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Accuracy and Reliability of Qualitative Echocardiography Assessment of Right Ventricular Size and Function in Neonates

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Abstract

Background: Subjective assessment of right ventricular (RV) function by neonatal echocardiography lacks validation. Incorrect diagnostic assignment in patients with suspected pulmonary hypertension (PH) may lead to unnecessary treatment or missed treatment opportunities.

Methods: Six evaluators [experts (n=3), novice (n=3)] were asked to independently rate RV characteristics (global function, dilation, septal flattening) based on standardized echocardiography images. We randomly selected 60 infants, 35 weeks gestation at birth, of whom 30 were clinically unwell with acute pulmonary hypertension (aPH) and 30 were healthy controls. aPH was defined by echocardiography presence of right-left shunting across transitional shunts or elevated right ventricular systolic pressure as estimated by the magnitude of the regurgitant jet across the tricuspid valve with impaired oxygenation. Inter-rater comparative evaluation within groups and between groups were performed using Kappa statistics.

Results: Global agreement between evaluators for subjective assessment of RV function [0.3 (0.03), p<0.001], size [0.14 (0.02), p<0.001] and septal flattening [0.2 (0.02), p<0.001] was uniformly poor. Agreement in RV function assessment was marginally better for both expert [0.32 (0.08), p<0.001 vs 0.13 (0.081), p<0.001] and novice [0.4 (0.08), p<0.001 vs 0.06 (0.07), p<0.001] evaluators. Overall, the diagnosis of aPH vs control was misclassified in 18% of cases.

Conclusion: This study demonstrated significant variability in qualitative assessment of RV size and function by trained evaluators, regardless of level of expertise attained. The reliability of objective measures of RV hemodynamics requires prospective evaluation.

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Conflict of Interest

There are no conflicts of interest to declare.

Keywords

Echocardiography; pulmonary hypertension; right ventricular function; reliability testing

Background

Neonatal pulmonary hypertension (PH) is primarily characterised by increased pulmonary vascular resistance (PVR) and may be acute or chronic in origin [1]. Acute PH (aPH) commonly results from failure in the normal postnatal reduction in PVR leading to impaired oxygenation and right ventricular (RV) dysfunction. The incidence of moderate/severe aPH is estimated at 2–6 per 1,000 live births and affects up to 10% of all babies [2]. Despite recent advances in both diagnostic and therapeutic modalities early mortality for moderate/severe aPH remains 8–10% [3, 4] and the rates of disability at 1 year of age remain high, regardless of inhaled nitric oxide (iNO) use [5]. Chronic PH (cPH) presents later secondary to pulmonary vascular remodeling, particularly in context of evolving chronic lung disease (CLD) [6]. Persistent elevation in PVR may be associated with reduced RV function and RV dilation due to heterometric adaptation as this ventricle is particularly sensitive to increased afterload [7]. The consequences of RV dysfunction include increased risk of death or necessity for extracorporeal membrane oxygenation (ECMO) [8].

Echocardiography is the current standard of care for assessment of PH and RV function in neonates [9]. The American Society of Echocardiography recommends a combination of qualitative and quantitative methods for assessment of PH and RV function [10]. Subjective evaluation includes assessment of the degree of flattening at end-systole of the interventricular septum (IVS) [11, 12]. Qualitative echocardiography evaluation of the RV is often hindered by anterior or retrosternal location, heavily trabeculated myocardium and unique geometry. In addition, qualitative assessment of RV size and RV systolic function is recognized as inaccurate and has wide inter-observer variability in adult patients, particularly if there is mild or moderate impairment [13]. Diagnostic inaccuracy may lead to errors in clinical judgment and suboptimal therapeutic choices. Objective measurements such as Pulmonary Artery Acceleration time (PAAT) and Tricuspid Annular Plane Systolic Excursion (TAPSE), are being increasingly utilized to provide objective assessment of RV performance [14, 15]. Prompt diagnosis of PH and accurate assessment of the severity of myocardial impairment is essential to guide effective management aiming to minimize morbidity and mortality; yet, despite the availability of enhanced methods of evaluation, the standard of care in most programs is to perform qualitative assessment.

