Fate of infants with transposition of the great arteries in relation to balloon atrial septostomy

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SUMMARY The palliation afforded by balloon atrial septostomy to 124 infants with transposition of the great arteries was assessed in terms of survival to 6 months of age without the need for further intervention. Prediction of success or failure in relation to palliation was significantly affected by the presence of associated ventricular septal defect, left ventricular outflow tract obstruction, or persistent ductus arteriosus and by the maximum volume of balloon used to perform the septostomy. There was a significant association between balloon volume and size of atrial defect found at subsequent surgery or necropsy.

The results of definitive surgery for infants with transposition of the great arteries are optimal beyond 6 months of age at our centre,1 so that the management of such infants will depend on the increased risks of earlier surgery and the risks of the waiting period before surgery. Most of these infants die before 6 months of age without palliation,2 whereas balloon atrial septostomy3 has allowed the majority to survive to this age. Reports of the results of septostomy show a varying cumulative morbidity and mortality before definitive surgery despite this procedure,4–20 although an improvement has taken place more recently.21 22 Balloon septostomy catheters that can provide larger effective balloon volumes than those used when the procedure was first introduced are now available, and that, together with other factors, may have contributed to the improved survival figures also seen at our centre.

In this study we assessed the importance of balloon volume used at septostomy and the morbidity and mortality before definitive surgery of infants with transposition of the great arteries after a technically adequate septostomy had been performed.

Patients and methods
Case records of all infants with transposition of the great arteries managed at this hospital who underwent their first balloon septostomy between 1 January 1968 and 1 January 1980 were examined. Ten cases were excluded since the records did not include data on septostomy balloon volumes. Only infants with atrioventricular concordance, ventriculoarterial discordance, and normal pulmonary and systemic venous connections were included. Data extracted from case records are shown in Table 1. The information was processed on the University of Liverpool IBM computer. Where possible data were entered as actual values; coded variables are as shown.

CODING OF VARIABLES
The presence of a large ventricular septal defect was coded if a defect of over 3 mm was measured either at surgery or necropsy and, where such data were not available, if angiographic appearances suggested a defect of over 3 mm. Other defects were coded as small. A persistent ductus arteriosus was coded as large if it was described as large at surgery or necropsy of if the pulmonary artery to aortic systolic pressure ratio was above 0.8. A ductus present at initial catheterisation which was shown to have closed spontaneously at subsequent study or surgery was coded as absent. Left ventricular outflow tract obstruction was regarded as absent if the systolic pressure gradient between pulmonary artery and left ventricle was <20 mm Hg, as mild between 20 and 35 mm Hg, as moderate between 35 and 60 mm Hg, and as severe either if >60 mm Hg or if the left ventricular pressure was suprasystolic. Cases with left ventricular systemic pressure of <40 mm Hg were graded as having no obstruction, and those in which such data were not

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Table 1  Coding and frequency of variables (n = number of observations)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coding</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coded:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>Absent</td>
<td>Small</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>Absent</td>
<td>Small</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Coarctation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Small</td>
<td>Medium</td>
</tr>
<tr>
<td>Death by age 6 months</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Second procedure by aged 6 months</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Uncoded:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation before balloon atrial septostomy</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>Oxygen saturation after balloon atrial septostomy</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Oxygen saturation rise</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Maximum balloon volume</td>
<td></td>
<td>124</td>
</tr>
<tr>
<td>First pull volume</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Age at balloon atrial septostomy</td>
<td></td>
<td>124</td>
</tr>
<tr>
<td>Age at second study</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>Oxygen saturation at second study</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>Haemoglobin concentration at second study</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>LA pressure at second study</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>RA pressure at second study</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>PA pressure at second study</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>LV pressure at second study</td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>

LA, left atrial; RA, right atrial; PA, pulmonary artery; LV, left ventricular.

recorded were graded according to angiographic, surgical, or necropsy findings where available. Infants who underwent pulmonary artery banding were coded according to findings at subsequent study.

Maximum balloon volume used to perform the first septostomy procedure was recorded as the maximum volume of contrast fluid used to inflate the balloon. The balloon volume used for the first attempt to tear the septum during the first septostomy procedure was also noted.

Since we aimed to determine the efficacy of the technique of septostomy in terms of palliation we defined success of septostomy as survival after initial septostomy to 6 months of age without any further palliative or definitive procedure other than surgery for associated anomalies. Failures were coded either as deaths before 6 months of age or as second procedures before 6 months of age.

The diameters of 83 atrial defects resulting from the first septostomy had been recorded either at necropsy or at surgery. Diameters of a further seven defects were measured from necropsy specimens stored in formalin; no allowance was made for shrinkage. Defects resulting from repeat septostomy or other procedures were ignored.

