Contemporary incidence of stroke (focal infarct and/or haemorrhage) determined by neuroimaging and neurodevelopmental disability at 12 months of age in neonates undergoing cardiac surgery utilizing cardiopulmonary bypass†

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Abstract

OBJECTIVES: When evaluated prospectively, acute brain injury is reported in up to 75\% of neonates undergoing cardiopulmonary bypass (CPB), predominantly white matter injury rather than stroke. This study investigates the incidence of stroke (focal infarct and/or haemorrhage) detected by neuroimaging in contemporary clinical practice, whereby magnetic resonance imaging/computed tomography routinely occurs in response to clinical events, comparing those undergoing the Norwood procedure with those undergoing other neonatal procedures involving CPB, and defines the relationship between stroke and neurodevelopmental disability (NDD) at 12 months of age.

METHODS: One hundred and twenty neonates underwent CPB between July 2011 and December 2014: 25 Norwood procedures and 95 non-Norwood procedures. Data were retrospectively collected including clinical data and 12-month neurodevelopmental assessment using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III).

RESULTS: Stroke was detected in 12\% of neonates in current clinical practice: 24\% of the Norwood group vs 8\% of the non-Norwood group ($P = 0.03$). Significant predictors of stroke in the univariate analysis included the Norwood procedure, lowest operative temperature and use of extracorporeal membrane oxygenation ($P < 0.05$). The lowest operative temperature and use of extracorporeal membrane oxygenation remained significant in the multivariate analysis ($P < 0.05$). Fifty-seven percent were assessed using the BSID-III assessment, and 68\% demonstrated NDD in at least 1 subscale. In neonates who suffered stroke, the incidence of NDD was significantly greater in 4/5 subscales compared with those with no injury ($P < 0.05$). The Norwood group had a significantly greater incidence of NDD in 2/5 subscales when compared with the non-Norwood group ($P < 0.05$).

CONCLUSIONS: Stroke, established by neuroimaging in contemporary clinical practice, was detected in 12\% of neonates having CPB, and those undergoing the Norwood procedure have a 3-fold risk of injury. Stroke was associated with NDD at 12 months of age.

Keywords: Stroke • Neurodevelopment • Cardiopulmonary bypass • Neonates

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INTRODUCTION

The subtypes of congenital heart disease (CHD) requiring neonatal surgery are most often at the critical end of the phenotypic spectrum, involving correction of significant structural abnormalities. Optimizing neurological and developmental outcomes in neonates undergoing cardiac surgery is the current focus of care.

The incidence of acquired brain abnormalities in the neonatal cardiopulmonary bypass (CPB) group is high when evaluated prospectively. In such studies, where brain imaging has been performed before and after surgery, abnormalities have been reported in up to 75% of neonates with complex CHD [1–4]. The most common findings include pre-existing and new white matter injury (WMI) in more than half and haemorrhagic/ischaemic stroke occurring in approximately 10–15% of patients [5–7].

Neurodevelopmental disability (NDD) is defined by standardized, objective neurodevelopmental assessments at 1 year of age and at later time points. NDD has been reported in more than 50% of the neonatal CPB group at 1 year [8, 9]. Common manifestations include cognitive impairment, delays in speech, language, visual-motor and visual-spatial skills, attention deficit hyperactivity disorder as well as other learning and socialization dysfunctions [8, 10, 11]. These manifestations of NDD have been found to progress onto school age and beyond [12–14].

The aetiology of acute brain injury and NDD in neonates undergoing operation for CHD is multifactorial with both innate and acquired contributing factors [15]. WMI may be present at birth, with genetic and foetal environmental factors also influencing neurodevelopmental outcomes. Cardiac surgical techniques and postoperative care have been progressively refined; nevertheless, CPB in a neonate brings with it numerous potential haemodynamic, inflammatory and autoregulatory challenges for the developing brain [16]. Collectively, events surrounding surgery are now understood to have less impact on neurodevelopment than previously believed [17, 18].

