

Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39 821 newborns

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ABSTRACT

Objective To evaluate the use of pulse oximetry to screen for early detection of life threatening congenital heart disease.

Design Prospective screening study with a new generation pulse oximeter before discharge from well baby nurseries in West Götaland. Cohort study comparing the detection rate of duct dependent circulation in West Götaland with that in other regions not using pulse oximetry screening. Deaths at home with undetected duct dependent circulation were included.

Setting All 5 maternity units in West Götaland and the supraregional referral centre for neonatal cardiac surgery.

Participants 39 821 screened babies born between 1 July 2004 and 31 March 2007. Total duct dependent circulation cohorts: West Götaland n=60, other referring regions n=100.

Main outcome measures Sensitivity, specificity, positive and negative predictive values, and likelihood ratio for pulse oximetry screening and for neonatal physical examination alone.

Results In West Götaland 29 babies in well baby nurseries had duct dependent circulation undetected before neonatal discharge examination. In 13 cases, pulse oximetry showed oxygen saturations $\leq 90\%$, and (in accordance with protocol) clinical staff were immediately told of the results. Of the remaining 16 cases, physical examination alone detected 10 (63%). Combining physical examination with pulse oximetry screening had a sensitivity of 24/29 (82.8% (95% CI 64.2% to 95.2%)) and detected 100% of the babies with duct dependent lung circulation. Five cases were missed (all with aortic arch obstruction). False positive rate with pulse oximetry was substantially lower than that with physical examination alone (69/39 821 (0.17%) v 729/38 413 (1.90%), $P<0.0001$), and 31/69 of the "false positive" cases with pulse oximetry had other pathology. Thus, referral of all cases with positive oximetry results for echocardiography

resulted in only 2.3 echocardiograms with normal cardiac findings for every true positive case of duct dependent circulation. In the cohort study, the risk of leaving hospital with undiagnosed duct dependent circulation was 28/100 (28%) in other referring regions versus 5/60 (8%) in West Götaland ($P=0.0025$, relative risk 3.36 (95% CI 1.37 to 8.24)). In the other referring regions 11/25 (44%) of babies with transposition of the great arteries left hospital undiagnosed versus 0/18 in West Götaland ($P=0.0010$), and severe acidosis at diagnosis was more common (33/100 (33%) v 7/60 (12%), $P=0.0025$, relative risk 2.8 (1.3 to 6.0)). Excluding premature babies and Norwood surgery, babies discharged without diagnosis had higher mortality than those diagnosed in hospital (4/27 (18%) v 1/110 (0.9%), $P=0.0054$). No baby died from undiagnosed duct dependent circulation in West Götaland versus five babies from the other referring regions.

Conclusion Introducing pulse oximetry screening before discharge improved total detection rate of duct dependent circulation to 92%. Such screening seems cost neutral in the short term, but the probable prevention of neurological morbidity and reduced need for preoperative neonatal intensive care suggest that such screening will be cost effective long term.

INTRODUCTION

Cardiovascular malformations are the commonest type of congenital malformation, but a sizeable proportion are not detected by routine neonatal examination.¹⁻⁴ Cardiovascular malformations account for 6-10% of all infant deaths and 20-40% of deaths caused by congenital malformation.^{1,5} About 1-1.8 babies per 1000 live births have a duct dependent circulation, with a persistent ductus arteriosus being necessary for survival.^{4,6,7} These babies are at particular risk from the worldwide trend towards early discharge from maternity units, as the effects of ductal closure

may not be apparent at an early discharge examination. Some 10-30% of babies who die from congenital heart disease do not have their condition diagnosed before autopsy.¹⁸ In Sweden over the past decade increasing proportions of babies with critical congenital heart disease have been leaving hospital with their condition undiagnosed.³

Screening infants with non-invasive measurement of oxygen saturation has been proposed as an aid for early detection of duct dependent circulation, but the studies to date have been too small to enable proper estimates of sensitivity,^{6,7,9-13} and only two studies have included ascertainment of missed cases dying in the community.^{6,7} An attempt to estimate the sensitivity based on a meta-analysis was unsatisfactory because of the merging of studies with different probe sites, different cut-off values for saturation, and different oximeters measuring either functional or fractional saturation.¹⁴ We evaluated strategies to maximise sensitivity while minimising false positives in a screening test for duct dependent circulation with a new generation oximeter which measured functional oxygen saturation preductally (in right hand) and postductally (in either foot). We arrived at optimal screening cut-off values of <95% saturation or >3% difference between right hand and foot.¹⁵ We also found that the type of oximeter used had a significant effect on both the detection rate and false positive rate.¹⁵

Using these cut-off values and a new generation oximeter, we have now conducted a large, prospective, multicentre study of routine screening with pulse oximetry in the well baby units in the West Götaland region of Sweden. A cost effectiveness analysis estimated that pulse oximetry screening would have a higher false positive rate (1.3%) than clinical examination (0.5%) and that, although pulse oximetry screening might be cost effective, further research was required before it could be recommended.¹⁶ Our new study therefore incorporates further strategies to reduce false positive results from pulse oximetry screening. The aims of our study were:

- To identify the diagnostic accuracy of screening for duct dependent circulation with a new generation oximeter and to compare its detection rate with that of neonatal physical examination alone
- To estimate the excess number of neonatal echocardiographic investigations generated by the screening programme and by physical examination
- To compare the overall rate of detection of duct dependent circulation in West Götaland with that in other regions not using pulse oximetry screening
- To compare the incidence of sudden deaths due to undiagnosed duct dependent congenital heart disease in the population in West Götaland with that in other referring regions during the study period.

METHODS

Study population

Between 1 July and 5 September 2004, 200 babies born at Östra Hospital were included in a pilot study for optimising screening performance with pulse oximetry conducted by research fellows. Prospective screening of all babies in well baby nurseries in West Götaland started with a rolling start—at Östra Hospital on 6 September 2004, Mölndal Hospital on 20 September, Borås Hospital on 27 September, Skövde Hospital on 25 October, and Trollhättan Hospital on 8 November. The hospitals are situated between 4 m and 149 m above sea level. The study ended on 31 March 2007. Children were excluded from the oximetry screening if they were already admitted to neonatal special care units.

Cohort population

We included all babies born with duct dependent circulation between 1 July 2004 and 31 March 2007 in West Götaland (total live births=46 963) and between 1 January 2004 and 31 December 2007 in the other referring regions (total live births=108 604). (We used full 12 month periods for 2004 and 2007 in the other referring regions cohort in order to obtain correct birth numbers through official statistics.) We excluded those babies with a prenatal diagnosis of duct dependent circulation (two in West Götaland, nine in the other referring regions).

