Congenital Heart Disease

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REVIEW

Important Newborn Cardiac Diagnostic Dilemmas for the Neonatologist and Cardiologist–A Clinical Perspective

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ABSTRACT

Most congenital heart disease (CHD) is readily recognisable in the newborn. Forewarned by previous fetal scanning, the presence of a murmur, tachypnoea, cyanosis and/or differential pulses and saturations all point to a cardiac abnormality. Yet serious heart disease may be missed on a fetal scan. There may be no murmur or clinical cyanosis, and tachypneoa may be attributed to non-cardiac causes. Tachypnoea on day 1 is usually non-cardiac except arising from ventricular failure or a large systemic arteriovenous fistula. A patent ductus arteriosus (PDA) may support either pulmonary or systemic duct dependent circulations. The initially high pulmonary vascular resistance (PVR) limits shunts so that murmurs even from large communications between the systemic and pulmonary circulations take days/weeks to develop. At times despite expert input, serious CHD maybe difficult to diagnose and warrants close interaction between the neonatologist and cardiologist to reach a timely diagnosis. Such conditions include obstructed total anomalous pulmonary venous connections (TAPVC) and the need to distinguish it from persistent pulmonary hypertension in the newborn (PPHN)–the treatment of the former is surgical the latter medical. A large duct shunting right to left may overshadow a suspected hypoplastic aortic isthmus and/or coarctation. Is the right to left shunting because of severe aortic obstruction or resulting from a high PVR with little obstruction. The diagnosis of pulmonary vein stenosis (PVS) remains problematic often developing in premature infants with ongoing bronchopulmonary dysplasia (BPD), still being cared for by the neonatologist. While there are other diagnostic dilemmas including deciding the contribution of a recognised CHD in a sick neonate, this paper will focus on the above-mentioned conditions with suggestions on what may be done to arrive at a timely diagnosis to achieve optimal outcomes.

KEYWORDS

Obstructed pulmonary veins; persistent pulmonary hypertension; aortic coarctation; pulmonary vein stenosis; newborn

1 Introduction

Most problems in the newborn period clearly fall within the domain of neonatology. That may include many infants with CHD that have little or no impact on the well-being of the newborn infant. Prenatal

diagnosis in skilled hands readily detects most serious cardiac anomalies [1]. That forewarns the neonatologist to seek the involvement of the cardiologist [2]. That involvement also tends to occur if the infant develops increasing tachypnoea beyond the first postnatal day, cyanosis and/or differential pulses with advice often sought if the newborn is noted to have a murmur [3]. Premature infants with CHD benefit from the contributions from both disciplines [4]. There are however clinical situations where the diagnosis may be obscure and where there may be an overlap between what is best managed medically by a neonatologist versus that related to a significant CHD which requires early surgical intervention [5,6]. While those are few and far between, they nevertheless cluster within tertiary centres. The aims of this paper drawing on clinical experience, is to tease out what may be helpful in reaching a timely diagnosis to allow for the institution of appropriate treatment to achieve better outcomes. It will cover 3 conditions aiming to distinguish obstructed TAPVC from PPHN, a right to left shunting PDA maintaining the systemic circulation for an obstructed aortic arch from a tight coarctation rather than due to PPHN, and finally considering the diagnosis of PVS most commonly developing in premature infants with BPD who are usually still cared for by the neonatologist.

