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Usefulness of continuous positive airway pressure in differential diagnosis of cardiac from pulmonary cyanosis in newborn infants

P. SYAMASUNDAR RAO, BRENDA L. MARINO, AND ALEX F. ROBERTSON III

From the Department of Pediatrics, Sections of Pediatric Cardiology and Neonatology, Medical College of Georgia, Augusta, Georgia, USA

SUMMARY Differential diagnosis of cyanosis in the neonate is difficult and cardiac catheterisation may be required for a correct diagnosis. It has been suggested that the response of Pa_{O_2} to continuous positive airway pressure (CPAP) with 100% oxygen may be useful. The purpose of this study was to test further this hypothesis by studying all neonates investigated for cyanosis with a $Pa_{O_2} \leqslant 50$ torr in 0·8 to 1·0 F_IO_2. Arterial blood samples were obtained in an F_IO_2 of 0·21–0·4 and 0·8–1·0, and in an F_IO_2 of 0·8–1·0 with 8–10 cm CPAP, and were analysed for Pa_{O_2}, Pa_{CO_2}, and pH, bicarbonate being calculated. The final diagnoses were congenital heart disease (CHD) 21 cases, pulmonary parenchymal disease (PD) 10 cases, and persistent fetal circulation (PFC) 3 cases.

No significant difference in pH, bicarbonate, or Pa_{CO_2} was observed among the three groups or with CPAP. In the CHD and PFC infants CPAP produced no significant change in Pa_{O_2}. In the PD babies Pa_{O_2} increased by an average of 33 torr ($P<0·05$). Despite thus attaining statistical significance 2 PD infants had no increase in Pa_{O_2} with CPAP. An increase of $Pa_{O_2} > 10$ torr with CPAP suggests PD, and a nonsignificant increase in Pa_{O_2} does not rule out PD. Irrespective of initial Pa_{O_2}, final Pa_{O_2} in 0·8–1·0 F_IO_2 with CPAP >50 torr suggests PD, and <50 torr suggests CHD. The results indicate that CPAP may be used as an adjunct in differentiating cardiac from pulmonary disease.

In a distressed cyanotic newborn infant it is sometimes difficult to differentiate severe pulmonary disease from a congenital cyanotic heart defect. These infants frequently undergo cardiac catheterisation and selective cineangiography to have this distinction made. Cardiac catheterisation in the sick neonate carries considerable risk (Rudolph, 1968; Stranger *et al.*, 1974; Rigby and Rao, 1975). Clinical findings, electrocardiogram (ECG), chest *x*-ray, blood gas and pH values (particularly Pa_{CO_2}), and Pa_{O_2} response to 100% oxygen breathing are sometimes helpful (Lees, 1970; Rao and Strong, 1974; Jones *et al.*, 1976) but are not always reliable. In this prospective study we investigated the role of CPAP in differentiating cardiac from pulmonary causes of cyanosis in newborn infants.

Abbreviations	
CHD:	Cyanotic congenital heart disease
F_IO_2:	Fraction of inspired oxygen
Pa_{CO_2}:	Arterial carbon dioxide pressure
Pa_{O_2}:	Arterial oxygen pressure
CPAP:	Continuous positive airway pressure
PFC:	Persistent fetal circulation
PD:	Pulmonary parenchymal disease

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Materials and methods

Thirty-five newborn infants admitted to this intensive care nursery with a $Pa_{O_2} \leqslant 50$ torr while in an F_IO_2 of 0·8 to 1·0 were studied. A detailed perinatal history, physical examination by a neonatologist and/or a paediatric cardiologist, chest *x*-ray and an ECG were performed in all infants. These data and the information on their clinical course, findings of cardiac catheterisation and angiography, results of other studies, observations at surgery, and necropsy findings in the infants who died were used in the final diagnosis. All infants requiring immediate

surgical intervention or respirator ventilation upon arrival in intensive care were excluded.

Arterial blood was obtained either from a previously introduced umbilical artery catheter (the tip of the catheter being positioned at the level of D8–10 in the descending aorta) or by right radial artery puncture while the infant was in room air, or at the F_{IO_2} that the baby was in at the time of arrival to intensive care. The infant was then placed in a hood and 80–100% warmed and humidified oxygen was administered for 10–15 minutes and another arterial blood sample drawn. The infant was then fitted with a specially designed face mask and an adapter with three ports. One port was connected to a manometer, the second to the inspiratory gas source, and the third to a wide-bore tubing which served as the expiratory drain. The wide-bore tubing was connected to a Baby Bird outflow valve. 100% oxygen was administered at a flow rate equal to about four times the infant's estimated minute volume to prevent CO_2 accumulation and the outflow valve adjusted to administer 8–10 cm water pressure.

