraction, however, the correlation was very good (r=0·89) and the standard error was small (3·95%). When compared by a paired *t* test, values calculated from the single plane were not different from those obtained using both planes (p=0·33). Within the range of interest (40–70%), ejection fraction calculated from single plane images was very close to values calculated from biplane images. Therefore, we included in the present study the ejection fraction calculated from single plane cineangiograms in cases in which biplane angiograms were not available. Indexed volumes, however, are given only for patients who had biplane angiograms performed.

Mean velocity of circumferential fibre shortening was determined in all patients from the systolic excursion of the left ventricular internal minor equator as described by Karliner *et al*[9]; this has been shown to be a good indicator of normal and abnormal left ventricular myocardial function.[10] The normal figure for the mean value in children according to Fisher is 1·55(0·37) circ/s.[11]

CORRELATION OF OTHER VARIABLES WITH LEFT VENTRICULAR FUNCTION
The following factors related to preoperative state were evaluated: age at operation, preoperative haemoglobin concentration and haematocrit, aortic oxygen saturation at preoperative catheterisation, history of hypoxic spells, and preoperative left ventricular end diastolic volume. Hypoxic spells are defined as episodes of acute cyanosis with anxiety and tachypnoea, with or without loss of consciousness, requiring medical attention and usually prompting the administration of beta blocking drugs. One well documented episode was sufficient for inclusion in the group with "spells" if the case history showed that similar episodes had occurred before; most of these children, however, had numerous documented episodes. As for the factors related to the operative procedure the duration of cardiopulmonary bypass and aortic cross clamping was evaluated.

STATISTICAL METHODS
To assess the influence of the above factors on left ventricular ejection fraction and mean velocity of circumferential fibre shortening, multivariate analysis was performed using the SPSS-6000 Package[12] on a CDC Cyber computer. Left ventricular ejection fraction and mean velocity of circumferential fibre shortening were the dependent variables. All interval-scaled independent variables (for example, haemoglobin concentration, haematocrit, etc) were tested in
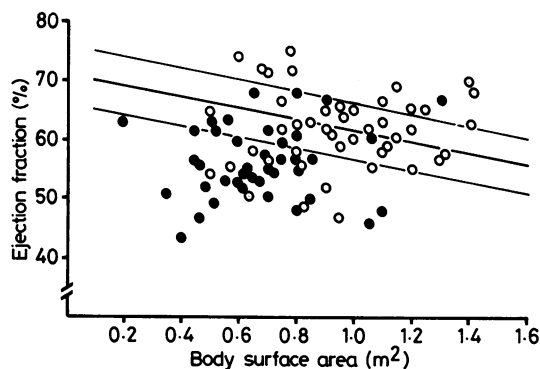
Fig. 1 *Left ventricular ejection fraction (postoperatively) in relation to body surface area in patients with (●) and without (○) a history of hypoxic spells. The continuous lines denote the mean and the upper and lower limits of normal, according to Graham.[7]*

conjunction with nominal independent variables (hypoxic spells) in an analysis of covariance. Bypass time and aortic cross clamping were first treated as interval-scaled variables. In a second analysis, they were treated as nominal variables using arbitrary cut off times (bypass time less or more than 120 minutes, aortic cross-clamping time less or more than 70 minutes).

Results

LEFT VENTRICULAR VOLUME
For comparison of preoperative and postoperative data, biplane left ventricular angiograms were available both before and after operation in 19 patients of >2 years of age. None of these patients had a shunt or Brock operation before complete correction. Indexed left ventricular end diastolic volume was below normal in the preoperative period (58·8(10) ml/m^2 (mean (SD))). After correction, it increased significantly to normal values (77·3(11) ml/m^2 (p<0·01)).

LEFT VENTRICULAR FUNCTION
For the determination of left ventricular ejection fraction 78 preoperative values and 84 postoperative values were available. On average, the left ventricular ejection fraction was lower than normal before as well as after operation when compared with normal data. Preoperatively, the left ventricular ejection fraction ranged from 44% to 75% and postoperatively from 43% to 75%. The mean value was 59·6(6·5)% preoperatively and 58·4(6·9)% postoperatively; normal values for children are 63(5)% according to Graham et al[7] and 71(7)% according to Fisher et al.[11] Thus the degree of left ventricular dysfunction in this series was moderate. There was no significant difference between preoperative and postoperative mean

ejection fractions. Figure 1 shows postoperative left ventricular ejection fraction in relation to body surface area, and the limits of normal according to Graham et al[7]; 46% of patients had a left ventricular fraction below normal values for body surface area. If values ≥58% are considered to be normal at all ages[13] 44% had abnormal left ventricular function.

