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Clinical Trials in Hemodynamic Support

Past, Present, and Future

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KEYWORDS

• Hypotension • Low blood flow • Clinical trials • Preterm infants • Inotropes

KEY POINTS

- Hypotension trials in preterm infants are marred by heterogeneity, small numbers, and a lack of a clear outcome measure.
- Identifying the underlying physiology for low blood flow states is the first step in devising definitive trials of hypotension.
- Comparison between a regimented approach and a physiologic approach to treatment should be the cornerstone of any future trials of hypotension in premature infants.

INTRODUCTION

Despite a significant number of randomized trials and meta-analyses of cardiovascular support in the preterm population,[1–3] the neonatal community is still at a loss on how to approach the preterm infant with low blood pressure (BP)/low blood flow states during the first days of life.[4,5] The trials to date are characterized by significant heterogeneity—in the populations studied, their inclusion criteria, and the interventions and endpoints chosen—but all are characterized by one important aspect—small numbers of enrolled patients (from 20 patients through to 90)—and all are underpowered to draw any short-term or long-term conclusions to direct clinical care.[6] The mantra of intervening when the mean BP falls below the mean gestational age in millimeters of mercury has remained set in stone for the majority,[7] and the primary agent used remains dopamine.[8,9] Familiarity with this approach has meant that it rarely has been challenged. A desire to oversimplify and homogenize what essentially is a heterogeneous, complex, and multifaceted pathophysiologic phenomenon has meant that 40 years on there still are not any concrete answers, other than that inotropes do (generally) increase BP.[10] Use of a regimented approach involving a single inotrope

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in a 1-size-fits-all intervention has to date failed to demonstrate tangible improvements in important neonatal outcomes but continues to be the mainstay of management.

One of the challenges in devising randomized controlled trials (RCTs) of hemodynamic support in this population undoubtedly is identifying the underlying pathophysiology. Premature birth imposes a significant stressor on the cardiovascular system, which is deigned to work in an adequate preload, low afterload environment supported by the placenta. Preterm birth essentially reverses this physiologic state to an impaired preload, high afterload milieu, further complicated by the persistence of fetal shunts, including the ductus arteriosus and the patent foramen ovale. The myocardium in premature infants possesses an immature contractile apparatus, resulting in systolic dysfunction, and a stiff noncompliant fiber structure, resulting in diastolic dysfunction, rendering the neonatal heart poorly tolerant of impaired preload and afterload conditions.[11,12] The cardiovascular system is challenged further by a lack of adequate adrenergic innervation,[13] the immaturity of the hypothalamic-pituitary-adrenal axis resulting in a deficiency of glucocorticoid production, and a propensity for the peripheral vessels to be in a high resting vascular tone.[14] Thus, it is easy to see how inotropes and their proposed effects differ substantially from pediatric populations, and drawing inferences from older age groups is both challenging and potentially misleading.[15–18]

This article reviews the many RCTs conducted to date in the preterm population. The challenges that have been encountered in performing these trials are reviewed and alternative studies proposed based on the lessons learned over the past number of years.

PREVIOUS TRIALS

At first glance it would appear that there should be significant evidence to support current management strategies because 24 RCTs have been performed and 6 Cochrane reviews conducted in the setting of low BP or low-flow states. These have included comparisons between inotropes and volume, individual inotropes, inotropes and steroids, inotropes and placebo, steroids and placebo, and lusitropes and placebo. These are summarized in the accompanying tables (**Tables 1** and **2**). The majority of the studies were performed in the 1990s, with fewer studies in the past 20 years. The majority have been single center studies and are discussed below.

Table 1
Randomized controlled trials conducted in 1990s

Author, Year	Agents	Number Enrolled	Gestation (weeks)/ Birthweight (g)
Roze et al,[22] 1993	Dopamine/dobutamine	20	<32
Greenough and Emery,[21] 1993	Dopamine/dobutamine	40	23–34
Gill and Weindling,[19] 1993	Dopamine/Fresh Frozen Plasma	39	<1500 g
Chatterjee et al,[24] 1993	Dopamine/dobutamine	20	<32
Klarr et al,[23] 1994	Dopamine/dobutamine	63	24–34
Hentschel et al,[25] 1995	Dopamine/dobutamine	20	25–36
Phillipos and Robertson,[30] 1996	Dopamine/epinephrine	20	<1750 g
Bourchier and Wesson,[37] 1997	Dopamine/hydrocortisone	40	<1500 g
Gaissmaier and Pohlandt,[39] 1999	Dexamethasone/placebo	17	No defined gestation

