Arterial oxygen tension and response to oxygen breathing in differential diagnosis of congenital heart disease in infancy

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Jones, R. W. A., Baumer, J. H., Joseph, M. C., and Shinebourne, E. A. (1976). *Archives of Disease in Childhood*, 51, 667. **Arterial oxygen tension and response to oxygen breathing in differential diagnosis of congenital heart disease in infancy.** Arterial oxygen tension was measured from radial artery samples in 276 infants referred for cardiological investigation. Values obtained during air breathing in infants with congenital heart disease showed considerable overlap between 'cyanotic' and 'acyanotic' groups, and are of limited diagnostic use. By contrast, values obtained while breathing oxygen in concentrations of over 80%, measured in 182 infants, allowed clear differentiation between these groups. All infants with acyanotic, but only 2 of 109 with cyanotic lesions, achieved an arterial oxygen tension of more than 150 mmHg. In the cyanotic group the response to oxygen breathing was significantly greater in common mixing situations and in the hypoplastic left heart syndrome than with either pulmonary outflow tract obstruction or transposition of the great arteries. Infants with transposition had a significantly lower mean arterial oxygen tension in air than infants with other forms of cyanotic congenital heart disease.

Of 23 infants whose final diagnosis was primary lung disease but in whom cyanotic congenital heart disease had been suspected, 7 achieved arterial oxygen tensions of more than 150 mmHg during oxygen breathing, and on this basis cardiac catheterization was not performed. We therefore conclude that measurement of the arterial oxygen tension while breathing high concentrations of oxygen should be routinely performed in the initial assessment of sick infants with suspected congenital heart disease.

Abbreviations

CMS: common mixing situation
HLHS: hypoplastic left heart syndrome
Pao₂: arterial oxygen tension
PDA: persistent ductus arteriosus
POTO: pulmonary outflow tract obstruction
RDS: respiratory distress syndrome
TGA: transposition of great arteries

The division of patients with congenital heart disease into 'cyanotic' and 'acyanotic' groups forms the basis of most attempts to classify this diverse

group of anomalies (Wood, 1956; Perloff, 1970). In the individual case, however, even this basic distinction may sometimes be difficult to make without resort to cardiac catheterization. Clinical assessment of arterial saturation is inaccurate (Comroe and Botelho, 1947; Goldman *et al.*, 1973), and many forms of cyanotic congenital heart disease with right to left shunt but increased pulmonary flow may achieve oxygen saturations above the level at which cyanosis becomes detectable. In addition, infants with acyanotic lesions may become cyanosed when heart failure or chest infection are present, and primary lung disease may mimic cyanotic congenital heart disease, especially in the neonatal period (Robertson, Hallidie-Smith, and Davis, 1967).

We have found that measurement of Pao₂ in high oxygen concentrations is extremely useful, both in

Received 2 January 1976.

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helping to delineate those infants with cyanotic congenital heart disease, and in the differential diagnosis of the individual lesion. Though other workers have stated this (Lees, 1970; Nadas and Fyler, 1972), no large series of infants has been reported where the clinical validity of this simple test has been assessed. This paper analyses our results in a large number of symptomatic infants referred with suspected congenital heart disease.

Patients and methods

386 infants under one year of age were admitted to Brompton Hospital between January 1973 and February 1975, with a provisional diagnosis of heart disease. Records were available for 384. Of these, 63 had arterial blood gases estimated while breathing air alone, and 182 had blood gases estimated while breathing high oxygen concentrations; in 154 of the latter blood gases were also estimated in air (Table I).

Blood gases were estimated in all infants from samples obtained by radial artery puncture. No record was made of whether the infants were crying. Samples were withdrawn anaerobically into 1 ml plastic syringes, the dead space of which had been filled with heparin 1000 units/ml, and refrigerated until analysis (within one hour of arterial puncture). P_{aO_2} was measured using the Corning 165 Blood Gas Analyser (Biomedical Engineering). pH and P_{aCO_2} were also measured.

Inspired oxygen concentrations of between 80% and 95% were obtained by using a Perspex head box (Warley and Gairdner, 1962) in 178 infants. 4 infants were intubated and required intermittent positive pressure ventilation, and in these the oxygen was delivered via the ventilator. High oxygen concentrations were administered for a minimum of 10 minutes before arterial blood sampling and were continued during the procedure.