For mean velocity of circumferential fibre shortening similar results were found, values being low before and after operation (1·24(0·35) circ/s and 1·24(0·34) circ/s) when compared with normal values of Fisher (1·55(0·37) circ/s). Again there was no difference between preoperative and postoperative mean values; 41% had a mean value below normal in the postoperative period.

POSSIBLE CAUSES OF LEFT VENTRICULAR DYSFUNCTION
Age at operation did not influence left ventricular function. There was no correlation between age (or body surface area) and ejection fraction (Fig. 1). The mean age of children with abnormal function was not different from that of those with normal function (7·1(3·4) v 6·6(2·6) years). Very few infants and children <2 years' old were, however, included in this study.

Preoperative left ventricular volume—To determine whether an underdeveloped left ventricle will function abnormally after operation, preoperative left ventricular volume was correlated with postoperative left ventricular ejection fraction. No significant correlation was found.

Chronic and acute hypoxia before operation—To assess whether chronic hypoxia and polycythaemia could be responsible for the deterioration in left ven-
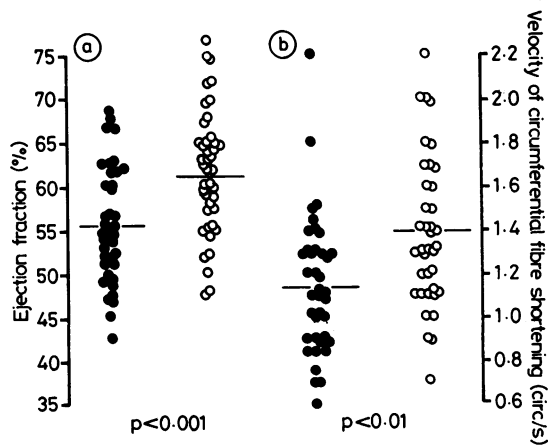

Fig. 2 *Comparison of (a) left ventricular ejection fraction, and (b) mean velocity of circumferential fibre shortening postoperatively in patients with (●) and without (○) a history of hypoxic spells. Bars represent mean values.*
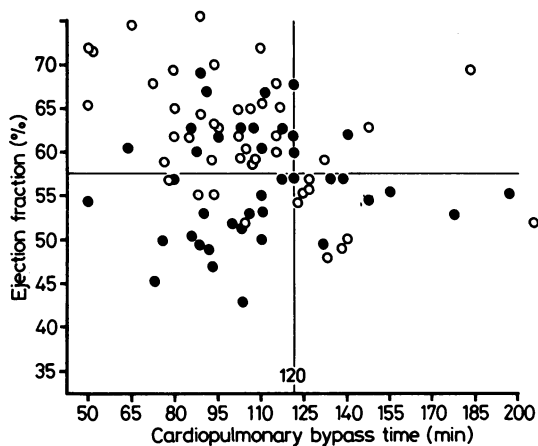
Fig. 3 *Postoperative left ventricular ejection fraction in relation to the duration of cardiopulmonary bypass in patients with* (●) *and without* (○) *a history of hypoxic spells.*

tricular function, correlations were made between function indices (postoperatively) and aortic oxygen saturation at preoperative catheterisation, preoperative haematocrit, and haemoglobin concentration. No significant correlation was found between these indices of function, and the degree of chronic hypoxia did not seem to influence left ventricular function.

Twenty six of 40 children with a history of hypoxic spells had abnormal left ventricular ejection fractions, compared with 10 of 48 patients without. Figure 2 shows postoperative left ventricular function indices for patients with and without hypoxic spells: the multivariate analysis indicates that this was the only preoperative factor that influenced left ventricular function significantly. Patients with a history of hypoxic spells had a significantly lower left ventricular ejection fraction than those without $(56 \cdot 2(6 \cdot 6)\%$ v $61 \cdot 2(4 \cdot 2)\%$, $p<0 \cdot 001)$ and a lower mean velocity of circumferential fibre shortening $(1 \cdot 14(0 \cdot 31)$ circ/s v $1 \cdot 38(0 \cdot 34)$ circ/s, $p<0 \cdot 01)$.

