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Examining the association of right ventricular dysfunction with moderate to severe bronchopulmonary dysplasia in preterm infants

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Abstract

Over the last three-and-a-half decades, many advances have been made in the care of preterm infants. Some of the most important developments have been in hemodynamic management, including the use of functional echocardiography exams. The Right Ventricle (RV) functional assessment has enabled investigators to track cardiac maturational changes in the first few months of life of Very and Extremely Preterm Infants (VEPIs). The present review investigates whether early RV dysfunction can be used to identify preterm infants with early Significant Bronchopulmonary Dysplasia (sBPD), that is, moderate to severe BPD. An early identification of RV dysfunction would allow for interventions to lessen BPD severity, ultimately reducing the incidence of significant complications associated with sBPD (e.g., adverse neurodevelopmental outcomes). Six studies have been selected for the final critical evaluation. They all indicate that RV dysfunction in preterm infants born < 32 weeks of postmenstrual age could be detected early in these infants' lives. However, the studies vary in methodology, are underpowered and use a limited number of functional tests to assess RV. Further studies with larger cohorts of VEPIs and a wider combination of RV functional tests, such as strain and strain rate, are thus needed to conclusively establish whether RV dysfunction can be reliably established at initial stage to serve as an early indicator of sBPD.

Introduction

The use of echocardiographic assessments of preterm infants-in particular, Very and Extremely Preterm Infants (VEPIs)-has gained momentum over the last 20 years, with more neonatologists becoming skilled in their use [1]. Various terms are used to describe this practice, including 'bedside Echocardiography (ECHO) examinations', 'neonatologist operated echocardiography' and 'functional echocardiography' [1]. Regardless of the exact name used, an echo has been shown as a useful complement to clinical hemodynamic assessments of newborn infants because it can help guide the management and the support of critically ill neonates [1].

Neonatologists in developed countries, such as the United States, Sweden and Japan, have consistently pushed the margins of viability [2,3,4]. It has been established that the more premature an infant is, the higher his/her risk of developing complications from prematurity, such as Bronchopulmonary Dysplasia (BPD), neurodevelopmental delays and growth failure [5,6]. Hence, the incidence of BPD is expected to increase since the VEPIs' survival rate is on the rise [7].

BPD is one of the most predominant and prognostically crucial sequelae in preterm neonates. Annually, there are 10,000-

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15,000 new cases of BPD in VEPIs in the United States alone [8,9]. Stoll et al. [10] reported that the BPD incidence rate among preterm infants born between 22 and 28 weeks of Postmenstrual Age (PMA) has increased over a 20-year period (1993-2012), reaching as high as 40% in the United States. According to Travers et al., [11] the BPD incidence could be even higher, up to 55%, in the same group of preterm infants in the United States. However, this high incidence rate of BPD in preterm infants born at ≤ 28 weeks of gestation in the United States is not as high in other parts of the world, such as Canada (20%) and Japan (25%) [12]. In the United Kingdom, the recent National Neonatal Audit Programme report [13] showed that the incidence rates of mild BPD and significant BPD (sBPD) over a three-year period (2015, 2016 and 2017) are 16.9% (n=3813) and 30.9% (n=6971), respectively, among total number of preterm infants born at < 32 weeks of gestation.

BPD develops through complex mechanisms. Thus, it remains a challenge for researchers and clinicians to agree on a descriptive and clinically practical definition [7] since BPD first described five decades ago by Northway et al [14].

Initially, radiological and pathological findings were used to define BPD. A clinical definition then emerged, stating that BPD-affected infants were those who needed oxygen for the first 28 days of life (DOL) [15]. However, its main limitation was that oxygen supplementation in the first 28 days postnatally might be related to other factors, such as extreme prematurity, rather than evolving BPD. Therefore, Shennan et al. [16] refined the definition by adding the use of oxygen at 36 weeks of PMA. However, this definition lacked the description of BPD severity, which led to a more descriptive definition that classified BPD into the following categories: none, mild, moderate and severe [17]. Infants were deemed as having mild BPD when they received oxygen or respiratory support for > 28 days but were in room air at 36 weeks of PMA. Infants with moderate BPD required supplemental oxygen, < 30% fraction of inspired oxygen concentration, at 36 weeks of PMA in comparison to the use of >30% oxygen or positive pressure at 36 weeks of PMA for the severe BPD group. The definition was further developed to include the physiological challenge of supplemental oxygen withdrawal to test for oxygen need at 36 weeks of PMA [18]. Despite the Canadian neonatal network's recent finding that the evaluation of respiratory support and oxygen supplementation at 40 weeks of PMA is more predictive of morbidities, its adoption in research can lead to under-recruitment since infants are usually discharged at 40 weeks of PMA [19]. Other researchers, such as Higgins et al. [20], further developed the BPD categories with the inclusion of the widely adopted respiratory support, the Heated, Humidified and High Flow Nasal Cannula (HHHFNC), over the last 10 years. Hence, it is evident that any consensus on the BPD definition is still a work in progress, and Jobe and Bancalari's [17] BPD classification remains widely accepted by researchers.