Screening study

All five maternity units in West Götaland took part (see above). Prospective screening of oxygen saturation was conducted preductally (palm of right hand) and postductally (either foot) with identical pulse oximeters (Radical SET, version 4 (average time set on 8 seconds) with multisite LNOP YI sensors, Masimo, Irvine, CA, USA) on all newborn infants before routine neonatal physical examination. The oximeters were locked with a key code to ensure unchanged settings throughout the study period.

All staff carrying out the screening (midwives, nurses, and nursery nurses) were trained in using the oximeters for one week by the same person (AWG) in each maternity unit immediately before the study started. The infants' age at screening, sex, and delivery mode (caesarean section or vaginal) and the technical quality of the measurement (optimal or not optimal) were recorded on a reporting form.

In order for the screening of all babies to be logistically feasible and to take no more than five minutes of nursing time, it had to be incorporated in ordinary nursing routines and was usually carried out before the daily weighing that preceded the discharge examination. This meant that pulse oximetry screening could be carried out as much as 16 hours before the discharge examination took place, and it was therefore decided before the study started that it would not be ethical to withhold optimal recordings of oxygen saturation $\leq 90\%$ from the treating physician. The protocol thus specified that if a saturation $\leq 90\%$ was

recorded the paediatrician on call would be immediately informed and the baby should be referred for an echocardiogram the same day.

Study protocol

When both preductal and postductal oxygen saturation was $\leq 95\%$ or the difference between the two measurements was $>3\%$ (≥ 2 standard deviations of inter-observer measurement variability¹⁵) the baby was provisionally considered to be screening positive, but a repeat measurement was performed. Babies with three repeated positive measurements were supposed to have an echocardiogram performed the same day according to the study protocol, but with some babies scheduled for early discharge only two pulse oximetry screenings were managed before the discharge examination was performed. Babies were considered screening positive until a measurement not fulfilling screening positive criteria was obtained. For saturations $\leq 90\%$, see above.

Neonatal physical examination—After the routine physical examination, the examining paediatrician completed a form to state (a) no suspicion of congenital heart defect, (b) weak suspicion of congenital heart disease, or (c) strong evidence of congenital heart defect and to state whether referral for echocardiography was indicated based on the physical findings. This form was filled in before the paediatrician was shown the results of the pulse oximetry screening.

Cohort study

We compared the overall rate of detection of duct dependent circulation in West Götaland with that in other regions not using pulse oximetry screening but which also refer children to the same supra-regional centre for congenital cardiac surgery (Queen Silvia Children's Hospital, Gothenburg). We retrieved data from the surgical and catheter procedure records, logbooks of children turned down for surgery, and deaths in the community (see below). All referring hospitals were asked to give details of infants who had died before being referred or declined referral during the study period. We examined the medical records of all babies with duct dependent circulation in the two cohort populations and recorded preoperative acidosis and 30 day mortality.

We retrieved data from Rattsbase, the national database of the National Board of Forensic Medicine, for information of all deaths due to undiagnosed cardiovascular malformations in children under 1 year of age in Sweden born between 1 January 2004 and 31 December 2007. We compared the number of deaths from undiagnosed duct dependent circulation (which all occurred within 30 days of birth) in West Götaland with that in the other referring regions.

Statistical analysis

The analysis was carried out with commercial software (GraphPad Prism version 4 and Statgraphics Plus v5.2). We calculated sensitivity, specificity, positive

predictive value, and negative predictive values for pulse oximetry screening and for blind neonatal physical examination alone. Categorical data were analysed with two tailed Fisher's exact test for small groups and χ^2 test for large populations. We used relative risk for comparison (except when there were no cases of adverse outcome in one group, when we used odds ratios) and calculated their 95% confidence intervals as appropriate. Confidence limits for population mortality were calculated as the confidence intervals of proportions as described by Motulsky.¹⁷

RESULTS

Screening study

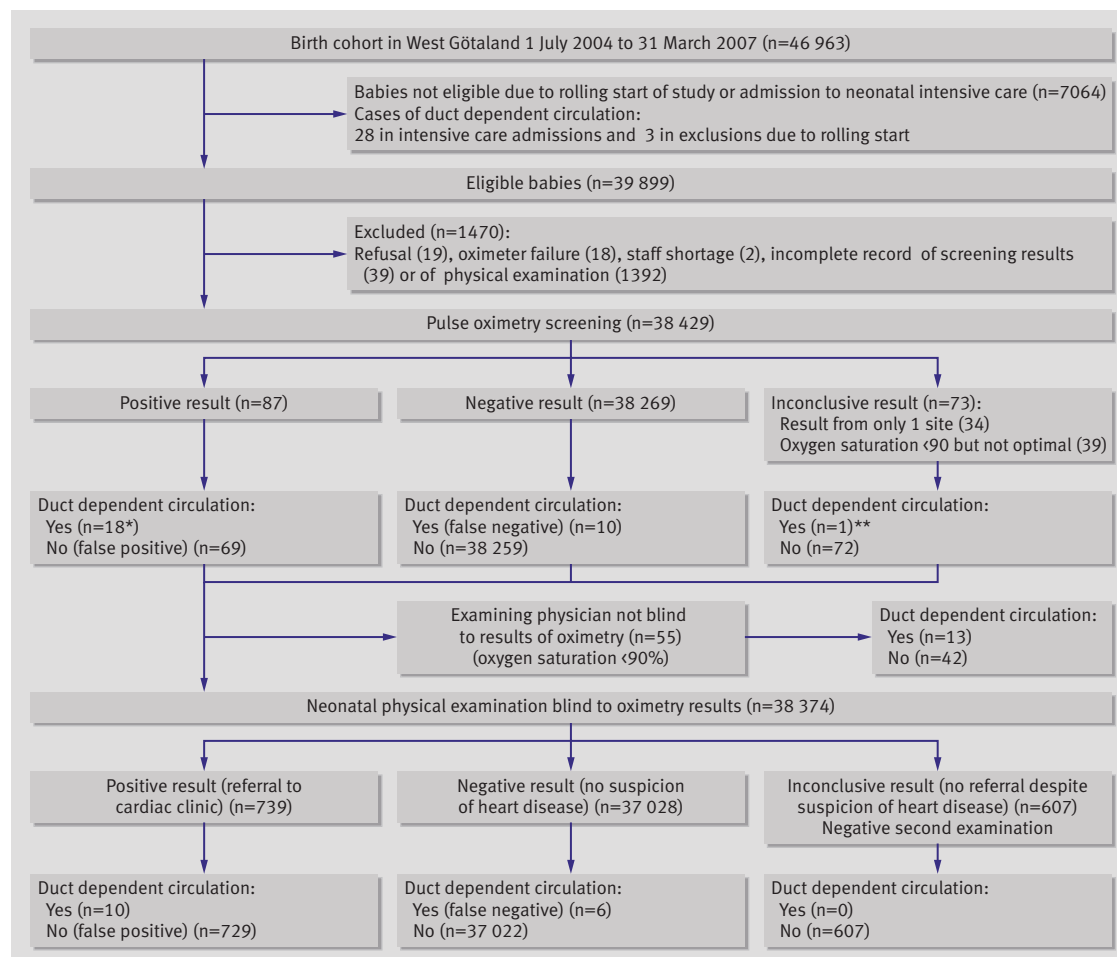
Because of the rolling start of our screening study in different well baby nurseries and prior admissions to neonatal intensive care units (about 10% of newborns), 7064 newborns were not eligible for the study (see fig). Of the 39 899 newborns eligible for the screening study (Östra n=13 455, Mölndal n=8953, Trollhättan n=7019, Borås n= 5382, and Skövde n=5090), 39 821 (99.8%) had completed the pulse oximetry protocols and 38 429 (96.3%) had complete data from both pulse oximetry and physical examination (see fig).

