Original Article

The value of peripheral perfusion index measurements for early detection of critical cardiac defects

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Background: Approximately 25% of congenital heart diseases (CHD) are estimated to be critical and require an intervention. In this study, we aimed to investigate the additional value of peripheral perfusion index (PPI) measurements to pulse oximetry screening for critical CHD (CCHD).
Methods: Infants born at Ege University Hospital between May 2013 and September 2015 were prospectively included in the study. In addition to physical examination, pre- and postductal oxygen saturations and PPI values were measured with a new generation pulse oximeter before discharge from the hospital.
Results: A total of 3175 newborns (33 with an antenatal diagnosis of CCHD) were included in the study. With the combination of physical examination, pulse oximetry screening and peripheral perfusion index (PPI) measurements, all newborns with CCHD were detected in our study including three infants without an antenatal diagnosis in whom pulse oximetry screening was negative.
Conclusion: PPI measurements may be valuable for early detection of obstructive left heart lesions where pulse oximetry screening has limitations in diagnosis.

1. Introduction

Congenital heart diseases (CHD) are the most common group of congenital malformations and occur in 9 out of every 1000 live births.[1,2] Critical congenital heart disease (CCHD) is defined as a cardiac defect which requires surgery or other cardiac interventions in the neonatal period especially in the first week of life. Approximately 25% of CHDs are estimated to be critical.[3,4] Until recently, screening for CHD relied on ultrasound scanning of the fetal heart chambers during the second trimester of pregnancy and postnatal physical examination which includes the evaluation of heart sounds, cyanosis and peripheral pulses. Unfortunately, both screening methods have a low detection rate and therefore many newborns with CCHD are discharged undiagnosed from maternity hospitals. Early detection of ductal-dependent lesions is crucial as closure of the ductus may lead to cardiovascular collapse and death.[5] Early suspicion for CCHD may bring early diagnosis. Prostaglandin infusion and palliative or corrective interventions may ensure optimum hemodynamics and prevent end organ injuries secondary to hypoxemia and cardiovascular collapse.[6,7]

Pulse oximetry screening is a simple, quick, well-established, accurate and non-invasive test for the objective detection of hypoxemia. Newborn pulse oximetry screening for CCHD may detect heart defects presenting with hypoxemia shortly after birth. A recent systematic review and meta-analysis of 13 studies concluded that pulse oximetry screening is a highly specific (specificity 99.9% CI 99.7 to 99.9) and a moderately sensitive test (sensitivity 76.5%, 95%CI 67.7 to 83.5) for detection of congenital heart diseases.[2,7,8] Since arterial oxygen saturation varies considerably in the first 24 h, many healthy newborns with oxygen saturations less than 95% may have false positive screening tests in the first 24 h of life. Therefore, pulse oximeter screening is recommended within 24–48 h of birth or just before discharge.[4,9]

Peripheral perfusion index (PPI) is a numerical value that reflects the relative strengths of different components of the infrared (IR) signal returning from the monitoring site reflecting the real-time changes in peripheral blood flow. It is displayed on the oximeter monitor, and its measurement is influenced primarily by the amount of blood at the monitoring site. The PPI upper and lower limits for Masimo Radical SET (Masimo Corp., Irvine, CA, USA), reported by the manufacturer, are 0.02–20.00%. The perfusion index has been suggested as a predictor of high illness severity in neonates and has been reported to show early postnatal changes in peripheral circulation of newborns. PPI is expected to be affected by a reduction in stroke volume in the arterial circulation and therefore low PPI values are expected in CCHD.[10–12] Detection of compromised circulation as early as possible may be of value for detection of heart diseases. In a study by Granelli et al., PPI values between 1 and 120 h of age showed an asymmetrical, non-normal distribution with median PPI value of 1.70 and interquartile range of 1.18–2.50.[12]

The Secretary of Health and Human Services added pulse oximetry (PO) screening to the Recommended Uniform Screening Panel and AAP has also supported this screening since 2011; however, this program is not yet routinely carried out in our country.[13,14] We have recently started routine pulse oximetry screening in our maternity hospital with simultaneous PPI measurements and we aimed to investigate the additional value of PPI in routine pulse oximetry screening for CCHD.

2. Methods

Infants born at Ege University Hospital between May 2013 and September 2015 were prospectively enrolled to the study. The study protocol was approved by the local ethics committee (2013, 13–4.1/7). Before initiation of the study, the medical staff who would perform screening tests were trained. Demographic information collected included the maternal and infant characteristics such as maternal age, prenatal care and pregnancy related problems, antenatal diagnosis or suspicion of any cardiac defects, gestational age, birth weight and need for neonatal intensive care unit (NICU) hospitalization.

