Late Diagnosis of Coarctation Despite Prenatal Ultrasound and Postnatal Pulse Oximetry

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abstract

OBJECTIVES: To determine what contribution prenatal ultrasound screening and neonatal pulse oximetry screening (POS) make to the timely diagnosis of neonatal coarctation of the aorta (CoA).

METHODS: We identified infants and fetuses diagnosed with isolated CoA in our referral area between 2003 and 2012 who died without surgery, underwent surgical repair before 2 months of age, or were terminated after a prenatal diagnosis. Clinical data were collected from hospital charts.

RESULTS: Only 3 of the 90 cases were diagnosed prenatally. Two of the 3 were born alive and in 1 case the couple opted for termination of pregnancy. Nineteen of the remaining 87 cases were born in units that used POS (hand and foot) and 4 of 19 screened positive. Of the remaining 83 cases, 46 were discharged undiagnosed (7 after nondiagnostic echocardiography), including 9 with a murmur and weak femoral pulses and 8 with a murmur and normal pulses. One was diagnosed postmortem after dying at home, and 22 of the remaining 45 discharged infants were in circulatory failure on readmission. Five of the patients who were not discharged died without surgery and undiagnosed CoA was the most probable cause of death in 2 of these patients.

CONCLUSIONS: The contribution of prenatal ultrasound screening and postnatal POS to the timely diagnosis of CoA was low. Careful physical examination of all newborns therefore continues to play a fundamental role in detecting this life-threatening cardiac defect, and better screening methods need to be developed.

WHAT’S KNOWN ON THIS SUBJECT: Neonatal coarctation of the aorta (CoA) is a life-threatening cardiac defect, but because symptoms may be lacking initially, newborns with this defect are frequently discharged from the hospital undiagnosed. Delayed diagnosis of CoA is associated with increased morbidity and mortality.

WHAT THIS STUDY ADDS: This population-based study analyzes the contribution of prenatal ultrasound and postnatal pulse oximetry screening to the timely diagnosis of neonatal CoA. Both screening methods had low sensitivity for CoA. Nearly half of all newborns with isolated CoA were discharged undiagnosed.
Routine neonatal examination often fails to detect duct-dependent congenital heart defects, and neonates with coarctation of the aorta (CoA) are at particular risk of being discharged undiagnosed.1–4 Newborn infants with CoA may be initially asymptomatic, but they will rapidly deteriorate after constriction of the arterial duct and risk death if not diagnosed in time to reverse the situation with prostaglandin E1 (PGE1). In a previous study, we found that newborns with critical congenital heart defects (CCHDs) were increasingly being discharged undiagnosed from the maternity ward in parallel with shorter postnatal stays and that aortic arch obstruction was the most frequently missed cardiac defect.2 Since then, prenatal ultrasound screening and neonatal pulse oximetry screening (POS) have been introduced in Sweden.5,6 In the current study, we aimed to determine to what degree these methods contributed to the early diagnosis of CoA in a complete population-based cohort. We also aimed to identify symptoms and signs that led to the diagnosis and to determine to what extent discharging undiagnosed cases resulted in circulatory collapse or preoperative death.

METHODS

Study Design and Population

This study was a population-based retrospective cohort study of all infants with isolated CoA born from January 1, 2003, to December 31, 2012 in our referral area for pediatric cardiac surgery who either underwent cardiac surgery before 2 months of age or died without surgery. Isolated CoA was defined as CoA without significant associated cardiac defects needing surgery. The additional defects that we accepted were as follows: a small ventricular septal defect (VSD), a bicuspid aortic valve without a gradient, a persistent left superior vena cava, and atrial isomerism. Cases with a marginal left ventricle and/or mitral valve anomalies were not included. Infants with associated extracardiac malformations and chromosomal aberrations, premature birth, and/or low birth weight were included.

We identified infants from our local surgery file, and patients who died before surgery were identified from the Causes of Death Registry (the Swedish National Board of Health and Welfare). We also searched the Swedish National Forensic Medicine database for infants with a diagnosis of CoA (International Classification of Diseases, 10th Revision, code Q25.1) and local fetal registries for cases diagnosed prenatally.

Variables Studied

Data from hospital charts were reviewed. Special attention was paid to results of routine neonatal physical examinations, age when the first sign or symptom of heart disease was noticed, POS results, and when CoA was diagnosed relative to hospital discharge.