Table 2
Randomized controlled trials conducted from 2000 to 2019

Author, Year	Agents	Number Enrolled	Gestation (weeks)/ Birthweight (grams)
Ruelas Orozco et al, 2000	Dopamine/dobutamine	66	Preterm infants
Osborn et al,[27] 2002	Dopamine/dobutamine	40	<30
Lundstrum et al,[20] 2002	Dopamine/volume	36	<36
NG,[38] 2006	Hydrocortisone/placebo	48	<32
Fillipi et al,[29] 2007	Dopamine/volume	35	<1500
Paradisis et al,[36] 2009	Milrinone/placebo	90	<30
Batton et al,[41] 2012	Dopamine/hydrocortisone/placebo	10	<28
Hochwald et al, 2013	Hydrocortisone/placebo	22	<30
Rios and Kaiser,[34] 2015	Dopamine/vasopressin	20	<28
Bravo et al,[35] 2016	Dobutamine/placebo	28	<33

Inotropes Versus Volume

Two studies compare volume versus inotrope, on both occasions dopamine. Gill and Weindling[19] included 39 hypotensive preterm infants and Lundstrom and colleagues[20] 24 infants (none of whom was hypotensive). These were the subject of a Cochrane review, which concluded that dopamine was better than albumin at increasing BP. Neither intervention was shown superior at improving blood flow or in improving mortality and morbidity.[1]

Inotrope Versus Inotrope

A majority of studies have compared dopamine versus dobutamine in hypotensive preterm infants,[21–26] and 1 study has compared both agents in low-flow states.[27] These studies are the subject of individual Cochrane reviews but the overall summary is that dopamine is more likely to increase BP and dobutamine more likely to increase cardiac output (CO).[2,28] The individual trials are characterized by small numbers of enrolled patients (20–66) and too few patients to infer any conclusive evidence for short-term and long-term outcome. Fillipi and colleagues[29] compared dopamine to dobutamine and found that dopamine increases BP greater than dobutamine but reduces serum T4 levels. Suppression was reversed, however, after treatment was stopped.[29]

Phillipos and Robertson[30] compared dopamine to epinephrine in hypotensive preterm infants and found epinephrine was more likely to increase left ventricular output compared with dopamine. Pellicier and colleagues[31] evaluated dopamine versus adrenaline in hypotensive preterm infants and found no difference in either agent in increasing BP or cerebral oxygenation. This study and the study by Osborn and colleagues[32] were the only trials to present long-term outcome data, but again the numbers are too small to draw any inferences.[33]

More recently, vasopressin has been compared with dopamine in a pilot trial, including 20 extremely preterm infants.[34] The investigators found that vasopressin increased BP in a fashion similar to dopamine but had less associated tachycardia. No differences in any clinically relevant outcomes were identified, which is not surprising, considering the number of enrolled patients.

Inotropes/Lusitropes Versus Placebo

Bravo and colleagues compared dobutamine with placebo in a pilot trial of 28 infants who had low-flow states as determined by a superior vena cava flow less than 41 mL/kg/min.[35] There was no difference in any clinically relevant outcome. Paradisis and colleagues compared milrinone with placebo in infants at risk of low-flow states. They found no difference between milrinone compared with placebo in prevention of low-flow states (90 patients in total). There was more tachycardia in the milrinone group, and a higher nonsignificant increase in the percentage of patients with hypotension.[36]

Steroid Trials

Corticosteroids have been utilized for both prevention and treatment of hypotension.[3] The treatment trials have been performed as either the primary agent to treat[37] or as a second-line agent.[38,39] All studies are characterized by small recruitment numbers, but their use has been associated with an increase BP and a reduction in the duration of inotrope administered.

Other Studies

The Treatment of Hypotension of Prematurity trial (dual-site study) is still enrolling. The design incorporated the inclusion of near-infrared spectroscopy (NIRS) monitoring in infants with low BP and compared dopamine with placebo. The total planned enrollment was 150 infants and is still enrolling after 10 years.