The aim of this study is to investigate the incidence of stroke (established by neuroimaging) in neonates undergoing CPB detected in contemporary clinical practice, where magnetic resonance imaging (MRI)/computed tomography (CT) imaging was conducted in response to clinical events. We sought to identify modifiable risk factors for stroke and NDD, and we compared outcomes in those undergoing the Norwood procedure (reflecting a high level of technical complexity and alterations to brain blood flow) with those undergoing other neonatal procedures involving CPB. Furthermore, we sought to define the relationship between stroke and NDD at 12 months of age.

MATERIALS AND METHODS

This project was approved by Sydney Children’s Hospital Network Ethics Committee (LNR/12/SCHN/513).

One hundred and twenty eligible neonates who underwent CPB between July 2011 and December 2014 were included in the study. Patients were grouped into those who underwent the Norwood procedure (n = 25) and those who underwent all other procedures involving CPB (non-Norwood, n = 95); the details of the surgical procedures are included in Table 1. Clinical data from the first year of life were retrospectively collected including operative and clinical information, neurological investigations and the results of a 12-month neurodevelopmental assessment using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). The BSID-III scaled scores were used for analysis as opposed to the composite scores as this allows for identification of sensitive differences in the language and motor scales that are not evident in the composite scores. The scales are age normed to have a mean of 10 and a standard deviation of 3, with a score between 8 and 12 classified as within normal limits. NDD was defined as a deviation from normative data, i.e. a score of 7 or less in each subscale.

Stroke was classified as haemorrhage (intraventricular or parenchymal) and/or focal infarction, and classification of injury followed the reporting methods of Beca et al. [5]. Stroke was identified from neuroimaging reports including ultrasounds (US), MRI and CT, and all but 1 incidence of detected stroke was confirmed by MRI or CT. Subdural haemorrhage was recorded but not considered as stroke due to its frequent occurrence in the healthy neonatal population. Incidence of WMI was also noted but was not included in further analysis due to the limited number of MRI scans performed in our clinical cohort. Imaging and reports were re-reviewed by 2 neuro-radiologists (K.P./R.G.). Patients for whom neuroimaging was not performed were recorded as having no detected abnormality or clinical indication of stroke; however, it is acknowledged that some of the ‘clinically silent’ strokes may have been undetected due to not reaching the threshold for imaging.

Statistical analysis was performed using IBM SPSS Statistics (Version 21). The nominal P < 0.05 was used to determine statistical significance, but all P-values are presented in Tables 1–2 and in all supplementary tables. See Supplementary Material, Supplementary Expanded Methods, for further information and a detailed description of the statistical analysis.

RESULTS

Patient demographics and details of surgical procedures are described in Table 1. Eleven patients died before the 12-month assessment (9%); 4 having undergone the Norwood procedure and 7 underwent non-Norwood procedures (16% vs 7%, respectively, P = 0.17). There were no significant differences in mortality rate or timing of death between the 2 groups. Of those who died, 5 (46%) patients suffered a stroke; however, stroke was not the primary cause of death in any of these patients. All deaths occurred during the first hospital admission.

Neurological morbidity

Neuroimaging was performed in 77 (64%) patients. Of the entire cohort, US was performed in 74 (62%) patients, CT on 14 (11%) and MRI on 11 (9%). Preoperative neuroimaging was performed in 44 (36%) patients: preoperative US (40), preoperative US and CT (2), preoperative US and MRI (1) and preoperative MRI (1); 96% of these scans were reported as normal. Postoperative imaging was performed in 53 (44%) patients: postoperative US (35), postoperative CT (4), postoperative US and CT (5), postoperative US and MRI (5) and postoperative US, CT and MRI (4). Neuroimaging was performed both pre- and postoperatively on 22 (18%) patients. Indications for primary imaging are described in Supplementary Material, Table S1.

