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Merits and Perils of Targeted Neonatal Echocardiography-Based Hemodynamic Research: A Position Statement

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Graphical Abstract

[See separate file].

Figure 1: Graphical abstract highlighting merits and considerations in TNE research.

Introduction

In the neonatal setting, point-of-care ultrasound is being used increasingly to help clinicians with the evaluation of heart function. Practices in neonatology, particularly with regards to acute and chronic hemodynamic managements, were traditionally more driven on dogma and predefined thresholds and not always supported by demonstrable physiology. For the first time, targeted neonatal echocardiography (TNE) provided neonatal intensivists with a bedside tool which made real-time assessment of neonatal hemodynamics status feasible in even the tiniest of babies. This opened the door towards more targeted physiological driven practices, allowing us to test historical approaches to clinical problems in a more precise way. Over the last ten years, evidence of the use TNE and its effect on clinical management has accumulated.

While TNE is helping to advance bedside decision-making, it also fosters an entirely new field of scientific interrogation. The wide availability of TNE has made it feasible for academicians to ask a variety of novel research questions pertaining to neonatal hemodynamics. However, despite the standardization of TNE training and the creation of a formalized curriculum, little attention has been paid to the establishment of an empirical framework to adjudicate scientific investigation. In this position statement, we reflect on the evolution of TNE in Canadian NICUs, appraise its strengths and limitations, and suggest guiding principles for clinicians and researchers to consider as they take this field forward.

Merits in the evolution of TNE

Clinicians have been using functional echocardiography in neonatal care in parts of Europe and Australasia for over two decades, while in North America, it has been more recently adopted. The first TNE program in Canada was established in 2006 at the Hospital for Sick Children in Toronto (El-Khuffash, Herbozo, Jain, Lapointe, and McNamara 2013). While for a few years that remained the only TNE program in Canada, over the last 6 years, a number of formal and standardized TNE programs have emerged in several NICUs across the country. This was in part facilitated by the endorsement of TNE by the American Society of Echocardiography which published a comprehensive practice and training guideline in 2011(Mertens et al. 2011) and resulted in a strong collaboration between neonatologists and pediatric cardiologists. The European group also published their guidelines for neonatologist performed echocardiography (NPE) in 2016 (Boode et al. 2016). This consensus-based guideline differed from the ASE in a few aspects, most importantly in that it does not mandate a period of training in a pediatric echocardiography laboratory. Instead, trainers of NPE are recommended to spend 12 months acquiring experience in infants with congenital heart disease, under the supervision of a pediatric cardiologist. Despite these variations, both groups strongly advocate for neonatologists with an interest in functional echocardiography to establish close clinical and academic links with their pediatric cardiology colleagues, and prescribes a minimum scanning exposure that trainees should have with neonates with structural heart defects other than patent ductus arteriosus and patent foramen ovale. One of the impacts of these consensus documents is the spread of TNE in clinical practice. At the time of writing this review, at least 14 tertiary NICUs in Canada are

known to have TNE capabilities, with more American centres coming on board. While consensus-based guidelines are excellent resources, it is important to note that at this time, they are not backed by a large body of evidence. We encourage clinicians, researchers and administrators to continue to build the evidence base for allowing the future refinement of TNE training guidelines.

Impact on clinical management

A number of studies have now confirmed that TNE in tertiary neonatal care frequently impacts clinical decision-making. From Canada, three centres have published their impact. In a study conducted on outborn patients, a review of 199 infants showed that TNE was associated with a change in clinical management among 41% of cases (El-Khuffash et al. 2013). A subsequent study from Calgary examining the utility of 303 TNEs from 129 patients showed that TNE altered clinical management in approximately 50% of cases in the first week of life, and in 22% of cases thereafter (Harabor & Soraisham 2015). More recently, we examined the role of TNE in a large tertiary perinatal centre and found that TNE resulted in a significant impact on clinical management, particularly infants with high illness severity and non-PDA pathologies (Papadhima et al. 2018). Outside of Canada, Corredera *et al* from Spain demonstrated that in their unit, TNE was associated with a modified management plan in 37% of cases, usually as it pertains to PDA management (Corredera et al. 2014).

However, there are some limitations to the current literature. These studies are retrospective in nature, and assume that changes in clinical management after a TNE were a direct result of the TNE consult itself. The intent of the attending clinicians in the absence of a

TNE consult cannot be accounted for. Similarly, in cases where there was no clinical change after TNE, a presumption may be made that the TNE had no clinical impact. However, in real life, confirmation of a clinical diagnosis and treatment pathway by TNE is important, and may prevent subsequent alterations in clinical management. There is therefore a need to formally evaluate the utility of TNE in neonatal care in a prospective manner.

