Intervention and Outcome for Neonatal Hypotension

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KEYWORDS

• Infant • Newborn • Blood pressure • Inotropes

KEY POINTS

- Epidemiologic studies of blood pressure (BP) produce percentiles of typical values but do not answer the question of what is a safe BP.
- Although there have been numerous small trials conducted, none have been powered to address clinically relevant outcomes.
- Only adequately powered prospective randomized controlled trials can answer the question of whether individual treatments of low BP have an impact on short- and longer-term outcomes.

INTRODUCTION

Blood pressures increase in the fetus throughout gestation, and the preterm neonate normally has a low systemic mean blood pressure (BP), which correlates with their gestational age. Immediately after birth, BP may decrease transiently—probably in part because of the significant changes in loading conditions of the left ventricle and the reversal of direction of the ductal shunt as pulmonary vascular resistance decreases—and then increase progressively.[1] Other factors such as growth restriction, chronic in-utero hypoxia, preeclampsia, maternal steroid treatment, and twin-twin transfusion syndrome can affect BP during the first few days.[2]

The question of what is a normal BP for a particular infant is therefore complex and cannot be answered with a single number for each gestational age or birth weight.[3] Epidemiologic studies of BP in large groups of infants have demonstrated the postnatal changes in BP, and although they can produce percentiles of typical values, they cannot answer the question of what is an appropriate, or safe, BP for an individual.[4–7]

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Many studies have shown that infants with BPs that are in the lower range for their gestational age tend to have increased complications (as reviewed later), but of course correlation does not prove causation, nor does it create an indication for treatment. However, many neonatal programs do intervene with preterm infants whose BPs are lower than usual, in the hope that doing so will decrease complications; that is a hope that is not supported by the trials that are reviewed in this article. The interventions for hypotension all have potential secondary effects, and their use should be determined by a good evidence base. Unfortunately, many trials have focused on the impacts of treatments on BP and not on whether the potential complications are reduced in turn.

The overreliance on the short outcome measure of "normalizing the mean BP" in hypotension clinical trials fails to recognize the complexity of the cardiovascular system in premature infants, especially in the first days of adaptation. Immaturity of the myocardium, poor tolerance of afterload, delays in reduction of pulmonary vascular resistance, relative hypovolemia, and high volume shunts through the ductus arteriosus or foramen ovale, along with the impact of various interventions such as positive pressure ventilation, can each contribute to cardiovascular compromise. Evaluation of the effect of any intervention in this setting presents many challenges, in addressing not only the intervention itself but also the underlying pathophysiology and the criteria chosen on which to intervene. Attempting to determine the impact of hypotension alone, compared with its treatment, is thus challenging. Indeed, even if it could be shown that a specific intervention for hypotension improved clinical outcomes, that does not necessarily mean that other interventions would have the same impact. Ideally, a trial evaluating an approach with observation alone, compared with a particular intervention at a certain threshold BP value, would provide evidence whether that specific way of maintaining a certain BP value results in better (or worse) outcome. However, large-scale trials in this area are lacking and thus the evidence base is rather tenuous. Large-scale cohort studies provide us with some important evidence but often have significant limitations. Often most of the BP measurements performed are noninvasive and intermittent, the duration of low BP is not documented, and the timing and type of interventions performed may not be described. Documentation of other potential confounding factors, such as placental transfusion and mechanical ventilation, the criteria leading to intervention, and the timing of outcome measures may not be reported. Despite these limitations such studies provide information, which are addressed later in the article. There have been numerous small trials comparing individual approaches, including inotropes and volume administration, but the criteria defining hypotension and the outcome measures vary from study to study. The largest has a sample size of only 90 patients,[8] and most of these studies have sample sizes less than 40 and are single-site trials, limiting their generalisability. In this article the authors review some of the short-term and long-term impacts of hypotension and intervention and provide some suggestions around how we can best interpret the data available to us in order to inform future studies.