The primary aim of this study was to evaluate the reliability of qualitative assessment of RV size, RV function and septal wall positioning in a representative cohort of term or near term neonates with PH and RV dysfunction versus healthy controls (HC). We hypothesize that the reliability and validity of assessment of RV performance by subjective review of neonatal echocardiography images by trained evaluators is poor.

Methods

Study Design:

This was an observational study of standardized echocardiography images of 30 neonates with aPH and 30 healthy controls. The study was conducted by the Developmental Hemodynamics Group at the University of Toronto, Canada between June and November 2016. Institutional ethics board approval was obtained.

PH cohort:

A total of 30 cases were randomly selected from a historical cohort of 49 neonates with a diagnosis of aPH. Cases were considered eligible if born ≥ 35 weeks gestational age, birth weight was $\geq 2,500$ g and a clinical diagnosis of aPH receiving care in the neonatal intensive care unit (NICU) of The Hospital for Sick Children, Toronto Canada between 2012 and 2015. The diagnosis of aPH was confirmed according to a comprehensive echocardiography imaging protocol [16, 17]. Strict inclusion criteria in the aPH cohort included: (i) echocardiography diagnosis of PH [defined as the presence of a bidirectional or right-to-left shunting across the patent ductus arteriosus (PDA) and/or patent foramen ovale (PFO) and/or tricuspid regurgitant (TR) jet with an estimated right ventricular systolic pressure (RVSP) greater than $\frac{1}{2}$ systemic systolic pressure beyond 12 hours of age], (ii) comprehensive imaging dataset stored as raw data to facilitate detailed offline analysis, (iii) requirement for respiratory support with a fraction of inspired oxygen of ≥ 0.4 . Exclusion criteria included major forms of congenital heart defect except PDA, PFO or ventricular septal defect (VSD) ≥ 2 mm, major developmental lung disorders, abdominal wall defects and renal defects with oligohydramnios, or known chromosomal anomaly. The following clinical data points were collected for identified PH cases: gestation, birth weight, necessity for cardiopulmonary resuscitation (CPR) at birth, 5 minute Apgar score, use of surfactant, iNO treatment, duration of invasive ventilation and oxygen therapy, inotrope use, duration of hospital admission, requirement for ECMO or death.

Control Cohort:

Thirty patients were randomly selected from a historical cohort of 50 healthy term neonates who were previously recruited by our group for prospective echocardiography studies designed to characterize physiologic data during the transitional period. [16, 17]. The latter cohort was recruited between December 2011 to September 2012 in the Mother and Baby Unit, Mount Sinai Hospital, Toronto, Canada. This cohort included healthy, singleton, term (gestational age 37 to 42 weeks) babies with birth weight between the 10th and 90th percentiles. All infants were born after uncomplicated, low risk pregnancies. Exclusion criteria were maternal disease (diabetes mellitus, pre-eclampsia, chorioamnionitis), antenatal diagnosis of placental dysfunction as defined by absent/reversed end-diastolic flow in the umbilical arteries on fetal ultrasound, the prenatal use of antidepressant medications and any newborn disease (perinatal compromise defined as an umbilical cord pH < 7.0 and /or Apgar score < 5 at 5 minutes of age, the necessity for active resuscitation at birth, admission to the NICU, any congenital malformation, a documented episode of neonatal hypoglycaemia, or clinical examination suggestive of genetic or cardiovascular abnormalities. Any neonate with incidental findings of congenital heart defects on echocardiography (except PFO, small

PDAs, mild peripheral pulmonary artery stenosis) was excluded. Patient confidentiality was ensured via use of random unique study identifiers and no patient specific data was collected.