2 Conditions Reviewed

2.1 Obstructed Total Anomalous Pulmonary Venous Connections/Persistent Pulmonary Hypertension of the Newborn

Both the above entities have a significant overlap in their clinical presentation while their management starkly differs. Total anomalous veins may be of three subtypes–'supracardiac': Draining into the innominate vein or superior vena cava, 'cardiac': Draining into the coronary sinus, or in 25% 'infracardiac' draining into the portal system [7]. TAPVC is difficult to diagnose prenatally especially if not associated with the heterotaxy syndrome [8,9]. A review undertaken in the UK only diagnosed 1.9% of isolated TAPVC on prenatal screening [10]. In contrast better figures were obtained from specialised centres with the San Francisco group missing only 1 out of their 26 diagnosed prenatally, though 5 terminated and 1 was lost to follow-up [9]. The first two more common subtypes if unobstructed as they usually are, may present insidiously with mild tachypnoea, recurrent chest infections and borderline low saturations in the high 80s or low 90s, but may be picked up earlier by pulse oximetry testing, prompting detailed clinical assessment [11–13]. The ECG will show RV hypertrophy. The chest radiograph suggests mild cardiomegaly, prominence of the pulmonary conus and with time pulmonary plethora. It will also exclude other pathology. There may or may not be a murmur, depending on any associated heart defect. Unexplained and continued tachypnoea prompts an echocardiogram for a definitive diagnosis [12].

Infracardiac TAPVC may present acutely with cyanosis since they tend to be obstructed because of the high hepatic resistance [5,7]. Chest radiographs may show a proximal "snow storm" or ground glass appearance, reflecting pulmonary oedema [5,14]. These infants develop pulmonary hypertension which is pulmonary venous (post-capillary) in origin. One is tempted to administer inhaled nitric oxide (iNO). However, this is a condition (alongside PVS, cor triatriatum or left ventricular diastolic dysfunction) where there is inability of the blood to leave the lungs freely. Sudden pulmonary vasodilatation with a potent pulmonary vasodilator tends to be ineffective, unphysiological and can lead to sudden and severe deterioration [5]. However, iNO has an important role in the post-operative care [15], as post-operative pulmonary hypertension may persist despite relief of the obstruction [16,17]. A significant decrease in PVR and pulmonary artery pressure may be noted when iNO is given post-operatively [18]. A failure of the post-operative newborn with pulmonary hypertension to respond to iNO successfully discriminated between anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction [19].

PPHN or persistent fetal circulation results from the disruption in the normal perinatal fetal-neonatal circulatory transition [20]. The common haemodynamic construct is a sustained increased elevation of PVR resulting in shunting of deoxygenated blood from the pulmonary to the systemic circulation

potentially causing severe hypoxia [21]. A typical infant presents with hypoxaemic cardio respiratory failure, pre/postductal difference in oxygen saturations of >5%. However it should be noted that such a gap can also be found in left sided obstructive heart abnormalities such as coarctation of the aorta (see 2.2). PPHN is seen in 1 to 2 per 1000 live births; mostly in term and post-term infants. Common underlying diagnoses are meconium aspiration syndrome and perinatal asphyxia, and characterised by release of vaso-constrictive humoral factors and/or suppression of pulmonary vasodilators, both leading to vasospasm. Medication intake during pregnancy such as serotonin reuptake inhibitor fluoxetine after 20 weeks, may also lead to sustained elevation of the PVR [22], as well as space occupying lesions such as a diaphragmatic hernia, congenital cystic adenomatoid malformation, etc. [21]. Physical examination in such infants is characterised by cyanosis with or without increased work of breathing. One may hear a loud summated S2 in the pulmonary area compared to the aortic area, and occasionally a soft ejection systolic murmur. Simultaneous pre/post-ductal arterial blood gas values or transcutaneous oxygen saturations suggests right to left ductal shunting. A gradient of 10% or more suggests PPHN but does not rule out CHD. The chest X-ray may be normal, show pathology especially if there is a space occupying lesion or pulmonary hypoplasia, and/or oligaemic lung fields. The ECG shows normal RV dominance, occasionally RV hypertrophy and/or myocardial ischaemia. Increase lability in oxygenation status, a fall in oxygen saturation even with minor weaning of fractional inspired oxygen, at times laboured breathing, presence of underlying predisposing factors (meconium aspiration/asphyxia) may all favour PPHN over CHD. Distinguishing PPHN and cyanotic CHD on clinical grounds can be challenging but essential since management is quite different [23]. Clinical cues to narrow the diagnosis have been recently summarised [24]. Absence of risk factors (such as meconium aspiration syndrome, perinatal asphyxia or sepsis), no/minimal signs of respiratory distress, presence of heart murmur, reduced femoral pulses, abnormal heart configuration/cardiomegaly, blood pressure gradient between upper and lower body and lack of response to high concentrations of oxygen are indicators of the presence of critical CHD.