An orogastric tube was passed and left open to atmospheric pressure to minimise the risk of gastric distension. In 5 infants oesophageal pressure was measured; when the CPAP was 8–10 cm of water the oesophageal pressure was about 1 cm less than the applied CPAP. After the infant was maintained on 10–15 minutes of CPAP another arterial blood sample was obtained. The arterial blood was analysed immediately after it was drawn for Pao_2, $Paco_2$, and pH using an Instrumentation Laboratory 213 pHbloodgas Analyser. Bicarbonate concentration was calculated from the Henderson-Hasselbalch equation. F_{IO_2} was analysed with an IMI 3300 Oxygen Analyser. No complications were encountered during the study. Statistical analysis was performed by Student's *t* test.

Results

Based on the final diagnoses, the infants were divided into three groups: CHD 21 infants, PD 11, and PFC 3. The CHD included transposition of the great arteries with intact ventricular septum 7, transposition of the great arteries with ventricular septal defect and pulmonary stenosis 4, tetralogy of Fallot 3, single ventricle with pulmonary stenosis or atresia 2, pulmonary atresia with intact ventricular septum 2, tricuspid atresia 1, Taussig-Bing anomaly 1, and total anomalous pulmonary venous connection to portal vein 1. Diagnoses were made by cardiac catheterisation alone in 4 infants, by catheterisation and surgery in 15, and by catheterisation, surgery, and necropsy findings in 2. Before the catheterisation and angiographic studies the cause of cyanosis, whether cardiac or pulmonary, was unclear in 11 of these 21 infants. However, the data in all 21 infants were analysed to ensure objectivity in the selection for inclusion in the study. Thus, all CHD infants with $Pao_2 \leqslant 50$ torr while in an F_{IO_2} of 0·8–1·0 were included. The data for the whole group are not significantly different from those of the 11 infants with unclear clinical diagnosis.

The PD cases were categorised as severe hyaline membrane disease 9, pulmonary haemorrhage 1, and severe bilateral pneumonia 1. Diagnoses were made on the basis of physical findings, laboratory data, and clinical course in 9 of the PD babies, and by necropsy findings in the remaining 2.

All the infants with PFC had cardiac catheterisation and selective cineangiography. There was no evidence of structural cardiac defects. The pulmonary arterial pressures were at systemic level with right-to-left interatrial and/or ductal shunting. In 1 infant the necropsy findings suggested PFC. The remaining 2 infants made an uneventful recovery.

The birthweight, estimated gestational age, and the age at CPAP study are given in Table 1. Birthweight and gestational age were lower ($P<0·01$) in the PD group than in the CHD group and this difference is consistent with the associated prematurity in the PD group.

Arterial blood samples in room air were obtained in 14 CHD babies and 1 PD infant. The F_{IO_2} was between 0·3 and 0·4 in 5 CHD, 8 PD, and 2 PFC infants. The remaining 5 infants were not placed in an $F_{IO_2} < 0·4$. However, arterial blood gas analysis was performed in all patients in an F_{IO_2} of 0·8–1·0 and after CPAP. Arterial blood samples were obtained via the umbilical artery catheter in 30 infants and by right radial artery puncture in 5. In each infant the same sampling site was used for the three determinations. pH, $Paco_2$ and plasma bicarbonate values in each of the three groups were similar ($P>0·1$) in an F_{IO_2} of 0·21 to 0·4 and 0·8 to 1·0, and did not significantly change ($P>0·1$) after CPAP for 10–15 minutes (Table 2). There were also no significant group differences.