A complete anatomical diagnosis was obtained from cardiac catheterization and angiography, supplemented by post-mortem examination when this was performed. Information from these sources was available in 92% of infants with heart disease. Of the remaining 8%, all but one was thought to have acyanotic heart disease not requiring cardiac catheterization. The remaining infant

died before further investigation and necropsy was not performed.

Results

Patients. Infants were divided into groups of those with cyanotic and those with acyanotic heart disease. For the two groups, P_{aO_2} in air and in high oxygen concentrations, as well as the rise in P_{aO_2} with change in inspired oxygen concentration (P_{aO_2} in oxygen minus P_{aO_2} in air), were compared. Infants with cyanotic congenital heart disease were divided into diagnostic categories and P_{aO_2} was likewise compared between the groups. Statistical significance was assessed by using the unpaired 't' test.

Arterial blood gases were analysed in 72% of infants in the study (Table I). In those under one week of age blood gases were analysed in 87% (87 out of 99), whereas in the older infants (those aged 1 month to 1 year) blood gas analyses were thought at the time to be clinically indicated in only 57% (103 out of 179).

Cyanotic and acyanotic congenital heart disease. 31 of the 276 infants with blood gas data were excluded as the inspired oxygen concentration at the time of blood sampling was not stated. The mean P_{aO_2} in air of infants with cyanotic congenital heart disease was 39 mmHg, and in oxygen 54 mmHg. In infants with acyanotic heart disease mean P_{aO_2} in air was 73 mmHg and in oxygen 268 mmHg. Though the mean P_{aO_2} in air was significantly different ($P < 0.001$) between the two groups, the overlap between them did not allow discrimination between cyanotic and acyanotic heart disease in the majority (68%) of infants (Fig. 1).

In high oxygen concentrations, however, P_{aO_2} was highly discriminating between the two groups (Fig. 2). None of the group with acyanotic heart disease had a P_{aO_2} of less than 150 mmHg, while

TABLE I
Proportion of infants under study in whom blood gases were analysed

	Age			
	<1 week	1 week to 1 month	1 month to 1 year	All patients
Total no. of patients	99	106	179	384
Blood gases in air and oxygen	54	53	47	154
Blood gases in oxygen alone	10	7	11	28
Blood gases in air alone	16	19	28	63
Blood gases: inspired oxygen concentration not stated	7	7	17	31
Blood gases not analysed	12	20	76	108

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FIG. 1.—Comparison of PaO_2 in air between infants with cyanotic and acyanotic congenital heart disease. Area of overlap between the two groups is from 30 to 100 mmHg. 68% of infants have PaO_2 values within this range, and in the majority discrimination between cyanotic and acyanotic heart disease is not possible.

FIG. 2.—Comparison of PaO_2 in high oxygen concentrations between infants with cyanotic and acyanotic congenital heart disease. Overlap between the groups is such that only 2 infants with cyanotic heart disease had values >150 mmHg.

FIG. 3.—Rise in PaO_2 (ΔPaO_2) on breathing high oxygen concentrations compared with PaO_2 on breathing room air. Values are shown for infants with cyanotic and acyanotic congenital heart disease. Overlap between the groups is shown.

only 2 infants with cyanotic congenital heart disease had PaO_2 values of more than 150 mmHg (both had CMS and high pulmonary blood flows). The rise in PaO_2 (Fig. 3) also clearly distinguished the two groups but gave no better discrimination between them than did PaO_2 in high inspired oxygen concentrations.

Infants with primary lung disorders. 23 infants referred with suspected cyanotic congenital heart disease were subsequently shown to have primary lung disorders. In 7 PaO_2 in high oxygen concentrations rose above 150 mmHg and on this basis cyanotic congenital heart disease was excluded. 3 of the remainder had localized x-ray changes of pneumonia; one of these had a PaO_2 of 100 mmHg in oxygen, which would not rule out cyanotic congenital heart disease.

Eleven of the remaining 13 infants underwent cardiac catheterization and all showed evidence of a right to left shunt via a PDA. A patent foramen ovale was shown in all infants catheterized, through which right to left shunting was found in 5. Pulmonary venous desaturation, despite high inspired oxygen concentrations, was shown in the remainder. The last two neonates (whose PaO_2 did not rise above 150 mmHg with high inspired oxygen concentrations) were not subjected to cardiac catheterization as they were thought clinically to have unequivocal severe hyaline membrane disease.