Echocardiography is still required to rule out CHD as well as to confirm the clinical diagnosis of PPHN and to assess its severity. Delayed diagnosis of critical CHD may lead to a worsening prognosis. When in doubt while awaiting echocardiography, often unavailable in peripheral centres, a prostaglandin E1 (PGE1) infusion may be started in anticipation of a potential heart defect. In PPHN PGE1 might have a mild pulmonary vasodilating effect [20,25] and in severe PPHN it will preserve postductal systemic circulation by keeping the duct open [26]. However PGE1 may lead to clinical deterioration of infants with certain CHD such as TAPVC. It is also important to recognise that other critical CHD may mimic PPHN such as transposition of the great vessels, pulmonary atresia with an intact ventricular septum and tricuspid atresia. The PGE1 infusion can be weaned and stopped after transfer to a tertiary centre and following confirmation of the final diagnosis by echocardiography.

Distinguishing between obstructed TAPVC and PPHN remains an important dilemma for both the neonatologist and cardiologist as the management of one is surgical while that of the other is medical, with improved outcomes with iNO at times aided by intravenous or oral pulmonary vasodilators for the latter if it persists [25]. A higher preductal versus a postductal saturation favours PPHN but not always [27]. A chest X-ray will be helpful as noted above, as it may show underlying pathology such as meconium aspiration, a diaphragmatic hernia or neonatal pneumonia. The heart size will be normal in both conditions while the pulmonary vasculature will tend to be reduced in PPHN but may show a ground glass appearance in obstructed TAPVC [14]. An ECG will not be discriminatory as it may well show persistent RV dominance/hypertrophy in both conditions. Cyanosis will also be present in both conditions with or without tachypnoea. The echocardiogram essentially shows what appears to be normal intracardiac anatomy. However in obstructed TAPVC all the flow through the atrial septal defect or stretched patent foramen ovale will be right to left [5], while in PPHN there will be bidirectional shunting at atrial and duct level. Ideally one may be able to clearly show by imaging and colour Doppler that in

PPHN the pulmonary veins enter the left atrium thereby excluding TAPVC. However it is important to remember that the pulmonary vein confluence in TAPVC usually lies behind the left atrium and in some views the veins may appear to be entering the left atrium. If one can visualise the connecting vein which travels caudally from the pulmonary vein confluence to and through the diaphragm, the diagnosis will be confirmed [5]. Colour Doppler interrogation of such a vessel will show that the direction of flow is downwards, similar to that of the descending aorta but opposite to the upward flow in the inferior vena cava or azygos vein. The Doppler velocity is low and continuous. Multiple intrahepatic venous dilatations communicating with an unusually wide portal vein may also be noted if the diagnosis is delayed [28].

While PPHN usually occurs in situations well recognised by the neonatologist/paediatrician, it is essential that the cardiologist definitively excludes obstructed TAPVC. PGE1 prescribed for the latter condition like iNO theoretically may result in worsening of the baby's state because of potentially increasing the pulmonary flow while there is obstructed drainage requiring early surgery. Nevertheless, it is often used at least initially to facilitate transport and may help support the systemic circulation [5,29]. A hyperoxaemic test [30] if used at all [21], may be helpful if faced with the dilemma of whether a cyanotic infant has obstructed pulmonary veins or PPHN when echocardiography and/or a cardiologist is not readily available. The former will tend to give lower PO2 readings while the latter a greater rise in 100% O2 [21].