Moreover, sBPD adversely affects several systems of the body. For example, it is associated with an increase in systemic vascular resistance and can subsequently lead to systemic hypertension [21]. Research has also indicated that BPD is a strong predictor of neurodevelopmental delay and faltering growth of preterm infants [22].

In short, the lungs affected by sBPD can negatively impact on other body systems. The present review therefore hypothesises that a dysfunction of one organ can potentially disturb the function of other organs. For example, this may be the case for the lungs and the heart [23]. The development of premature lungs involves the growth and the maturation of the alveolar tree, as well as the vascular bed; the aim is to develop a sufficient surface for gas exchange and ultimately, for normal pulmonary function. The disruption in the growth of any of these areas affects the development of others [24]. For instance, arresting the normal growth of the alveoli results in the presence of fewer and larger acinar cells in BPD-affected premature lungs. This in turn adversely affects pulmonary vascular growth, which is evidenced not just by a simple decrease in growth but also by an adaptive dysmorphic pattern in vascular growth [24]. This situation leads to the paucity of capillary vessels in the walls of the abnormally enlarged alveoli and a simplification of the capillary network.

Furthermore, infants with sBPD are more prone to hypoxic episodes, which also promote more pulmonary vasculature remodelling, an elevated tone, altered reactivity, vasoconstriction and increased Pulmonary Vascular Resistance (PVR) [25]. Eventually, these histological and remodelling changes increase the Right Ventricle (RV) afterload by pushing up pulmonary pressure Ambalavanan & Mourani, [25] which can be detected as early as in the first few weeks of life [24]. This explains why many infants with sBPD develop Pulmonary Hypertension (PH) [24]. Consequently, chronic afterload increase and hypoxic episodes can cause RV dysfunction and hypertrophy that can evolve into RV failure [26]. Moreover, mortality rates among infants with sBPD have been shown to increase by up to 40% when PH is also present [27], so early detection of progressing sBPD is important to allow for attenuating measures to minimise BPD severity.

A symbiotic relationship may therefore exist between sBPD and cardiac dysfunction that persists from infancy until later in life-particularly where the RV is concerned. This hypothesis, which is the focus of the present literature review, is of paramount importance because it suggests that future studies investigate the possibility of the presence of cause-and-effect or association patterns. The present review thus lays the foundation for further research on the utilisation of functional assessments of the RV as a surrogate measure of the effectiveness of sBPD treatment. Similarly, future research could investigate the possibility that RV cardiac dysfunction could be used as an early identifier of preterm infants with progressing sBPD. Such findings would help clinicians intervene sooner to prevent or at least attenuate the pathological processes associated with sBPD.

Methods

The clinical query was performed by using a systematic and well-structured methodology to conduct a coherent and efficient search process [28]. Three main question-formulating approaches could be taken when reviewing scientific literature: browsing, problem solving and background/foreground questions [29]. Since the relevant studies for this review compared two cohorts of preterm infants, a cohort with sBPD and another with either mild or no BPD would be the most appropriate. Therefore, the foreground quantitative question approach would be the most suitable to examine whether RV dysfunction would be linked to sBPD. The Population, Intervention, Comparison, Outcome, Time, Study (PICOTS) design (rather than just PICO) was used to formulate the research question [30]. The PICOTS question included the following:

P: The population was defined as comprising VEPIs with sBPD.

I: The intervention under study was the performance of a quantitative ECHO measurement(s) of RV function.

C: The control group included preterm infants with mild BPD or no BPD.

O: The outcome assessed was the presence of RV dysfunction.

