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Selective criteria for differential diagnosis of infants with symptoms of congenital heart disease

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SUMMARY 147 case records of infants referred to the Brompton Hospital in the first year of life with a provisional diagnosis of congenital heart disease were examined. Statistical analyses were performed to evaluate selective criteria for the allocation of these infants into a group with lung disease, or into 1 of 5 major haemodynamic groups—namely, acyanotic, complete transposition of the great arteries, pulmonary outflow tract obstruction, common mixing situations, or hypoplastic left heart syndrome. Arterial Po_2 in high oxygen concentration, cardiothoracic ratio, and pulmonary vascular markings on the admission chest *x*-ray; respiratory rate; P-wave morphology, the electrical sign of the T-wave in lead V_{4R}, and the presence or absence of Q-waves in leads V_{4R} and V_6 on the electrocardiogram were significant. A decision tree for the differential diagnosis of infants with suspected congenital heart disease into 5 haemodynamic groups and a group with lung disease is presented, and its predictive value is assessed.

In the first year of life, congenital heart disease may be suspected in the presence of cyanosis, tachypnoea, tachycardia, hepatomegaly, and failure to thrive.[1] However, each of these signs may appear in seriously ill patients with disease affecting organs other than the heart.[2–3] More subtle cardiac signs—such as palpation of the pulses and precordium, auscultation of the heart sounds and of the site, intensity and timing of cardiac murmurs—require special skills and are subjective.[1 4] We present a decision tree for the differential diagnosis of infants with suspected congenital heart disease into those with lung disease and those with 1 of 5 major haemodynamic groups based on readily measurable objective criteria, chosen by statistical analysis.

Methods

147 case records of infants referred to the Brompton Hospital in the first year of life with a provisional diagnosis of congenital heart disease were examined. Data concerning the following clinical information were abstracted:

(1) Arterial blood Po_2 in air, and in high oxygen concentration ($F_{IO_2} > 0{\cdot}08$).[5]

(2) Mean frontal QRS axis, determined from the electrocardiogram (ECG).[1]

(3) P-wave morphology: P-waves $>2{\cdot}5$ mV in amplitude or $>0{\cdot}08$ second in duration were considered abnormal. Tall but not prolonged P-waves in leads II and III together with pointed P-waves in leads V1 and V2 with tall initial positivity were considered to indicate right-atrial hypertrophy. Flat-topped P-waves in leads I and II of normal height but prolonged duration with two peaks $>0{\cdot}02$ second apart were considered to indicate left-atrial hypertrophy.

(4) Electrical sign of the T-wave in lead V_{4R}; positive, negative, isoelectric (TV_{4R}).[1]

(5) Voltage of the R-wave in lead V_{4R} (RV_{4R}).

(6) Presence or absence of Q-waves in leads V_{4R} (QV_{4R}) and V_6 (QV_6).

(7) Respiratory rate was counted for 2 minutes.

(8) Cardiothoracic ratio was determined by summing the greatest diameters of the cardiac silhouette and the internal thorax on either side of the midline and dividing the thoracic by the cardiac diameter.[1]

(9) Pulmonary vascular markings on the initial chest *x*-ray were classified as clearly increased, clearly decreased, and indeterminate or normal. The first chest *x*-ray film taken on admission of each patient to the Brompton Hospital was interpreted blindly by a single observer (D W).

Anatomical diagnosis was obtained from cardiac catheterisation and angiography, supplemented by necropsy if performed. Information obtained from these sources was available in 92% of infants with heart disease. Of the remaining 8%, all but one was

thought to have acyanotic congenital heart disease not requiring cardiac catheterisation. The remaining patient died before investigation and necropsy was not performed.

Infants were allocated to a lung disease group or to 1 of 5 haemodynamic groups, according to the main physiological disturbance produced, which in some (but not all instances) corresponded to a specific anatomical defect. It should be stressed that none of these infants was asymptomatic and that each had been referred from another hospital to a designated centre for infants with congenital heart disease. Thus they were a group selected because of symptoms and did not represent a sample of all infants with congenital heart disease. Specifically, asymptomatic infants with heart murmurs were excluded.