Table 1 *Clinical details of the infants in the 3 groups studied*

Group (n)	*Birthweight (kg) (mean ±SD)*	*Gestational age (w) (mean ±SD)*	*Median age at CPAP (h) (range)*
Cyanotic heart disease (21)	3·1 ± 0·6	39·5 ± 1·3	30 (4–436)
Pulmonary disease (11)	2·4 ± 0·6	36·0 ± 1·6	18 (4–36)
Persistent fetal circulation (3)	3·3 ± 0·5	37·0 ± 1·0	12 (4–24)

Table 2 *pH, $PaCO_2$, and bicarbonate values in the 3 groups*

Groups (n)	*pH units (mean ±SD)*			*P value of △ pH in*	*$Paco_2$ torr (mean ±SD)*			*P value of △ $Paco_2$*	*Bicarbonate (mEq/l) (mean ±SD)*			*P value of △ bicarbonate in*
	F_IO_2 *0·21–0·4*	F_IO_2 *0·8–1·0*	*CPAP*	F_IO_2 *0·8–1·0 & CPAP*	F_IO_2 *0·21–0·4*	F_IO_2 *0·8–1·0*	*CPAP*	*in F_IO_2 0·8–1·0 & CPAP*	F_IO_2 *0·21–0·4*	F_IO_2 *0·8–1·0*	*CPAP*	F_IO_2 *0·8–1·0 & CPAP*
Cyanotic heart disease (21)	7·36 ±0·09	7·34 ±0·14	7·3 ±0·13	>0·1	33·6 ±7·9	34·4 ±8·2	37·0 ±9·2	>0·1	18·3 ±3·3	17·9 ±4·0	17·6 ±3·5	>0·1
Pulmonary disease (11)	7·30 ±0·04	7·29 ±0·10	7·27 ±0·09	>0·1	38·4 ±4·7	40·8 ±13·0	41·6 ±14·3	>0·1	18·5 ±3·3	18·9 ±5·3	18·3 ±4·4	>0·1
Persistent fetal circulation (3)	7·27 ±0·04	7·28 ±0·11	7·24 ±0·12	Not calc	44·0 ±2·8	40·8 ±16·6	47·8 ±21·7	Not cacl	16·6 ±3·3	20·0 ±5·1	17·2 ±4·7	Not calc

In the CHD group there was an average increase of 6 torr (SD ±6) in Pao_2 from an F_IO_2 of 0·21–0·4 to an F_IO_2 of 0·8–1·0 (Fig.), which is consistent with previous observations (Lees, 1970; Jones *et al.*, 1976). With the use of CPAP in the CHD group there was an average 3 torr fall in Pao_2 which is non-significant ($P>0·1$). In the PD group Pao_2 increased with an F_IO_2 of 0·8 to 1·0 by an average of 6 torr (SD ± 10). With CPAP the Pao_2 increased (35 ± 39 torr)* in the PD group and this change was statistically significant ($P<0·05$). The Pao_2 response to CPAP in CHD *vs* PD groups was also statistically significant ($P<0·001$). Despite attaining statistical significance, individual CHD and PD infants showed a markedly varied response to CPAP (Table 3). In the CHD group CPAP produced a decrease in Pao_2 in 12, no change in 1, and an increase of <10 torr in 8. In the PD group Pao_2 decreased in 1, increased by <10 torr in 1, increased by 10–25 torr in 5, and increased by 43, 47, 52, and 140 in the remaining 4. The final Pao_2 on 0·8 to 1·0 F_IO_2 with CPAP was <50 torr in the CHD group and >50 torr in the PD group. This might have been a distinguishing feature between these two groups except that one infant in each group (Case 10 of the CHD group and Case 9 of the PD group) did not follow this general pattern.

In the PFC group the Pao_2 in room air and in 1·0 F_IO_2 were similar and did not significantly change after CPAP. This response was similar to that in the CHD group (Fig.).

Discussion

An accurate clinical diagnosis of the cause of cyanosis in the neonate, particularly the differentiation of CHD from PD, is sometimes difficult and cardiac catheterisation with angiography may be necessary for diagnosis. Cardiac catheterisation of CHD babies provides an accurate anatomical diagnosis on which therapy can be based. However, catheterisation of infants with PD increases the morbidity and mortality considerably and should be avoided. Although the usual clinical and laboratory data, arterial blood gas values, and Pao_2 response to 100% O_2 inhalation are helpful in the differential diagnosis, they are not completely reliable.