Defects classified as CCHD are hypoplastic left heart syndromes (HLHS), pulmonary atresia with intact ventricular septum, simple transposition of the great arteries (TGA), interruption of the aortic arch, total anomalous pulmonary venous return (TAPVR), or tricuspid atresia, as well as all infants dying or requiring medical interventions within the first 28 days of life with coarctation of the aorta, aortic valve stenosis, pulmonary stenosis, tetralogy of Fallot (TOF), double outlet right ventricle (DORV), Ebstein anomaly, or pulmonary atresia with ventricular septal defect.[15]

We considered 7 CCHDs as "primary" targets of the screening: HLHS, pulmonary atresia, dextro-transposition of the great arteries, truncus arteriosus, TOF, tricuspid atresia and TAPVR. The 5 "secondary" targets of the screening were as follows: coarctation of the aorta, DORV, Ebstein anomaly, interrupted aortic arch and single ventricle.[16]

All newborns underwent physical examination after birth and pulse oximetry screening was performed on all newborns using an AAP-endorsed screening algorithm.[17] In this screening, postductal measurements were performed from the left foot for standardization. Newborns with normal physical examination and negative screening tests constituted the healthy group. All measurements were performed after 24 h of age.

Preductal and postductal oxygen saturation (SpO_2) and PPI levels were measured within 24–48 h of birth or just before discharge. The SpO_2 values were recorded after the signal became artifact-free.

Infants with a positive pulse oximetry screening test were evaluated with echocardiography. Echocardiography was also performed on all infants with a family history of CHD, postnatal physical examination findings suggesting CHD, such as heart murmur, cyanosis and weak peripheral pulses. Echocardiography was performed immediately after birth on neonates with a history of antenatal CCHD.

All infants with a gestational age of <34 weeks were excluded from the study.

3. Data analysis

Data was analyzed with Social Sciences (SPSS) for Windows 19.0 software, IBM Corporation, Armonk, NY. Numeric

variables with ROC analysis were performed and cut-off values were determined. Values were reported as mean and SD. A p value < 0.05 was considered statistically significant.

4. Results

A total of 3175 newborns born at Ege University Hospital Department of Obstetrics and Gynecology during May 2013—September 2015 were prospectively enrolled in the study. The mean gestational age was 38.32 ± 1.49 (34—43) weeks and birth weight was 3245.49 ± 483.26 (1825—5250) grams. Numbers of patients in the study groups were as follows: Group 1: Newborns without an antenatal CCHD diagnosis (n = 3142) and Group 2: Newborns with an antenatal CCHD diagnosis (n = 33). Demographic variables of the patients are summarized in Table 1.

Among infants in Group 1 (n = 3142), 13 newborns were pulse oximetry screen-positive (0.4%). In this screen-positive group, 7 patients had a postnatal CCHD diagnosis as follows: TGA (n = 2), coarctation of aorta, hypertrophic cardiomyopathy with aortic stenosis, pulmonary atresia with atrioventricular septal defect, TAPVR and truncus arteriosus. These 7 patients had screen-positive results with SpO_2 results <95%. The remaining 6 infants with positive screening tests were diagnosed as normal with reassuring echocardiography results.

The remaining 3129 newborns in Group 1 were screen-negative (99.6%). However, in this screen-negative group, 3 patients had a heart murmur during physical examination and echocardiography revealed TOF, coarctation of the aorta and pulmonary stenosis.

Thirty-three patients in Group 2 were evaluated due to their antenatal CHD diagnosis, and 20 of these infants (60.6%) were pulse oximetry screen-positive and 13 patients (39.4%) were screen-negative. Echocardiographic evaluation revealed a CCHD diagnosis in 18 infants, all of whom had a SpO_2 <95%. Two other patients with a screen-positivity due to the pre- and postductal SpO_2 difference of 4% had postnatal diagnosis of atrial septal defect and patent ductus arteriosus and were not considered as critical CHD. Of the 13 screen-negative patients with antenatal CCHD diagnosis, 5 had a postnatal CCHD diagnosis (two patients with coarctation of aorta, two patients with HLHS and one patient with TGA). The remaining eight patients with screen-negative results had echocardiographic results as follows: 4 patients with patent ductus arteriosus and patent foramen ovale, 1 patient with patent foramen ovale and minimal mitral insufficiency, 2 patients with stenosis in juxta ductal region and 1 patient with a normal echocardiography report. These results are summarized in Fig. 1.