Echocardiography Assessment:

Targeted Neonatal Echocardiography (TNE) assessments were performed as part of a hemodynamic consultation completed by trained experts upon request by the attending neonatologists. All echocardiography evaluations were performed, using a Vivid 7 or Vivid E9 ultrasound system and either a 10 or 12 MHz transducer (GE Medical Systems, Milwaukee, WI, USA), according to a comprehensive, standardized imaging protocol as previously devised by our group [16, 17]. The protocol was based, but not limited to, the guidelines outlined by the American Society of Echocardiography [10, 18]. The offline analysis of all study group echocardiograms was performed at a dedicated work station (EchoPAC version BT10, GE Medical Systems).

Evaluators:

All evaluators were trained neonatologists who had completed standardized training in TNE methodology according to published standards and were practising at level III/IV neonatal intensive care units. Evaluators were designated as 'experts' (n=3) if they had at least three years of experience and had interpreted more than 500 TNE studies. The designation of 'novice' (n=3) was applied to trained neonatologists who had completed a minimum of one-year training and interpreted more than 150 TNE studies. Data was collected on evaluator age, sex and duration of practice as an echocardiography consultant.

Image Evaluation:

All studies were reviewed and images de-identified by one investigator [JRP], a neonatologist with training in echocardiography, who did not participate as an evaluator. A series of image clips were acquired from 7 pre-specified and standardized imaging planes for each neonate and used to evaluate RV size, RV function and septal curvature. No images in which intra- or extra-cardiac shunt was identifiable were used. Each evaluator qualitatively assessed the images regarding RV size, septal curvature and RV function. RV size was classified as normal, mildly dilated or moderate/severely dilated. RV systolic function was classified as normal, mild or moderate/severe dysfunction. Septal curvature was classified as normal (round throughout the cardiac cycle), flat at end-systole, or bowing into the left ventricle at end-systole (Figure 1). Echocardiography diagnosis of PH, according to previously mentioned diagnostic criteria, was confirmed from the official report and validated by independent study review. All sixty subjects [PH cases (n=30), controls (n=30)] were reviewed by the 6 evaluators [experts (n=3), novices (n=3)]. All evaluators were blind to the clinical course and any objective assignment of RV function, size and septal curvature. Both PH cases and control studies were arranged in random order and scored by each of the 6 independent evaluators.

Statistical analysis:

A sample size of convenience was used to determine the number of patients in each group, as there are no prior data appraising the reliability of qualitative assessment. Cohen's kappa coefficient was used to estimate agreement between raters and the gold-standard classification. Kappa values over 0.75 are considered to represent excellent agreement, 0.40 to 0.75 are fair to good, and values below 0.40 are considered to represent poor agreement. We evaluated the rate of diagnostic misclassification by each rater for both healthy patients and patients with PH. Misclassification in healthy controls was defined by the recording of either moderate-severe RV dilation, moderate-severe dysfunction or any dilation and any dysfunction. We excluded septal flattening from this classification as it a common finding in healthy patients during the transitional period. Misclassification in patients with acute PH was defined by the recording of three normal findings (normal size, function, and septal position) in patients. We compared the frequency of misclassification between experts and novices, and between healthy controls and patients with PH. A p value < 0.05 was considered significant.

Results

Both groups were comparable in terms of baseline demographics, although the Apgar score was lower in aPH patients. The average age at which echocardiograms were performed were 18.8 (6.2) hours and 20.1 (7.1) hours after birth in the healthy (control) population and aPH groups respectively ($p>0.05$). None of the healthy controls received mechanical ventilation. Twelve (40%) of the PH infants required high frequency oscillatory ventilation (HFOV) and 18 (60%) required conventional ventilation. No patient required ECMO.

Evaluators [novice (n=3) and expert (n=3)] provided a subjective interpretation of RV function, size and septal motion in all 30 cases of aPH and all 30 controls. Experts were characterized by longer duration of clinical practice as an echocardiography practice as a hemodynamic consultant [expert: 8.3 ± 4.1 years vs novice: 1 ± 0 years, $p=0.04$]. Expected differences in baseline neonatal characteristics between cases and controls were noted (Table 1), but there was no difference among evaluators in sex [expert: male = (3/3) vs novice (2/3), $p=1.0$] or age [expert: 41.3 ± 4.9 years vs novice: 35 ± 1 years, $p=0.1$].

