Critical Congenital Heart Disease Screening Using Pulse Oximetry

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Congenital heart disease (CHD) is the most common congenital malformation, occurring at a frequency of 8-12 per 1000 live births.[1] Critical congenital heart disease (CCHD) occurs at a frequency of 1.2-1.7 per 1000 live births and accounts for 10%-15% of all cases of CHD.[2,3] Although there is variation in how the term is defined, CCHD is generally accepted as referring to any congenital cardiac lesion that requires intervention or may cause significant morbidity or mortality in the first weeks of life. The public health impact of CHD is considerable, as CHD is responsible for 7.4% of all infant deaths,[4] of which 10% are not diagnosed until autopsy.[5] Chang et al[6] reported that 50% of infants with previously undiagnosed CCHD died at home or in emergency departments. Up to 30 infant deaths per year have been attributed to undiagnosed CHD in California alone. In 2007, Aamir et al[7] reviewed the birth records in New Jersey and found 47 patients during a period of 5 years with a delayed diagnosis of CCHD (57% <4 weeks, 66% <2 months). Many of these patients were subject to multiple diagnoses, admissions, and procedures, suggesting an increased financial cost with delayed diagnosis. Delays in diagnosis can also lead to significant morbidity and worse outcomes after interventions.[8,9] Because of its frequency in the population, potential for serious and life-threatening presentation, and availability of effective interventions, CCHD is an excellent candidate for a screening examination.

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Current Detection Methods

The ideal screening test for CCHD should be accurate in recognizing disease in the preclinical state, have an excellent safety profile, be reasonably priced, have a wide availability, and lead to improved outcomes. Many of the existing methods of detecting CCHD have shortcomings in these areas. Obstetric ultrasound, typically performed between 18 and 22 weeks of gestation, is a common way in which structural cardiovascular abnormalities are diagnosed. However, controversy exists as to what images should be included in the "routine" obstetric examination of the fetal heart, which affects the sensitivity of this examination,[2,10] and detection rates remain low.[11] When abnormalities are detected, referral for comprehensive fetal echocardiography is often indicated; however, access varies widely by geographic region. Furthermore, certain lesions such as transposition of the great arteries (TGA) can be challenging to detect by physicians without expertise in CHD. Last, infants born to mothers who have had limited or no prenatal care do not have the benefit of access to this potential screening.

Fetal echocardiography is another method of detection of CHD, and it may improve preoperative acidosis, postoperative intensive care course, and surgical survival,[12-14] although data regarding mortality reduction are mixed.[15] It is often performed because of an abnormal cardiac screen on obstetric ultrasound, detection of other congenital malformations, an abnormal nuchal fold thickness or triple screen, a family history of CHD, or maternal medical conditions such as diabetes. However, it has significant cost, and even in urban settings with easy access to fetal echocardiography, fewer than one-half of newborns admitted postnatally for CHD are detected with fetal echocardiography.[16]

The immediate postnatal period provides another opportunity for screening for CHD via the routine newborn physical examination. Unfortunately, many forms of CCHD do not present with obvious heart murmurs. Cyanosis may not be easily apparent until saturations are <80%[17] and may be more difficult to appreciate in individuals with dark skin pigmentation. Mellander et al[18] showed that in a population of infants requiring cardiac catheterization or surgery within the first 2 months of life (excluding patients diagnosed prenatally), 57% of infants with CCHD had been discharged home at 72-120 hours of life. Ductal-dependent CCHD was diagnosed after discharge in 20%, and 43% of these infants were in shock at admission. Although a more recent study has placed the missed diagnosis rate at 25%,[19] figures vary widely, and it is reasonable to conclude that a more sensitive and uniform newborn screen is needed.

AAP	American Academy of Pediatrics
AHA	American Heart Association
CCHD	Critical congenital heart disease
CHD	Congenital heart disease
HHS	Department of Health and Human Services
RUSP	Recommended Uniform Screening Panel
SACHDNC	Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of the great arteries

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How Pulse Oximetry Works

Oxygenated blood absorbs red light at a wavelength of 640 nm and deoxygenated blood absorbs light in the infrared spectrum at 940 nm. Pulse oximeters contain 2 light-emitting diodes at different wavelengths and sensors that measure the amount of red and infrared light emerging from the tissue. The ratio of oxygenated to deoxygenated hemoglobin can be calculated from this, and an oxygen saturation level displayed. Because most forms of CCHD rely on the ductus arteriosus to supply blood flow to the pulmonary circulation, the systemic circulation, or, preferentially, the lower half of the body, hypoxemia or a saturation difference is often present.