For pulse oximetry CCHD screening, the sensitivity was calculated as 75.9%, and the specificity was 99.7%. The percentage of false-positive results was 0.3% and the percentage of false-negative results was calculated as 24.2%. Among 33 patients with postnatal CCHD diagnosis, 8 patients had screen-negative results for pulse oximetry.

PPI values of the patients with CCHD diagnosis were compared to the newborns without CCHD. The cut-off values for PPI between the 5th, 50th and 95th percentiles were calculated for pre- and postductal measurements. For preductal measurements, the 5th, 50th and 95th percentiles were 1.2, 2.9 and 5.2 respectively. For the 5th percentile, the sensitivity of preductal PPI measurement was calculated as 63.6%, and the specificity was 97.2%.

The cut-off PPI values for postductal measurements between the 5th, 50th and 95th percentiles were 1.1, 2.7 and 5.0, respectively. For 5th percentile, the sensitivity of postductal PPI measurement was calculated as 60.6%, and the specificity was 96.3%. We also evaluated our PPI values with a 0.7 as a cut-off value, which is commonly referred to in the literature as a cut-off value for PPI. These results are summarized in Table 2.

According to 5th percentile preductal and/or postductal PPI values of 1.2 and 1.1, in that order, we could diagnose 23 of the 33 CCHD infants. Of these 23 patients, 16 patients (16 with a positive pulse oximetry screening) were in the primary targets group for CCHD. The remaining 7 patients (5 with a positive pulse oximetry screening) were in the secondary targets group for CCHD screening. The results for all calculated PPI cut-off values are summarized in Table 3.

The false positive results for 5th percentiles of PPI are calculated for pre- and postductal measurements. The false positive rate was calculated as 2.7% for 1.2, as a preductal cut-off value and 3.6% for 1.1, as a postductal cut-off value.

In our study, in addition to antenatal CCHDs, we performed echocardiography on patients with positive pulse oximetry screening and on those with physical examination findings. Three significant CHDs were diagnosed postnatally (coarctation of aorta, atrioventricular septal defect and aortic stenosis). The patient with aortic stenosis had negative pulse oximetry screening, but the PPI measurement was positive. This patient required a balloon angioplasty when he was 3 months old. Using the pulse oximetry screening algorithm together with PPI measurements, the five remaining patients were diagnosed with echocardiography performed due to heart murmur (Figs. 1 and 2).

| Table 1	Demographic variables of the patients.		
	Group 1 No antenatal diagnosis of CCHD	Group 2 Antenatal diagnosis of CCHD	All patients
Total patient number (n)	3142	33	3175
Gestational age (weeks)	38.33 ± 1.49	37.81 ± 1.53	38.32 ± 1.49
Mean (range)	(34—43)	(34—43)	(34—43)
Birth weight (g)	3248.30 ± 482.27	2985.66 ± 510.76	3245.49 ± 483.26
Mean $\pm$ SD (range)	(1730—5250)	(1825—3677)	(1730—5250)
Gender (male)	49.7%	81.3%	50.0%
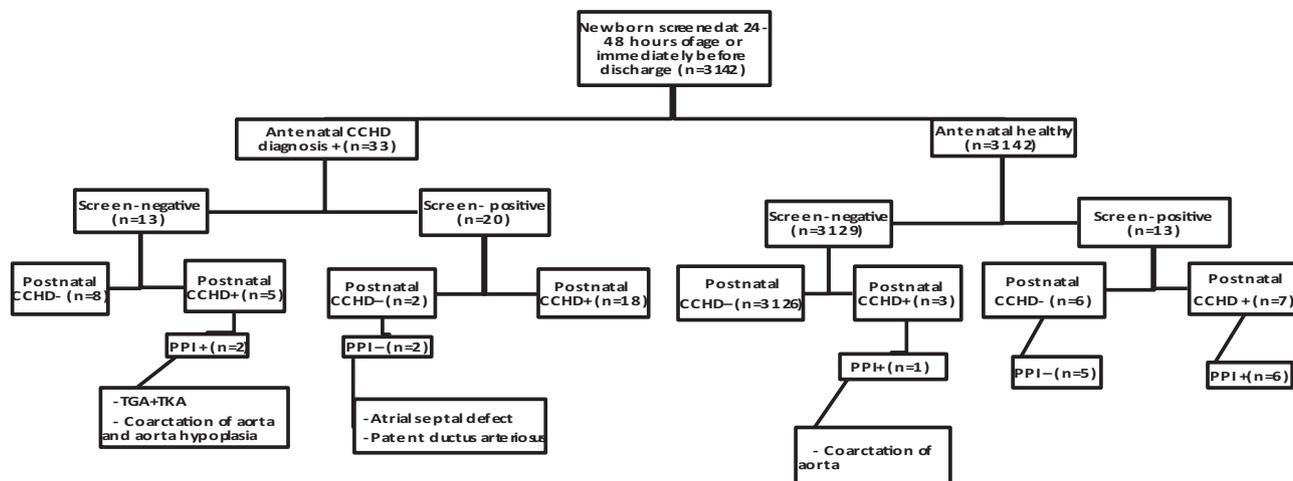
Figure 1 Study flow chart (Cut off values for perfusion index is 1.2 for right hand and 1.1 for left foot).