CARDIAC OUTPUT AND MYOCARDIAL PERFORMANCE MEASUREMENT USING ECHOCARDIOGRAPHY

Adequate cellular metabolism requires a normal and sustained *cardiac output* (and end-organ perfusion) in addition to a *normal blood oxygen (O_2) content.* Cardiac output is determined by preload, afterload, myocardial contractility, and heart rate.

Those determinants of cardiac output also have important interactions with each other, which are often forgotten when attempting to determine the underlying cause of a low blood flow state. Contractility is influenced by preload due to the *length-tension relationship:* this relationship describes the interaction between increased preload and improved contractility. Increased preload results in increased sarcomere length and tension, leading to an increase in the force of contraction up to a physiologic threshold beyond which myocardial dilation can occur. The *force-velocity relationship* governs the interaction between contractility and afterload: it describes the inverse relationship between increasing afterload (force generated during the shortening of the muscle fiber) and the velocity of fiber shortening. Finally, the *force-frequency relationship* governs the interaction between contractility and heart rate (**Fig. 1**) and describes the increase in contractile force with increasing chronotropy (heart rate) if there is adequate preload.[9] The use of echocardiography in the neonatal field has increased significantly over the last 10 years to provide a noninvasive and objective assessment of cardiac function and output. The use of echocardiography can, in theory, help to provide a more comprehensive assessment of the various components of cardiovascular hemostasis necessary to maintain adequate cellular metabolism. The traditional use of echocardiography has centered on measurement of cardiac output; however, more recent advances have potentially enabled the measurements of surrogate markers of preload and afterload. In addition, more recent echocardiography markers such as deformation analysis may distinguish between dysfunction secondary to adverse loading conditions versus dysfunction secondary to compromised contractility.

Left and right ventricular outputs can be obtained to determine systemic and pulmonary blood flow states.[10] However, those measurements should be interpreted with

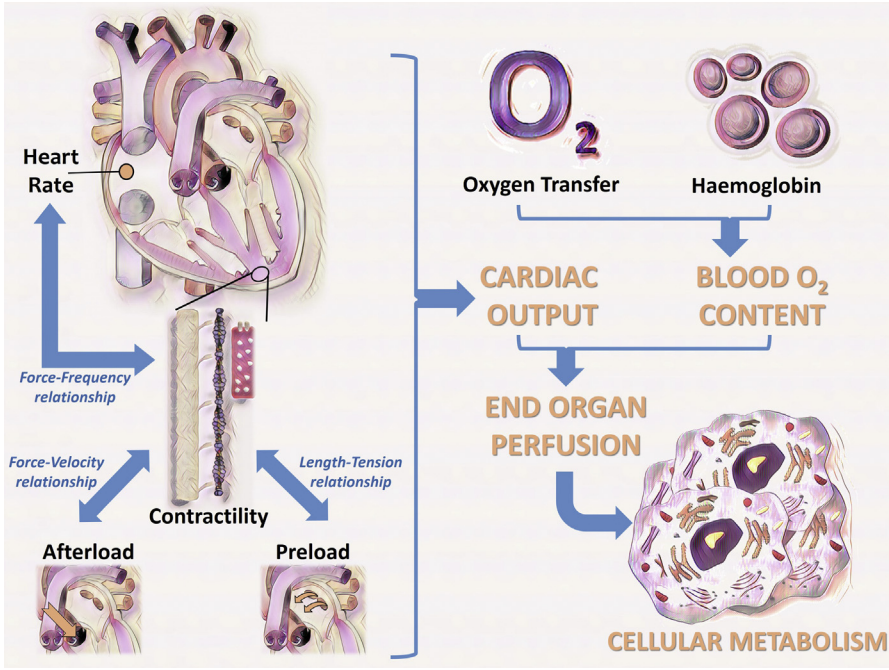

Fig. 1. Factors influencing cardiac output and endorgan perfusion.

caution, as they are complicated by the presence of intra- and extracardiac shunts. Superior vena cava (SVC) flow measurement provides a shunt independent assessment of blood flow to the upper body.[11] Low SVC blood flow has been associated with adverse short- and long-term outcomes.[12–14] However, the positive predictive value of low SVC flow measurement for adverse outcome is low.[15] Concerns around inter- and intrarater variability also need to be considered; the same operator should perform sequential scans where this is warranted and feasible.