A recent pilot randomized trial evaluated intervening at different threshold values.[40] The investigators compared 3 intervention thresholds: active (<30 mm Hg), moderate (<gestational age mm Hg), and permissive (signs of poor perfusion or <19 mm Hg). The investigators concluded that the BP threshold used to trigger treatment affects inotrope usage but more importantly that it was possible to perform this type of study design.

MORE RECENT MULTISITE TRIALS

The most interesting finding of the more recent RCTs has been the inclusion of a placebo arm, highlighting the concern that perhaps intervention may be more harmful than beneficial. Determining this can be challenging. These trials are discussed.

The Extremely Low Gestational Age trial was a feasibility trial conducted across 16 National Institute of Child Health and Human Development sites.[41] The study had a factorial design evaluating dopamine, hydrocortisone, and placebo. It provided some interesting findings, namely (1) that the incidence of hypotension was approximately 33% in infants less than 27 weeks' gestation, (2) consent was challenging, and (3) clinician equipoise may have had an impact on enrollment. Ultimately, of 58 eligible babies, only 10 were enrolled, either because families were not approached (20) or refused consent (28). These certainly are important considerations in future trials.

The Hypotension in Preterm Infants trial was a pragmatic trial, which originally aimed at enrolling 820 infants.[42] Delays with drug production, however, meant that trial initiation was delayed for more than 5 years and ran into funding issues as a result of the delayed start. When recruitment did commence, it progressed slowly, related somewhat to restricted inclusion criteria but also to consent-related matters. Only preterm infants with an invasive line in situ and with a cranial ultrasound free of significant abnormality were eligible. There was no deferred consent permitted. The timeline to enrollment proved to be relatively short, with a median time to enrollment of less than 6 hours, which is short considering the requirements to obtain truly informed consent. These requirements precluded a large number of infants being enrolled and in

total 58 infants from a possible 200 were enrolled over a 2.5-year time frame across 10 sites.

In the Dobutamine for NEOnatal CIRCulatory failure defined by novel biomarkers (NEO-CIRC) trial, the NEO-CIRC consortium was funded in the same manner as the HIP project. The goal was the development of a neonatal formulation of Dobutamine and for this to be evaluated in a RCT. The age group was to include infants less than 33 weeks gestation with low BP and low systemic blood flow. The group met difficulties, however, acquiring a neonatal formulation of the drug, and the trial has yet to commence. A single-site pilot trial was conducted.[35]

CHALLENGES

These more recent studies have been designed to evaluate meaningful short-term and long-term outcomes. They highlighted several significant concerns, however. First, they are difficult to get started. These multinational and multisite studies require significant interaction with multiple agencies across different countries and highlight the need for consistency across the various agencies. Enhanced interaction between the Food and Drug Administration (FDA) and European Medicines Agency (EMA), and between academia and industry, such as occurs with the International Neonatal Consortium, may help overcome some of these hurdles. The Voluntary Harmonisation Procedure may assist with the approval process across European countries.

When studies are commenced, enrollment can be challenging. Significantly, the provision of timely informed consent was a major factor. As can be seen from the HIP trial the median time of enrollment was 6 hours. This is a relatively short time period considering the need to perform several tasks in addition to ensuring appropriate clinical care, placement of central lines, provision of adequate information, drug preparation, randomization, and study inclusion. The high dropout rate from eligible hypotensive infants to numbers included may have been related to the short time to obtain consent competing with the need to start intervention. Such factors may have contributed to a lack of clinician equipoise and thus an unwillingness to approach and enroll patients. This is a difficult area to tease out but may be an important factor for consideration in future studies. In the absence of alternative consent, procedures trials in this area will remain challenging.

Conducting the trial presents its own challenges. Staffing availability to prepare the drug in a blinded fashion means that studies may not be able to enroll on a 24-hour basis, instead enrolling only during day time hours and outside of weekends when staff may be available. The ready availability of a neonatal-specific formulation produced under Good Manufacturing Practice standards would overcome these obstacles and also may be a safer way to deliver the drug to the infant. These studies are costly to perform and require significant investment. Development of a neonatal specific formulation can incur significant costs. Conducting the trial on a 24-hour, 7-day-a-week basis will incur significant costs at the individual sites, but also significant monitoring costs are required to ensure the study is conducted to the highest standards. For example, in the HIP trial, there were 225 serious adverse events recorded. These challenges can be overcome with appropriate investment in future studies, but future trial design is critical.