Influence of the operative procedure—When the duration of cardiopulmonary bypass and aortic cross clamping are treated as an interval-scaled variable in the multivariate analysis, no significant correlation is found with left ventricular function indices (Fig. 3). Nevertheless a very long procedure was associated with depressed left ventricular ejection fraction: of the 19 patients with a bypass time >120 minutes, 15 (75%) had depressed postoperative left ventricular ejection fraction and only four a normal ejection fraction (Fig. 3). Among the patients with a shorter bypass time, the number with a decreased ejection fraction is much smaller (22/65, 33%). When bypass time is treated as a nominal variable in the multivariate analysis (<120 minutes or >120 minutes) a

significant effect on left ventricular ejection fraction is found $(p<0 \cdot 05)$, and this is independent of the variable "hypoxic spells".

The same tendency is seen with prolonged aortic cross clamping: 16 of 22 (72%) patients with aortic cross clamping had an abnormal ejection fraction compared with 20 of 60 (33%) patients with a shorter cross clamping time. This did not, however, reach statistical significance.

Discussion

Abnormal left ventricular function after total correction of tetralogy of Fallot was first reported by Jarmakani *et al.*[3] Indeed, these authors found left ventricular ejection fraction to be depressed in many patients and often to a more severe degree than was found in our study. Subsequently, Sunderland *et al* reported normal left ventricular function in children operated for tetralogy before 2 years of age, stressing the need for early correction.[14] Rocchini *et al*[15] found abnormal left ventricular function only in patients with residual lesions—that is, residual ventricular septal defect with a significant left to right shunt or severe residual pulmonary stenosis. Thus the subject of left ventricular function in tetralogy remains somewhat controversial, and the causes of dysfunction are open to discussion.

In the present study, we measured left ventricular ejection fraction and mean velocity of circumferential fibre shortening in a large number of children undergoing surgical correction and tried to determine the causes of abnormal left ventricular function. Since very few infants were included in this series, we cannot comment on the effects of operation very early in life. Children with tetralogy followed from birth in our hospital undergo elective corrective surgery between 2 and 3 years of age. Many of the patients included in this study were, however, referred from abroad and not followed by us from birth. This explains the relatively high mean age of 6·6 years and the inclusion of patients as old as 16 years. Some of the children coming from developing countries had had severe hypoxia for months or years.

We found moderately decreased ejection fractions in 46% of the patients; because the vast majority of our patients had a satisfactory repair residual lesions cannot be held responsible. We found no significant difference on average between preoperative and postoperative ejection fractions. It must be emphasised that preoperative and postoperative ejection fraction cannot be directly compared. Firstly, many of the patients received beta blocking drugs at the time of the preoperative study but none at the time of the postoperative catheterisation. Secondly, different loading conditions exist for the left ventricle in

preoperative and postoperative patients—in particular, preload is decreased before surgery; ejection fraction is said to be partly dependent on preload,[16][17] although there is controversy on this subject.[18] Both propranolol and volume underload would tend to decrease ejection fraction; thus low values in the preoperative study are not totally unexpected. Postoperative left ventricular function is therefore emphasised in the present study. A host of factors could be responsible for left ventricular dysfunction in tetralogy of Fallot. Left ventricular volume is often (though not always) small in tetralogy before operation, as reported by Jarmakani et al.[3] The present study confirms this finding. After operation, the left ventricle increases to normal size; when measured with serial echocardiograms it appears that this process is completed within two to four weeks after operation.[19]

To assess whether this rapid change in size could influence left ventricular function we correlated preoperative left ventricular volume with postoperative left ventricular ejection fraction but found no significant correlation. Thus a small left ventricle preoperatively is not a risk factor for postoperative dysfunction, although it may increase the risk of death in the immediate postoperative period.[19][20]