The relation between data available at the time of septostomy and failure of palliation was analysed by logistic regression, thus enabling intercorrelated variables to be analysed simultaneously.

CLINICAL DATA
Of 124 infants, 92 (74%) were male and 32 (26%) were female. Age at septostomy ranged from day 1 to day 131 (median day 5, mode day 2); six septostomies were performed after the fifth week of life. Weight at septostomy ranged from 2·0 to 7·9 kg (median and mean 3·47 kg).

Eighty three (67%) infants had an intact ventricular septum, 13 (10%) had a small ventricular septal defect, and 28 (23%) a large defect. Ninety five (77%) had no persistent ductus arteriosus; 12 (10%) a small ductus, seven (6%) a large ductus, and 10 (8%) a ligation performed. Left ventricular outflow tract obstruction was absent in 58 (62%), mild in 19 (20%), moderate in 12 (13%), and severe in five (5%). Aortic coarctation was found in nine (7%) cases.

Systemic arterial oxygen saturation before septostomy ranged from 17% to 85% (median 60%). Immediately after septostomy, the range was 35% to 95% (median 76%).

Maximum balloon volume ranged from 1·5 to 6·0 ml (median 2·2 ml, mean 2·9 ml, mode 2 ml). First pull volumes ranged from 1 to 4 ml (median 1·8 ml). Second study

A second study was performed between the first and fifty-ninth month in 87 cases (median seventh month). Median arterial oxygen saturation was 64% (range 23-85%). Haemoglobin concentration ranged
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from 11·8 to 25·2 g/dl (median 18·9 g/dl). As a result of a single septostomy in 90 cases, there were 40 large defects (≥15 mm diameter), 27 moderate sized defects (10–14 mm), and 23 small defects (<10 mm). There were 60 (48%) failures of initial septostomy, including 38 (31%) who died before 6 months of age and 35 (28%) who underwent a second palliative procedure before 6 months of age.

**Results**

Factors known at the time of balloon septostomy were analysed in terms of their relation to failure of palliation. Since several of these predictor variables may be intercorrelated, it is most appropriate to analyse them simultaneously. This was achieved by predicting the probability of failure of palliation using logistic regression analysis.

The final set of predictor variables used satisfied the criterion that the inclusion of a variable in the regression equation should lead to a significant reduction in deviance. The following variables failed to meet this criterion and were thus not considered to have a significant predictive effect: age at septostomy, weight, sex, presence of coarctation, and systemic oxygen saturations before and immediately after septostomy.

The final equation used was:

\[ \ln(p/1-p) = 1.30-0.843 \times (MBV) + a + b + c \]

where MBV is maximum balloon volume (ml); a = 0 if ventricular septal defect was absent, 1·19 if small, 1·61 if large; b = 0 if persistent ductus arteriosus was absent, 2·78 if small, 1·90 if ligated, 1·96 if large; c = 0 if left ventricular outflow tract obstruction was absent, 0·60 if mild, 1·99 if moderate, 1·72 if severe, 2·70 if unknown. This equation enabled failure (estimated \( p > 0·5 \)) to be correctly predicted in 100 (81%) cases.

There was a trend towards increasing success of palliation in the later years of the study, the most notable difference between year groups being between 1968–75 and 1976–79 (\( p < 0·001 \)). Adding the year of septostomy to the regression equation did not, however, yield a further significant reduction of deviance. Thus we were unable to show any improvement in success of palliation in more recent years over and above that explained on the basis of increased balloon volume. Maximum balloon volumes of over 3 ml were exclusive to the years 1976–79. Further comparison of year groups showed that there was a higher incidence of recorded ventricular septal defects and left ventricular outflow tract obstruction in 1976–79 (\( p < 0·05 \)), presumably from increased accuracy of diagnosis. There was an almost significant decrease in the incidence of major thrombosis (thrombosis of the inferior vena cava or its major branches or a cerebrovascular accident) in 1976–79 compared with 1968–75 (\( p = 0·06 \)).

A persistent ductus arteriosus whether small or large had a deleterious effect. The relation between the presence of a persistent ductus and failure and mortality at 6 months of age is shown in Table 2.

The relation between left ventricular outflow tract obstruction and failure varied according to the degree of obstruction, mild degrees having a beneficial effect. Similarly, the presence of a large ventricular septal defect had a beneficial effect, although this was not true of a small defect.