RV Function Assessment, Septal Curvature & RV dilation:

There was overall poor agreement between evaluators for subjective assessment of RV function (Table 2). There were, however, no differences in Kappa values between expert and novice assessors. Agreement was marginally higher in patients with aPH than control patients. Agreement between qualitative assessment of septal curvature and RV size was poor in all evaluators, with no difference between experts and novices (Table 2). Agreement on septal wall motion was marginally higher in cases with aPH.

Diagnostic Misclassification Rate:

The overall rate of diagnostic misclassification rate was 18% (Table 3). The frequency of misclassification was higher in patients who were clinically healthy ($p<0.01$) (Table 4). There was a trend towards higher rate of misclassification by novice raters in comparison to

experts ($p=0.07$). On subgroup analysis, the rate of misclassification by novice evaluators was higher in healthy patients compared to cases of aPH ($p<0.01$).

Discussion

This is the first study in neonates to evaluate the reliability of qualitative assessment of right heart function using transthoracic echocardiography. Unique attributes of the RV including its specific geometry, anterior or retrosternal location and significantly trabeculated myocardium may hinder accurate assessment of RV size and function by qualitative means, especially in the setting of RV impairment, and explain the wide inter-observer variability of such RV assessments in adult patients [13]. Incorrect diagnostic assignment may lead to institution of treatment in patients without PH which shifts the pendulum towards increased probability of drug related harm without any discernible benefit. Contrary, failure to correctly diagnose patients with PH may lead to delays in institution of treatment. We hypothesized that the reliability of assessment of RV performance by subjective review of neonatal echocardiography images by trained evaluators was poor. Our result confirmed that both experts and novices demonstrated equally poor reliability for subjective assessment of RV function, classification of septal curvature and RV size. Such findings emphasize that regardless of the level of expertise obtained in TNE, subjective evaluation of RV function is inherently difficult and error prone. These data prompt the critical need for prospective investigation of objective measures of pulmonary hemodynamics.

RV function has been evaluated by echocardiography since the 1980's [19, 20]. Studies in adults have compared echocardiography measurements of RV function against other objective modalities to establish their utility and reliability. RV fractional area change (FAC) has been shown to correlate well with cardiac MRI-derived RV ejection fraction in adults ($r=0.8$, $p<0.001$) [21]. Adult studies have also demonstrated that RV ejection fraction measured by nuclear ventriculography correlates positively with myocardial performance index as assessed by 2D echocardiography. In addition, Kjaergaard *et al* reported that TAPSE may be superior to 3D echocardiography or single-photon emission computed tomography (SPECT) for estimation of RV ejection fraction when validated against cardiac MRI measurements [22, 23]. The utility of quantitative echocardiography was recognized in 2012 by Ling *et al* who compared objective echocardiography measures of RV function (FAC and TAPSE), qualitative assessment of RV size and RV systolic function by 15 evaluators, with cardiac magnetic resonance considered the reference standard for grading RV size and RV systolic function [13]. They reported that quantitative echocardiography measurements improved evaluators accuracy for diagnosing normal and mild RV systolic dysfunction from 52% to 84% ($p < 0.001$) and from 36% to 56% ($p = 0.001$) respectively. In addition, objective echocardiography methods improved inter-reader agreement for classification of the included subjects as normal or abnormal from a kappa value 0.43 to 0.66 (moderate to good agreement) for RV systolic function [13]. The authors surmised that quantitative echocardiography improves the accuracy and reliability of RV size and functional assessments, especially in the delineation of normal vs abnormal states. In this study, we did not evaluate the impact of objective cut-offs, derived from quantitative measurements, on the magnitude of inter-rater agreement as clinically relevant thresholds have not been well established for neonates. This needs to be investigated in future studies.