The hypothesis that chronic hypoxia may be responsible for left ventricular dysfunction was not confirmed by the present study since there was no correlation between aortic oxygen saturation or haematocrit (preoperatively) and left ventricular function. Episodes of acute hypoxia, however, seem to play a role. Hypoxic spells often occur in tetralogy of Fallot; in the present study, a history of such episodes appears to be a significant predictor of abnormal left ventricular function, which is independent of other factors. The finding that chronic hypoxia is tolerated well but that adverse effects occur in patients with acute episodes is not surprising; it may be explained by what is known about myocardial metabolism in cyanotic congenital heart disease. Indeed, myocardial substrate consumption at rest is not different from normal in tetralogy, even in the presence of appreciably decreased oxygen saturation.[21-23] When the heart is stressed—for example, by atrial pacing (or by exercise)—oxygen requirements increase, but oxygen saturation in arterial blood will often decrease: indeed, in classical tetralogy with a reactive infundibulum atrial pacing produces a pronounced fall in aortic oxygen saturation.[23] As a result of the imbalance between oxygen supply and demand anaerobic metabolism occurs with a fall in myocardial lactate extraction or even with lactate production and an increase in phosphate in coronary venous blood.[23] The same findings have been reported by Graham et al in the experimental animal made hypoxic by anas-

tomosing the inferior vena cava to the left atrium, and using isoproterenol to increase myocardial oxygen demand.[24] It is very likely that hypoxic spells will cause similar changes in cardiac metabolism. Such children will have repeated periods of inadequate oxygen supply to the myocardium both during their acute episodes of hypoxia and during exercise or other stress situations. As a result, necrosis of some myocardial fibres will occur, with subsequent fibrosis. Myocardial fibrosis has indeed been found in right as well as left ventricles in tetralogy by Krymsky[25] and by Shakibi et al[26] especially in older children and adults. Loss of myocardial fibres and interstitial fibrosis will in turn cause left ventricular dysfunction.

Open heart surgery with cardiopulmonary bypass is known to result in some degree of myocardial damage.[27] It was therefore important in the present study to assess the possible influence of the operative procedure and technique on left ventricular function. Although a direct correlation between left ventricular function indices and duration of cardiopulmonary bypass or aortic cross clamping was not found, the statistical analysis indicates that a bypass time of >2 hours is associated with a significantly decreased ejection fraction. Thus, in addition to hypoxic spells, a prolonged operative procedure may influence postoperative left ventricular function. The two factors were independent of each other in the multifactorial analysis.

This study confirms that hypoxic spells must be considered to be a serious warning sign, indicating a risk of damage through tissue anoxia not only to the brain but also the myocardium, with subsequent ventricular dysfunction. Although propranolol is useful in most patients and prevents such episodes of acute hypoxia in about 80% of cases[28] we advocate early surgical repair for children subject to them.

References

1 Epstein SE, Beiser GD, Goldstein RE, Rosing DR, Redwood DR, Morrow AG. Hemodynamic abnormalities in response to mild and intense upright exercise following operative correction of an atrial septal defect or tetralogy of Fallot. Circulation 1973; 47: 1065–75.

2 Borow KM, Green LH, Castaneda AR, Keane JF. Left ventricular function after repair of tetralogy of Fallot and its relationship to age at surgery. Circulation 1980; 61: 1150–8.

3 Jarmakani JMM, Graham TP Jr, Canent RV Jr, Jewett PH. Left heart function in children with tetralogy of Fallot before and after palliative or corrective surgery. Circulation 1972; 46: 478–90.

4 Kavey REW, Thomas FD, Blackman MS, Sondheimer HM. Right and left ventricular dysfunction and ventricular arrhythmias after repair of tetralogy of Fallot [Abstract]. Am J Cardiol 1982; 49: 987.

5 James FW, Kaplan S, Schwartz DC, Chou TC, Sandker MJ, Naylor V. Response to exercise in patients after total surgical correction of tetralogy of Fallot. *Circulation* 1976; **54**: 671–9.

6 Dodge HT, Sandler H, Ballew DW, Lord JD Jr. The use of biplane cineangiocardiography for the measurement of left ventricular volume in man. *Am Heart J* 1960; **60**: 762–76.

7 Graham TP Jr, Jarmakani JM, Canent RV Jr, Morrow MN. Left heart volume estimation in infancy and childhood. *Circulation* 1971; **43**: 895–904.