Pulse oximetry screening

Table 1 shows details of the 29 babies in the screening study who were found to have duct dependent circulation, including the results from pulse oximetry screening and the physical examination. Of the 28 infants with complete screening data, 18 (64%) had positive pulse oximetry results. In the final infant, repeated inability to obtain a pulse oximetry reading in the feet led to an incompletely filled in screening form, but the child was referred for echocardiography and diagnosed with coarctation of the aorta, and is counted as screening positive. Thus, pulse oximetry in isolation gave abnormal screening results in 19/29 (66%) of apparently well babies with duct dependent circulation.

The sensitivity of the pulse oximetry for detecting pulmonary duct dependent circulation and transposition of the great arteries was 9/9, but the sensitivity for essentially acyanotic left heart obstruction was, unsurprisingly, lower (10/20). However, one child with positive pulse oximetry result and interrupted aortic arch was discharged home without echocardiography in violation of the study protocol, and thus the real life sensitivity of the pulse oximetry was 18/29 (62%). Table 2 shows the sensitivity, specificity, positive and negative predictive values, and likelihood ratio for pulse oximetry. A positive pulse oximetry screening gives a relative risk of 719.8 (95% confidence interval 350.3 to 1479; $P<0.0001$) of having duct dependent heart disease.

In accordance with the study protocol, the examining neonatologist was immediately informed of the pulse oximetry results for the 12 babies with oxygen saturation $\leq 90\%$, and for one with saturation of 91%. Thus, these 13 were excluded from the evaluation of neonatal physical examination alone.



Flow of infants through study and detection of neonatal heart disease by pulse oximetry screening and by physical examination alone. *1/18 with positive pulse oximetry screening was discharged home without echocardiogram (protocol violation).

**Pathological pulse oximetry screening as no signal could be obtained in feet.

In terms of which screening criteria were positive, both preductal and postductal oxygen saturations were $<95\%$ in 13 babies, while in five babies a difference of $>3\%$ between preductal and postductal saturations was the only positive criterion. However, many babies with complex cyanotic heart disease were positive on both criteria, so in total 14 babies had a saturation difference $>3\%$, of whom eight (57%) had duct dependent systemic circulation (table 1). Babies without critical congenital heart defect or lung pathology had a median oxygen saturation of 99% (interquartile range 98% to 100%) both preductally and postductally. The median age at screening was 38 hours (interquartile range 5.5 to 95.5, range 1 to 406), and 90% of the babies were screened at ≤ 72 hours of age. The earliest permitted discharge in West Götaland is 6 hours after birth, and 1317 babies (3.3%) were screened that early.

Neonatal physical examination alone

Physical examination alone detected 10/16 cases of duct dependent circulation (that is, a sensitivity of 63%) (table 2), but, as the examining neonatologist was informed of the pulse oximetry results for the 13 babies

with oxygen desaturation $\leq 90\%$, this sensitivity estimate cannot be directly compared with that for pulse oximetry. A valid comparison of sensitivity of physical examination versus pulse oximetry plus physical examination can instead be made from the cohort data (see below).

The positive predictive value of neonatal examination was significantly lower than that of pulse oximetry (1.35% v 20.69%) and likelihood ratio was lower (32.4 v 344.8). This difference would have remained significant even in the extremely unlikely event of all 13 exempted babies being detected as true positives on physical examination alone, which would have given a positive predictive value of 3.06% (95% confidence interval 1.95% to 4.55%). Thus, pulse oximetry has at least seven times the positive predictive value of physical examination.

The clinical findings from physical examination that provoked referral for echocardiography in the 10 detected babies with duct dependent circulation were systolic murmurs (n=5), poor or absent femoral pulses with a murmur (n=4), and poor femoral pulses alone (n=1). Thus poor or absent femoral pulses was the

Table 1 Details of the 29 babies in the screening study in West Götaland (1 July 2004 to 31 March 2007) who were found to have duct dependent circulation, including the results from pulse oximetry screening and physical examination