Shannon *et al.* (1972) used positive end-expiratory pressure (PEEP)† of 8–10 cm water to differentiate CHD from PD. In their study Pao_2 fell by an average of 33 torr with CPAP in the CHD group and Pao_2 rose by 141 torr on average in the PD group. From these observations they suggested that

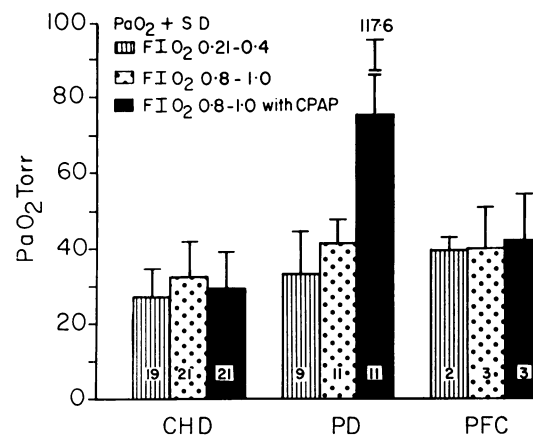

Fig. *The Pao_2 is expressed as mean + standard deviation in an F_IO_2 of 0·21–0·4 and 0·8–1·0, and of 0·8–1·0 with CPAP in babies with CHD, PD, and PFC. The number of infants in each group is noted. Note significant increase in Pao_2 in PD group after CPAP.*

*A large standard deviation in this group is due to a very high Pao_2 (189 torr) with CPAP in Case 10 of the PD group (Table 3).

†The CPAP referred to in this study is similar to Shannon's PEEP and the term CPAP is generally used for this form of respiratory manoeuvre without ventilator. Hereafter we will only use the term CPAP.

Table 3 *PaO_2 in 1·0 F_IO_2 and CPAP in each infant in the study*

Case no.	*PaO_2*	
	F_IO_2 *0·8–1·0*	F_IO_2 *0·8–1·0 & CPAP*
	Cyanotic heart disease	
1	31	21
2	41	33
3	22	24
4	38	24
5	41	44
6	20	21
7	23	23
8	40	38
9	31	29
10	46	56
11	31	30
12	49	38
13	49	28
14	26	18
15	31	38
16	28	18
17	25	17
18	33	40
19	37	27
20	20	21
21	26	28
	Pulmonary disease	
22	47	56
23	32	57
24	37	89
25	49	92
26	48	52
27	33	51
28	38	58
29	37	60
30	40	34
31	49	189
32	45	92
	Persistent fetal circulation	
33	26	29
34	44	43
35	49	54

CPAP be used to help differentiate cardiac cyanosis from pulmonary cyanosis, and that CPAP helped to avoid cardiac catheterisation in PD babies. We tested further the usefulness of CPAP in the differentiation of CHD from PD. Our data showed that CPAP produced no significant change in Pao_2 in the CHD group, but in the PD group Pao_2 increased significantly, and the results may be interpreted as being very similar to those of Shannon.

On close examination, however, several differences become apparent. First, in the CHD group, although Pao_2 fell on an average of 3 torr with CPAP, this decrease was not as marked (33 torr) as in Shannon's study. Second, in the PD group Pao_2 increased with CPAP (average of 35 torr) but not as dramatically as in Shannon's infants (average of 141 torr). Finally, although the change in the Pao_2 in the CHD *vs* PD group was statistically significant, 2 babies in the PD group did not follow the general trend. These differences can perhaps be explained on the basis of the severity of the pulmonary disease and the type of cardiac disease in the infants studied.

The Pao_2 in an F_IO_2 of 0·9–1·0 in lung and heart disease in Shannon's study was 66 ± 10 (SD) and 77 ± 26 torr respectively, and in ours 41 ± 6 and $32 \cdot 8 \pm 9$ torr. This major difference in the 'control' Pao_2 appears to be related to the method of selection of infants for inclusion in the study. Whereas Shannon's babies were unselected with regard to the degree of hypoxia, we required a Pao_2 in 0·8–1·0 F_IO_2 of $\leqslant 50$ torr. Thus, our PD babies had more severe lung disease than Shannon's. With regard to cardiac disease, 4 of the 7 infants in Shannon's study had either hypoplastic left heart syndrome or ventricular septal defect with patent ductus arteriosus; both these lesions cause increased pulmonary blood flow with consequent high Pao_2. Our infants had either decreased pulmonary blood flow secondary to right ventricular outflow obstruction (tetralogy physiology) or transposition of the great arteries with poor mixing; both these groups tend to have low Pao_2.