The transposition of great arteries group included all patients with concordant atrio-ventricular but discordant ventriculo-arterial connections, some also had a ventricular septal defect or pulmonary stenosis. The common mixing situations group included those anomalies which resulted in admixture of the pulmonary and systemic venous return, the admixed blood being distributed to the pulmonary and systemic circulations. All patients with hypoplastic left heart syndrome had aortic atresia. The heterogeneous group with pulmonary outflow tract obstruction included patients with pulmonary atresia with or without ventricular septal defect as well as those with tricuspid atresia with restricted pulmonary flow and tetralogy of Fallot.

All those with acyanotic heart disease were thought to be in heart failure. Similarly, those with lung disease were tachypnoeic and were thought at the referring hospital possibly to be in heart failure.

Table 1 *Six groups into which 147 infants were placed according to the primary anatomical diagnosis of each at cardiac catheterisation or necropsy*

Acyanotic congenital heart disease (acyanotic)		n=32
Ventricular septal defect	(n=22)	
Patent ductus arteriosus	(n=5)	
Isolated coarctation of the aorta	(n=3)	
Atrio-ventricular canal	(n=2)	
Hypoplastic left heart syndrome		n=8
Transposition of the great arteries		n=27
Pulmonary outflow tract obstruction		n=37
Tetraology of Fallot	(n=14)	
Pulmonary atresia	(n=16)	
Tricuspid atresia	(n=7)	
Common mixing lesions		n=15
Total anomalous pulmonary venous drainage	(n=7)	
Common atrium	(n=2)	
Double outlet right ventricle	(n=2)	
Single ventricle	(n=4)	
Lung disease		n=28
Respiratory distress syndrome	(n=11)	
Other pulmonary problems	(n=17)	

Statistical analysis and results

Infants were divided into 6 groups based on the anatomical diagnosis made at cardiac catheterisation or necropsy (Table 1).

Analysis of variance. This was carried out to determine whether variation of given continuous variables was greater within or between the 6 groups. The results of the analysis are illustrated by ranking the means of the haemodynamic groups for a given continuous variable and indicating the significant differences.

Po_2 (*in air*) F=9·32 (P<0·001)

	Mean	
Acyanotic	58·3	mmHg
Lung disease	50·6	
Hypoplastic left heart syndrome	45·9	
Common mixing situations	36·9	
Pulmonary outflow tract obstruction	34·8	
Transposition of great arteries	33·2	

The extremes of this ranking are significantly different, a difference of about 10 mmHg being significant at the 5% level. Common mixing situations, pulmonary outflow tract obstruction, transposition of great arteries have a lower group mean Po_2 in air than aycanotic, lung disease, or hypoplastic left heart syndrome.

Po_2 (*in high* O_2) F= 34·62 (P<0·001)

	Mean	
Acyanotic	246·5	mmHg
Lung disease	151·4	
Hypoplastic left heart syndrome	125·6	
Common mixing situations	73·8	
Pulmonary outflow tract obstruction	49·4	
Transposition of great arteries	41·6	

Significant differences below the 5% level were found between the groupings shown.

Respiratory rate F=5·26 (P<0·01)

	Mean	
Common mixing situations	70·3	respirations/min
Hypoplastic left heart syndrome	68·8	
Transposition of great arteries	65·6	
Acyanotic	63·4	
Lung disease	59·9	
Pulmonary outflow tract obstruction	49·2	

Pulmonary outflow tract obstruction group mean for respiratory rate was significantly lower than the other groups at the 0·1% level.

Cardiothoracic ratio $F=3\cdot15$ ($P<0\cdot001$)

	Mean	
Hypoplastic left heart syndrome	0·68	}
Acyanotic	0·64	}
Common mixing situation	0·63	}
Transposition of great arteries	0·61	}
Pulmonary outflow tract obstruction	0·60	}
Lung disease	0·56	}

The group means for hypoplastic left heart syndrome and lung disease were significantly different from each other, and from acyanotic, common mixing situations, transposition of great arteries, and pulmonary outflow tract obstruction, taken together.

The analysis of variance was not significant for QRS axis or RV_{4R}.