T: The timeframe under study included patients who were born prematurely and had their RV function assessed at any stage before they reached 38 weeks of PMA. This time period was chosen because the review focused on examining whether evolving sBPD could cause early RV dysfunction.

S: The studies would either have a cohort or a case-control design.

The pearl-growing technique (i.e., examining relevant review articles) would lead to the identification of other important research papers. Thus, it was utilised to find the relevant review papers in several databases, such as Web of Science, that eventually guided the discovery of other relevant databases, which facilitated the extraction of additional suitable citations [31]. Next, a systematic electronic search of several bibliographic databases (Medline, PubMed, CINAHL, Web of Science, Embase, Google Scholar, Cochrane Library and DelphiS indexes) was performed, and e-journals were examined through ProQuest. Medical subject headings were applied (Appendix 1). Boolean operators, such as 'AND' and 'OR', were also used to enhance the efficiency of the search [32]. The following search terms (including truncations) were used: 'right ventricle function', 'bronchopulmonary dysplasia', 'chronic lung disease' and 'preterm/premature infant'. The included studies were those published over the last 20 years (since this was the period when the use of ECHO exams first became widespread in neonatal intensive care units) Raimondi et al., [1], written in English and that focused on VEPIs, examined RV functioning using ECHO tests and quantitative ECHO measurements of RV function and used a cohort or a case-control design. The excluded studies had no full text available, performed ECHO exams outside the time period under study (between birth and < 38 weeks of PMA) or consisted solely of animal studies or reviews, letters to the editor or expert opinions (e.g., examined new ECHO methods). Furthermore, the main findings of the literature search regarding the definition of BPD were as follows: 1) The description of BPD was still being further developed 2) Jobe and Bancalari's [17] definition and categorisation of BPD were still widely utilised by researchers in this field. Only the studies that classified BPD patients according to the respiratory support and oxygen requirements at 36 weeks of PMA were included in the final critical appraisal.

Ultimately, out of the 23 initially identified studies, only 6 met the eligibility criteria (Figure 1). The other 17 were rejected because they did not examine any subgroups of BPD (4), performed ECHO outside this review's target age range (4), had a different focus (3), were designed as case-series or overly small case-control studies (2), only studied the link between PH and BPD (1), investigated new ECHO methods (1) or consisted of a device review (1) or an animal study (1).

Observational studies, such as those using case-control and cohort designs, were the most suitable for assessing the topic in question. To assess the quality of the selected papers, the Critical Appraisal Skills Programme [34] checklist was used, which enabled a systematic analysis of each paper's quality [35]. The checklist data questionnaire was modified by dividing it into internal versus external validity (Table 2). All studies had focused questions and utilised appropriate statistical analyses.

A qualitative critical evaluation was deemed the most appropriate method of assessing the validity of the eligible studies due to their clinical heterogeneity [36]. The dissimilarities among the diagnostic ECHO tests used to assess RV function and the different ages at which they were performed (Table 3) made objective quantitative comparison unfeasible.

Each selected study was reviewed for compliance with the ethical principles of the World Medical Association Declaration of Helsinki, [33]. Table 1 summarises the results.

Table 1: Checklist of ethical principles.

	S1	S2	S3	S4	S5	S6
An adequate literature search was performed to justify the trial.	Yes	Yes	Yes	Yes	Yes	Yes
An ethical committee approval was obtained.	Yes*	No	Yes	Yes	Yes	Yes
Participant confidentiality was noted.	No	No	No	No	No	No
Voluntary, informed and written consent was provided by all participants.	No	No	Yes	Yes	Yes	Yes
The results were made publicly available.	Yes	Yes	Yes	Yes	Yes	Yes
The funding sources were stated.	Yes	Yes	No	No	Yes	Yes
Conflicts of interest were declared.	Yes	No	Yes	Yes	Yes	Yes

• The authors implied that ethical approval was sought through their institutional trial committees.