Several studies have reported on these assessments of cardiac output when comparing one agent against another agent,[8,16–20] with varying findings. Each study has small numbers of enrolled infants but it would seem that dopamine usually leads to a reduction in left ventricular output presumably secondary to increased afterload, whereas dobutamine usually increases cardiac output and decreases systemic vascular resistance, thus having little predictable impact on the BP, and epinephrine, at least in low or moderate doses, usually increases BP and cardiac output.[21] However, these are oversimplifications of a more complex problem.

Characterization of ventricular performance with myocardial deformation has recently been suggested as a validated method to assess both ventricular contractility and loading conditions in preterm infants. Deformation analysis describes a change in shape of a segment of the myocardium, or the myocardium as whole, from its baseline shape in diastole to its (deformed) changed shape in systole and can occur in several planes in the left ventricle (longitudinal, radial, and circumferential) and predominantly in the longitudinal plane in the right ventricle.[22] Strain is the measure of the amount of deformation occurring over the cardiac cycle, whereas strain rate measures the speed at which deformation occurs and returns to baseline.[23] Strain is highly influenced by loading conditions and therefore changes in strain can reflect change in preload or afterload. Increasing preload (or a decrease in afterload) leads to an increase in the magnitude of strain, whereas increasing afterload (or a decrease in preload) leads to a decrease in the magnitude of strain.[24,25] However, recent animal and adult human data have convincingly demonstrated that strain rate shows a close relationship with invasive measures of intrinsic contractility and exhibits observable properties further supporting load independency.[26,27] Therefore, changes in strain rate occur independent of loading condition and are more likely to reflect changes in contractility.[9,28,29] Characterization of adverse loading conditions and impaired contractility with advanced strain and strain rate measures provide a deeper understanding of myocardial performance phenotyping in preterm infants. This can set the scene for a more comprehensive appraisal of the underlying pathophysiology of low blood flow states. Assessment of those physiologic endpoint can pave the way for a targeted treatment approach in order to rectify those components and set the scene for future trials of low blood flow states. However, normative values, therapeutic interventions, and response to treatment need further study in this population.[30]

OTHER MODALITIES FOR THE ASSESSMENT OF HEMODYNAMIC COMPROMISE

Noninvasive cardiac output monitoring using the theory of electrical conductance through body tissues is gaining interest. There are 2 main derivatives of the technique termed electric velocimetry (EV) and transthoracic bioreactance (TBR). There are new devices on the market that can derive left ventricular stroke volume, cardiac output, and SVR (by integrating cardiac output and BP readings) using either EV or TBR. EV

measurements have a relatively low bias when compared with echo but with relatively wide limits of agreement; a patent ductus arteriosus (PDA) can also affect the agreement between EV and echo.[31,32] Bioreactance demonstrates a constant systematic bias when compared with echo, cardiac output readings obtained by TBR being lower than echo by 30%.[33] TBR can however demonstrate important hemodynamic changes in certain disease states during therapeutic hypothermia and following PDA ligation.[34,35] The techniques seem to be quite unreliable in the presence of shunts, and further studies are required before the introduction of those modalities into routine clinical use in the newborn. Their use in the trial setting may be of benefit, especially if echocardiography eliminates the presence of a shunt. Studying trends of changes in cardiac output, derived systemic vascular resistance, and end-organ perfusion may provide a clearer picture of the physiologic response to various inotropes. This may increase our understanding of the effect of different inotropes on the premature infant circulation and refine our design of randomized controlled trials (RCTs) in hypotension in the future.