The improvement in Pao_2 in the PD group may be explained on the basis that CPAP stabilises and keeps the small airways open (Gregory *et al.*, 1971; Shannon *et al.*, 1972). The lack of, or minimal increase in, Pao_2 with CPAP in 2 PD infants suggests that the intrapulmonary right-to-left shunting in these babies was not affected by CPAP. The fall in Pao_2 in Shannon's CHD group was thought to be secondary to increased pulmonary vascular resistance and the consequent increase in right-to-left shunting (Shannon *et al.*, 1972). This explanation appears untenable because a change in pulmonary vascular resistance in the presence of severe obstruction to right ventricular outflow tract (as seen in both our study and Shannon's) should not affect pulmonary blood flow unless the pulmonary vascular obstruction is more severe in magnitude than the right ventricular outflow tract obstruction.

Furthermore, a recent study (Egan and Hessler, 1976) suggested that the pulmonary vascular resistance may either decrease or increase with CPAP and this is dependent on its effect on alveolar gas tensions and degree of lung inflation. Current data (Sugarman *et al.*, 1972; Kirby *et al.*, 1975) suggest that CPAP reduces the pulmonary venous return. This reduction in fully oxygenated pulmonary venous blood increases right-to-left shunting and a consequent fall in Pao_2 in infants with right ventricular outflow tract obstructive lesions. In the transposition group the decreased pulmonary venous return may result in decreased interatrial left-to-right shunting with a consequent reduction in Pao_2. Similarly, CPAP may also reduce systemic venous return with a consequent reduction in cardiac output. Impaired ventricular function and increased right and left ventricular afterload have

also been postulated (Cassidy *et al.*, 1977; Robotham *et al.*, 1977) and these will also reduce the cardiac output. Reduction of cardiac output can also increase hypoxia.

In the PFC group the results are similar to those seen in intracardiac right-to-left shunting in CHD, and PFC cannot be distinguished from CHD on the basis of the Pao_2 response to CPAP in an F_IO_2 of 0·8–1·0. Levin *et al.* (1976) suggested that simultaneous determination of temporal (or right radial) artery and descending aortic Po_2 may help differentiate PFC from CHD. No difference in Pao_2 was seen in CHD infants but a higher temporal artery Po_2 was observed in PFC babies because of right-to-left shunting at ductal level in the latter group. All 3 PFC infants had simultaneous radial artery and descending aorta Po_2 measured in 0·8–1·0 F_IO_2; in 2 there was no difference in Po_2 and in one the radial artery Po_2 was 88 torr higher than that of the descending aorta. This difference can be seen only when the major right-to-left shunting in PFC is at ductal level and will be helpful in the diagnosis. Should the main right-to-left shunting be at the atrial level, as it was in 2 of our cases, the Po_2 will be similar and PFC cannot be distinguished from CHD.

The following inferences may be drawn with regard to the usefulness of CPAP in the differentiation of CHD from PD. (1) CPAP with 1·0 F_IO_2 may be used as an adjunct in the differential diagnosis of cyanotic newborn infants. (2) In CHD babies CPAP does not produce an increase >10 torr but such an insignificant change in Pao_2 does not rule out PD. (3) In most PD babies Pao_2 increases by >10 torr with CPAP and is highly suggestive of PD. A Pao_2 response >10 torr with CPAP practically excludes CHD. (4) Irrespective of the Pao_2 in room air and in 1·0 F_IO_2, the Pao_2 with the additional CPAP may be of value; Pao_2 >50 torr strongly suggests PD and Pao_2 <50 torr indicates CHD. However, there are occasional exceptions. (5) Pao_2 response to CPAP in the PFC group mimics the intracardiac right-to-left shunting seen in CHD and cannot be distinguished from that observed in CHD. The use of CPAP may not be without risk in infants with normal pulmonary compliance in that pneumothorax may be produced (Gregory *et al.*, 1971), though none of our babies had this complication. 9 of the CHD babies had a fall in Pao_2 of 8 torr or more. The further decrease in an infant with an already low Pao_2 may be a potential hazard. However, none of our infants deteriorated after CPAP nor developed metabolic acidosis.

In conclusion, our results suggest that CPAP is useful in the differential diagnosis of CHD from PD but with occasional exceptions. It is useful when used in conjunction with other clinical and laboratory data including the recently developed noninvasive techniques such as echocardiography and nuclear angiography (Meyer and Kaplan, 1973).

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Correspondence to Dr P. S. Rao, Department of Pediatrics, Section of Pediatric Cardiology, Medical College of Georgia, Augusta, Georgia 30902, USA.