8 Hermann HJ, Bartle SH. Left ventricular volumes by angiocardiography: comparison of methods and simplification of techniques. *Cardiovasc Res* 1968; **2**: 404–14.

9 Karliner JS, Gault JH, Eckberg D, Mullins CB, Ross J Jr. Mean velocity of fiber shortening. A simplified measure of left ventricular myocardial contractility. *Circulation* 1971; **44**: 323–33.

10 Peterson KL, Skloven D, Ludbrook P, Uther JB, Ross J Jr. Comparison of isovolumic and ejection phase indices of myocardial performance in man. *Circulation* 1974; **49**: 1088–101.

11 Fisher EA, DuBrow IW, Hastreiter AR. Comparison of ejection phase indices of left ventricular performance in infants and children. *Circulation* 1975; **52**: 916–25.

12 Nie NH, Hull HC, Jenkins JG, Steinbrener K, Bent DH. *Statistical package for the social sciences*. 2nd ed. New York: McGraw-Hill, 1975.

13 Jarmakani JMM, Graham TP Jr, Canent RV Jr, Capp MP. The effect of corrective surgery on left heart volume and mass in children with ventricular septal defect. *Am J Cardiol* 1971; **27**: 254–8.

14 Sunderland CO, Matarazzo RG, Lees MH, *et al*. Total corrction of tetralogy of Fallot in infancy. Postoperative hemodynamic evaluation. *Circulation* 1973; **48**: 398–405.

15 Rocchini AP, Keane JF, Freed MD, Castaneda AR, Nadas AS. Left ventricular function following attempted surgical repair of tetralogy of Fallot. *Circulation* 1978; **57**: 798–802.

16 Yang SS, Bentivoglio LG, Maranmao J, Goldberg M. From cardiac catheterization data to hemodynamic parameters. Philadelphia: FA Davis, 1972.

17 Nixon JV, Murray RG, Leonard PD, Mitchell JH, Blomqvist CG. Effect of large variations in preload on left ventricular performance characteristics in normal subjects. *Circulation* 1982; **65**: 698–703.

18 Rankin LS, Moos S, Grossman W. Alterations in preload and ejection phase indices of left ventricular performance. *Circulation* 1975; **51**: 910–15.

19 Oberhänsli I, Friedli B. Echocardiographic study of right and left ventricular dimension and left ventricular function in patients with tetralogy of Fallot before and after surgery. *Br Heart J* 1979; **41**: 40–53.

20 Friedli B. Left ventricular volume and function in tetralogy of Fallot: possible causes of left ventricular dysfunction [Abstract]. *Eur J Cardiol* 1979; **10**: 325.

21 Rudolph W. Myocardial metabolism in cyanotic congenital heart disease. *Cardiology* 1971; **56**: 209–15.

22 Scheuer J, Shaver JA, Kroetz FW, Leonard JJ. Myocardial metabolism in cyanotic congenital heart disease. *Cardiology* 1970; **55**: 193–210.

23 Friedli B, Haenni B, Moret P, Opie LH. Myocardial metabolism in cyanotic congenital heart disease studied by arteriovenous differences of lactate, phosphate, and potassium at rest and during atrial pacing. *Circulation* 1977; **55**: 647–52.

24 Graham TP Jr, Erath HG Jr, Buckspan GS, Fisher RD. Myocardial anaerobic metabolism during isoprenaline infusion in a cyanotic animal model: possible cause of myocardial dysfunction in cyanotic congenital heart disease. *Cardiovasc Res* 1979; **13**: 401–6.

25 Krymsky LD. Pathologic anatomy of congenital heart disease. *Circulation* 1965; **32**: 814–27.

26 Shakibi JG, Aryanpur I, Nazarian I. The anatomic correlate of ventricular dysfunction in tetralogy of Fallot. *Jpn Heart J* 1979; **20**: 53–62.

27 Kirklin JW, Conti VR, Blackstone EH. Prevention of myocardial damage during cardiac operations. *N Engl J Med* 1979; **301**: 135–41.

28 Garson A, Gillette PC, McNamara DG. Propranolol: the preferred palliation for tetralogy of Fallot. *Am J Cardiol* 1981; **47**: 1098–104.