Final diagnosis	Pulse oximetry screening		Physical examination		
	Preductal/postductal oxygen saturation (%)	Test result	Murmur present (day of life)	Femoral pulses	Referral for echocardiography
Referred for urgent echocardiography according to protocol*					
TGA	47/22	+ve	No	Normal	N/A
TGA	59/59	+ve	No	Normal	N/A
TGA, PA, DILV	65/72	+ve	Yes	Normal	N/A
PA, VSD	75/84	+ve	Yes	Normal	N/A
PA, VSD	78/83	+ve	Yes	Normal	N/A
Critical AS, CoA	86/46	+ve	Yes	Very weak	N/A
TGA, DILV	85/89	+ve	Yes	Normal	N/A
Critical AS	93/80	+ve	Yes	Weak	N/A
CoA, VSD	99/86	+ve	No	Weak	N/A
TGA, CoA, VSD	87/93	+ve	Faint	Normal	N/A
Critical PS	70/60	+ve	Faint	Weak	N/A
HLHS	90/91	+ve	Yes	Weak	N/A
TGA, DILV, CoA	91/93; 94/91	+ve	Faint	Very weak	N/A
Blind neonatal examination					
Critical SAS	98/89; 98/94	+ve	Yes (day 2)	Normal	Yes
HLHS	90/93; 92/92; 91/94	+ve	Faint (day 2)	Normal	Yes
CoA	97/postductal value (foot) unrecordable	Pathological result	No (day 1)	Weak	Yes, arrhythmia
IAA, TGA, DILV	97/92; 97/93; 95/90	+ve	Yes (day 4)	Weak	Yes
HLHS	96/82; 95/81	+ve	Yes (day 2)	Difficult (crying)	Yes
IAA, TA	95/96	-ve	Yes (day 1)	Increased	Yes
Aortic atresia, AVSD, CoA	96/96; 90/92	-ve	No (day 1) Yes (day 2)	Normal	No Yes (no urine)
CoA, ASD	100/99; 99/100	-ve	Yes (day 1)	Impalpable	No
			Yes (day 2)	Impalpable	Yes
CoA	98/99	-ve	Yes (days 1-4)	Normal	Yes
			Faint (day 5)	Impalpable	
CoA	99/100	-ve	Yes (day 3)	Palpable	Yes
			No (day 4)	Impalpable	
CoA, VSD, ASD	97/98	-ve	Yes (day 1)	Impalpable	Yes
Discharged home without diagnosis and echocardiography					
IAA, AP window	98/92; 99/95	+ve	No (day 1)	Normal	No (protocol violation)
			Circulatory collapse day 8		
CoA	99/93; 95/95	-ve	No (day 2)	Normal	No
			Circulatory collapse day 7		
CoA, VSD	98/100	-ve	No (day 2)	Normal	No
			Circulatory collapse day 4		
IAA, ASD	97/99	-ve	No (day 1)	Normal	No
			Circulatory collapse day 4		
CoA	99/97	-ve	No (day 1)	Normal	No
			Circulatory collapse day 4		

TGA=transposition of the great arteries, PA=pulmonary atresia, DILV=double inlet left ventricle, VSD=ventricular septal defect, AS=aortic stenosis, CoA=coarctation of the aorta, PS=pulmonary stenosis, HLHS=hypoplastic left heart syndrome, SAS=subvalvar aortic stenosis, IAA=interrupted aortic arch, TA=truncus arteriosus, AVSD=atrioventricular septal defect, ASD=atrial septal defect, AP=aorto-pulmonary.

*Physical examination performed with knowledge of oxygen saturation results.

alerting sign in half of these children, and contributed to the detection of two babies with duct dependent systemic circulation who would otherwise have been missed with oximetry screening (see table 1). Even among the 13 babies whose oximetry results were revealed to the examining physician, poor femoral pulses was an important indicator of duct dependent systemic circulation in six infants (table 1).

Combining pulse oximetry and physical examination

As different cases were missed by clinical examination and by pulse oximetry, the combination of neonatal physical examination and oximetry screening had a higher sensitivity than either of the methods individually (82.76% (95% confidence interval 64.23% to 95.15%)), although the higher number of false positives from physical examination lowered the positive

Table 2 | The performance of screening methods in the detection of duct dependent circulation in newborn infants in West Götaland (1 July 2004 to 31 March 2007)

Performance	Physical examination alone (n=38374)	Pulse oximetry (n=38429)	Physical examination plus pulse oximetry (n=38429)
Sensitivity (95% CI) (%)	62.50 (35.43 to 84.80)*	62.07 (42.3 to 79.31)	82.76 (64.23 to 94.15)
Specificity (95% CI) (%)	98.07 (97.93 to 98.21)	99.82 (99.77 to 99.86)	97.88 (97.73 to 98.03)
Positive predictive value (95% CI) (%)	1.35 (0.65 to 2.47)	20.69 (12.75 to 30.71)	2.92 (1.88 to 4.31)
Negative predictive value (95% CI) (%)	99.98 (99.96 to 99.99)	99.97 (99.95 to 99.99)	99.99 (99.97 to 100.00)
Likelihood ratio	32.37	344.8	39.08
False-positive rate (%)	1.90	0.17†	2.09
No of true positives	10*	18‡	24‡
No of false negatives	6*	11§	5§
No of false positives	729	69	798
No of true negatives	37 022	38 259	36 881
Relative risk (95% CI) (%)	83.6 (30.5 to 229.5)	719.8 (350.3 to 1479)	215.4 (82.4 to 563.0)

*Blind physical examination alone cannot be compared directly with the other two methods as the number of babies with duct dependent circulation was 16 in this group.

†False positive rate calculated on total numbers of patients completing pulse oximetry (n=39 821).

‡Patient who was diagnosed after repeated failures of obtaining a pulse oximetry signal in the feet is counted as true positive.

§Patient who fulfilled screening criteria but was discharged due to protocol violation is counted as false negative.

predictive value to 2.92 (1.98 to 4.31) (see table 2). Of the infants detected by oximetry, at least four had no physical signs that would have led to a referral for echocardiography (table 1). Five babies with duct dependent circulation were discharged without diagnosis during the study; all had duct dependent systemic circulation due to aortic arch obstruction, but, as one was discharged with a positive oximetry result in violation of study protocol, the potential detection rate in apparently well babies was 86% (25/29) (table 1).

False positive results with pulse oximetry

The “false” positive rate for oximetry screening was 69/39 801 (0.17%) (see fig). Table 3 shows that 45% (31/69) of the “false positive” babies detected by pulse oximetry had other significant heart malformation, lung problem, or infection. In terms of benefit derived by early detection of babies with pathology other than duct dependent heart disease, table 3 suggests that 12% required cardiac surgery, 29% required further follow-up, and that neonatal intensive care was required in ≥ 5 days for 26% and < 5 days in 13%. It seems reasonable to conclude that early detection of sepsis, lung pathology, and congenital heart disease requiring surgery is of definite benefit to the baby (all required neonatal intensive care), and that detection of asymptomatic pulmonary hypertension and transitional circulation (in 14 (20%)) has possible benefit (6/14 required neonatal intensive care, see table 3).

After subtracting babies with other significant congenital heart disease, persistent pulmonary hypertension, and transitional circulation from the false positives, we are left with only 41 babies with positive oximetry results who had normal cardiac findings on echocardiography. Thus there were 2.3 echocardiograms with normal findings per baby with duct

dependent heart disease detected by pulse oximetry screening (41/18). Of the 24 normal babies who had false positive results, 22 were positive on having $< 90\%$ saturation. The two false positive babies whose only positive screening criterion was a $> 3\%$ difference in oxygen saturation had other pathology.