Prenatal Ultrasound Screening and Postnatal POS

During the study period 97% of pregnant women in Sweden had a second-trimester ultrasound, including a 4-chamber view of the fetal heart. Outflow views and the 3-vessel-and-tracheal view were steadily introduced and were routinely applied by 65% and 61% of all units, respectively, by the end of 2012. Neonatal POS was increasingly implemented and was practiced by most units toward the end of the study period. All units that carried out screening used the Granelli protocol, with measurements in the right hand and 1 foot.5

Newborn Physical Examination and Echocardiography

In most Swedish units newborn infants routinely receive 1 examination by a pediatrician before discharge, performed at a minimum of 6 hours after birth. According to national guidelines, this examination includes registering skin color, respiratory rate and pattern, auscultation of the heart and lungs, and palpation of the femoral pulses. If the discharge is before 12 to 24 hours, most units perform a second examination at 2 to 5 days of age at the same time as the phenylketonuria blood test. The first routine postdischarge physical examination of all infants is performed at 4 to 6 weeks of age at the children’s health center.

Specialized sonographers or pediatric cardiologists performed all echocardiographic examinations in our tertiary center and in 1 of the referring hospitals, and those performed by sonographers were reviewed by pediatric cardiologists. In all other hospitals echocardiograms were performed by pediatricians, usually with several years of training in pediatric echocardiography, or by pediatric cardiologists.

Ethics

The study was approved by the Regional Ethical Review Board in Göteborg on July 9, 2013 (Registration number T542-L3, Addition 137-12).

Statistical Analysis

Medians and ranges were used for the continuous variable of age and percentages were used for categorical variables. For comparisons between 2 groups, Fisher’s exact test was used for dichotomous variables and the Mann-Whitney U test for continuous variables.

Definitions

Circulatory failure was defined as the need for intensive care with metabolic acidosis (pH <7.26) or elevated lactate (>5 mmol/L) and signs of organ dysfunction.
RESULTS

Patients
We identified 90 cases. Eighty-nine were born alive at 21 referring hospitals (n = 76) or in our tertiary center (n = 13). The incidence was calculated on the basis of 72 infants born in Gothenburg or in any of the hospitals that had a stable referral pattern during the complete study period. There were 359,287 live births in these areas from 2003 to 2012, which translated to an incidence of 20 per 100,000.

Of the 89 live-born infants, 52 (58%) were boys and 14 were preterm (<37 weeks) or had a birth weight <2500 g. None had perinatal asphyxia, defined as an Apgar score of ≤5 at 10 minutes after birth. Two patients had Turner syndrome, 1 had a 10q22.3-q23.1 deletion, and 1 had a deletion on chromosome 7. Four patients with normal chromosomes had extracardiac malformations, with 1 case each having jejunal atresia, diaphragmatic hernia, hypospadias, and malformation of the left hand.

Prenatal Diagnosis
Three cases were diagnosed prenatally, including 1 termination of pregnancy. One was delivered in our hospital, treated with PGE1 and operated on at 2 days of age. The other, born in a referring hospital, was followed with repeated echocardiography in the outpatient clinic until ductal constriction at 5 days of age when the CoA became evident. He was given PGE1, transported, and operated on the following day.

Role of POS
Nineteen of the 87 infants detected after birth were born in units using POS, and 4 of these (21%) screened positive with oxygen saturation levels on their right hand and one foot of 100/85, 99/89, 97/90, and 98/76 (%, hand/foot). Routine neonatal physical examination revealed additional clinical findings in 3 of these 4 infants.

Clinical Presentation
The first signs of heart disease in the 83 infants not detected by POS were noted at a median age of 2.2 days (range: 0–41.5 days). Forty-three presented with a systolic murmur. Of these, 21 had weak femoral pulses (Table 1). In 10 infants, the first sign was weak femoral pulses but no murmur; 14 presented with tachypnea, and 14 with circulatory collapse. One neonate died at home, without readmission or evaluation before death, and CoA was detected postmortem. Finally, 1 neonate with no signs of heart disease underwent echocardiography because of a prenatal diagnosis of Turner syndrome.

Diagnosis After Discharge
More than half (53%) of the 87 patients whose CoA was not detected antenatally were discharged undiagnosed from the maternity ward (n = 41) or neonatal care unit (n = 5) after a median length of hospital stay of 2.4 days (range: 0.4–9.7 days). Of these, 28 had a normal routine neonatal physical examination (Table 1) and were discharged at a median age of 1.9 days (range: 0.4–6.9 days). Seven of the 28 had a follow-up visit planned. The remaining 18 neonates were discharged despite clinical findings at a median of 2.7 days of age (range: 1.0–9.7 days) (Table 1); 14 had follow-up planned. Seven were examined with echocardiography before discharge with a normal or inconclusive result. Of the 46 who were discharged undiagnosed, 1 patient died at home and was diagnosed postmortem and 22 were in circulatory failure at readmission or shortly afterward. These included 1 infant who received cardiopulmonary resuscitation at home by the parents and had an initial pH of 6.47.