The relatively high degree of transparency of brain tissue in the near-infrared (NIR) range enables real-time noninvasive detection of tissue oxygen saturation using transillumination spectroscopy.[36] NIRS-measured hemoglobin oxygenation parameters may reflect functional changes in cerebral hemodynamics and brain tissue oxygenation during neonatal cardiopulmonary bypass and deep hypothermic circulatory arrest.[37] In the premature population, NIRS illustrates lower cerebral regional saturations in hypotensive infants[38] and can also demonstrate a reduction in cerebral oxygenation in infants chronically exposed to a PDA.[39] NIRS is also used to measure splanchnic perfusion with evidence suggesting that this technique may be able to distinguish between complicated and uncomplicated necrotizing enterocolitis (NEC).[40] Its use in guiding hemodynamic management can potentially reduce short-term morbidities in preterm infants[41] but again further studies incorporating NIRS are necessary.

HYPOTENSION AND SHORT-TERM CLINICAL OUTCOMES

Intraventricular Hemorrhage

Perhaps the greatest area of concern relates to the relationship between hypotension and brain injury. It is easy to appreciate the biological plausibility: low BP, lower than the limits of autoregulation (or in the presence of impaired autoregulation), may result in low cerebral blood flow resulting in brain injury, typically intraventricular haemorrhage (IVH). However, although there is a close temporal relationship in that most of the significant injury occurs in the first few days of life and that most hypotension in at-risk patients occurs on the first day,[42] many other factors need to be considered. Numerous observational studies have demonstrated an association between low BP and IVH over the years,[21] each of which has its own limitations. These associations have undoubtedly resulted in common practice standards. For example, the practice of maintaining a mean BP greater than 30 mm Hg is derived from data obtained from 33 preterm infants 26 to 30 weeks gestation,[43] in which the investigators found that infants with a mean BP of less than 30 mm Hg for at least 1 hour had significantly more severe lesions and early deaths than those with a mean greater than 30 mm Hg in the first 24 hours of life. None of the infants with a mean BP greater than 30 mm Hg had severe lesions. In another study of 100 preterm infants in the first 48 hours of life with invasive BP recordings infants in whom grades 2 to 4 periventricular-IVH developed (n = 28) had consistently lower mean arterial pressure (MAP)

than those who had no hemorrhage or a grade 1 hemorrhage only.[44] Watkins and colleagues[7] identified an association between prolonged duration of a mean BP less than the tenth percentile for birth weight and the frequency of IVH. Much of these data are derived from the 1980s and 1990s and are not entirely representative of the population of infants today at the greatest risk of brain injury. Kuint and colleagues,[45] in a matched case control study including 218 infants with mean birth weight of approximately 28 weeks, found that the only parameter predicting IVH grade 2 to 4 was the lowest MAP, with an odds ratio (OR) of 1.3 (95% confidence interval [CI] 1.12–1.51). Batton and colleagues investigated 15 different BP definitions in a cohort of infants delivered between 23 and 27 weeks gestation in an attempt to identify a BP threshold less than which initiating therapy would be beneficial. However, of the 15 definitions of low BP used they found that therapy was not prescribed to 3% to 49% of infants with low BP but was administered to 28% to 41% of infants without low BP, suggesting that factors other than BP were leading to withholding or commencing intervention.[46] They also described the dynamic changes in mean BP over the first 24 hours of life.[1]

The German Neonatal Network explored the association between short-term outcome and hypotension in preterm infants less than 32 weeks gestation. The investigators examined the lowest mean BP on day 1 in almost 5000 preterm infants. They examined 2 definitions of hypotension, namely (1) the lowest mean arterial pressure during the first 24 hours of life (minMAP24) lower than gestational age (in weeks) and (2) minMAP24 lower than median minMAP24 of all patients of the corresponding gestational age. They analyzed these definitions in the subgroup of infants who did not receive any vasoactive drugs (4260 infants) and found that lower BP was also associated with higher risk of development of IVH (16.5% vs 13.9%, $P = .019$). Infants with minMAP24 in the lowest quartile for gestational age also had a greater risk of severe IVH (18.4% vs 14.3%, $P = .004$). In a multivariate model minMAP24 was found to be a predictor for the occurrence of IVH (OR 0.97/mm Hg, 95% CI 0.95–0.99, $P = .006$), bronchopulmonary dysplasia (BPD) (OR 0.96/mm Hg, 95% CI 0.94–0.98, $P<.001$) and death (OR 0.95/mm Hg, 95% CI 0.90–0.99, $P = .026$).[47] Alderliesten and colleagues evaluated the association between hypotension and adverse outcome in preterm infants less than 32 weeks. In this matched case control study low BP alone was not associated with adverse outcome. Instead they found that low cerebral oxygenation values were associated with adverse long-term outcome.[48]