The utility of objective measures of RV function in neonatal health and disease is currently under investigation. Normative reference ranges, in prospective cohorts of premature and term neonates, for measurements such as RV FAC have been published [24]. There is also a keen interest to ensure that novel echocardiography techniques such as speckle-tracking echocardiography (STE), utilized to provide objective measures of RV function, are reliable and reproducible [25]. Neonatologist performed TNE may play a pivotal role in the overall management of the neonate with suspected aPH through the timely and accurate diagnosis of PH, exclusion of PH mimics such as cyanotic congenital heart disease and objective evaluation of RV and LV function [1]. Peterson *et al* reported the use of echocardiographic predictors of survival and necessity of ECMO, high frequency oscillatory ventilation (HFOV) and iNO in 63 neonates with pulmonary hypertension [26]. They postulated that the early identification of at-risk infants, using echocardiography markers, may prompt earlier or more aggressive intervention enabling enhanced patient outcome. A recent retrospective study demonstrated that objective echocardiographic measures of cardiac function provided an accurate evaluation of PH treatment response. Specifically, the investigators demonstrated improved tissue Doppler indices of RV strain, RV strain rate, LV s' and a' waves after milrinone administration to patients 34 weeks with PH not responding to iNO [27]. These studies, however, did not evaluate the predictive impact of qualitative assessment on adverse outcomes.

The estimated incidence of cPH in patients with confirmed CLD is 14–44% [2]. Khemani *et al* studied a cohort of 42 infants born < 32 week's gestation who developed CLD, and were diagnosed with pulmonary artery hypertension at a postnatal age of 2 months, and demonstrated a high risk of death for those infants with confirmed severe pulmonary artery hypertension [28]. While such data emphasizes the importance of early recognition of cPH, prompt diagnosis remains a challenge. In the absence of intra-atrial or PDA shunts, echocardiography diagnosis of cPH is often reached based of subjective evaluation of IVS curvature, RV hypertrophy and RV dilatation. Recent neonatal studies have focused on the utility of objective and advanced echocardiography techniques, including tissue Doppler imaging and deformation analysis, in patients with CLD to detect cPH and/or RV dysfunction earlier. Studies are emerging that report failure of subjective conventional echocardiographic measurements to detect differences in cardiac function between infants with and without CLD which are successfully delineated utilising objective tissue Doppler imaging measurements [29, 30]. Strain echocardiography methods have also demonstrated decreased RV longitudinal strain in children born < 32 week's gestation with moderate to severe CLD and PH despite conventional echocardiographic techniques indicating normal ventricular function [31]. The rate of misclassification in healthy patients ranged from 19% to 34% in experts vs novices respectively. The rate of misclassification in patients with aPH ranged from 9% to 10% in experts vs novices respectively. Incorrect diagnostic assignment may lead to delays in pulmonary vasodilator treatment in patients with cPH or inappropriate use of these agents in patients with normal pulmonary hemodynamics. The impact to the health care system of non-judicious use of these expensive treatments or delays in management may be significant.

In conclusion, our study demonstrated significant variability in qualitative assessment of RV size and function by trained evaluators, regardless of level of expertise attained. A limitation

of this study is the lack of quantitative measures to compare and contrast with qualitative echocardiography assessment. Quantitative measurements when combined with qualitative assessment may enhance the diagnostic reliability of PH and associated RV dysfunction. Normative data for novel quantitative techniques are currently being established and verified although thresholds for intervention remain unclear. Echocardiography may also play a role in the objective assessment of new or potential therapeutic modalities for PH including sildenafil, hydrocortisone, melatonin and citrulline [32–34]. Further neonatal studies should evaluate if utilising objective echocardiography techniques of RV function in the setting of PH improves short and long term neonatal medical and neurodevelopmental outcomes.

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Figure 1:
Septal curvature was classified as normal (round throughout the cardiac cycle) (A), flat at end-systole (B), or bowing into the left ventricle at end-systole (C)

Table 1.