Table 2 The evaluation of the results according to a PPI cut-off value of 0.7.

	Pre-ductal	Post-ductal	Pre/post-ductal (either)
Sensitivity (%)	33.3	36.4	42.4
Specificity (%)	99.2	98.4	97.6
Positive predictive value (%)	30.6	19.4	16.7
Negative predictive value (%)	99.3	99.3	99.3

Table 3 Analysis of cut-off values for pre- and post-ductal measurements.

| Cut-off values for pre-ductal measurements	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Number of missed patients in primary targets of CCHD	Number of missed patients in secondary targets of CCHD
5 p (1.2)	63.6	97.2	19.4	99.6	8	4
0.7	33.3	99.2	30.6	99.3	15	7
1	57.5	98.5	22.8	99.5	7	7
Cut-off values for post-ductal measurements						
5 p (1.1)	60.6	96.3	14.8	99.5	8	5
0.7	36.4	98.4	19.4	99.3	13	8
1	57.5	96.3	14.3	99.5	9	5

5. Discussion

In this study, we hypothesized that a PPI measurement in addition to pulse oximetry screening and physical examination may be helpful in early detection of CCHD. Using pulse oximetry screening protocol, seven patients without an antenatal CCHD were diagnosed (coarctation of aorta, TAPVR, TGA, pulmonary atresia and truncus arteriosus). Regarding PPI measurements with cut off values of 1.2 for the right hand and 1.1 for the left foot, we could also diagnose one other patient with coarctation of the aorta and aorta hypoplasia, in whom pulse oximetry SpO$_2$ screening was negative. In left heart obstruction, which may compromise peripheral perfusion in the early phase of left heart failure, PPI may help with diagnosis of these patients. The two remaining patients who were both negative for PO and PPI screenings were diagnosed as ventricular septal defect with pulmonary stenosis and tetralogy of Fallot.

CHDs are the most common group of congenital malformations and occur in 1% of live births. CCHDs still have a higher mortality rate compared to other malformations. CCHD accounts for 20% of deaths in the neonatal period and is therefore a significant cause of mortality in the first month of life.

Despite improvements in antenatal ultrasonography, delayed CCHD diagnosis occurs in approximately 10% of patients.[18] Evidence shows that certain CCHD lesions are more likely to be diagnosed antenatally by abnormal 4-chamber heart view. On the other hand, some heart defects may be missed from the antenatal screening whereas the 4-chamber heart view is normal such as in TOF and TGA. In addition, TAPVR and coarctation of the aorta can be missed due to subtle prenatal ultrasonographic signs.[19]
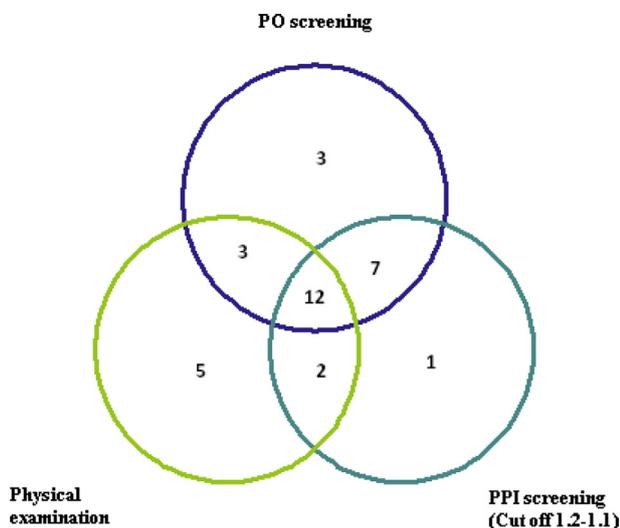
Figure 2 Diagnostic screening results in patients with CCHD.