2.2 Right to Left Shunting PDA: Hypoplastic Aortic Isthmus, Coarctation of the Aorta/PPHN

At times in the newborn it may be difficult to exclude a significant coarctation of the aorta and/or a hypoplastic isthmus in the presence of a large PDA shunting right to left. The latter not only confounds the clinical signs resulting in good volume femoral pulses [6], but echocardiographically the duct may mask the coarctation if it overlies the juxtaductal area. Antenatal suspicions may be suggested by noting a dilated right ventricle [31] but as the duct overlaps the area of narrowing, clear imaging of the site may be lacking. Hypoplasia of the aorta isthmus if visualised may be helpful further aided by colour Doppler imaging which may show turbulence at that site as it enters the descending aorta [31]. Pulse wave Doppler interrogation of the narrowed region may show a "saw-tooth appearance, infrequently seen because of the patency of the duct [32]. Despite these findings aortic coarctation may still be missed in 25% of cases even when the scans are carried out at a specialised centre, particularly if there is no follow-up third trimester scan [33]. Nevertheless if a coarctation of the aorta is suspected it would be prudent for such deliveries to take place in a tertiary centre with newborn intensive care facilities and ideally on-site paediatric cardiac surgery.

Coarctation of the aorta in the newborn may be readily picked up if the duct gradually closes with the infant developing mild tachypnoea and weak femoral pulses [6]. Echocardiography will confirm the diagnosis with similar findings as seen prenatally especially if the closing duct is away from the site of narrowing. In situations where PPHN is suspected, a large duct maybe observed shunting right to left but with clear views of an unobstructed aortic arch. At times however there may be a suggestion of possible coarctation and/or aortic isthmus hypoplasia with the relevant area overshadowed by the duct. How then should the infant be managed especially if there was the prenatal finding of a larger right ventricle compared to the left?

Some aspects of early assessment and management overlap between what might be reasonable at a tertiary centre (with relatively easy access to paediatric cardiology) versus smaller centres. These include keeping the infant monitored with pulse oximetry, regular assessment of femoral pulses (presence and strength), urine output and frequent capillary blood gases to assess lactate levels. These observations are in addition to clinically examining these infants for colour and perfusion as well as parenteral signs of "unwellness" (lethargy, poor feeding). In addition at a tertiary centre, these infants will be frequently monitored by echocardiography; the earliest sign of ductal narrowing which reveals an underlying

coarctation, will prompt administration of PGE1 previously withheld, and transfer to a surgical centre and/or listing for surgical repair. If unrecognised in smaller centres without cardiology input, the presentation may be one of gradual deterioration or sudden collapse [6,13]. A high index of suspicion will however enable appropriate therapy and early transfer on a PGE1 infusion to maintain duct patency and to keep the baby "safe" during transport [29]. The infusion may then be stopped at the tertiary centre if the diagnosis is unclear, setting into motion the above strategy to facilitate a definitive diagnosis. Routine use of PGE1 in such suspected cases as sometimes occurs even at a tertiary centre, may delay diagnosis and intervention. If the baby is well at the outset, and there is a suggestion but not confirmation of a coarctation/hypoplastic aortic segment, and despite the duct showing mostly a right to left shunt which may be related to a high PVR, then provided the baby is watched carefully along the lines stated above, it may be reasonable not to commence PGE1. That will allow the duct to close on its own accord, allowing for better visualisation of the area under question. Once signs suggestive of a coarctation develop on clinical review, an echocardiogram done then may provide better visualisation of the periductal area confirming the diagnosis. Occasionally a CT angiogram of that site may help clarify the anatomy and/or determine the extent of the narrowing or distal arch hypoplasia [34].