Of the entire clinical cohort, 14 (12%) patients were identified as having an ischaemic and/or haemorrhagic stroke. This was
of stroke. Of those who had a stroke, 12 (40%) and severe (>3 foci or >5% of hemisphere) in 1 (20%). No patients were identified as having WMI without stroke (Supplementary Material, Table S2), acknowledging that WMI was detected in 5 patients who had a stroke (4%) and this was classified as: mild (≤3 foci and 2 mm) in 2 (40%), moderate (>3 foci and ≤10 foci, or >2 mm but <5% of hemisphere) in 2 (40%) and severe (>10 foci or >5% of hemisphere) in 1 (20%). No patients were identified as having WMI without stroke (Supplementary Material, Table S2), acknowledging that WMI can only be assessed on MRI. Of those who had a stroke, 12 (86%) had associated clinical events, most commonly seizures (57%) that were more prevalent in the Norwood group (P < 0.01), Table 2.

The Norwood procedure, the lowest operative temperature, the use of extracorporeal membrane oxygenation (ECMO), length of stay (LOS) in hospital and LOS in intensive care unit were significantly associated with detected stroke in the univariate logistic regression analysis (P < 0.05, total R² = 0.29), Supplementary Material, Table S3. The Norwood procedure, the lowest operative temperature and the use of ECMO were entered into a backward selection multivariate analysis where the lowest operative temperature and the use of ECMO remained significant predictors of stroke (P < 0.02, total R² = 0.08), Supplementary Material, Table S4. LOS in hospital and LOS in intensive care unit were not included in the multivariate analysis as these variables have an expected association with stroke and are likely influenced by a stroke occurring rather than being predictive of stroke.

### Neurodevelopmental assessment

Of those who survived till 12 months of age (n = 109), 68 (62%) had 12-month neurodevelopmental assessment using BSID-III. Forty-one (38%) patients were alive who did not have a BSID-III assessment, and reasons for no assessment and median scores for each of the subscales are described in Supplementary Material, Table S2.
scales remained in 51% of the cohort.

occurred in 68% of the entire cohort, and delay in 2 or more sub-

the no injury group (P < 0.05), Fig. 1, and a significantly greater number of patients who suffered delays in expressive language and gross motor skills when compared with all other neonates undergoing cardiac surgery involving CPB. With our current understanding of acute risk and later outcomes, these figures should provide a guide in the discussion of risk with parents prior to neonatal bypass surgery. Previous figures derived from studies where neonates and lower risk older children are combined (e.g. stroke risk of 0.5–2%) do not adequately estimate the risk of stroke during the neonatal period [19, 20].

Rates of stroke detected in those who underwent the Norwood procedure (24%) were 3 times greater than the other neonatal group (8%). There are many potential explanations for this finding beyond the scope of this study, namely that the Norwood group (i) requires more complex perfusion strategies because of known associations with placental insufficiency and abnormalities of cerebral blood flow [21] and (iv) may have genetic abnormalities in gene pathways affecting both brain and heart development [22].

Significant factors for stroke in the univariate analysis included the Norwood procedure, the lowest operative temperature, the use of ECMO, LOS in hospital and LOS in intensive care unit. Several operative factors previously reported to be associated with brain injury were found to have no significant relationship with stroke in our series, including lower birth weight [6], duration of CPB [5] and the use and duration of deep hypothermic circulatory arrest [5]. Significant predictors of stroke in the multivariate analysis included lower operative temperature and the use of ECMO (total R² = 0.08). Deep hypothermia during CPB in complex cardiac procedures is a routine practice and has been well established as a neuroprotective strategy. Lower operative temperatures are typically a reflection of surgical complexity, particularly with regard to the Norwood procedure, which is likely to be the contributing factor for increased risk of stroke in these patients rather than low temperature itself.

The use of ECMO being a risk factor for brain injury in neo-

nates has previously been described by Polito et al. [23], whilst the use of ECMO in our clinical practice is only initiated in critical circumstances and cannot be considered a modifiable risk factor.