Correlation coefficient. An investigation of the relative importance of the continuous variables considered by analysis of variance for differentiating between the 6 groups was made by calculating the correlation coefficients for every possible pair of continuous variables, both overall and within the 6 groups (Table 2).

Overall, a close correlation between Po_2 (in air) and Po_2 (in high O_2) was the most pronounced feature. These two criteria taken together were statistically the most accurate for differentiating between the groups. Significant correlations (Table 2) were found between Po_2 (in air) and Po_2 (in high O_2) in transposition of great arteries, common mixing situations, lung disease, and pulmonary outflow tract obstruction. Positive but insignificant r values were found for the hypoplastic

Table 2 *Correlation coefficients for every possible pairing of 6 continuous variables both overall and within the 6 groups of infants. Only those r values that achieve significance are shown*

		Po_2 (in high O_2)	QRS-axis	RV_{4R}	Respiratory rate	Cardiothoracic ratio
Transposition of great arteries	Po_2 (in air)	0·528**	0·479**	0·350*	—	—
	Po_2 (in high O_2)	—	0·662***	—	—	—
	QRS-axis		—	—	—	0·466*
	RV_{4R}			—	0·374*	—
	Respiratory rate				—	—
	Cardiothoracic ratio					—
Hypoplastic left heart syndrome	Po_2 (in air)	—	—	0·54*	—	—
	Po_2 (in high O_2)	—	—	0·59*	0·78**	—
	QRS-axis		—	—	—	—
	RV_{4R}			—	0·61*	—
	Respiratory rate				—	—
	Cardiothoracic ratio					—
Common mixing situations	Po_2 (in air)	0·69**	—	—	—	0·55*
	Po_2 (in high O_2)	—	0·52*	—	—	0·54*
	QRS-axis		—	—	—	—
	RV_{4R}			—	—	0·47*
	Respiratory rate				—	—
	Cardiothoracic ratio					—
Lung disease	Po_2 (in air)	0·473***	—	—	—	—
	Po_2 (in high O_2)	—	—	0·556**	0·567**	—
	QRS-axis			0·519**	—	—
	RV_{4R}			—	—	—
	Respiratory rate				—	0·470**
	Cardiothoracic ratio					—
Acyanotic	Po_2 (in air)	—	—	—	—	—
	Po_2 (in high O_2)	—	—	—	—	—
	QRS-axis		—	—	0·474**	—
	RV_{4R}			—	0·464**	—
	Respiratory rate				—	0·407*
	Cardiothoracic ratio					—
Pulmonary outflow tract obstruction	Po_2 (in air)	0·834***	—	—	—	—
	Po_2 (in high O_2)	—	—	—	—	—
	QRS-axis		—	—	—	—
	RV_{4R}			—	—	—
	Respiratory rate				—	—
	Cardiothoracic ratio					—

*** $P<0\cdot001$, ** $P<0\cdot01$, * $P<0\cdot05$.

left heart syndrome and acyanotic groups. Overall statistical significance was not achieved with any other pairings of continuous variables.

The χ^2 test. This was applied to the discontinuous variables (Tables 3–7).

P-wave morphology

Normal P-wave morphology predominated in all groups. Right-atrial hypertrophy was occasionally seen in pulmonary outflow tract obstruction, acyanotic, common mixing situations, and transposition of great arteries. Left-atrial hypertrophy was seen once in acyanotic and once in transposition of great arteries.

Table 3 *P-wave morphology*

	Normal	*Right atrial hypertrophy*	*Left atrial hypertrophy*
Pulmonary outflow tract obstruction	26	4	0
Acyanotic	22	3	1
Lung disease	25	0	0
Hypoplastic left heart syndrome	10	0	0
Common mixing situations	8	6	0
Transposition of great arteries	22	3	1

$\chi^2_{10} = 20{\cdot}23$, $P < 0{\cdot}05$.

Table 4 *Electrical sign of T-wave in lead V_{4R}*

	Positive	*Negative*	*Isoelectric*
Pulmonary outflow tract obstruction	19	6	3
Acyanotic	4	19	4
Lung disease	6	12	3
Hypoplastic left heart syndrome	4	5	2
Common mixing situations	5	8	0
Transposition of great arteries	9	16	3

$\chi^2_{10} = 21{\cdot}57$, $P < 0{\cdot}05$.