2.3 Pulmonary Vein Stenosis/Bronchopulmonary Dysplasia

Neonatologists continue to care for premature babies especially if they have gone on to develop BPD. In preterm infants the diagnosis of BPD is made at 36 weeks corrected gestational age. For example, for an infant born at 25 weeks gestational age, the gap between birth and the diagnosis is 11 weeks. BPD may also be accompanied by gradually evolving PVS [23,35]. Previous investigators have outlined the association as well as commented upon the natural history. A multi-centre study found that 29/39 (74%) infants who had PVS, had BPD. The postnatal age at diagnosis of PVS was >6 months [36]. Of concern, interrogation of pulmonary vein flow may not always be performed as part of a routine chronic pulmonary hypertension evaluation. As PVS is a diagnosis which evolves, a single interrogation as part of confirming normal anatomy, may be erroneously considered 'sufficient' as far as pulmonary vein connections imaging is concerned. The clinical and physiological effects of PVS may be non-specific and can be easily missed. Rarely it may be congenital and associated with CHD [37]. The infant may have unexplained tachypnoea, the need for respiratory support, a lack of response to diuretics but no murmur. Signs of a loud summated second heart sound may be noted. A chest radiograph may show features of pulmonary oedema and an ECG right ventricular hypertrophy.

The clinical and physiological effects of abnormal LV function may overlap those of PVS, although there are likely to be major differences in end-diastolic LA pressure and inter-atrial shunting [38]. Echocardiography as noted earlier may aid the diagnosis of PVS using colour Doppler interrogation from the 'crab-view' (modified short axis). While there is no standard definition, increased pulmonary vein peak flow velocity >1.1 m/s and continuous non-phasic flow (loss of the typical biphasic Doppler pattern) are suggestive of PVS [39]. Drossner et al. [36] echocardiographically identified PVS in 26 subjects with continuous, turbulent flow with a calculated mean gradient >5 mm Hg. A further study found that the median age at diagnosis was 7.4 months and 11 (42%) infants had BPD [35]. A recent natural history study of chronic pulmonary hypertension noted that preterm infants who had BPD (of whom 89% was classified as severe) had a concurrent diagnosis of PVS in 26% of subjects [23]. An earlier study of premature infants identified PVS in 26% of infants with BPD associated pulmonary hypertension who underwent catheterization [40]. An unremitting clinical course, lack of response to diuretics and no improvement (or deterioration) with pulmonary vasodilators such as iNO or sildenafil should raise the suspicion of PVS and/or LV functional disease. CT angiography of the pulmonary veins may be required to confirm the diagnosis [41].

3 Conclusions

PPHN and obstructed TAPVC may have similar clinical features presenting with cyanosis, without murmurs, but with important differences in their management–the former requiring intensive medical treatment and the latter urgent cardiac surgery. PPHN may be associated with meconium aspiration/ perinatal asphyxia/chest space occupying lesion etc., which may show up on a chest X-ray. There is a higher preductal versus postductal oxygen saturations. In contrast obstructed TAPVC rarely shows differential cyanosis with the chest X-ray suggesting a ground glass appearance. Of importance the echocardiogram in PPHN shows bidirectional shunting at atrial and duct level with the pulmonary veins entering the left atrium, while in obstructed TAPVD "pure" right to left shunting occurs at atrial level with usually an anomalous vein transversing downwards to the portal systems arising from a pulmonary vein confluence behind the left atrium.

Suspected coarctation of the aorta and/or a hypoplastic aortic isthmus may be obscured by an overlapping large PDA. If delivered at a tertiary centre allowing the duct to close may provide a better view of the juxta-ductal area on echocardiography, promptly repeated following a weakening of the femoral pulses. If neonatal coarctation of the aorta is suspected away from a tertiary centre, transfer on PGE1 is advisable. That may be stopped with careful monitoring if imaging does not confirm a coarctation because of a large overlying PDA. CT angiography may provide good imaging of the aortic arch if echocardiography fails to provide a definitive diagnosis.

PVS remains difficult to diagnose but should be considered if there is persistent tachypneoa, pulmonary hypertension and continuous non-phasic flow in one or more pulmonary veins, especially in a setting of bronchopulmonary dysplasia. CT angiography may be helpful.

Dedication: This paper is dedicated to the memory of Dr Andrew Ramsden, former Director of Monash Newborn, who fostered close collaboration between neonatologists and paediatric cardiologists with benefit to all.

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