The Canadian Neonatal Network evaluated the relationship between admission systolic BP and adverse outcome including mortality and severe brain injury.[49] The investigators identified a U-shaped curve, suggesting that low- and high-admission systolic BPs were associated with worse outcome in preterm infants less than 26 weeks gestation. Limitations included a lack of standardized measurement techniques and lack of timing, absence of duration of BP measurements, and no control for volume or epinephrine administration in the delivery room. When infants who received inotropic medications were removed, there remained an association between low systolic BP and IVH.

In a propensity score matched subgroup from the Epipage 2 cohort, untreated hypotensive infants were more likely to have the primary adverse outcome (death or serious brain injury or NEC or retinopathy or severe bronchopulmonary dysplasia) compared with treated infants who were hypotensive but had no other signs of low perfusion (51% vs 38%)[50]; the serious brain injury part of the outcome was seen in 22% of the untreated and 10% of the treated matched babies, suggesting that intervention may be warranted. This finding is in contrast to data from a previous single-center study where the approach to management of low BP was characterized by a

more global assessment of the infant, not relying solely on BP values, before deciding to intervene. Infants treated with this permissive approach had as good an outcome as normotensive patients.[51]

Observational studies, however, no matter how well performed, cannot discriminate between correlation and causation. Even when causation can be proved, they provide no evidence regarding the efficacy of different treatments. Most of such studies show a correlation between lower BP and IVH.

Necrotizing Enterocolitis

NEC is a multifactorial problem, of which intestinal perfusion is one important factor.[52,53] Early studies suggested that NEC was caused by early hypotension/ischemia.[52] Data from the Canadian Neonatal Network identified that NEC was associated with lower gestational age, treatment of hypotension, and PDA.[54] Recently Samuels and colleagues[55] performed a systematic review of prognostic studies of risk factors for NEC. Hypotension was identified as one of the risk factors. The authors evaluated an approach defined as permissive hypotension[51] and found no difference in the incidence of NEC between groups who were normotensive, hypotensive and not treated, and hypotensive and who received intervention. However, such studies are not powered to make such determinations. Bravo and colleagues[56] randomized preterm infants with low SVC flow to dobutamine or placebo (28 infants in total) and found that there was no difference in the incidence of NEC between groups, nor in comparison to those infants who had normal SVC flows. To date this is the only RCT including a placebo arm to have reported NEC as an outcome. Some of the other RCTs comparing 2 inotropes in patients with low BP do report NEC rates,[17,57] but the small number of patients included, and hence low numbers with NEC, make it impossible to draw any conclusions.

LONG-TERM OUTCOMES

The relationship between hypotension and long-term outcome is even more challenging to address, given the complexity of factors that influence long-term outcome. Martens and colleagues[58] followed 266 live born infants with a gestational age less than 32 weeks as part of the Leiden Follow-up Project. They evaluated preterm infants at term with the Prechtl examination and found an association between those with hypotension (defined as a mean arterial BP <30 mm Hg on at least 2 occasions) and abnormal neurologic assessment. Goldstein and colleagues evaluated the association between hypotension and long-term outcomes for infants less than 1500 g. Hypotension was defined as a systolic BP less than 35 mm Hg for infants with a birth weight less than 750 g and less than 40 mm Hg for 750 to 1500 g. They found a correlation between the duration of BP less than this threshold and lower psychomotor developmental index on the Bayley scales of infant development at 2 years.[59] Kuint followed-up their matched case control study to 2 years and in a stepwise logistic regression analysis, which included neonatal hypotension, medically treated hypotension, BPD, IVH, and periventricular leukomalacia (PVL) among other factors, found that PVL and treated neonatal hypotension were the only parameters predicting major neurologic disability, with an OR of 63.1 (95% CI 13.3–299, $P<.001$) and 5.4 (95% CI 1.29–22.7, $P = .01$), respectively.[45] Fanaroff and Fanaroff[60] in a retrospective study of 156 extremely preterm infants found an association between symptomatic hypotension and delayed motor development and hearing loss (OR 8.9). Logan and colleagues[61] as part of the follow-up of the ELGAN study found no association between early postnatal hypotension and developmental delay at 24 months in a large