Table 5 *Presence or absence of Q-wave in lead V_6*

	Present	*Absent*
Pulmonary outflow tract obstruction	4	23
Acyanotic	5	23
Lung disease	2	20
Hypoplastic left heart syndrome	4	6
Common mixing situations	6	6
Transposition of great arteries	2	23

$\chi^2_5 = 14{\cdot}32$, $P < 0{\cdot}02$.

Table 6 *Presence or absence of Q-wave in lead V_6*

	Present	*Absent*
Pulmonary outflow tract obstruction	14	12
Acyanotic	20	7
Lung disease	11	11
Hypoplastic left heart syndrome	1	9
Common mixing situations	0	11
Transposition of great arteries	7	17

$\chi^2_5 = 26{\cdot}71$, $P < 0{\cdot}001$.

Table 7 *Pulmonary vascular markings on initial chest x-ray*

	Increased	*Decreased*	*Indeterminate or normal*
Pulmonary outflow tract obstruction	5	20	6
Acyanotic	27	1	2
Lung disease	0	0	18
Hypoplastic left heart syndrome	3	2	3
Common mixing situations	8	1	5
Transposition of great arteries	14	4	7

$\chi^2_{10} = 179{\cdot}32$, $P < 0{\cdot}001$.

TV_{4R}

Positive T-waves predominated in pulmonary outflow tract obstruction. Negative T-waves predominated in the acyanotic, lung disease, and transposition of great arteries groups.

QV_{4R}

Q-waves were predominantly absent from lead V_{4R} in the acyanotic, lung disease, pulmonary outflow tract obstruction, and transposition of great arteries groups. Q-waves were present in and absent from lead V_{4R} in equal numbers in the common mixing situations and hypoplastic left heart syndrome groups.

QV_6

Q-waves were present in lead V_6 in the majority of infants in the acyanotic group. Q-waves were present in and absent from lead V_6 in equal numbers in the pulmonary outflow tract obstruction and lung disease groups. The transposition of great arteries, and hypoplastic left heart syndrome groups were predominantly without Q-waves in lead V_6. The common mixing group had no Q-waves in lead V_6.

Pulmonary vascular markings

In the pulmonary outflow tract obstruction group, pulmonary vascular markings were predominantly decreased, while in the acyanotic group, pulmonary

vascular markings were predominantly increased. In the lung disease group, normal pulmonary vascular markings were seen in all the cases. The hypoplastic left heart group had equal numbers of cases with increased, decreased, and normal pulmonary vascular markings.

