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COMMENT

Alternative facts? Using big data to identify high and low blood pressure values

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Investigation of the relationship between blood pressure (BP) and clinically significant outcomes such as death, severe intraventricular hemorrhage (IVH), and altered or impaired neurodevelopment dates back >40 years.[1] After four decades, optimal assessment and management of the immature cardiovascular system remains elusive. While BP increases spontaneously in the immediate postnatal period for extremely preterm infants, a wide range of BP values is observed at each postnatal hour such that the identification of "normal" or "acceptable" BP values is difficult. In addition, the presence of multiple confounding variables in most studies combined with a lack of safety and efficacy data for commonly prescribed antihypotensive therapies makes it challenging to know when therapeutic intervention is warranted for a specific infant at a specific postnatal age under specific hemodynamic circumstances.

In this issue of *Pediatric Research*, Vesoulis and colleagues[2] add "fuel to the fire" by examining the relationship between continuous BP values obtained over the first 168 h and severe IVH in a cohort of extremely preterm infants with a mean gestational age (GA) at birth of 25.2 weeks. Utilizing a massive database with >85 million BP measurements (an average of >540,000 data points per patient), the authors examined the relationship between BP measurements, other patient characteristics, and the incidence of severe IVH. They reported that infants with severe IVH had significantly more extreme mean arterial BP (MABP) values (≤23 mm Hg or ≥46 mm Hg) and spent a significantly greater period of time with a MABP outside this "optimal" range (defined by analysis of BP measurements for the study population) as compared to infants without a severe IVH or without any IVH. Infants with a severe IVH were also less likely to receive antenatal corticosteroids and more likely to receive inotropic medications. The authors note several important limitations based on the study inclusion criteria and heterogeneity of the patient population investigated and appropriately caution against over-interpretation of their results. Nonetheless, the manuscript is well written with several important findings, which merit further discussion.

First, there are no "normal" BP values for extremely preterm infants and "abnormal" BP values are not easily determined. As noted by the distribution of time spent at each 2 mm Hg "bin" in Fig. 2, observed BP values vary significantly for preterm infants and only a small percentage of time is spent at each numeric MABP value over the first postnatal week. As shown in Fig. 1 and reported previously by others,[3] BP increases in the immediate postnatal period in extremely preterm infants similar to more mature infants. This lack of "normal" values means "abnormal" values are also difficult to identify, likely vary for extremely preterm infants, and probably change with advancing postnatal age. A strict numeric cut-off for defining low BP values—such as a MABP numerically equivalent to the infant's GA at birth[4]—is inconsistent with the observed values. Since this definition of low BP also does not reliably identify infants at increased risk for adverse outcomes (as noted in this study in which infants with a severe IVH spent a similar portion of time with a MABP below this threshold as infants without a severe IVH) and is not a threshold for therapeutic intervention associated with improved rates of clinically relevant patient outcomes, a MABP numerically equivalent to the infant's GA at birth to define hypotension does not have evidence to support its routine use for clinical care or as the basis for future investigations.

Second, as other authors have suggested, significant BP variability can contribute to adverse outcomes related to the brain. This is presumably due to associated changes in cerebral perfusion in which a rapid rise in BP and cerebral perfusion occurs without sufficient time to allow for arteriole cerebral vasoconstriction, thus exposing germinal matrix blood vessels to a sudden and significant increase in pressure, which may lead to rupture and hemorrhage. However, the underlying cause of BP variability is often not known. Vesoulis et al. speculate that this may be related to "therapeutic overshoot." Other potential explanations include medical complications (dislodged or occluded endotracheal tube, pneumothorax), procedures (suctioning of the trachea, endotracheal intubation, echocardiography, intravenous catheter placement), hands-on nursing care, and tactile or auditory stimulation. Future studies are needed to clarify the concept supported by the current study, which advocates for limiting stimulation and intervention in an effort to decrease BP variability and minimize injury to the brain.

Third, the administration of inotropic medications to extremely preterm infants is associated with an increased risk of adverse outcomes. In this study by Vesoulis et al., infants with a severe IVH were more than twice as likely to receive an inotrope as those without a severe IVH (69% versus 30%, $p < 0.01$). Extremely preterm infants who receive antihypotensive therapies have higher mortality and morbidity rates versus untreated infants of a similar GA.[5,6] While the presence of confounding factors makes it difficult to determine whether this association is causative or simply the result of sicker infants more commonly receiving these therapies, evidence suggests that these risks persist even when considering variables such as the frequency of low BP values, severity of illness, inclusion of infants in extremis who are likely to die irrespective of therapeutic interventions, and the underlying cause of perceived low BP.[5–8] The

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study by Vesoulis et al. was not designed to determine the cause of IVH and it is unclear whether this association is due to changes in cerebral perfusion related to inotropes or a different underlying pathophysiology, which happens to also be associated with an increased risk of inotrope use. At minimum, this study highlights the need to be vigilant when administering inotropes to extremely preterm infants with prompt titration when BP starts to rise and an awareness that the use of these medications is associated with a greater chance of adverse outcomes.

Fourth, antenatal corticosteroids benefit the brain in addition to the lungs. The decrease in severe IVH rates reported by Vesoulis et al. is consistent with previous studies, which also demonstrated a decreased risk of IVH when corticosteroids were administered prior to preterm birth.[9] Irrespective of whether this is an association that reflects circumstances at delivery rather than a cause and effect relationship, the current study provides additional support to the clinical practice of urgently administering corticosteroids whenever preterm birth is suspected.

Lastly, and perhaps most importantly, additional data from well-designed studies are needed. Randomized trials of BP management in this population have remained elusive to date due to challenges with obtaining informed consent, provider equipoise, and a lack of consensus regarding the appropriate criteria for therapeutic intervention.[10–12] While several studies have reported encouraging results, currently there is also insufficient evidence of improved outcomes in extremely preterm infants for the routine clinical use of other methods of hemodynamic assessment such as echocardiography, near infrared spectroscopy, bioimpedence, or pulsatility index. Owing in part to this lack of evidence, hemodynamic assessment and management for preterm infants in the immediate postnatal period is highly variable.[7,13,14]

While BP is often monitored continuously in the immediate postnatal period, there remains limited understanding of how best to interpret or respond to observed values. The findings reported by Vesoulis and colleagues are important examples of this dilemma. Uncertainty in medicine is common, particularly when caring for critically ill preterm infants. The association between severe IVH and both high and low MABP values reported in this study adds to our current understanding of cardiovascular management in extremely preterm infants. There is substantial evidence suggesting an increased risk of adverse outcomes associated with the use of therapies intended to increase BP—perhaps because an unintended consequence of these therapies is a rapid or higher rise in BP than desired with resulting adverse consequences, such as a severe IVH. Until better safety and efficacy data of various options for therapeutic intervention are available through much-needed clinical trials, the best option may be to take a "first, do no harm" approach in which the use of inotropic medications in extremely preterm infants is limited to those with strong evidence of impaired perfusion (e.g., oliguria, metabolic acidosis, failure of BP to rise spontaneously, evidence of hypovolemia, strong suspicion of sepsis) in whom the potential risks and benefits are favorably balanced.

AUTHOR CONTRIBUTIONS

B.B. takes full responsibility for all aspects of authorship of this manuscript.

ADDITIONAL INFORMATION

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