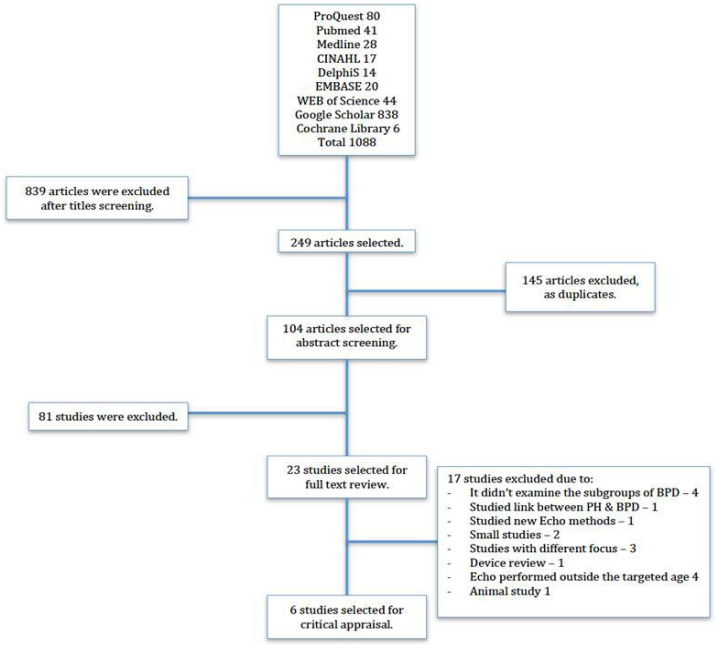

Figure 1: Diagram of the search process and audit trail.

Table 2: Critical appraisal of the selected articles.

Studies	Participants	Study design	Internal validity	External validity
S1. Levy et al., 2015 [37]	*N* = 115 Infant PMA 23–28 w at birth	Prospective longitudinal case control	Investigators were blinded to patient details. Efforts were made to reduce inter- and intra-observers' variability. Analyses compared preterm infants with significant BPD to preterm infants with mild or no BPD.	RV-FAC could be incorporated as one of the ECHO measurements of the RV function.
S2. Choi et al., 2016 [38]	*N* = 73 Infant PMA < 32 w at birth	Retrospective case control	In this retrospective study, investigators were not blinded to the BPD severity.	Suitably trained clinicians could perform these ECHO measurements.
S3. Sehgal et al., 2016 [39]	*N* = 30 (28 analysed) Infant PMA < 32 w at birth	Prospective case control	Efforts were made to minimise confounding factors. The two cohorts were similar in having no PDA at the time of the ECHO. No infant was on pulmonary vasodilator therapy or inotropes. No infant required surgical PDA ligation. Investigators were blinded, and measurements were averaged over three cardiac cycles. The final number of recruits was small.	Suitably trained clinicians could perform these ECHO measurements.
S4. Yajamanyam et al., 2016 [40]	*N* = 72 Infant PMA < 32 w at birth	Prospective case control	There were reasonable numbers of recruits in each group. Only 67 cases (including controls) were similar. Controls were more mature. A single experienced investigator who was not blinded to the BPD severity performed the ECHOs. TR and septal flattening were the safety measures to identify cases of significant PH.	Suitably trained clinicians could perform these ECHO measurements.
S5. Bokiniec et al., 2017 [41]	*N* = 82 Infant PMA < 32 w at birth	Prospective case control	The investigators were highly experienced in performing neonatal ECHO measurements but was not blinded to the BPD severity. Investigators also did not perform ECHO exams between Days 1 and 27, so important data about RV function development may have been missed. A more mature cohort of controls was included.	Suitably trained clinicians could perform these ECHO measurements.
S6. Haque et al., 2017 [42]	*N* = 45 (34 analysed) Infant PMA < 32 w at birth	Prospective case control	The study had a strong design. An experienced sonographer performed the ECHO exams. Images were analysed by paediatric cardiologists blinded to the BPD severity. Measurements were averaged over three cardiac cycles. The major issue was under-recruitment.	The ECHO measurements were performed by an experienced sonographer and analysed by paediatric cardiologists. Practical application might be an issue since an on-site paediatric cardiology service might be needed. However, other clinicians could be trained in ECHO assessments, or links could be established with local paediatric cardiac services.

PMA: postmenstrual age, w: weeks, sBPD: significant bronchopulmonary dysplasia (moderate to severe), BPD: bronchopulmonary dysplasia, TDI-MPI: tissue Doppler imaging–myocardial performance index, PDA: patent ductus arteriosus, RV-FAC: right ventricle–fraction area change, TR: tricuspid regurgitation

Table 3: ECHO details and significant results.