Negative Result of Early Echocardiography
The median age at echocardiographic diagnosis was 5.6 days (range: 0.3–50.7 days). The first echocardiographic examination did not show CoA, but the diagnosis was made before discharge in 21 of 41 infants discharged without diagnosis. The median age at diagnosis was 2.7 days (range: 0.5–14.3 days). One patient died at home, and 1 had a follow-up visit planned. The remaining 19 infants were discharged.

TABLE 1 Presenting Signs and/or Symptoms

<table>
<thead>
<tr>
<th>Presenting Sign/Symptom</th>
<th>Total (N = 83), n</th>
<th>Infants Discharged Undiagnosed (n = 46), n</th>
<th>Infants Not Discharged Before Surgery (n = 37), n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Signs/Symptoms Before Discharge</td>
<td>Signs/Symptoms on Readmission</td>
<td>Signs/Symptoms Before Discharge</td>
</tr>
<tr>
<td>Murmur only</td>
<td>22</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Murmur and weak or absent femoral pulses</td>
<td>21</td>
<td>6 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Weak or absent femoral pulses</td>
<td>10</td>
<td>3 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>14</td>
<td>1</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>14</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Death at home</td>
<td>1b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Screening echocardiogram in Turner syndrome</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No signs or symptoms</td>
<td>0</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

Cases diagnosed prenatally or detected by POS were excluded. Numbers in parentheses are infants developing circulatory collapse.

a Excluding those who had signs/symptoms before discharge.
b Indicates preoperative death.
not diagnose CoA in 16 cases. Three of these were performed at our tertiary center. In total, 7 of 16 patients were examined before they were discharged because of weak femoral pulses with murmur (n = 4), murmur alone (n = 2), or weak femoral pulses alone (n = 1). Three of the 16 were discharged without previous echocardiography and were examined with echocardiography at an early follow-up visit that was arranged because of weak femoral pulses with murmur (n = 1), murmur alone (n = 1), or tachypnea (n = 1). Three infants who were not discharged were diagnosed only after repeated echocardiographic examinations. Finally, 3 neonates identified from the Causes of Death Registry had undergone nondiagnostic echocardiography in a referring hospital before death. These are described in the Preoperative Mortality section. There was no significant difference between these 16 patients compared with the rest of the group with respect to age at onset of symptoms (1.4 [range: 0.1–13.5] days versus 2.6 [range: 0.0–41.5] days).

Conditions Potentially Influencing Age at Diagnosis

Twenty-one infants had a hemodynamically insignificant VSD that did not require surgical closure. Murmurs were no more common (11 of 21) in infants with a VSD than without a VSD (32 of 66), and the risk of being discharged before surgery did not differ (10 of 21 vs 36 of 66). The risk of being discharged before surgery was also not significantly different between those with a known tricuspid (20 of 34) or bicuspid (14 of 31) aortic valve or between boys and girls (27 of 51 and 13 of 36). There were no statistically significant differences between infants with or without a VSD, with a tricuspid or bicuspid aortic valve, between boys and girls, or between those born prematurely or at term with respect to age at onset of symptoms or age at diagnosis.

Use of PGE1

PGE1 was given to 61 (70%) neonates before surgery; in 8 cases the infusion was started before the CoA was diagnosed.

Preoperative Mortality

Six infants died before surgery (Table 2). One was born at 26 weeks of gestation weighing 1090 g and required assisted ventilation. CoA was diagnosed 1.2 days after birth and PGE1 was started. At 8 days she developed necrotizing enterocolitis and died the next day. Three infants died within 24 hours of birth. One had group B streptococcal sepsis and early echocardiography was considered normal. Another had a diaphragmatic hernia and no echocardiogram was performed. The third infant had pulmonary hypertension with reduced biventricular contractility on early echocardiography. Neither the aortic isthmus area nor the ductus arteriosus could be visualized. He received PGE1 at 17 hours of age but died 2 hours later. There was no other obvious cause of death and CoA was diagnosed postmortem. One full-term neonate died at 9 days of age. She was small for gestational age, with a birth weight of 2275 g, and presented with a murmur on day 7.