False positive results with neonatal physical examination

Physical examination alone generated 739 referrals for echocardiography (fig) with a false positive rate (729/38 374 (1.91%)) more than 10 times higher than that for pulse oximetry ($P < 0.0001$). In the screened West Götaland population there were, in addition to the babies with duct dependent circulation, 30 babies with other heart malformations that required surgery or catheter intervention during the first year of life. Of these 30 babies, 24 were among the 739 referrals from physical examination (seven were referred because of Down’s syndrome). Thus physical examination failed to detect six (20%) of the babies with less critical heart disease. The relative risk for pulse oximetry screening generating a false positive was 0.093 (0.073 to 0.119) compared with screening by physical examination alone ($P < 0.0001$).

Cohort population

Between 1 July 2004 and 31 March 2007, the birth prevalence of duct dependent circulation in West Götaland was 62/46 963 (1.32/1000). Two were detected prenatally and not included in our cohort study. In all other referring regions, not using pulse oximetry screening but some with prenatal screening by echocardiography, 109/108 604 newborn infants had duct dependent circulation (birth prevalence 1.00/1000). Of these, 100 were included in our cohort comparison (9 were detected prenatally and excluded). The risk of leaving hospital with undiagnosed duct dependent circulation was 28/100 (28%) in the other referring regions versus 5/60 (8%) in West Götaland ($P = 0.0025$; relative risk 3.36 (95% confidence interval 1.37 to 8.24)) (see table 4). The difference was mainly because of the improved detection of pulmonary duct dependent circulation (where we included transposition of the great arteries) in West Götaland (odds ratio 18.83 (1.07 to 331), $P = 0.0030$). The detection of systemic duct dependent circulation also tended to be better, but not significantly so ($P = 0.12$).

Among the 12 babies with duct dependent pulmonary circulation who had been discharged home (all in the regions other than West Götaland), as many as 11 had transposition of the great arteries (see table 5). Thus a surprisingly large proportion, 11/25 (44%) of all patients with transposition of the great arteries left hospital undiagnosed in other referring regions, testifying to the inadequacy of physical examination alone in detecting even profound arterial desaturation in newborn babies.

In the 28 cases of undiagnosed duct dependent heart disease in the other referring regions, transposition of the great arteries constituted 39%, simple coarctation of the aorta 26%, and complex coarctation 18% (table 5).

Table 3 | Pathology found in 69 babies with false positive results from pulse oximetry screening for duct dependent circulation in West Götaland (1 July 2004 to 31 March 2007)

Pathology found	No (%) of babies	Subsequent management			
		Stay in neonatal intensive care		Follow-up only	Surgery
		≥5 days after screening	<5 after screening		
Other critical congenital heart disease*	4 (6)	4/4	0/4	0/4	4/4
Other milder congenital heart disease	10 (14)	4/10	1/10	5/10	4/10
Persistent pulmonary hypertension	6 (9)	3/6	0/6	3/6	N/A
Transitional circulation†	8 (12)	0/8	3/8	2/8	N/A
Infections	10 (14)	6/10	4/10	N/A	N/A
Pulmonary pathology	7 (10)	5/7	1/7	1/7	N/A
Normal (verified from hospital charts)	24 (35)	N/A	N/A	N/A	N/A

*Pulmonary atresia with multiple aorto-pulmonary collaterals (n=2), tricuspid atresia with pulmonary stenosis and ventricular septal defect (n=1), total anomalous pulmonary venous return (n=1).

†Right to left shunting across foramen ovale without pulmonary hypertension.

After exclusion of hypoplastic left heart syndrome (Norwood surgery), and premature birth (that is, comparison of babies with a normal surgical risk), the mortality of babies who left hospital with undiagnosed duct dependent circulation was 4/27 (18%) versus 1/110 (0.9%) for babies with duct dependent circulation detected in hospital ($P=0.0054$, relative risk 16.3 (1.90 to 140.0)). Severe acidosis at diagnosis was also significantly more common among those babies who left hospital undiagnosed (14/28 (50%) *v* 26/132 (20%), $P=0.0016$, relative risk 2.54 (1.53 to 4.21)), and in all the babies with duct dependent circulation from other referring regions versus those from West Götaland (33/100 (33%) *v* 7/60 (12%), $P=0.0025$, relative risk 2.8 (1.3 to 6.0)). Among the population from other referring regions 19/33 (58%) of babies with severe acidosis had systemic duct dependent circulation.

Griebsch et al introduced the concept of timely diagnosis in their cost benefit analysis,¹⁶ defined as occurring in hospital and in time to prevent severe acidosis before the diagnosis is made. Thus patients discharged with duct dependent circulation without diagnosis and patients who collapsed in hospital without diagnosis would not be considered to have had a timely diagnosis. With these criteria, we found absence of timely diagnosis of duct dependent circulation in 45/100 (45%) of patients in other referring regions compared with 11/60 (18%) of patients in West Götaland ($P=0.0006$, relative risk 2.46 (1.38 to 4.37)).

Mortality from undiagnosed duct dependent heart disease

Between 1 July 2004 and 31 March 2007 no children with undiagnosed duct dependent circulation died in West Götaland (0/60) compared with 5/100 in the

other referring regions ($P=0.16$). Two of the infants who died had duct dependent pulmonary circulation and would definitely have been detected by pulse oximetry screening, one had hypoplastic left heart syndrome and would probably have been detected, and two had coarctation of the aorta. In relation to the number of children born, there were thus 4.6 deaths due to unrecognised duct dependent circulation per 100 000 live birth in the other referring regions (95% confidence interval 0.6 to 8.6).

DISCUSSION

Principal findings

In asymptomatic babies we found that the combination of neonatal physical examination plus pulse oximetry screening for duct dependent heart disease had a detection rate of 82.8% (86.2% if protocol violations are ignored), with a low false positive rate of 0.17% for pulse oximetry. Because of the large sample size our estimate provides an authoritative assessment of this screening method. However, about half of the babies with duct dependent disease presented clinically before discharge examination, so that in total the introduction of pulse oximetry screening meant that in our region of West Götaland 92% of all babies with a duct dependent circulation were diagnosed before leaving hospital. This is a significantly higher proportion than that encountered among babies from other Swedish regions not using pulse oximetry screening (72%; $P=0.0025$).