Study	Echocardiogram parameters	Type/s of echocardiogram performed	Significant outcomes
S1. Levy et al., 2015 [37]	Four ECHOs performed on preterm infants on DOL 1 and 3, then at 32–36 w of PMA Only two ECHOs on term infants (control group)	RV-FAC	- A faster rate of RV-FAC maturation in preterm infants occurred at 32–36 w of gestation. - The maturation process was unfavourably affected by the presence of significant BPD. The infants with moderate to severe BPD had a lower RV-FAC in the late preterm period.
S2. Choi et al., 2016 [38]	One ECHO performed between 35–37 w of PMA	TR, RV-MPI via PWD, RV-MPI via TDI	- No significant difference was found between TR and RV-MPI via PWD groups. - RV-MPI via TDI was significantly higher in the severe BPD group compared to the no or mild BPD groups ($P < 0.05$). - A linear regression analysis indicated a significant correlation between BPD severity and RV-MPI via TDI ($P = 0.01$).
S3. Sehgal et al., 2016 [39]	One ECHO performed at 36 w of PMA	TR, TAPSE, RV-MPI via TDI, RV-FAC, E/E'	- TR was measurable in 7/18 (40%) of the BPD group, with 3/7 with TR Vmax > 2.7 m/s. No controls had a measurable TR. - MPI ($P < 0.0001$) and E/E' ($P < 0.0001$) were significantly elevated in BPD patients compared to controls. - RV-TDI peak systolic velocities were significantly lower ($P < 0.0001$) in BPD patients compared to controls. - RV-FAC was significantly lower in BPD patients compared to controls.
S4. Yajamanyam et al., 2016 [40]	One ECHO performed at 36–37 w + 2 d of PMA	TR, septal flattening, RV-MPI via TDI, RV-IVRT	- Significantly higher RV-MPI via TDI was observed in patients with severe BPD compared to the groups with no ($P < 0.001$) or mild ($P = 0.006$) BPD. - Significantly longer RV-IVRT was found in patients with severe BPD compared to the groups with no ($P = 0.001$) or mild ($P = 0.031$) BPD. - BPD patients were further divided into subgroups to assess whether they received dexamethasone and whether they were discharged on supplemental O2. - 14/50 BPD patients who received dexamethasone had significantly higher RV-MPI ($P = 0.015$) but had no significant difference in RV-IVRT and no ventricular hypertrophy in comparison to subgroup who did not receive dexamethasone. - RV-MPI was significantly higher in the 30 patients who were discharged with O2 therapy compared to the other 20 with no O2 therapy at discharge ($P = 0.004$). RV-IVRT did not differ in both subgroups.
S5. Bokiniec et al., 2017 [41]	Three ECHOs performed on DOL 1 and at 28 w and 36 w of PMA	TR, TV–E/A ratio, AcT/RVET, RV-MPI via PWD and TDI	- RV-MPI assessment success rates were 73.6% and 77.2% for TDI and PWD, respectively. - RV-MPI via PWD was higher in preterm infants with sBPD compared to preterm infants with no ($P = 0.014$) or mild ($P = 0.031$) BPD when measured on the 28th DOL. However, these results were not replicated by RV-MPI via TDI.
S6. Haque et al., 2017 [42]	One ECHO performed at > 36 w of PMA	TR, RV-FAC, TAPSE, RV-MPI via PWD, RV-TDI, RV-SR-MDI	- The only significant difference detected was the regional peak systolic strain in the free wall middle segment (1/6 segments), which was lower in patients with sBPD ($P < 0.01$).

DOL: day of life; w: weeks, d: day; PMA: postmenstrual age; sBPD: significant bronchopulmonary dysplasia (moderate to severe BPD); TDI-MPI: tissue Doppler imaging–myocardial performance index; RV–FAC: right ventricle–fraction area change; TR: tricuspid regurgitation; TAPSE: tricuspid annular plane systolic excursion; TV–E/A ratio: tricuspid valve–early to late diastolic waves ratio; PWD: pulsed-wave Doppler; RV–SR–MDI: right ventricle–strain rate–myocardial deformation imaging; AcT: pulmonary artery acceleration time; RVET: *right ventricle ejection time; RV–IVRT: right ventricle–isovolumic relaxation time*

Results

Six studies (S1-6) were selected for critical evaluation. The complex methods used in each study (meta-analysis, meta-ethnography and meta-study) required high levels of experience and knowledge. Therefore, each study was evaluated separately [43].