### DISCUSSION

Understanding and reducing the risk of brain injury and later NDD is crucial in optimizing long-term outcomes for children with CHD and minimizing the downstream demand on health and welfare resources. We report the incidence of stroke in neonates undergoing cardiac surgery detected in contemporary clinical practice and correlate these findings with 1-year neurodevelopmental outcomes in the same population, with a particular focus on the relationship between stroke and NDD, as well as outcomes in those undergoing the Norwood procedure when compared with all other neonates undergoing cardiac surgery involving CPB.

Stroke was detected by neuroimaging in 12% of neonates who underwent cardiac surgery involving CPB. With our current understanding of acute risk and later outcomes, these figures should provide a guide in the discussion of risk with parents prior to neonatal bypass surgery. Previous figures derived from studies
our results support the need for high surveillance and the awareness of potential stroke in this group.

Despite independent and multivariate factors being identified as significant predictors of stroke in our cohort, they accounted for only 29% of variation in outcomes, with only 8% of variance being accounted for in the multivariate model, suggesting that other variables not measurable or identified in this series contribute towards the risk of stroke and supporting that the aetiology of brain injury and NDD is multifactorial with other potential factors such as brain immaturity, genetic factors and epigenic insults likely impacting outcomes [4, 5, 15].

Beca et al. [5] have demonstrated that when assessed prospectively, very high rates of acute brain injury may be detected (~75%) in neonates and infants after cardiac surgery, most of which is WMI [1–3, 5]. Detection of WMI was limited in our study due to the small number of MRI scans performed in our clinical cohort; however, the rate of stroke detected independent to WMI (12%) was similar to the stroke rate identified by Beca et al. [5–7], where all patients underwent postoperative MRI imaging (10–15%). Our findings suggest that our clinical threshold for imaging was effective in identifying most stroke but highlights that WMI is likely under-reported in routine clinical practice. It is

Figure 1: Proportion of NDD: the Norwood procedure group versus non-Norwood procedure group. CI: confidence interval; NDD: neurodevelopmental disability; OR: odd ratio.

Figure 2: Proportion of NDD: stroke versus no stroke. CI: confidence interval; NDD: neurodevelopmental disability; OR: odd ratio.
expected that patients with WMI alone were not identified in our series, because the clinical threshold for imaging was not reached for other reasons. Furthermore, in patients where stroke was identified by CT and MRI was not performed, WMI may not have been identified as this is best assessed by MRI.

US was performed in a large number of patients in our cohort to exclude major structural abnormalities with no further imaging performed. The reliability of US in detecting brain abnormalities is questionable in recent reports. Rios et al. [24] identified that US only detected 3% of preoperative brain injuries in CHD neonates compared with 26% detected with MRI in the same population. The continued use of US in this context should be further investigated.

The rate of NDD in our cohort was similar to previous reports [8, 9, 25] with rates of delay in at least 1 BSID-III subscale occurring in 68% of our cohort, and delay in 2 or more subscales occurring in 51% of our cohort at 12 months of age, validating the understanding that NDD following neonatal cardiac surgery is common. Although worse neurodevelopmental outcomes following brain injury in neonates undergoing cardiac surgery have been reported previously [26], this is the first study to report the relationship between clinical stroke detected by neuroimaging (independent to WMH) and later NDD, demonstrating that neurodevelopmental function following stroke is importantly altered, with outcomes in cognitive function, receptive language and fine motor skills being the most affected. Patients who underwent the Norwood procedure were also found to have worse neurodevelopmental outcomes compared with all other neonates undergoing CPB. Other investigators have shown that patients undergoing the Norwood procedure have worse neurodevelopmental outcomes than population norms [27]. Our study, albeit with small numbers of Norwood patients, highlights the difference between Norwood patients and other neonates undergoing surgery involving CPB.

The association between clinically detected stroke and the incidence of NDD appears intuitive but has not, to our knowledge, been demonstrated previously and is a clinically important finding. In smaller strokes, which constitute the majority of events, motor recovery is often quick and apparently complete. In that context, it is easy for the clinical narrative associated with the stroke to be relegated to the past, something that has been recovered from. However, this study shows that stroke has an important impact on neurodevelopment at 12 months of age.