Infants with cyanotic congenital heart disease. These infants were divided into diagnostic categories according to the haemodynamic situation producing cyanosis. Four different groups were recognized.

(1) Complete TGA. (2) POTO; the anomalies listed in Table II were included in this group, all of which are characterized by shunting of blood away from the lungs. (3) CMS; the anomalies listed in Table III were included in this group. In

TABLE II
Anomalies resulting in POTO and cyanosis

Fallot's tetralogy	31
Primitive ventricle + pulmonary stenosis or pulmonary atresia	10
Pulmonary atresia ± ventricular septal defect	10
Tricuspid atresia ± small ventricular septal defect	6
Pulmonary stenosis + patent foramen ovale	3
Double outlet right ventricle + pulmonary stenosis	3
Hypoplastic right ventricle	1
Corrected transposition + pulmonary stenosis + ventricular septal defect	1
Total (blood gases done in 55)	65

TABLE III
Anomalies producing CMS

Total anomalous pulmonary venous drainage	15
Tricuspid atresia + large ventricular septal defect	6
Truncus arteriosus type I	4
Double outlet right ventricle	4
Primitive ventricle	4
Primitive ventricle + coarctation	4
Primitive ventricle + single atrium	3
Double outlet right ventricle + coarctation	2
Primitive ventricle + mitral atresia	1
Total (blood gases done in 33)	43

this group are included those anomalies where admixed systemic and pulmonary venous blood is distributed to both great arteries. (4) HLHS.

The mean Pao_2 of the different groups was compared in air and oxygen; the rise in Pao_2 in response to rise in inspired oxygen concentration was also compared (Fig. 4, Table IV). In air the

TABLE IV
Comparison between different groups with cyanotic congenital heart disease

	P values		
	Air	Oxygen	Rise
TGA/POTO	<0.02	NS	NS
POTO/CMS	NS	<0.01	NS
CMS/HLHS	NS	NS	NS
TGA/CMS	<0.01	<0.001	<0.05
POTO/HLHS	NS	<0.001	<0.01
TGA/HLHS	<0.001	<0.001	<0.001

NS, not significant.

mean Pao_2 was significantly higher in infants with POTO (39 mmHg), CMS (42 mmHg), and HLHS (47 mmHg) than in those with TGA (30 mmHg). In oxygen the mean Pao_2 was significantly higher in infants with CMS (64 mmHg) and HLHS (79 mmHg) than in those with TGA (39 mmHg) and POTO (45 mmHg). Mean Pao_2 rise in infants with CMS (21 mmHg) and HLHS (36 mmHg) was significantly greater than in infants with TGA (9 mmHg); the mean Pao_2 rise in infants with HLHS was significantly greater than in those with POTO (12 mmHg). There was no significant difference in mean Pao_2 between infants with common mixing situations and those with HLHS.

In infants with TGA comparison was made between those with a ventricular septal defect and those with intact ventricular septum. In air the mean Pao_2 of the former (39 mmHg) was significantly higher than of the latter (25 mmHg) ($P < 0.02$).

However, there was no significant difference between the groups in high inspired oxygen concentrations, nor in their response to changes in inspired oxygen concentration.

Infants with TGA were also divided into those with and those without a PDA as shown at cardiac catheterization. No significant differences were shown.

Discussion

The spectrum of congenital heart disease seen was comparable to that in other series (Lambert, Canent, and Hohn, 1966; Rowe and Mehrizi, 1968; Campbell, 1973), and is representative of symptomatic infants referred to a specialist centre for investigation. This study was undertaken to ascertain whether measurement of Pao_2 and its response to high oxygen concentrations would provide clinical information in the initial assessment of these infants. Pao_2 in oxygen proved to be far more useful than measurement in air, allowing clear differentiation between cyanotic and acyanotic groups, and in the former providing useful clues to the type of congenital defect present. The extent of the rise in Pao_2 after oxygen administration gave no additional information. In 7 infants referred with suspected cyanotic congenital heart disease, the values for Pao_2 in oxygen supported our clinical diagnosis of primary lung disease, thereby obviating the need for cardiac catheterization.