Echocardiography at 8 days revealed a dilated right ventricle and pulmonary artery, suggesting pulmonary hypertension. The ductal area could not be visualized. Shortly thereafter the infant died of sudden circulatory collapse. Last, 1 neonate died at home at 11 days of age after having been discharged at 3.3 days without symptoms. Dyspnea was reported by the parents before the infant was found dead at home.

Surgery and Postoperative Mortality

Surgery was performed in 83 infants at a median age of 8 days (range: 2–52 days). Resection with end-to-end anastomosis was performed in 54, extended end-to-end anastomosis in 14, aortic arch reconstruction on extracorporeal circulation in 11, and repair with subclavian flap technique in 4 cases. There were 2 postoperative deaths. Both were preterm (birth weights of 1350 and 2090 g); 1 patient died of necrotizing enterocolitis at 7 days of age and the other died of a respiratory syncytial viral infection at 7 months of age.

DISCUSSION

Neonates with isolated CoA have an excellent long-term prognosis if they receive timely diagnosis and surgical repair.7 In this population-based study we report that nearly half of all newborns with isolated CoA were discharged undiagnosed and both

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Echocardiography Performed</th>
<th>CoA</th>
<th>Prematurity</th>
<th>GBS</th>
<th>SGA</th>
<th>Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 weeks</td>
<td>Yes</td>
<td>CoA</td>
<td>Prematurity</td>
<td>No</td>
<td>No</td>
<td>9 days</td>
</tr>
<tr>
<td>38 weeks</td>
<td>No</td>
<td>CoA</td>
<td>Prematurity</td>
<td>No</td>
<td>&lt;24 hours</td>
<td>&lt;24 hours</td>
</tr>
<tr>
<td>39 weeks</td>
<td>Yes</td>
<td>Normal</td>
<td>GBS sepsis</td>
<td>No</td>
<td>&lt;24 hours</td>
<td>&lt;24 hours</td>
</tr>
<tr>
<td>42 weeks*</td>
<td>Yes</td>
<td>Normal</td>
<td>None</td>
<td>No</td>
<td>9 days</td>
<td></td>
</tr>
<tr>
<td>38 weeks*</td>
<td>Yes</td>
<td>PHT</td>
<td>SGA</td>
<td>No</td>
<td>Yes</td>
<td>11 days</td>
</tr>
<tr>
<td>40 weeks*</td>
<td>No</td>
<td>--</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>11 days</td>
</tr>
</tbody>
</table>

CDH, congenital diaphragmatic hernia; GBS, group B Streptococcus; PHT, pulmonary hypertension; SGA, small for gestational age; ---, not applicable.

* Death potentially preventable by prenatal or early postnatal diagnosis.

** The aortic arch could not be visualized.
prenatal ultrasound and postnatal POS had low sensitivity for this condition. The proportion who were discharged undiagnosed was not that different from what we found in a previous population-based study covering the period 1993–2001. Therefore, although the general problem of delayed detection of CCHDs decreased in our referral area, in parallel with increasing prenatal detection rates and the introduction of POS, this improvement was not evident for CoA. Almost half of those who were discharged developed circulatory failure, and 1 of these infants died at home. Our study did not address if preoperative circulatory collapse negatively influenced the neurodevelopmental outcome. Whether this is the case should be the subject of a longer-term follow-up study.

Our findings agree with previous reports that CoA had the highest proportion of delayed diagnosis of all CCHDs. Wren et al studied 170 newborns with CoA and reported that 11 were diagnosed prenatally, 68 before discharge, 87 after discharge, and 4 after death. Chang et al found that 1.7 infants per 100 000 live births died after a missed or late diagnosis of a CHD and that the most common diagnoses among those were hypoplastic left heart syndrome and CoA. Peterson et al found that 62% of 801 newborns with CoA were diagnosed after 3 days of age, and 2 were diagnosed postmortem.

Prenatal diagnosis of CoA lowers the preoperative risk of death or circulatory collapse. The proportion of newborns who were diagnosed prenatally in our study was low, however, which is similar to several other population-based studies. Some areas of Europe have achieved higher prenatal detection rates as a result of training programs for sonographers and accessible expert feedback from fetal cardiologists. Although similar programs have been implemented in parts of our referral area, resulting in increasing prenatal detection of CCHDs, CoA is still rarely detected.