A NEW WAY OF THINKING

Determinants of Adequate Cellular Metabolism

Future RCTs need a paradigm shift away from the desire to treat and correct hypotension to the aim of restoring adequate cellular metabolism. It needs to be recognized

that hypotension (whichever way it is defined) is one of the markers used to assess adequate circulation along with other equally important elements.[43] Adequate cellular metabolism is dependent on normal CO (and end-organ perfusion) in addition to a normal oxygen-carrying capacity, which in turn is dependent on hemoglobin levels and lung function. CO is dependent on an intact intrinsic contractile mechanism, adequate filling (preload), and a manageable systemic and pulmonary vascular resistance (afterload). Contractility is influenced further by interactions with heart rate (force-frequency relationship), preload (length-tension relationship), and afterload (force-velocity relationship). The reader is directed to other texts for further detailed explanation of those relationships.[44] BP is a product of CO and systemic vascular resistance (SVR). Therefore, examining BP in isolation without knowledge of SVR or CO may not reveal the underlying pathophysiologic cause (if any) of low blood flow and potentially impaired cellular metabolism.

Understanding this complex physiology makes one thing clear: the use of BP in isolation to determine adequate blood flow is overly simplistic; treatments that are directed at correcting BP without due consideration given to other important determinants are unlikely to result in improvements in outcomes and may cause harm.[45] In addition, not only should mean BP be considered but also the relevance of systolic and diastolic components prior to making any inference on the circulatory status of a preterm infant.[46] An infant with a systolic/diastolic pressure of 60/15 compared with another with a BP of 35/25 mm Hg has a similar mean BP (of approximately 30 mm Hg) but is likely to have completely different underlying physiology. The former could be in a state of a high CO, low SVR resulting from sepsis and warm shock and likely to benefit from volume correction and vasopressor support whereas the latter could have low CO and high SVR due to pulmonary hypertension (or cold shock) and may benefit from a chronotropy and vasodilatation. It becomes clear that using mean BP as a sole guide to make any meaningful hemodynamic interventions needs to be reconsidered.

A More Comprehensive Assessment of Hemodynamic Compromise

To modify the approach to future trials of hemodynamic support, the ability to identify true hemodynamic compromise needs to be improved and the underlying pathophysiologic reason for this compromise characterized further.[47] In other words, identifying whether hemodynamic compromise is a result of impaired preload, afterload, contractility, or the oxygen-carrying capacity (or a combination of those factors) can facilitate a more targeted and more meaningful approach to management. Therefore, the determination of an adequate circulation should be the result of a composite appraisal of clinical indices, such as the 2 components of arterial BP, measures of end-organ perfusion, and echocardiography. The value of these parameters likely is highest when used in combination and longitudinally to document trends or response to therapeutic interventions. Therapeutic decisions rarely should be made based on any 1 parameter in isolation. The decision to intervene is likely to depend on the underlying disease process; this in turn enables a more targeted approach to treatment.

There are no set criteria to define true hypotension in neonates. The definition used most widely is a mean BP below the gestational age as a guide for the cutoff for treatment.[48] Currently, little attention is placed on systolic and diastolic arterial pressures when characterizing circulatory stability or selecting a cardiovascular intervention. Normative population-based data for systolic arterial pressures are available.[49,50] Systolic arterial pressure is a useful surrogate of the adequacy of contractile force and CO; it also reflects adequate filling and preload. A low value can indicate a diminishing stoke volume due to impaired contractility or impaired filling. Diastolic arterial

pressure reflects SVR and volume status of the infant. It is compromised in fluid loss, left-to-right shunts, and leakage due to vasoactive shock. A high diastolic BP may indicate increased afterload. Combined systolic and diastolic hypotension usually is an end-stage phenomenon of a rapidly progressive condition. Delineating the cause may be a challenge.[46]

The use of other modalities, such as NIRS and echocardiography, can further enhance the ability to identify end-organ perfusion and decipher the underlying pathophysiologic mechanisms of low CO.[47] The use of those modalities is described in further detail in other articles in this series. Recently, newer echocardiography modalities, such as deformation analysis, have been shown to possess the capability of distinguishing whether myocardial dysfunction (low CO) is a result of impaired intrinsic contractility or low preload/increased afterload.[51]

A Physiology-Based Treatment Approach

The multimodal approach to diagnosing and identifying the cause of hemodynamic compromise paves the way to a targeted approach to treatment. Characterizing the predominant physiologic cause of low CO and impaired cellular metabolism enables a more accurate use of vasopressors and volume support to suit a particular physiologic situation (**Table 3**). Individualization of care for hemodynamic compromise recently has been described as a potential approach.[52] This recognizes the heterogeneous nature and complexity of low blood flow states in the premature infant and proposes a treatment approach depending on the underlying physiologic basis for this compromise. The use of regimented (single inotrope-based) protocols needs to be reconsidered and evaluated.