The effectiveness of the intervention for NDD is increased when performed at a younger age and with more frequent interventions [28], suggesting that interventional services, such as physiotherapy and speech pathology, should be introduced as early as possible for those who suffer stroke or demonstrate NDD on early assessments.

In this study, a BSID-III score of 7 was used as a cut-off to describe NDD. A score of 5–7 is generally considered 'mild' NDD but nevertheless is a threshold for referral to interventional services. A high proportion of patients in our cohort were found to score lower than this, signifying moderate to severe delay. This was particularly prevalent in the stroke group with rates of moderate to severe delay ranging from 13% to 50% across the separate subscales compared with 2–7% in those with no stroke.

Because of the high number of individuals displaying NDD across our entire cohort, our findings support the recommendation of universal long-term neurodevelopmental assessment in all infants with CHD as advised by American Heart Association guidelines [14] and continued education in the cardiac and paediatric community about the increased risk of delayed neurodevelopment in this population including the recommendation for essential routine screening [29]. Structural brain imaging with MRI should also be considered in all patients undergoing complex neonatal surgery. At our centre, routine MRI is now standard protocol for all neonates undergoing Norwood surgery, and we are advocating for resources to allow this to become routine clinical practice in all neonates with CHD undergoing cardiac surgery involving CPB.

Limitations

Although this is the largest contemporary study investigating the incidence of stroke detected in routine clinical practice, the retrospective nature of this study has several limitations. Most importantly, because of the infrequent use of MRI and CT in clinical practice, some stroke and other important abnormalities (i.e. WMH) may have been under-reported in this cohort. The majority of neuroimaging was US, which has been found to have poor reliability in detecting brain abnormalities. Additionally, because of the lack of standardization in the frequency, timing and type of neuroimaging performed, ascertainment bias may be present when describing the incidence of stroke detected. Although this is a limitation of our study, our results provide an understanding of the rates of abnormality detected in current clinical practice and support the use of routine MRI screening to detect all abnormalities, particularly ‘clinically silent abnormalities’ in complex CHD. Furthermore, the results provide realistic prognostic figures that are beneficial in presurgical counselling with families. As this was not a prospective protocol, not all patients had 12-month neurodevelopmental assessments, and standardization of clinical notes and recorded information were not possible.

The single-institution nature of the cohort has limitations including restricted generalizability across different practice settings and small sample sizes. The patient numbers were relatively low for various variables examined, including the number of patients who required ECMO or had deep hypothermic circulatory arrest, and the number of strokes detected; consequently, the results may be underpowered to determine differences in outcomes resulting from variances in intraoperative management strategies and in determining the association between these variables and stroke outcomes. Seizure events not associated with abnormal cross-sectional brain imaging were not classified as stroke and this might under-recognize the significance of isolated seizures. Limitations also exist in the 12-month BSID-III assessment, as although the tool provides an early indicator of individuals who may need intervention, the use of the BSID-III at 12 months of age is controversial, and scores obtained may be influenced by motivation, attention and interests and the test may not assess all the skills a child might be capable of using. The 12-month BSID-III assessment has also been found to overestimate ability [30]. A review of the same cohort with follow-up NDD assessment at a later stage would be beneficial in understanding the lasting implications of our findings.

CONCLUSION

Clinically detected stroke identified by neuroimaging affects 12% of neonates having CPB. Neonates undergoing the Norwood procedure are at a 3-fold increased risk of stroke compared with
all other neonates having CPB. A diagnosis of stroke, made after brain imaging prompted by a clinical event, is associated with worse performance on neurodevelopmental assessment at 12 months of age, with 75% of those who suffered a stroke falling below average in 2 or more subdomains. The incidence of stroke is a potentially modifiable risk factor for later neurodevelopmental disorder. Routine neurodevelopmental screening and early interventions are required to optimize long-term functioning and outcomes in neonatal cardiac surgery patients.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at ICVTS online.

**Conflict of interest:** none declared.

**REFERENCES**