There was a positive correlation between maximum balloon volume and first pull volume so that their effects on failure could not be separated, although the effect of maximum balloon volume appeared to be the greater. Failure rate was lower for volumes of over 3 ml than for those of 2–3 ml.

**Table 2** Failure and mortality in relation to presence of persistent ductus arteriosus, maximum balloon volume, and defect size

<table>
<thead>
<tr>
<th>Persistent ductus arteriosus</th>
<th>No of cases</th>
<th>Failure (%)</th>
<th>Death by 6 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>95</td>
<td>38 (40)</td>
<td>20 (21·1)</td>
</tr>
<tr>
<td>Small</td>
<td>12</td>
<td>10 (83·3)</td>
<td>8 (66·7)</td>
</tr>
<tr>
<td>Large</td>
<td>10</td>
<td>8 (80)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Ligated</td>
<td>7</td>
<td>4 (57·1)</td>
<td>2 (28·6)</td>
</tr>
<tr>
<td>Maximum balloon volume (ml):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>61</td>
<td>35 (57·4)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>41</td>
<td>8 (19·5)</td>
<td></td>
</tr>
<tr>
<td>Defect size:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>23</td>
<td>15 (65·2)</td>
<td>11</td>
</tr>
<tr>
<td>Medium</td>
<td>27</td>
<td>18 (66·7)</td>
<td>7</td>
</tr>
<tr>
<td>Large</td>
<td>40</td>
<td>7 (17·5)</td>
<td>1</td>
</tr>
<tr>
<td>( x^2 (2 df) )</td>
<td>21·18</td>
<td>18·55</td>
<td>( p &lt; 0·0001 )</td>
</tr>
<tr>
<td>( x^2 (2 df) )</td>
<td></td>
<td></td>
<td>( p &lt; 0·0001 )</td>
</tr>
</tbody>
</table>

**DEFECT SIZE**

There was a significant rank association between maximum balloon volume and defect size, larger balloons being associated with larger defects (\( p = 0·001 \)). Defect size had no significant relation to age or weight at septostomy, the presence of associated defects, or systemic oxygen saturation changes at first study. There was a significant association between defect size and failure or mortality at 6 months (Table 2).

The second study was performed at an earlier age with smaller defects (\( p = 0·04 \)), and systemic arterial oxygen saturations were lower with smaller defects (\( p = 0·03 \)). There was a significant fall in saturation from the time of septostomy to the time of the second study even in the presence of large defects (\( p < 0·05 \)). Left atrial, right atrial, and pulmonary artery pressures were all significantly lower in the presence of large defects (\( p < 0·05 \)).
SECOND STUDY
A second catheterisation was performed at an earlier age in failures (p<0.001), so that haemodynamic data are not strictly comparable between failure and success groups. Systemic arterial oxygen saturation was lower in failures (p<0.001), and before 1976 haemoglobin concentration was lower in failures than successes (p=0.037) but not for 1976-79 (p=0.5). There were many missing pressure data, making interpretation difficult. Pulmonary artery pressure tended to be higher in the failure group, but this was not quite significant at the 5% level.

Thrombosis of the inferior vena cava or its major branches and cerebrovascular accidents grouped together were associated with poor survival at 6 months (p=0.008). There was no association between thrombosis and either haemoglobin concentration or systemic arterial oxygen saturation at the second study.

MORBIDITY, MORTALITY, AND FAILURE ASSOCIATED WITH LARGE BALLOONS
Of 41 infants who underwent septostomy with balloon volumes between 3.5 and 6 ml, two had transiently abnormal neurological signs within one week of septostomy with subsequent normal developmental progress. There were no cases of atrial rupture. Two deaths occurred within one month of septostomy; one infant was moribund before septostomy and died within 24 hours of the procedure; the other developed necrotising enterocolitis. Thirty eight infants were alive at 3 years of age and one had died suddenly at 7 months of age.

Four infants with simple transposition underwent repeat septostomy between 2 weeks and 4 months of age, and all four are alive after definitive surgery between 11 and 14 months of age. Another infant successfully tolerated definitive surgery at 4 months of age.

Discussion
Early survival of infants with transposition of the great arteries has been dramatically improved by the palliative technique of balloon atrial septostomy. Nevertheless, a considerable cumulative morbidity and mortality up to the time of definitive surgery has been seen despite this procedure.4-20 More recent reports reflect an improving outlook for the first year of life after palliation.21 22 At our centre the use since 1976 of a new generation of balloon catheters, capable of dilating to balloon volumes of 4 ml without distortion of their configuration,24 coincided with an improving outcome for these infants. Before 1976 catheters in use had a maximum effective balloon capacity of 3 ml, further dilatation leading to elongation rather than an increase in transverse diameter. Many factors have probably contributed to the recent improvement in early survival. Nevertheless, maximum balloon volume was significantly associated with failure of septostomy regardless of year, and there is little doubt that the use of larger balloons has contributed appreciably to the improved survival in the later years of the study. Larger balloon volumes were also associated with larger defects seen subsequently at surgery or necropsy; defect size was itself significantly associated with success of palliation and survival to 6 months of age.