Pulse oximetry has been used in its current form since the early 1980s[20] and has been validated by comparison with arterial blood gases.[21] During the past decade, there have been advances in the technology used in these devices to address their performance in historically challenging settings, including patient movement or poor perfusion.[22] Newer devices have been shown to have improvements with regard to patient motion,[23] false or missed hypoxic or bradycardic alarms,[24] and time needed to obtain a reliable reading.[25] New pulse oximeters are also extremely precise even when the anatomic location of the sensor is varied.[26] Guidance for industry on the premarket notification [for 510(k) clearance] of pulse oximeters is available from the US Food and Drug Adminsitration.[27] Pulse oximeters are extremely accurate—in the range of arterial saturations of 85%-100%, which is the range that would be most important in a newborn screening program for those forms of CHD that are likely to cause early morbidity and mortality.

Clinical Studies

One of the earliest studies using pulse oximetry as a screening test for CCHD was performed by Hoke et al[28] from 1993-1995. This study screened 2876 newborns admitted to well-baby nurseries and 32 newborns with known CCHD. The primary target was the early detection of ductal-dependent left-sided heart obstructive disease, and although this was a relatively small study, it laid the groundwork for more comprehensive investigations that followed.

In 2009, the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) released a scientific statement on the role of pulse oximetry in screening for CCHD.[29] The writing group reviewed the existing published evidence and rated screening for CCHD with pulse oximetry as class IIb, level of evidence C, suggesting that there were no adequate large studies and that expert opinion was mixed. The writing group also called for additional population-based studies to evaluate the false-positive and false-negative rates and the detection rate of pulse oximetry as a screen for CCHD. It also highlighted the need to consider the effect of early detection on hospital costs. Importantly, the group wrote that prenatal ultrasound alone is insufficient for detection based on population data and that delayed or missed diagnoses are associated with significant brain injury and higher mortality. The AHA/AAP scientific statement concluded that "methods to improve the early detection of CCHD appear warranted" and called for larger population-based studies on implementation.

Recently, several studies have contributed data that address the concerns raised in the AHA/AAP statement (Table I). The data have been substantially larger than previously published data. In 2009, de-Wahl Granelli et al published a cohort study of 39 821 neonates screened with upper and lower extremity oxygen saturation measurements to evaluate for CCHD as defined by ductal-dependent lesions.[30] The main outcomes were the sensitivity, specificity, positive and negative predictive values, and likelihood ratios for screening with physical examination and pulse oximetry versus physical examination alone. A screen was considered positive if both extremity measurements were <95% or if there was a >3% difference between the measurements. Screens were repeated 2 or 3 times depending on discharge planning; if the results remained within the classification of a positive screen, an echocardiogram was performed. A saturation of <90% immediately resulted in an echocardiogram. The sensitivity, specificity, positive predictive value, and negative predictive value of pulse oximetry alone are shown in Table I. The false-positive rate with pulse oximetry of 0.17% (69 patients) compared favorably with 1.9% with physical examination alone. This study also addressed the important question of differential outcomes, a key issue in evaluating screening for CCHD, as worse acidosis and mortality rates were present in the control (physical examination alone) cohort. Furthermore, 8% of infants with ductal-dependent disease left the hospital in the study cohort versus 28% in the control cohort. The authors addressed cost and feasibility, estimating that 2.3 normal echocardiograms per true-positive test were performed, and an estimated 5 minutes of nursing time per child was required. Importantly, 31 of the 69 infants with false-positive results had other significant (noncardiac) diseases that required treatment. The authors concluded that CCHD

Table I. Summary of recent large population-based studies of newborn pulse oximetry screening (published since the 2009 AHA/AAP scientific statement[29])

Author	No. of births screened	Sensitivity	Specificity	False-positive rate	Positive predictive value	Negative predictive value
de-Wahl Granelli (2009)[30]	39 821	62%	99.8%	0.17%	20.7%	99.97%
Riede (2010)[32]	41 445	77.8%	99.9%	0.10%	25.9%	99.99%
Ewer et al (2011)[31]	20 055	75%	99.1%	0.84%	9.23%	99.99%