DESIGNING A FUTURE TRIAL OF HEMODYNAMIC SUPPORT

The Cardiology Working Group proposed several possible trial designs previously, including potentially a targeted BP trial and other designs incorporating placebo arms.[52] Although these proposals were suggested approximately 15 years ago, there has been little progress over the ensuing years. There is now a need to reconsider alternative trial designs. A regimented protocol approach usually using a single inotrope to placebo (or another regimented protocol) for the treatment of hypotension based on an arbitrary diagnosis of a mean BP being lower than the gestational age in weeks has been the mainstay of practice. It is time to recognize that this approach is overly simplistic and ignores the complexity of the neonatal circulation. It is important to have pragmatic inclusion criteria for infants in future trials and consider novel ways of tackling the barriers to effective consent and enrollment in this critical care setting.

Table 3
Physiology-based approach to managing low blood flow states

	Echocardiography			Blood Pressure		
Underlying Physiology	Ejection Fraction	Strain	Strain Rate	Systolic	Diastolic Blood Pressure	Suggested Management
Reduced preload	↓	↓	—	—/↓	↓↓	Fluids/vasopressor
Increased afterload	↓	↓	—	↓	↑	Vasodilator/inotrope
Impaired contractility	↓	↓	↓	↓	—/↓	Inotrope

↓, decreased; ↑, increased, —, no change.

One future trial design (Fig. 1) could compare the current approach of treating hypotension—using a regimented protocol employing a single inotrope to normalize BP (standard approach)—to a more physiology-based approach, which uses clinical, echocardiographic, and potentially NIRS parameters to identify evidence of a low blood flow state, characterize the underlying physiologic basis for this compromise, and implement a targeted individualized approach aimed at correcting the underlying pathophysiology (physiologic approach). Selection criteria should be broad enough to include a large number of infants with the recognition that hemodynamic compromise may not be reflected by a single marker, such as BP. Infants in the standard arm