The median age at diagnosis in our study was 5.6 days. Ward et al reported that symptoms of CoA developed at 2 to 5 days of age, when the constriction of the arterial duct was critical enough, ending in cardiovascular collapse at 8 to 12 days of age. According to data from the Swedish National Board of Health and Welfare, the mean stay at a maternity unit after giving birth was 1.9 days in 2012 and 75% of women were discharged before 2 days. Is it therefore possible to improve early postnatal detection of CoA when most newborn infants are discharged before the age at which symptoms usually become evident?

In our study some infants with weak or absent femoral pulses were discharged without previous echocardiography. Although our data did not permit calculation of the positive predictive value of weak or absent femoral pulses, we believe a newborn infant with such findings should undergo echocardiography the same day and always before discharge. Whether echocardiography should be routinely performed also in newborns with isolated murmurs is more controversial. The pediatrician is confronted with a significant number of neonates with murmurs, most of which are innocent. Ainsworth et al proposed that all neonates with a murmur should undergo an early pediatric cardiac assessment and reported that 0.6% of all newborns had murmurs and approximately half were due to cardiac defects. Singh et al performed echocardiography on all neonates with an asymptomatic heart murmur that persisted after 48 hours, reporting that the incidence of such murmurs was 205 in 21 957 (0.9%) and that 2% of infants with murmurs had major structural heart defects. One of the 205 infants had CoA. The incidence of isolated CoA in our study was 20 per 100 000 and a murmur was the only indication of a heart problem in 25% of cases. Therefore, assuming an incidence of isolated murmurs of 0.6% to 0.9%, only 6 to 8 of 1000 newborns with a murmur would have CoA.

Only 4 of 19 infants with CoA screened positive during POS, which in all was a result of the differences in oxygen saturation between the right hand and 1 foot. POS screening was gradually implemented and by 2014 it covered almost 100% of all births. Several large studies have shown that POS increases the early detection of CCHDs and minimizes the risk of preoperative circulatory collapse but has low sensitivity for aortic arch obstructions. The explanation is presumably a large left-to-right shunt across the foramen ovale, resulting in a near-normal saturation in the blood shunted right-to-left across the ductus arteriosus in combination with some blood flow across the narrow aortic isthmus. It is also possible that in some neonates with CoA the aortic isthmus narrowing may be so mild at the time when POS is performed that there is a pure left-to-right ductal shunt until the duct constricts with concomitant narrowing of the isthmus. Thus, newborn infants should be carefully examined before discharge, including palpation of the femoral pulses, even in units that use POS.

The peripheral perfusion index, as displayed on the pulse oximeter monitor, might be a promising additional tool for improving early detection of critical CCHDs with duct-dependent systemic circulation. A prospective study to evaluate its performance to detect coarctation should be performed.

Early echocardiography failed to detect CoA in 16 of the cases in our study. Three of these newborns deteriorated at home but were stabilized on readmission and an additional 3 had undergone...
echocardiography before death and the CoA could not be visualized. It is common knowledge among pediatric cardiologists that in some newborns with aortic isthmus hypoplasia, it is not possible to determine whether the systemic circulation is duct-dependent when echocardiography is performed while the ductus is still open. Sequential echocardiographic assessments should be planned in such cases until the duct has closed.

As explained in the Methods section many newborns in Sweden receive only 1 examination by a pediatrician. An additional routine postdischarge examination at 2 to 5 days of age of all neonates discharged before 48 hours could possibly contribute to earlier detection of some cases of coarctation.

CONCLUSIONS
A large proportion of neonates with CoA were discharged undiagnosed, resulting in circulatory collapse in approximately half of them. POS, which is a good screening method for most CCHDs, showed low sensitivity for CoA. Therefore, careful palpation of the femoral pulses and wide indications for early echocardiography are necessary, even in hospitals that have implemented POS. Also, early repeat echocardiography should be performed if signs or symptoms persist even if findings at the first echocardiographic examination are interpreted as normal or inconclusive. The prenatal detection rate of CoA is still low and needs to be improved in parallel with a critical evaluation of neonatal screening routines.

ACKNOWLEDGMENTS
We thank pediatric cardiac surgeon Dr Boris Nilsson for providing access to the local surgical file and for the description of the surgical techniques used and pediatric cardiologist Dr Annika Öhman for help with the registry search. We also thank all of the colleagues who contributed data on their patients.

ABBREVIATIONS
CCHD: critical congenital heart defect
CoA: coarctation of the aorta
PGE1: prostaglandin E1
POS: pulse oximetry screening
VSD: ventricular septal defect

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