cohort of infants. Batton addressed the issue of early BP changes, treatment, and the effect on outcome in their prospective cohort study of infants delivered between 23 and 27 weeks. They found infants in receipt of antihypotensive therapy had a higher rate of death/neurodevelopmental disability irrespective of early BP changes.[62] Similarly, the German Neonatal Network data also showed an association between inotrope administration and adverse outcome as defined by IVH.[47] Treatment with inotropes was associated with a higher rate of IVH but the investigators acknowledged that the administration of vasoactive medications may have been due to complications and so this finding needs to be interpreted cautiously. In a large cohort of almost 8000 infants less than 29 weeks from the Canadian Neonatal Network infants in receipt of inotropes had an increased risk of death, severe IVH, NEC, and BPD. The overall rate of inotrope administration was 9.8% for the group overall in receipt of inotrope on day 1 and day 3, a rate similar to the GNN data. Therefore, statistically there are associations supporting a relationship between hypotension and adverse outcomes[59] but also conflicting evidence suggesting no such statistical association.[61] The exact same can be said of intervention/treatment of hypotension, some studies suggesting worse outcome and others suggesting no difference in outcome. What is clear from more recent observational data is that significant site variability persists, but there seems to be an overall reduction in the use of inotropes in very preterm infants in the last decade.[47,49]

SUMMARY

The conventional use of BP in isolation to diagnose inadequate blood flow and to determine whether to institute therapy is overly simplistic, which is reflected in the marked variability between documented low BP and inotrope administration. Although there is probably an association between lower BP and more short-term complications, which are probably associated with poorer long-term outcomes, it is not clear whether this is causative. In some publications the association with more frequent outcomes disappears after correcting for inotrope use, one possible explanation of which is that hypotension is a marker of ill health and higher risk but that active intervention is what leads to the complications.

Only adequately powered prospective RCTs can answer the question of whether individual treatments of low BP are helpful or harmful (or have no impact) in terms of short- and long-term outcomes. Indeed, one could ask whether the current paradigm of trials to examine hypotension treatment is appropriate. Trials of cardiovascular support among preterm infants with evidence of poor oxygen delivery might be more appropriate. However, until, and unless, hypotension treatment in isolation is abandoned by clinicians, RCTs of hypotension treatment will remain relevant.

Future trial design examining short-term physiologic optimal outcome measures should move away from targeting a change in BP alone as a marker for reestablishing adequate cardiovascular homeostasis. The inclusion of additional monitoring tools including echocardiography, noninvasive cardiac output monitoring, and NIR spectroscopy should be used to determine inclusion and serve as important short-term physiologic outcome measures. Finally, clinically important outcomes of survival and short- and long-term complications of prematurity must be considered as the primary outcomes of such trials.

DISCLOSURE

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Best Practices

What is the current practice?

Neonatal Hypotension

Best practice/guideline/care path objectives

- No uniform guideline exists to define and manage low BP in the very preterm infant
- Often intervention occurs when the mean BP is less than the equivalent gestational age value
- Volume followed by dopamine as the primary inotrope is the most consistent intervention
- The current evidence base only permits an association to be made between low BP and short- and long-term outcome
- There is currently no high-quality evidence to support the development of best practice guidelines for management of hypotension in preterm infants

What changes in current practice are likely to improve outcomes?

Major Recommendations

Adequately powered RCTs are necessary to determine

1. Criteria to guide intervention
2. Type of intervention

Summary statement

It remains unclear if intervention is associated with an improved outcome in preterm infants with low BP. Future trials assessing intervention criteria and the type of intervention chosen are now necessary.

Data from Refs.[1,22,43,44]

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