Impact on patient outcomes

Even though there is a great deal of evidence showing the impact of TNE on clinical practice, its ability to influence patient outcomes remains under-evaluated. The few studies published in this field are retrospective in nature, and include a small number of patients with a specific disease process. Shah and Kluckow, in a retrospective case-control study, found that in 26 preterm infants born after preterm prolonged rupture of membranes, the availability of TNE was associated with earlier identification of pulmonary hypertension, which was linked to a prompter initiation of treatment and improved survival (Shah & Kluckow 2011). In a study of a similar design, Jain *et al* compared preterm infants undergoing PDA ligation who were assessed routinely with TNE post-ligation and treated with milrinone for low left ventricular output with a historical cohort, and found that the cases had improved postoperative cardiorespiratory stability (Jain et al. 2012). A more recent study examined the impact of integrated evaluation of hemodynamics on 18 infants, and found that TNE was associated with a shorter time to recovery in patients with late-onset compromised systemic circulation (Amer, Kalash, Seshia, and Elsayed, 2017).

Given the paucity of currently available data from prospective studies, there is clearly an urgent need for high-quality and comprehensive evaluation of the direct impact of TNE on

patient outcomes. Such studies will not only justify the adoption of this technology in NICUs, but will target its use to the most in-need population and at the most appropriate time, maximizing its impact.

One of the areas where good-quality retrospective studies have been conducted is in the role of TNE in identifying malpositioned catheter tips of central venous lines. There have been a few retrospective studies confirming its utility (Harabor and Soraisham 2014; Weisz, Poon, James, and McNamara 2014), and these findings have been confirmed by several prospective studies which compared TNE and radiography assessment of umbilical venous catheter placement, and found that TNE may be a more optimal in determining line malpositioning (Franta, Harabor, and Soraisham 2017; Karber, Nielsen, Balsam, Messina, and Davidson 2017; Pulickal et al. 2013).

A great deal of academic work is still needed to be done in this field to understand its utility in clinical and research settings.

Considerations for the future: perils

The role of TNE in physiologic studies

Typically, physiological studies in the neonatal field are conducted using animal models. Such experimental studies are crucial in providing mechanistic insights into disease pathophysiology and identify therapeutic targets. Increasingly, non-invasive methods such as TNE are also being incorporated into animal experiments, as they provide the desirable ability to provide sequential assessments. While this has opened a new field to researchers, there are certain limitations to its translatability to human subjects. These include inter-species

differences, the effect of the interplay of multiple co-existing disease processes, and the influence of concurrent therapies. In addition, the TNE measurements used in these animal studies have not undergone rigorous validation. Nevertheless, the use of TNE has opened the door to appraise physiologic alterations in humans. This is especially important in neonatology, due to the limited feasibility of continuous invasive monitoring.

Unfortunately, its translatability into day-to-day clinical practice has lagged behind, due to some key obstacles. The patient population in the NICU can be highly variable. Both the physiological processes and the effect of diseases on them may vary with gestational maturity. For instance, the immature myocardium of the preterm heart is known to have an intrinsic diastolic dysfunction that may not be seen in term infants. Hence, there is a need to have robust gestational age-specific normative data. This is still missing for a number of TNE measurements. The existent normative data may also need to be re-evaluated, given the major advances in perinatal care over the last two decades, such as the increased uptake of magnesium sulphate, prophylactic indomethacin, antenatal steroids, delayed cord clamping (Demarini, Dollberg, Hoath, Ho, and Donovan 1999; Wu, Azhibekov, and Seri 2016).

Another limitation of the currently available normative data is the lack of consideration of postnatal age. For example, data acquired on day 1 for a 25-week infant may not necessarily be applicable to a two-week old 23-week infant. Further, normative data might apply to certain developmental phases for the preterm infant, but not others. For example, the extremely preterm infant is innately less tolerant of hemodynamics disturbances in its transitional period, and the consequences of low cardiac output states may lead to significant intraventricular hemorrhages. In addition, infants who tend to receive TNE typically do so for a medical indication; therefore, it may be challenging to apply retrospective data acquired from presumed healthy infants. Ideally,

normative data should be established at a population level with a large cohort size, and be validated against long-term clinical outcomes. This has yet to be done.