The detection rate of blind physical examination alone was 62.5%. In the region using pulse oximetry screening there were no deaths in the community from undiagnosed critical heart disease, but there were five deaths, 5% of babies with duct dependent circulation, in the regions not using pulse oximetry screening. This

Table 4 | Failure to diagnose duct dependent circulation in neonates (1 July 2004 to 31 March 2007) in West Götaland with pulse oximetry screening and in other referring regions not using pulse oximetry. Values are numbers (percentages) of cases of duct dependent circulation unless stated otherwise

Type of duct dependent circulation	West Götaland	Other referring regions	Comparison
Systemic circulation	5/30 (17)	16/48 (33)	$P=0.12$
Lung and mixing circulation	0/30 (0)	12/52 (23)	$P=0.0030$
Total	5/60 (8)	28/100 (28)	$P=0.0025$; relative risk 3.36 (95% CI 1.37 to 8.24)

Table 5 | Details of the 28 cases of undetected duct dependent circulation in neonates (1 January 2004 to 31 December 2007) in Swedish referring regions not using pulse oximetry screening

Diagnoses	Sequelae	
	Severe acidosis	Death within 30 days
Pulmonary and mixing duct dependent circulation		
TGA	No	No
TGA	No	No
TGA	Yes	No
TGA	Yes (+ preoperative seizures)	No
TGA	Yes (ECMO, preoperative cerebral haemorrhage)	No
TGA, VSD	No	No
TGA, VSD	No	No
Complex TGA	N/A	Yes, undiagnosed
Pulmonary flow duct dependent circulation		
TGA, PA, VSD	No	No
TGA, PA	No	No
PA	N/A	Yes, undiagnosed
Systemic and mixing duct dependent circulation		
TGA, CoA, VSD	Yes, brain infarction, cerebral haemorrhage, preoperative seizures	No
Systemic flow duct dependent circulation		
HLHS	N/A	Yes, undiagnosed
Critical AS	No	No
IAA, truncus arteriosus	Yes (pH 6.80)	No
IAA, VSD	No	No
CoA, VSD	Yes (pH 6.90)	No
CoA, VSD	N/A	Yes, undiagnosed
CoA, VSD	No	No
CoA, VSD	N/A	Yes, undiagnosed
CoA, AVSD	No	No
CoA	Yes	No
CoA	Yes	No
CoA	Yes	No
CoA	No	No
CoA	No	No
CoA	Yes (pH 7.14)	No
CoA	No	No

ECMO=extracorporeal membrane oxygenation, N/A=information not available as infant died at home (severe acidosis would have preceded death), TGA=transposition of the great arteries, PA=pulmonary atresia, VSD=ventricular septal defect, AS=aortic stenosis, CoA=coarctation of the aorta, HLHS=hypoplastic left heart syndrome, IAA=interrupted aortic arch, AVSD=atrioventricular septal defect.

improved detection was achieved by an alteration of nursing routines, that was estimated to increase nursing time spent per baby by maximum five minutes, and occasioned only 2.3 extra echocardiograms without pathology per case of true positive duct dependent heart disease detected by pulse oximetry.

Furthermore, we could demonstrate that the infants who left hospital undiagnosed had a much greater proportion of severe acidosis at the time of diagnosis (50%) than those diagnosed while in hospital (20%; $P=0.0012$), and that the proportion of babies showing

severe acidosis at diagnosis was significantly lower in the population subjected to pulse oximetry screening ($P=0.0025$). As acidotic babies require neonatal intensive care, this finding alone would be likely to make pulse oximetry screening cost effective. Our observation that the survival of duct dependent heart disease (excluding hypoplastic left heart syndrome) is better in babies detected in hospital (mortality 0.9%) than in those discharged undiagnosed (mortality 14.8%; $P=0.0054$) is also consistent with earlier reports that survival of serious duct dependent heart disease such as transposition of the great arteries,¹⁸ hypoplastic left heart syndrome,¹⁹ and coarctation of the aorta is improved by antenatal diagnosis.²⁰

There is no routine fetal echocardiography in our region, leading to a low rate of antenatal detection of duct dependent heart disease (3.3%), much lower than the nearly 20% antenatal detection of all critical heart disease over the past few years in Newcastle.⁴ They report about 60 terminations for cardiac causes, which may be one contributory reason why their birth prevalence of 1.0 per 1000 is lower than that of 1.3 per 1000 found in our study.

Strengths and weaknesses of our study

The major strengths of our study are the large number of babies prospectively screened, and use of the Swedish personal identity number system together with the forensic database, so that we can be certain that no deaths in the community or elsewhere have been overlooked in the screened cohort.

A weakness of our study design was that it was impossible for ethical reasons to withhold seriously deranged pulse oximetry values from the attending medical staff, which meant that our evaluation of the success of physical examination alone to detect duct dependent heart disease excluded the most severely cyanotic types of duct dependent disease. This is the main reason why we included a contemporary comparison cohort from the other Swedish regions that refer their patients to our hospital for surgery but do not use pulse oximetry screening. This comparison group showed that, without pulse oximetry screening, 23% of patients even with cyanotic duct dependent pulmonary circulation left hospital undiagnosed, and there was no significant difference in the other referring regions between the number of cases with pulmonary versus systemic duct dependent circulation that was missed ($P=0.62$).

There may be other differences besides the use of pulse oximetry screening that contributed to the lower detection rate in the other referring regions (some differences between the referring hospitals were documented in a previous study³). However, the detection rate in the referring regions was as good as or marginally better than that documented in the Newcastle region over 20 years,⁴ so it was probably a representative average. Furthermore, comparison of the detection rate in West Götaland Region in the present study with the detection of duct dependent heart disease in a previous retrospective survey in

1993-2001 in the same region (a study that probably underestimates missed cases as there was no systematic retrieval of cases dying in the community)³ also shows that detection with pulse oximetry screening is superior to physical examination alone (55/60 (92%) *v* 192/241 (80%), $P=0.037$).

All the maternity units taking part in the pulse oximetry screening were at low altitudes, so any maternity unit situated at high altitude would be advised to assess oxygen saturation in their normal babies before adopting our cut-off values. However, saturations $\geq 95\%$ are on the relatively flat part of the oxygen dissociation curve, and arterial pO_2 needs to be <11 kPa in newborn infants in order for the pulse oximeters used in our study to record saturations $<95\%$ (unpublished observation).

Results in relation to other studies

Previously published studies attempting to assess the potential of pulse oximetry for the screening for critical congenital heart disease have been too small (study populations ranging from 2114 to 11 281) to enable a confident estimate of sensitivity because of the prevalence of such disease being only 1-1.8/1000.^{6,7,9-13} Those studies which have not included ascertainment of missed cases dying in the community are making unsupported claims of sensitivity,⁹⁻¹³ since Wren et al showed that an average of 5% of all babies with critical heart disease died undiagnosed in the community,⁴ just as in our comparison cohort.