Overall, each study indicated that one or more of the measured ECHO parameters was or were negatively affected by sBPD (Table 3). For example, S1 detected a reduction of the RV-Fraction Area Change (RV-FAC) among the VEPIs affected with sBPD. S5 showed that the RV-Myocardial Performance or Tei index (RV-MPI) via the Pulsed-Wave Doppler (PWD) was higher in earlier development stages among VEPIs (i.e., when the infants were four weeks old). However, this result was only statistically significant when measured on the 28th DOL. In contrast, S2–4 found significant increases in RV-MPI but via Tissue Doppler imaging (TDI) rather than PWD; these studies also measured it at a later age (35-37 weeks of PMA). Meanwhile, S6 examined the strain rate of the RV using the speckle tracking method and found that the regional peak systolic strain in the free wall middle segment (1/6 total segments) was lower in patients with sBPD.

Discussion

All of the selected studies were underpowered to some degree, had the biases inherent to all observational studies and

employed dissimilar methodologies (Tables 2,3). The methodological heterogeneity of the selected studies represented the main limitation in performing a quantitative review, hence, qualitative assessment was utilised to critically appraise the chosen research papers. Nonetheless, they all indicated a probable link between RV dysfunction and sBPD, suggesting that abnormal pulmonary maturation due to progressing sBPD can be reflected in the correlated reduction in RV function.

S1 and S5 demonstrated that a reduction in RV function could manifest as early as in the first four weeks of life. Particularly, in S5, the measured ECHO parameter revealed a degree of RV dysfunction; however, it was statistically significant at only one point (i.e., on the 28th DOL of the three study measurements points), probably due to the exclusion of almost 25% of all RV studies from the analysis. These results support the conclusion that the surveillance of hemodynamic changes, such as the RV function in VEPIs via repeated ECHO assessments, is especially important in VEPIs with progressing sBPD. This conclusion is also in line with a fairly recent review's Nagiub et al., [44] recommendation of a routine ECHO assessment of these infants in the neonatal period (i.e., in the first 28 DOL).

The studies also demonstrated the achievability of using different RV function measurement techniques. Furthermore, RV-MPI measured via TDI in S2-6 (except S5) is probably more reliable than via PWD in detecting RV dysfunction because PWD measurements need to be taken from different cardiac cycles, which can be affected by heart rate variations between cycles [45]. The inability of S5 to demonstrate the suggested superiority of TDI to PWD in measuring RV-MPI perhaps reflects underrecruitment from the exclusion of a quarter of the performed ECHO studies. S3 also showed the effectiveness of using Tricuspid Valve (TV)-E/E' ratios to assess the cardiac diastolic function of the RV, where E represents the early filling velocity on a trans-TV Doppler, while E' denotes the early relaxation velocity on a tissue Doppler, which could be helpful in detecting the diastolic dysfunction of RV associated with sBPD. In contrast, S6 used speckle-tracking technology, although the study's low number of participants probably prevented this technique from reaching its full potential in assessing RV function in the context of sBPD. Regardless of the specific method used, appropriately trained professionals should perform the ECHO measurements to minimise inter- and intra-observer variations.

The main direction of the RV's contraction differs from that of the Left Ventricle (LV) in that the RV's longitudinal strain is predominant, while the LV has equally predominant longitudinal, radial and circumferential strains, mainly due to the RV's complex geometry and orientation [46]. Furthermore, while it is common to use Tricuspid Regurgitation (TR) as an assessment measure of PH, this may not be very reliable, given the inconsistent correlation between TR and PH found by Nagiub et al. [44]. Thus, the low-pressure and the high-output RV system function assessment may require incorporating a combination of ECHO measurements to provide a reliable assessment of the RV function. In other words, due to the complexity of the RV function, it requires a well-measured amalgamation of functional ECHO tests. However, this assessment consolidation must be balanced against the need to avoid significantly lengthening the duration of patient assessments. The need to include multiple measurements also underscores the importance of advisory links with paediatric cardiac experts [44].

Conclusion

This literature review was undertaken in line with the current trend towards moving away from examining each system in isolation. Instead, it sought to examine the interactions among different body systems, specifically in the presence of pathologies, such as sBPD in VEPIs.

It should also serve as an impetus for further research into the early detection of progressing sBPD by using RV functional assessments in the first 28 DOL. Paediatric cardiology support and the utilisation of a wide combination of RV functional ECHO tests by trained clinicians are recommended.

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