Another factor to consider with using normative data especially applicable to hemodynamic principles is that expected normal ranges may vary in well and disease states. For example, a left ventricular output obtained from a healthy infant at rest may not be "safe" for a sick infant with a higher metabolic demand. Lastly, while some hemodynamic parameters have undergone rigorous validation by comparing against gold standards, several others that are used in day-to-day clinical and research settings remain untested. With the availability of cardiac magnetic resonance imaging (MRI), such validation studies may now be feasible, even in neonates. Recent advancements in cardiac MRI techniques now offer a non-invasive surrogate of traditionally invasive gold-standard investigations, however, at this time, this modality is generally only used for stable newborn infants, despite hemodynamically unstable infants being the typical population of interest.

The need for academic rigor

So far, most studies using TNE methodology have used a small number of patients, and have focused on the description of the hemodynamic physiology observed in disease states. While this has been helpful in furthering our understanding of hemodynamic pathophysiology, at least at a macro level, it is our opinion that in the future, studies need more rigorous methodology to have a greater clinical impact. This should start at the stage of constructing the research plan itself. It is key, as in any other field of research, that careful planning and consultation be undertaken at this stage. Consideration should be given to formulating a clear and objective hypothesis and stating relevant primary and secondary outcomes.

One of the limitations of many of the previous TNE-based studies is the absence of justifiable sample sizes, which are often chosen out of convenience. This is understandable for descriptive physiological studies, however in order to generate research findings that are more generalizable and widely applicable, as well as have a long-standing impact on practice change, it is imperative that studies are adequately powered to detect differences in clinically meaningful outcomes. In the absence of having appropriate sample sizes, research findings need to be validated in secondary cohorts prior to their clinical implementation.

One way to generate a large sample size is to have a multi-centre TNE network. At this time, a national TNE database does not exist in Canada, but is a potential solution to increasing the feasibility of larger and more rigorous studies. For such a network to produce reliable results, it will require participating centres to standardize the types of measurements to be obtained and the techniques required in doing so. Intra- and inter-person variability is a known barrier in TNE-based research.

In addition, careful consideration should be given to identify potential sources of bias, and mitigating strategies should be incorporated from early in research planning. One unique obstacle in TNE-based research is the difficulty in blinding the operator. Due to resource limitations, TNEs are typically performed and/or analyzed by clinicians with expertise, who may be also either aware of or directly involved in patient management. One way to overcome this challenge is for the research scans and analysis to be performed by trained sonographers, or by careful blinding of personnel. Other factors to consider are the handling of repeat measures and the effect of varying postnatal age at the time of TNE assessments. Data acquired at multiple time-points on the same patient should not be considered independent observations, as this may

introduce bias related to clustering. Most contemporary statistical software packages provide the capability to control for repeated measures.

One of the unique features of TNE-based research is the ability to acquire a large number of variables from a single scan. While this allows for the opportunity to corroborate research results, it also increases the potential for type I error (i.e. identifying statistically significant but erroneous findings), which may be misleading. It is therefore important to adjust for multiple comparisons during statistical analysis. Further, unexpected secondary findings should be re-confirmed in subsequent studies. It is with these considerations that we advise TNE researchers to foster close collaboration with experts in clinical epidemiology. Such collaboration would be mutually beneficial, as physiology-driven epidemiological studies could have a major long-lasting impact on patient care.

Next steps

Targeted neonatal echocardiography provides many opportunities to expand our knowledge of sick and healthy infants across all gestational ages. To continue to move this field forward, future work should cultivate a more refined approach to hemodynamic problems by using validated TNE techniques on important clinical cardiovascular disease states that require mechanistic assessments. More focused effort should be spent in corroborating echocardiographic findings with the clinical picture, by harmonizing the extraction of TNE data with clinical variables. Commonly used cardiovascular therapies should be studied with more emphasis, as there are many holes in our current knowledge of their physiological mechanisms of action across the various gestational and postnatal age groups. Finally, following infants with

hemodynamic disturbances to assess both their short- and long-term outcomes will help fill in gaps in our understanding of the repercussions of abnormal cardiovascular health states.

Conclusions

Over the last two decades, and with the efforts of national and international leaders, TNE is being widely endorsed in the neonatal community with a growing number of people being trained in its use. For this field to continue advancing its impact, clinicians and researchers of the future need to be well trained in both scanning, and its strengths and limitations in analysis. TNE research should be designed and executed in a methodologically rigorous fashion. Ultimately, through the combination of TNE-based research and clinical integration, the goal of neonatal care of providing the right therapy, for the right patient, at the right time may be better realized.