Thus six months' palliation from septostomy in most cases depends on the production of a defect of adequate size, which from our data usually means a defect of ≥15 mm diameter as measured subsequently at surgery. Production of a large defect at septostomy does not, however, guarantee its permanence. The importance of technique in producing an adequate defect has been emphasised25 26: first pull volumes of under 2 ml may lead to stretching rather than tearing of the septum with good immediate results but inadequate long term palliation.26 Data on whether first pull or maximum balloon volumes or other operative techniques determine adequate tearing of the atrial septum are sparse; Hawker et al found that success and failure groups had been treated with similar first pull diameters of about 12 mm,15 but the balloons were of not more than 3 ml effective volume. Our data cannot differentiate the effects of first pull and maximum volumes, although the latter appears to have more influence on the success of the procedure.

The success rate was highest with maximum volumes of over 3 ml and first pull volumes of at least 2 ml, using catheters that retain a roughly spherical configuration at these volumes. That stretching and subsequent shrinkage of the atrial septum do occur after attempts at balloon septostomy is suggested by the fact that failures and successes had similar changes in systemic arterial oxygen saturations after septostomy, but failures had relatively sharp falls in saturation to subsequent study with smaller defects measured at surgery or necropsy. Furthermore, many such infants experience long lasting palliation after a repeat septostomy. Rarely, shrinkage of an atrial defect may occur after atrial septectomy.27

The insertion of a suitably sized catheter via a femoral vein is occasionally difficult. A further difficulty may be excessive resistance26 to passage of the balloon through the atrial septum. Nevertheless, Henry et al used balloon volumes of over 3 ml in 42 of 43 infants and produced defects of >15 mm in 27, 10-15 mm in four, and <10 mm in four.21 Blade atrial septostomy29 is available for infants in whom the atrial septum may be too tough to tear.

Concern has been expressed about the possible
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hazard of atrial rupture during septostomy with large balloons.\textsuperscript{30} In our experience, this complication is independent of balloon volumes of up to 6 ml; indeed the use of balloon volumes of between 3.5 and 6 ml has not been associated with excessive incidence of any complication compared with smaller balloons.

Interpretation of the association between other variables and failure of septostomy is hampered by the unavailability of data on all cases, particularly findings at the second study. The accuracy of diagnostic categorisation of associated lesions such as ventricular septal defect and left ventricular outflow tract obstruction is also open to doubt in view of the discrepancy in the diagnostic frequency of these lesions between group years. Our data do, however, reflect the malignant nature of even a small persistent ductus arteriosus cited by others.\textsuperscript{4,22} There was, however, a significantly lower mortality associated with this lesion in 1976–79, suggesting improved management. We cannot deduce whether the presence of a large atrial defect modifies the adverse effects of a persistent ductus, such as by reducing right ventricular over-load, although large defects were generally associated with lower pulmonary artery pressures than were small defects.

The timing of definitive surgery for infants with transposition of the great arteries will depend on the risks of early surgery and the risks of waiting to the optimal age for surgery in each case. Relatively poor survival data after balloon atrial septostomy have led some centres to advocate elective definitive surgery within the first weeks of life\textsuperscript{11,28} or in the presence of adverse factors.\textsuperscript{22} Our data suggest that, given the benefit of modern medical management, most of these infants may survive to elective surgery beyond 6 months of age in the presence of a large atrial defect. Failure of septostomy to allow survival beyond the first 6 months of life may be regarded as either failure to produce a long lasting large defect or failure in the presence of such a defect. Echocardiography\textsuperscript{31} allows failure to be defined non-invasively.

Consistent production of such a defect requires the use of balloon catheters capable of expanding to adequate volumes without distortion of their configuration; such modern balloons have a partly cuboid rather than spherical configuration, which may favour tearing of the atrial septum rather than stretching of the interatrial opening. Interpretation of data on the fate of infants with transposition of the great arteries after balloon atrial septostomy should take into account the type of balloon used.

We recommend that balloon septostomy should be performed with first pull volumes of 2–2.5 ml; subsequent pulls should be performed with increasing volumes leading to a maximum of 4–4.5 ml. Greater volumes are not usually necessary and may increase the risk of the procedure.

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