Depending on the cut-off criteria, the false positive rate of pulse oximetry screening varied between 0.009% and 5% in these studies. Richmond et al showed that the introduction of repeat pulse oximetry brought their false positive rate down from 5% to 1%.⁶

The detection rate of physical examination alone, 62.5% in our study, agrees with the 62% postnatal in-hospital detection rate reported by Wren et al as being fairly consistent over a 20 year period, from their large retrospective survey in the Newcastle region, with on average 30% of their babies with critical heart disease leaving hospital undiagnosed.⁴ In the Newcastle study, however, the patients presenting via the neonatal intensive care units were included in the in-hospital detection rate.

Few of the earlier studies of pulse oximetry screening have compared it with the detection rate of physical examination alone in well babies, but Bakr and Habib reported a sensitivity of 46% for clinical examination in the detection of any major congenital heart disease.¹¹ Reviewing the literature and the data from the Newcastle study, Griebisch et al estimated a detection rate of 32.3% for critical heart disease and a false positive rate of 0.5% for clinical examination.¹⁶ In our study both the detection rate from clinical examination (62.5%) and the false positive rate (1.91%) were higher, possibly influenced by our design, which meant that each examining paediatrician had to make an active statement as to whether heart disease was suspected.

Our previous observations on patients with coarctation maintained on prostaglandin infusions suggested

that the introduction of a comparison of preductal and postductal oxygen saturation might increase the detection rate of coarctation,¹⁵ but in the present study only a third (3/9) of infants with coarctation of the aorta as the main diagnosis had abnormal saturation screening results (table 1). Even with the combination of physical examination with pulse oximetry, four of the nine patients with acyanotic arch obstruction had no detectable abnormality.

What is the optimal screening regimen?

A large Norwegian multicentre study that appeared after we submitted our manuscript used the same pulse oximeter and probes as in our study, but the participants measured only postductal oxygen saturation with a cut-off point of $<95\%$ in two repeated measurements.²¹ They claimed a sensitivity of 77%, but this is optimistic as they did not actively ascertain patients dying in the community with undiagnosed heart disease, and the reported incidence of critical heart disease (35/50 008) is surprisingly low at only 0.7/1000 compared with the 1.3/1000 in our study. Other pulse oximetry screening studies that did actively ascertain patients that died at home from missed heart disease reported prevalences of duct dependent heart disease in the screened population virtually identical to ours, at 1.3/1000 and 1.2/1000.^{6,7}

If we apply the Norwegian study's cut-off criteria ($<95\%$ oxygen saturation postductally in two measurements²¹) to our screened population, we get a detection rate of 17/28 (60.7%)—that is, their criteria missed one positive result on our screening criteria and did not add any additional positives (see table 1). What is directly comparable between our study and the Norwegian study is the false positive rate, which is 3.5 times higher with their criteria (0.6%) than with the criteria used in our study (0.17%), which has cost benefit implications, as does our positive predictive value of 20.69 compared with their value of 8.3.

Although it is superficially attractive to simplify screening by measuring only postductal circulation, this overlooks the fact that in complex heart disease with a combination of transposed great vessels and an arch obstruction the postductal saturation may well be $>95\%$ in a child with duct dependent circulation, as was the case in 2/66 (3%) in our previous study.¹⁵ In practice, once you have the baby and pulse oximeter together it takes less than a minute extra to measure oxygen saturation in both hand and foot instead of foot only, and it does provide useful additional information. As patients with duct dependent systemic circulation are the ones most likely to develop early circulatory collapse with neurological and other morbidity, we feel that the fact that a $>3\%$ difference between preductal and postductal saturation substantially increases the likelihood of a duct dependent systemic circulation being present is a useful diagnostic pointer towards urgent further investigations and possibly prophylactic treatment with prostaglandins. We found the addition of the $>3\%$ difference as a criterion did not increase the

false positive rate in normal babies but did detect a few more cases with pathology.

Reasons for reduced clinical detection of duct dependent heart disease

Earlier studies have suggested that duct dependent systemic circulation is more often missed than pulmonary duct dependent circulation^{3,4} and that duct dependent systemic circulation is the most common cause of death in the community from unrecognised critical heart disease.^{1,4} For example, Wren et al found that 54% of babies leaving hospital with undiagnosed heart disease had coarctation of the aorta and 44% had an interrupted aortic arch.⁴ In our cohort study, however, all cases of duct dependent pulmonary circulation were detected by pulse oximetry screening in West Götaland but constituted 12/28 (43%) of missed cases of duct dependent circulation in the other referring regions, where 11/25 (44%) of the cases of the most cyanotic heart lesion of all, transposition of the great arteries, were missed before discharge.

This is a noteworthy change that has occurred in parallel with reduced lengths of stay in maternity units, as the previous retrospective analysis in the same Swedish regions in 1993-2001 found that only 5/106 infants with duct dependent pulmonary circulation left hospital undiagnosed,³ a significantly lower proportion than the 12/52 seen in the other referring regions in the current study ($P=0.0016$). Factors that might influence these figures include average length of stay on the maternity ward after delivery, which has steadily declined in Sweden from 3.3 days after vaginal delivery in 1993 to 2.2 days in 2005.²² In West Götaland, where no baby died from undiagnosed duct dependent circulation during the study period, 63.2% of mothers and babies left the maternity unit ≤ 48 hours after delivery during 2005, close to the national average during the study period of 62.3%.

However, as some of the missed cases were not discharged early from hospital, we feel that other factors must also be present. Postnatal examination routines have altered, and many units now carry out only one, rather than two, neonatal physical examinations (4/5 participating units in West Götaland). This may be important as there has been a simultaneous move from babies being kept together in large, well lit nurseries where they are frequently observed by nursing staff (and where it may be more noticeable that a baby is more cyanosed than its neighbour) in favour of babies rooming with their mothers under more domestic lighting conditions. This might be an important factor in the reduced detection of duct dependent pulmonary circulation. Some maternity units have stopped examining femoral pulses routinely (though not in West Götaland); since half of the babies with duct dependent circulation detected at neonatal physical examination had poor or absent femoral pulses as a major alerting sign (see table 1), the omission of palpation of femoral pulses is likely to reduce the detection of duct dependent circulation on clinical examination.

Comparative mortality rates from undiagnosed duct dependent heart disease

In the Stockholm region in Sweden seven infants died suddenly from undiagnosed duct dependent heart disease (1 with pulmonary atresia and 6 with obstructive left heart disease) in 1982-2001, only 1.6 deaths per 100 000 live births.²³ This compares with 4.4/100 000 in the Newcastle area in 1985-2004, which is similar to the 4.6/100 000 found in the other referring regions for 2004-2007 in this study. Factors that might influence these figures are firstly, average length of stay on the maternity ward after delivery, which in Sweden was 5.6 days in 1982, and altered postnatal examination routines as discussed above. Lastly, transport distances for collapsed babies may influence survival.