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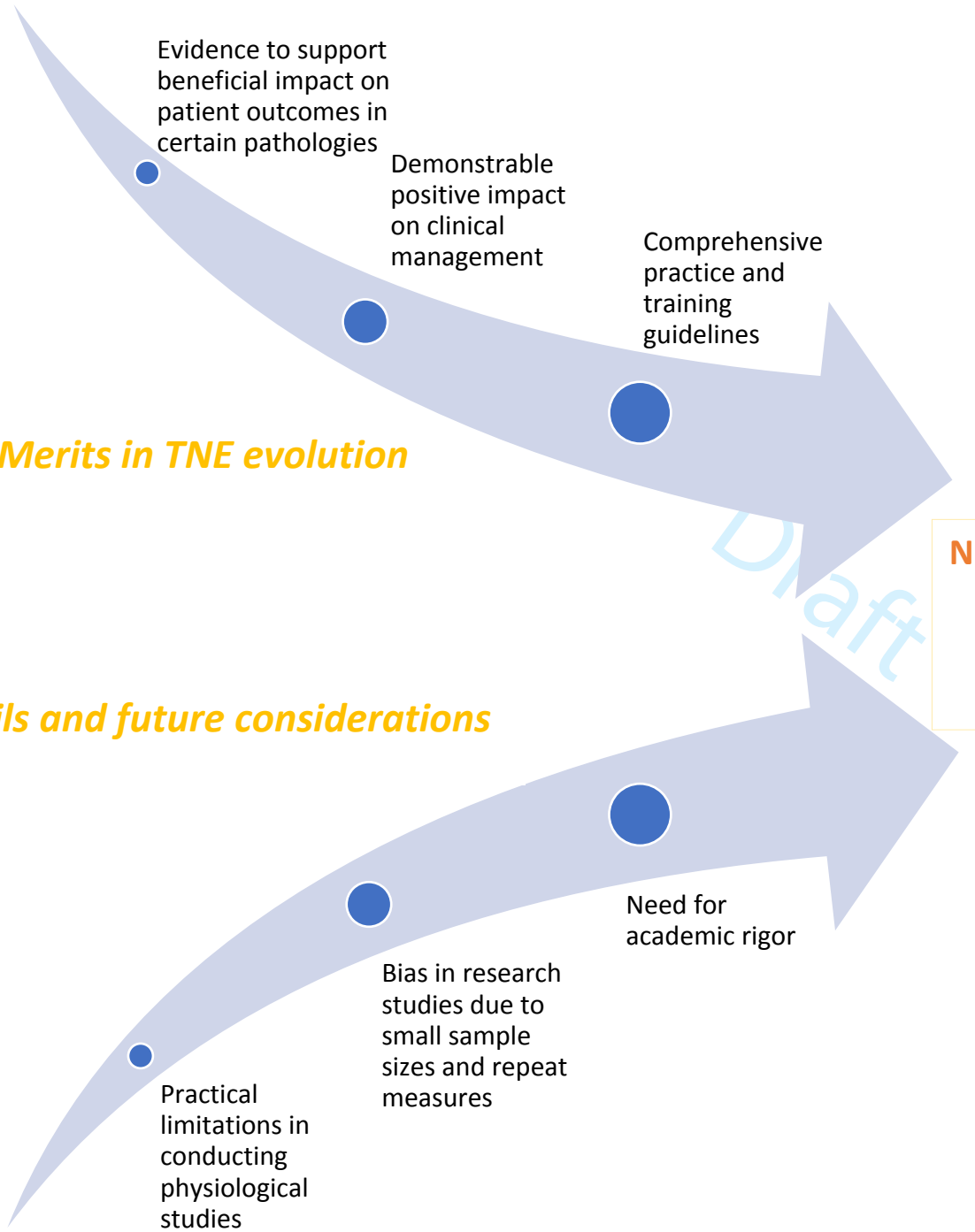
Evidence to support beneficial impact on patient outcomes in certain pathologies
Demonstrable positive impact on clinical management
Comprehensive practice and training guidelines
Merits in TNE evolution
Perils and future considerations
Practical limitations in conducting physiological studies
Bias in research studies due to small sample sizes and repeat measures
Need for academic rigor
Need for:
Physiology-Driven Epidemiological Studies
Prospective Evaluation of Impact
Correlation with Patient Outcomes