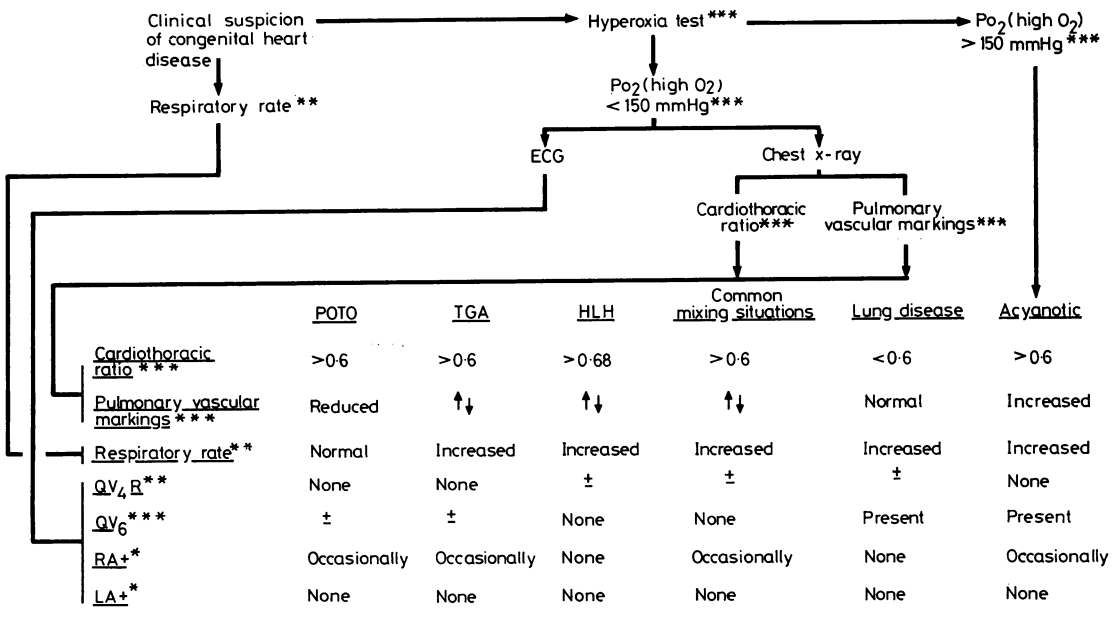
Discussion

There have been many attempts to classify congenital heart defects on the basis of clinical presentation.[3 6–10] We chose several objective and readily measured criteria and tested their statistical power in differentiating between 6 groups of patients: 5 with congenital heart disease and 1 with lung disease (Table 1).

Levin *et al.*[11] noted that 65% of 66 infants with D-transposition of great arteries were tachypnoeic on presentation and that other signs of a major congenital cardiac anomaly were usually absent in these infants. In the present study, tachypnoea was seen in all groups except the pulmonary outflow tract obstruction group.

We noted that Po_2 (in air) alone did not differentiate reliably between acyanotic and other lesions, whereas the addition of Po_2 (in high O_2) (the hyperoxia test) improved the reliability of differentiating between acyanotic and other lesions to the 1% level of significance. We agree with Jones *et al.*[5] that in infants who achieve a Po_2 (in high O_2), >150 mmHg, cyanotic congenital heart disease may be effectively ruled out. However, episodes of enhanced cyanosis may be seen in infants with a ductus-dependent circulation during

Table 8 *A decision tree for the differential diagnosis of infants with symptoms of congenital heart disease into a group with lung disease and 5 other major haemodynamic groups based on statistical analysis of selective criteria. The decision tree is constructed in the form of a flow diagram. In order to allocate a particular infant prospectively to 1 of the 6 groups, the data obtained from individual selective criteria should be combined sequentially following the steps outlined in the flow diagram. (Levels of significance at each step are indicated).*



	POTO	TGA	HLH	Common mixing situations	Lung disease	Acyanotic
Cardiothoracic ratio ***	>0·6	>0·6	>0·68	>0·6	<0·6	>0·6
Pulmonary vascular markings ***	Reduced	↑↓	↑↓	↑↓	Normal	Increased
Respiratory rate**	Normal	Increased	Increased	Increased	Increased	Increased
QV_4R**	None	None	±	±	±	None
QV_6***	±	±	None	None	Present	Present
RA+*	Occasionally	Occasionally	None	Occasionally	None	Occasionally
LA+*	None	None	None	None	None	None

Acyanotic	Acyanotic congenital heart disease	POTO	Pulmonary outflow tract obstruction
ECG	Electrocardiogram	QV_4R	Q-wave in lead V_4R on ECG
HLH	Hypoplastic left heart syndrome	QV_6	Q-wave in lead V_6 on ECG
LA+	Left atrial hypertrophy diagnosed by ECG	RA+	Right atrial hypertrophy diagnosed by ECG
TGA	Transposition of great arteries		

P<0·001 *** P<0·01 ** P<0·05 *

Example 1. A 7-day-old boy weighing 3·2 kg, born at 38 weeks by elective caesarean section, had tachypnoea (60 respirations/min) and a murmur which gave rise to a suspicion of congenital heart disease. P_{O_2} (in high O_2) was 113 mmHg. Cardiothoracic was 0·55. Pulmonary vascular markings were normal. Tachypnoea was present. Q-wave was absent in lead V_{4R} and present in lead V_6. There was no left or right atrial hypertrophy on ECG. The infant was classified in the *lung disease* group. This infant recovered over the next 3 days and was thought to have *transient tachypnoea of the newborn.*

Example 2. An 8-week-old girl was cyanosed and had failed to gain weight. P_{O_2} (in high O_2) was 67 mmHg. Cardiothoracic ratio was 0·65 and pulmonary vascular markings were reduced. Respiratory rate was 40/min. Q-waves were absent from lead V_{4R} and present in lead V_6. Right atrial hypertrophy was present in ECG. This infant was classified in the *pulmonary outflow tract obstruction* group. At cardiac catheterisation she proved to have *situs solitus*, concordant pulmonary atresia with ventricular septal defect.