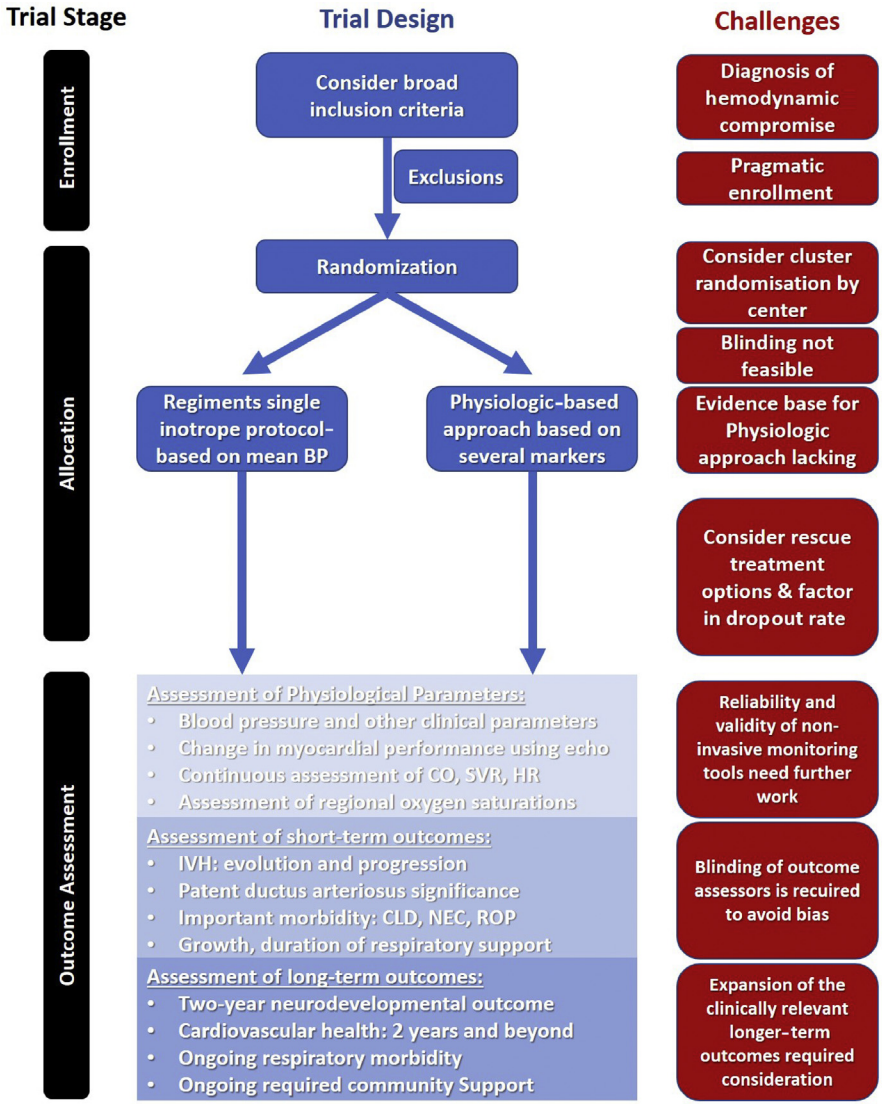


Fig. 1. Proposed future clinical trial design and challenges. CLD, chroinc lung disease; HR, heart rate; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity.

should receive treatment only if the mean BP is less than gestational age in weeks whereas infants in the physiologic arm will undergo active monitoring for evidence of low blood flow states, which includes monitoring of systolic and diastolic BP, echocardiography to assess loading conditions, contractility and the resultant overall function, and NIRS to assess end-organ perfusion. This approach also should consider the oxygen-carrying capacity of blood, including an assessment of hemoglobin and lung function. Thought also should be given to management of intracardiac and extracardiac shunts, including the consideration of the management of pulmonary hypertension or treatment of a hemodynamically significant patent ductus arteriosus if present. Both arms should institute careful monitoring of the physiologic responses to the treatment, including CO and myocardial performance, BP, and end-organ perfusion. Endpoints are critical and the selection of important short-term and long-term outcomes relevant to the infants' and their families' needs to be clearly defined. Respiratory morbidity, overall cardiovascular health, nutritional status, and neurologic outcomes all should be considered. Because blinding of the interventions is unrealistic, efforts should be made to blind the outcome assessments. The approach to consent the families also requires careful consideration with the exploration of deferred consent, antenatal consent, or a perhaps even cluster trial design trials (see **Fig. 1**). Equipoise may be a problem for some clinicians who steadfastly believe that echocardiography is essential to management and thus may not consider enrolling infants to the standard approach.

Such an undertaking will require an international, multicenter collaborative approach and a significant investment in training in the reliable use of echocardiography and other monitoring modalities, such as NIRS. Consensus on thresholds for determining hemodynamic compromise in the physiologic arm is required. This may be a challenge due to the lack of a suitable evidence base. Trials of this nature undoubtedly need a significant monetary investment, as highlighted previously, and an infrastructure that is well set up to sponsor, insure, and monitor the progress of this trial. Prior to embarking on a large-scale trial of this nature, a feasibility trial in a local setting should be carried out in order to identify challenges throughout the entire process. Embarking on such trials requires significant interaction between industry, academia, FDA, EMA, and other agencies. The International Neonatal Consortium is one such international collaboration and may help into the future with defining normative blood ranges, standardization of noninvasive BP devices, future clinical trial design, clinically relevant endpoints, neonatal specific formulations, and consent issues. Significant investment is required, through industry or a combination of industry and academia. The recent C4C funding platform through the Innovative Medicines Initiative provides an opportunity to conduct studies on such a scale.

SUMMARY

The current approach to trials of hemodynamic support has failed to identify the ideal methods of managing hemodynamic compromise in premature neonates, because the trials to date have, by and large, asked the wrong question and looked for the wrong answer. The first step in rectifying this is the recognition of the need for a radical change in the approach to such trials. The complex and unique nature of the cardiovascular system in preterm infants, the heterogeneous nature of the etiology of hemodynamic compromise, and the evolution of understanding of the physiology coupled with the advancement of diagnostic and monitoring tools should set the scene for a new approach and pave the way forward to making meaningful advances in this area of newborn care.

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