Demographics and clinical characteristics of patients with clinical evidence of pulmonary hypertension vs control patients

	Pulmonary Hypertension (n=30)	Controls (n=30)	p
<i>Gestational age (weeks)</i>	39.8 ± 1.4	39.4 ± 1.3	ns
<i>Birth weight (kilograms)</i>	3.6 ± 0.5	3.5 ± 0.5	ns
<i>Male gender</i>	19 (63)	17 (57)	ns
<i>5-minute Apgar score</i>	5.3 ± 2	8.6 ± 0.8	<0.01
<i>Required resuscitation (n)</i>	9 (30)	0 (0)	n/a
<i>Received surfactant replacement (n)</i>	4 (13)	0 (0)	n/a
<i>Pulmonary vasodilator therapy (n)</i>	30 (100)	0 (0)	n/a
<i>Inhaled nitric oxide (n)</i>	23 (77)	0 (0)	n/a
<i>Inotrope treatment (n)</i>	26 (90)	0 (0)	n/a
<i>Survival (n)</i>	28 (93)	30 (100)	n/a
<i>Referred for ECMO (n)</i>	0 (0)	0 (0)	n/a
<i>Duration of ventilation (n)</i>	15 [9, 21]	0 [0, 0]	n/a

Table 2:

Qualitative assessment of RV function, dilation and septal curvature as adjudicated by expert and novice evaluators in patients with pulmonary hypertension and healthy cohort, Kappa value (standard error of Kappa)

	All patients (n=60)	Healthy Cohort (n=30)	PH cohort (n=30)
RV Function			
All	0.3 (0.03), p<0.01	0.11 (0.05), p=0.01	0.33 (0.04), p<0.0001
Expert	0.32 (0.06), p=0.003	0.13 (0.01), p=0.1	0.32 (0.08), p<0.001
Novice	0.35 (0.06), p=0.003	0.06 (0.07), p=0.3	0.4 (0.08), p<0.001
RV Dilatation			
All	0.14 (0.02), p<0.001	0.12 (0.04), p=0.004	0.12 (0.03), p<0.0001
Expert	0.15 (0.06), p=0.003	0.13 (0.02), p<0.001	0.17 (0.07), p=0.009
Novice	0.13 (0.05), p=0.003	0.22 (0.07), p=0.002	0.02 (0.06), p=0.38
Septal curvature			
All	0.2 (0.02), p<0.001	0.08 (0.03), p=0.004	0.22 (0.03), p<0.0001
Expert	0.23 (0.05), p<0.001	0.09 (0.08), p=0.13	0.23 (0.08), p=0.001
Novice	0.21 (0.05), p<0.001	0.06 (0.07), p=0.18	0.29 (0.07), p<0.001

Table 3.

Frequency of incorrect diagnostic impression for each rater in healthy patients and those with pulmonary hypertension

Rater	Misclassification rate in Healthy Patients (n=30)	Misclassification rate in Pulmonary Hypertension (n=30)	Overall Misclassification of Patients (n=60)
Expert 1	5	3	8 (13%)
Expert 2	5	4	9 (15%)
Expert 3	7	2	9 (15%)
Novice 1	10	3	13 (22%)
Novice 2	9	5	14 (23%)
Novice 3	12	0	12 (20%)

Table 4.

Global rating for misclassification rate in healthy patients and those with pulmonary hypertension

Rater	Misclassification rate in Healthy Patients	Misclassification rate in Pulmonary Hypertension	Overall Misclassification of Patients
Overall	48/180 (27%)	17/180 (9%) [*]	65/360 (18%)
Experts	17/90 (19%)	9/90 (10%)	26/180 (14%)
Novices	31/90 (34%)	8/90 (9%) [*]	39/180 (22%)

^{*}
p<0.05 vs healthy patients,

[#]
p<0.05 vs experts.

Denominator is 180 for all patients [(n=30) x 6 raters] and 90 for the expert or novice subgroups [(n=30) x 3 raters]