Example 3. A 10-day-old girl who weighed 3·8 kg after a vaginal delivery at term became listless and refused to feed. P_{O_2} (in high O_2) was 100 mmHg. Cardiothoracic ratio was 0·69. Pulmonary vascular markings were increased. Respiratory rate was 100 respirations/min. Q-waves were present in lead V_{4R} and absent from lead V_6. There was no left or right atrial hypertrophy on ECG. The infant was classified in the *hypoplastic left heart syndrome* group. On echocardiography, aortic atresia with hypoplasia of the left ventricle and mitral valve was visualised. Aortic atresia was confirmed on aortography.

When the decision tree was used to classify the infants in the study, all 8 infants were classified correctly to the *hypoplastic left heart* group, 20 of 28 infants were classified correctly to the *lung disease* group, 28 of 32 infants were classified correctly to the *acyanotic* group, 23 of 27 infants were classified correctly to the *transposition of great arteries* group, 29 of 37 infants were classified correctly to the *pulmonary outflow tract obstruction* group, and 12 of 15 infants were correctly classified to the *common mixing* group.

the administration of high O_2.[1 4] The hyperoxia test must be used with caution when the presence of a ductus-dependent circulation is suspected.

On the initial chest *x*-ray film, taken on admission to the Brompton Hospital, a cardiothoracic ratio $>0·6$ was associated with heart disease, whereas a cardiothoracic ratio $<0·6$ was most likely to be seen with lung disease ($P<0·01$). A particularly large cardiothoracic ratio was seen in the hypoplastic left heart syndrome group ($P<0·05$). The assessment of pulmonary vascular markings was subjective. However, with the division of pulmonary vascular markings into clearly increased, clearly decreased, and indeterminate or normal groups, a close correlation was observed between pulmonary vascular markings and expected pulmonary blood flow, those with high flows having increased respiratory rates. Infants with a low respiratory rate and reduced pulmonary vascular markings were most likely to be found in the pulmonary outflow tract obstruction group ($P<0·05$).

We did not find the ECG to be as helpful as the hyperoxia test or the chest *x*-ray film in differentiating between infants in the 6 groups. The analysis of variance was not significant for QRS axis, and the χ^2 test was not significant for RV_{4R}.

Shinebourne *et al.*[12] however, pointed out the significance of a superior QRS-axis in the differential diagnosis of infants with congenital heart disease. It is probable that with a larger series of patients in which the study groups could be broken down into individual anomalies, some of the ECG criteria might prove significant. For example, distinguishing patients with pulmonary atresia and an intact ventricular septum from those with an additional ventricular septal defect might result in significant differences in RV_{4R}; similarly a QRS-axis between 270 and 360° (superior axis) might distinguish patients with atrioventricular canal from the rest of the acyanotic group, or those with tricuspid atresia from the remainder of those with pulmonary outflow tract obstruction. Looking at individual anomalies in the present study, cases of hypoplastic left heart syndrome, Fallot's tetralogy, total anomalous pulmonary venous drainage, and ventricular septal defect were seen with a superior-QRS axis.

P-wave morphology, electrical sign of the T-wave in lead V_{4R}, and the presence or absence of Q-waves in leads V_{4R} and V_6 could also be helpful in differentiating between the study groups ($P<0·05$, 0·05, 0·02, and 0·001 respectively).

Despite relatively small numbers of infants with individual anomalies, and the retrospective nature of our data, we were able to show significant correlations between certain selective criteria for the differential diagnosis of infants with symptoms of congenital heart disease into 5 major haemodynamic groups and a group with lung disease. Clearly, the diagnosis of each anomaly must rest on more definitive methods of investigation. Nevertheless, the decision tree presented in Table 8 has potentially useful applications in clinical practice. When the table was used to classify the babies in the present study, 81% were classified correctly.

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