Cost benefit analysis

Griebsch et al calculated a detailed prediction of costs for different types of screening according to UK health service costs in 2001, and estimated a cost of £4894 per timely diagnosis achieved by pulse oximetry screening.¹⁶ However, our observed positive predictive value for oximetry screening was much higher (20.69% *v* 6.6%) and false positive rate much lower (0.17% *v* 1.3%) than in Griebsch et al's model, and when we use their basic cost estimates and give the highest possible cost to echocardiography (consultant time) our cost for 18 timely diagnoses made by pulse oximetry (would have been 19 except for the protocol violation) is £3430 per timely diagnosis made. As the cost for an infant leaving hospital with duct dependent circulation and returning in circulatory collapse was calculated to be £3453,¹⁶ introduction of pulse oximetry screening should be, at a minimum, cost neutral since each additional case diagnosed saves at least as much as each case missed costs.

In contrast, clinical examination in our study engendered many more false positives than Griebsch et al predicted (1.91% *v* 0.5%) and had a lower positive predictive value (1.35% *v* 7.8%), so, in spite of a higher detection rate (62.5% *v* 32.3%), the cost per timely diagnosis for clinical examination in our study came out between £7700 (for those actually referred for echocardiography from physical examination alone) and £2526 (in the unlikely event that all the infants with pulse oximetry results of $\leq 90\%$ saturation would have been referred to echocardiography from physical examination alone).

However, as well as the acute costs, a timely diagnosis of transposition of the great arteries, hypoplastic left heart syndrome, or coarctation of the aorta improves the survival of affected babies.¹⁸⁻²⁰ The experience from the Swedish regions not using pulse oximetry screening (see table 5) also shows that there is serious long term neurological morbidity to be expected (increasing the costs of not making a timely diagnosis), as 5/23 of the surviving patients with undiagnosed duct dependent circulation had preoperative cerebral haemorrhages ($n=2$) or preoperative seizures ($n=1$), which are a recognised predictor of poor neurological outcome,²⁴ or extreme acidosis (pH 6.80-

WHAT IS ALREADY KNOWN ON THIS TOPIC

About 1-2 babies per 1000 live births have an immediately life threatening cardiac malformation, and 30% of such infants leave hospital without the malformation being recognised and either return to hospital in circulatory collapse or die at home

Pulse oximetry screening has been advocated as a possible tool to improve detection, but sensitivity and cost effectiveness remain unproved in the absence of sizeable prospective studies

WHAT THIS STUDY ADDS

As inpatient maternity stays have reduced, an increasing proportion of babies with duct dependent pulmonary circulation leave hospital undetected

Pulse oximetry screening performed both preductally and postductally detects 100% of infants with pulmonary duct dependent circulation and, when combined with routine clinical examination, detects 92% of all infants with duct dependent circulation before hospital discharge, and has a higher detection rate than physical examination alone

Introduction of pulse oximetry screening is cost neutral in the immediate perspective, as each additional case that receives a timely diagnosis costs the same as the treatment of a child that is readmitted in circulatory collapse, but there are probably additional long term cost benefits from reduced neurological morbidity

6.90) causing serious concern for eventual neurological outcome (n=2).

Implications of the study

Our study shows that pulse oximetry screening of all well babies in maternity units is practically feasible with a minimum use of nursing time, and that it significantly improves detection of duct dependent heart disease before hospital discharge. The low false positive rate, the fact that other important pathology is unearthed by the screening, and the likely reduced need for preoperative neonatal intensive care suggest that such screening will be cost effective.

Areas for future research

The detection of acyanotic aortic arch obstruction remains a problem area with pulse oximetry screening alone. However many new generation pulse oximeters now also display a peripheral perfusion index, which records what proportion of saturated haemoglobin in the blood displays pulsatile flow (that is, is roughly proportional to pulse volume). We have published normal values for this index in healthy newborns, and showed that peripheral perfusion index is pathologically low (<0.70) in 5/9 infants with duct dependent obstruction of the left heart or aortic arch.²⁵ Incorporating cut-off values for perfusion index into routine pulse oximetry screening would probably increase sensitivity for detection of left heart obstructive disease, but the implications for the false positive rate would have to be assessed.

The ideal way of optimising number of timely diagnoses is probably to have one pulse oximetry screening during the first 24 hours of life to prevent circulatory collapse in hospital of babies with duct dependent pulmonary circulation and hypoplastic left heart syndrome,²¹ to add peripheral perfusion index cut-off criteria, and to perform a second pulse oximetry

screening at discharge or when early discharge has taken place, at the time of Guthrie testing. Routine fetal echocardiography could improve detection of duct dependent circulation.⁴ However, prenatal detection of coarctation has also been a problem: a new method for assessing aortic isthmus diameter has some promise to improve this.²⁶

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Contributors: AWG supervised and coordinated the study, set and locked the pulse oximeters, informed and educated all staff involved, handled and analysed the data, participated in the statistical analyses, and drafted and helped revise the manuscript. MW participated in planning the study design, organising the pulse oximetry screening at Östra and Mölndal units, and retrieving their birth numbers. KS participated in planning the study design and retrieving data at Östra and Mölndal and was their neonatal contact person. MM was responsible for organising echocardiography at Queen Silvia Children's Hospital, jointly collected the reference population in the historical comparison cohort, and helped in manuscript revision. CB was responsible for organising the pulse oximetry screening at NÄL Hospital, and was their obstetric contact-person. LI was responsible for organising echocardiography at NÄL and was their paediatric contact person. ME was responsible for organising the pulse oximetry screening at Borås, retrieving birth numbers, and was their obstetric contact person. NS was responsible for organising echocardiography at Borås and was their paediatric contact person. AÅ was responsible for organising the pulse oximetry screening at Skövde, retrieving birth numbers, and was their neonatal contact person, BMEJ was responsible for organising echocardiography at Skövde, and was their paediatric contact person. JS provided the logbook over those not being referred for or denied surgery and jointly collected the reference population in the historical comparison cohort. MV retrieved and analysed infant data from the forensic database. IÖS conceived and was extensively involved in the design of the study, interpretation of the results, statistical analyses, and writing and revising the manuscript. All authors reviewed and approved the final manuscript. IÖS is guarantor for the study.

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