Therefore, internationally accepted screening programs should be routinely used, keeping in mind that in early screenings in the first 24 h of life, pulse oximetry may have greater false positivity.[15]

Interventions are made worldwide to increase the quality of the screening. Pflugeisen et al.[14] investigated the differences after transition to pre-and postductal protocol from post-ductal protocol and suggested pre-and post-ductal protocol could be implemented successfully.[14] Computer-based programs are also suggested to prevent protocol violations. Different studies of normal values for pulse oximetry from higher altitudes are reported.[20] Studies regarding the ideal screening period were performed, and to achieve an acceptable specificity testing infants >24 h after birth appeared to be the most reliable strategy.[4,9] Mahle et al.[4] reported the results of 10 studies examining pulse oximetry for CCHD and the sensitivity was 75% and the specificity was determined as 99.3%.[4] Different results are reported from several studies and the overall sensitivity differs from 60 to 87%, while the specificity is usually over 99%.[21,22] In a recent study from our country, sensitivity and specificity of pulse oximetry in the diagnosis of CCHD were determined to be 60% and 99.8%, respectively. In that study, three patients with coarctation of the aorta were missed by pulse oximetry screening.[23] Therefore, additional methods may be beneficial to increase the success of the screening programs.

Oximetry screening may miss some CCHD lesions which are at great risk for acute cardiovascular compromise and may result in serious morbidities and mortality.[4] The pulse oximetry screening may be limited in these obstructive left heart lesions especially in detecting coarctation of the aorta, aortic stenosis and HLHS.[24] Riede et al.[25] conducted a prospective multicenter trial in which 42,240 newborns from 34 institutions were included and the four false negative patients after pulse oximetry screening had diagnosis of coarctation of aorta (n = 3) and TGA (n = 1).[25] Therefore, a strategy aiming to improve the screening results of this group is necessary.

Using a screening protocol with pulse oximetry, we were able to screen our newborns, and in addition to the pulse oximetry screening algorithm, PPI and physical examination improved our screening results and all patients were diagnosed. Sensitivity of pulse oximetry screening was a little higher in our study, while the specificity was similar to AAP results.

PPI is affected by a reduction in stroke volume in the arterial circulation and therefore low PPI values are expected in patients with CCHD. Granelli et al.[12] established PPI reference values for newborns in the first few days of life and indicated that PPI values lower than 0.70 may indicate illness.[12] If the duct is small or closed, the lower limb will show desaturation and reduced pulse volume. In their screening, two of the patients were missed with physical examination and pulse oximetry screening with CCHD (coarctation of the aorta and HLHS). PPI measurement was positive for both patients immediately after the diagnosis.[12] Hakan et al. aimed to determine reference values of perfusion index (PI) in healthy newborns during the early neonatal period.[26] Preductal (right hand) and postductal (foot) PI values were assessed during the first 5 days of life by using a new generation pulse oximeter and on the first day, in term infants, the median (interquartile range [IQR]) preductal and postductal PI values were 1.35 (1.02−1.91) and 0.88 (0.62−1.22), respectively. The sensitivity of our results is lower than those of Granelli et al., and at this point, it seems more logical to accept a PPI level of 0.70 as a cut-off.

In our study, pulse oximetry screening missed the two patients with coarctation of the aorta but their PPI measurement was positive. In our study, one patient with aortic stenosis who underwent balloon angioplasty during the follow-up had normal oxygen saturation levels but PPI measurement was positive. This may be due to early changes in peripheral perfusion before its reflection to oxygen saturation levels. Although the main aim of the screening is to detect newborns with CCHD, in combination of pulse oximetry with PPI values, in the future, significant CHDs may be detected with screening methods.

With the combination of physical examination, pulse oximetry screening and PPI measurement, all newborns with CCHD were diagnosed in our study. In a recent study, Zuppa et al.[27] screened 5750 asymptomatic newborns at 48th−72nd h of life, and despite detailed physical examination and pulse oximetry screening one patient with coarctation of the aorta was missed and diagnosed at 28th day of life after emergency care submission due to vomiting and tachycardia.[27] Therefore, using the two screening methods in combination with physical examination significantly improves the results.

6. Conclusion

PPI measurements in addition to pulse oximetry screening and physical examination may be helpful in preventing late detection of CCHD. Using a simultaneous combination of physical examination, pulse oximetry screening and PPI measurements, all newborns with CCHD were diagnosed in our study. PPI measurement is especially beneficial in obstructive left heart lesions where pulse oximetry screening may be of limited effectiveness in diagnosis.

Conflict of interest

Acknowledgements

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