Under the conditions of the present study, we have found that a Pao_2 of 150 mmHg while breathing oxygen in concentrations of over 80% provides a convenient 'watershed' separating cyanotic from acyanotic congenital heart disease (Fig. 2). In practice, few infants with cyanotic lesions achieved Pao_2 values of more than 100 mmHg, and most infants with acyanotic lesions achieved values far greater than 150 mmHg. The latter would be expected on theoretical grounds, for by use of the shunt equation relating alveolar to arterial oxygen tension (Strang and Macleish, 1961), it can be calculated that Pao_2 of 150 mmHg in 80% oxygen corresponds to a right to left shunt of approximately 25% of the cardiac output. However, intrapulmonary shunts of this size may occur in normal newborn infants (Nelson *et al.*, 1963), and in those with acyanotic congenital heart disease and increased pulmonary flow (Lees, Way, and Ross, 1967). In addition, the crying often induced by arterial puncture may produce intracardiac right to left shunting (Prec and Cassels, 1952). These factors may explain why several infants with acyanotic lesions failed to achieve Pao_2 values of more than 150–200 mmHg.

In cyanotic congenital heart disease arterial desaturation may be due to several different mechanisms, each depending on the haemodynamic situation present. Thus, in the present study, infants have been grouped according to the haemodynamic rather than anatomical defect present. In air, those with TGA, the commonest cyanotic lesion in the series, had a mean PaO_2 value significantly lower than in any other form of cyanotic congenital heart disease. Since arterial desaturation in TGA is due to inadequate mixing of pulmonary and systemic circulations, those infants with additional ventricular septal defect would be expected to have higher values than those with intact ventricular septum. In our series this difference was significant only during air breathing. Similarly no difference could be shown for infants with TGA with or without PDA.

Whereas other workers have stated that in cyanotic congenital heart disease PaO_2 is unlikely to rise above 100 mmHg while breathing pure oxygen (Liebman and Whitman, 1973; Lees, 1973), we have found that this occurred in 8 of the 109 infants studied. The maximum values during oxygen breathing were seen in infants with CMS and HLHS (Fig. 4), and may be explained by the high effective pulmonary blood flow (the proportion of the systemic venous return that is theoretically fully oxygenated by passage through the lungs) in these conditions, this being maximal when pulmonary vascular resistance falls in response to

oxygen administration. It is notable that the only 2 of 109 infants with cyanotic congenital heart disease who achieved PaO_2 values of more than 150 mmHg during oxygen breathing belonged to the CMS group. One infant had a primitive ventricle, the other a persistent truncus arteriosus. In addition to a high effective pulmonary blood flow, preferential 'streaming' of saturated and unsaturated blood in the common mixing chamber resulting in higher oxygen saturations in the aorta than the pulmonary artery, has been shown in both these conditions (Tandon, Hauck, and Nadas, 1963; Rahimtoola, Ongley, and Swan, 1966), and may explain the high values in these 2 infants.

In contrast to the haemodynamic situation in CMS, total and effective pulmonary blood flow in POTO is reduced (the chest x-ray showing oligoemia rather than plethora). In addition, obstruction to ventricular outflow is relatively fixed, and pulmonary flow does not increase in response to oxygen administration. Thus PaO_2 values rose only minimally (Fig. 4), and may indeed fall in some cases, perhaps due to constriction of a PDA which is contributing to pulmonary flow.

HLHS usually results in severe heart failure and low cardiac output in early infancy (Noonan and Nadas, 1958), and has been considered separately because of this characteristic presentation. Differentiation from heart failure due to acyanotic congenital heart disease, and from other causes of shock such as sepsis or haemorrhage, is aided by measurement of the PaO_2 in high oxygen concentrations. Though the highest mean PaO_2 values were seen in this group (Fig. 4), in none did this exceed 150 mmHg. HLHS might also be considered as an example of common mixing, since this usually occurs at atrial level, and the PaO_2 values in oxygen did not differ significantly between these two groups.

In infants with cyanotic congenital heart disease statistically significant differences between mean PaO_2 values in different haemodynamic subgroups has been shown. The degree of overlap between these groups (Fig. 4) means that in the individual case clear differentiation cannot be made. However, when considered together with the clinical, chest x-ray, and electrocardiographic findings, useful information is obtained.

In infants with acyanotic congenital heart disease cyanosis may occur when heart failure or chest infection are present, and is due principally to alveolar hypoventilation as indicated by a raised Paco_2 (Talner *et al.*, 1965), though intrapulmonary right to left shunting may also occur in infants with

FIG. 4.—Comparison of PaO_2 between groups of infants with cyanotic congenital heart disease. Mean and SD are shown for patients with TGA, POTO, CMS, and HLHS. Values are shown while infants breathe room air and high inspired oxygen concentrations. In the last column are values for the rise in PaO_2 in each group. Numbers above individual values indicate the number of patients in each group. Significance of differences between groups is given in Table IV.

increased pulmonary flow (Lees *et al.*, 1967). Differentiation from cyanotic congenital heart disease, particularly CMS, may be difficult since cyanosis in CMS is often minimal during air breathing and is abolished by oxygen administration. Furthermore, the chest x-ray may show cardiomegaly and pulmonary plethora in both groups. Measurement of Pao_2 in oxygen, however, allows differentiation in the majority of cases. In the present series all infants with acyanotic lesions, but only 2 of 31 with CMS, achieved values of more than 150 mmHg.

Primary lung disease may cause cyanosis due to alveolar hypoventilation, impaired gas diffusion, inequalities of ventilation, and perfusion (the most extreme example of which is the perfusion of totally unventilated alveoli), or extrapulmonary right to left shunting. In respiratory distress syndrome right to left shunts of up to 80% of the cardiac output may occur (Strang and Macleish, 1961) and cyanotic congenital heart disease may be mimicked, though the clinical and radiological findings usually allow differentiation between the two. The use of a positive end expiratory pressure in addition to oxygen breathing has been reported to be helpful in distinguishing infants with primary lung disease from those with cyanotic congenital heart disease, the Pao_2 rising in the former but falling in the latter group (Shannon *et al.*, 1972). Tooley and Stanger (1972) have pointed out the limitations of this test, infants with HLHS often raising their PaO_2 after addition of a positive end expiratory pressure, and infants with persistent pulmonary vascular obstruction showing no response. In the respiratory distress syndrome early measurement of Pao_2 in 100% oxygen has been suggested as a guide to prognosis (Boston, Geller, and Smith, 1966), and a Pao_2 of more than 150 mmHg may later help to exclude cyanotic congenital heart disease if this is subsequently suspected on clinical grounds.

When cyanosis in lung disease is due to extrapulmonary right to left shunting, this may occur via a PDA or patent foramen ovale. In these instances it is secondary to the raised pulmonary vascular resistance accompanying hypoxia, hypoventilation, or acidosis. This 'persistence of the fetal circulation' may occur in atypical respiratory distress syndrome (Robertson *et al.*, 1967) and also be secondary to hyperviscosity, hypoglycaemia, or persistent pulmonary vascular obstruction of unknown cause (Burnell *et al.*, 1972; Gersony, 1973; Brown and Pickering, 1974). In these circumstances the administration of high inspired oxygen concentrations ensures that the oxygen saturation of the pulmonary venous return is above 95%. If

right to left shunting is solely via a PDA, right radial (but not femoral or umbilical) artery samples will also be fully saturated.* Conversely, if shunting is through a patent foramen ovale, radial artery samples will be desaturated, and differentiation of primary lung disease from cyanotic congenital heart disease will not be possible on Pao_2 measurement. In this group the clinical, radiological, and electrocardiographic findings may also not permit differentiation. Thus, in our experience there will be a group of infants in whom cardiac catheterization offers the only means of excluding cyanotic congenital heart disease. In a specialized unit this must be recognized and accepted since the risks of cardiac catheterization in such a unit are low, a recent report from this hospital indicating a mortality of 1.7% in the first week of life (Miller, 1974).

A fall in Pao_2 after oxygen administration was seen in 16 infants with cyanotic congenital heart disease; all but one had POTO or TGA where a PDA might have contributed significantly to pulmonary flow and may have been constricted by the administration of oxygen. An alternative explanation is that of alveolar collapse secondary to 'wash-out' of alveolar nitrogen. Though these are theoretical hazards to the diagnostic administration of high oxygen concentrations, we have not found any infant whose condition has deteriorated as a result of the test.

In conclusion, we state that measurement of the Pao_2 during administration of oxygen that had already been given for the previous 10 minutes, provides essential information in the initial assessment of infants with suspected congenital heart disease. Accurate anatomical diagnosis, however, depends on the results of cardiac catheterization and angiography.

We are indebted to Dr. G. A. H. Miller who performed cardiac catheterization in many of our patients, and to Dr. R. A. H. Anderson and Elizabeth Thompson for considerable assistance in the preparation of this manuscript.

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