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Review

Evidence-based versus pathophysiology-based approach to diagnosis and treatment of neonatal cardiovascular compromise

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SUMMARY

With the advances in biomedical research and neonatal intensive care, our understanding of cardiovascular developmental physiology and pathophysiology has significantly improved during the last few decades. Despite this progress, the current management of circulatory compromise depends primarily on experts' opinions rather than high level of evidence. The lack of reliable, accurate, continuous and preferably non-invasive monitoring techniques has further limited our ability to collect the information needed for the design and execution of more sophisticated clinical trials with a better chance to provide the evidence we need. Given the lack of randomized, placebo-controlled trials investigating clinically relevant outcomes of novel treatments of neonatal cardiovascular compromise, we must now use the available lower level of evidence and our present understanding of developmental physiology and pathophysiology when providing cardiovascular supportive care to critically ill neonates. However, with recent advances in cardiovascular monitoring capabilities, direct and more objective assessment of the changes in cardiovascular function, organ blood flow, and tissue oxygenation have become possible. These advances have helped in our clinical assessment and enabled us to start designing more sophisticated interventional clinical trials using clinically relevant endpoints.

1. Introduction

In order to manage circulatory compromise, one must first recognize it. In older children and adults, hypotension is the single most important sign of uncompensated shock. Therefore, it does not come as a surprise that defining hypotension has been a focus of research in neonatology since its inception. Yet, despite decades of research and debate on the topic, we still know very little about what constitutes hypotension in the neonate. Although we have come to understand that blood pressure (BP) has a direct relationship with gestational and postnatal age, controversy continues to surround all other clinically relevant aspects of defining the normal range of BP. Many agree that a definition of hypotension based on the relation between BP and systemic/organ blood flow (especially blood flow to the brain), would be clinically meaningful. However, identifying a threshold below which vital organ autoregulation becomes impaired and cellular function disturbed or, even more importantly, permanent organ damage is sustained in a given patient is challenging. Identifying the exact cut-off may be unrealistic as the thresholds likely vary among individuals and may differ in the same patient at different points in time depending on the interplay of many other factors. Considering the uncertainty about the normal range of BP for a given gestational and postnatal age and individual patient characteristics, some have advocated a complete disregard of BP in sick preterm and term neonates. Instead, advocates of this approach only recommend assessment of organ perfusion by clinical and laboratory means to assess the need for provision of cardiovascular supportive care. However, despite its limitations, disregarding BP altogether does not enhance our limited ability to detect circulatory compromise and it ignores the physiologically determined need to maintain appropriate perfusion pressure for the circulation to enable oxygen delivery to the cells.

In clinical practice, some clinicians define the lowest acceptable BP by the 5th or 10th percentile of the population-based normative values as, historically, BP values below these cut-off ranges were shown to be associated with brain injury [1]. By another approach, hypotension is defined as the mean BP < 28–30 mmHg in very low

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birth weight infants. This definition is based on the limited data demonstrating a loss of cerebral autoregulation at 28–30 mmHg [2,3]. Finally, the arbitrary definition of hypotension by a mean BP value below the numerical value of the gestational age in the given patient is the most widely used definition by clinicians and researchers alike [4].

2. Why does hypotension matter?

Although some studies have shown no difference in outcome of hypotensive preterm infants compared to normotensive patients [5–7], the vast majority of available data point to an association between hypotension, however defined, and poor outcome [1,8–16]. It is not clear, however, whether causality is at play. Given the widespread practice of treating hypotension and the lack of data from randomized controlled trials (RCTs), it remains unknown whether hypotension, its treatment, the underlying pathology leading to hypotension and/or a combination of these factors are the causes of the medium- and long-term hemodynamic and neurodevelopmental adverse effects often seen in critically ill neonates [17]. It is likely that all of the potential causes play a role but the extent of the contribution of each factor to the adverse outcome is not known. Regardless of the controversy about the use or disregard of BP as one of the factors in determining the institution of treatment, low BP does lead to reduced cerebral blood flow (CBF) especially in preterm infants with impaired CBF autoregulation. As in preterm infants the autoregulatory BP range is much narrower than in older children or adults, the preterm infant is more prone to having a pressure-passive CBF. Therefore, concern over cerebral hypoperfusion in the setting of hypotension is often cited as a reason for monitoring BP and treating hypotension. It must be noted that the impact on clinically relevant outcomes of the pace and magnitude of correction of low BP have not been studied. Based on recent data on the changes in CBF and the lack of immediate re-establishment of CBF autoregulation in response to pharmacological normalization of BP in preterm neonates [2], it is tempting to speculate that aggressive treatment of hypotension by whatever means might be as harmful as leaving the brain hypoperfused.

The other reason for the need to identify the normal range of BP is to be able to recognize shock earlier. In the case of an event leading to circulatory compromise, such as sepsis, shock progresses through three phases. During the compensated phase, BP is maintained in the “normal range” by neuroendocrine compensatory mechanisms, and oxygen delivery to the vital organs (brain, heart and adrenal glands) remains largely unchanged. In the next, uncompensated state, the compensatory mechanisms fail and hypotension and generalized tissue hypoperfusion develop. If untreated or if the patient is unresponsive to treatment, shock will progress to its final, irreversible phase leading to multi-organ failure and death. In our quest to prevent shock from entering the irreversible phase, we must recognize it during its earlier phases. Hypotension is the main clinical sign that denotes failure of the compensatory mechanisms; therefore defining hypotension is one of the key steps to enable us to recognize the presence of uncompensated shock.

3. Pressure versus flow

In recent years, there has been much discussion on whether BP or flow is more important. According to the Poiseuille's law they are related, as flow is directly proportional to the pressure gradient. In other words, BP is the driving force behind moving the blood through the vasculature. Clinically, we use Ohm's law to assess the circulation, where the flow is directly related to the pressure gradient and inversely related to systemic vascular resistance (SVR). Unfortunately, SVR is a calculated value and cannot be directly measured. Accordingly,

$$\text{BP} = \text{cardiac output (CO)} \times \text{SVR}.$$

One can appreciate that BP will not change despite significant alterations in the hemodynamic status if, for example, CO falls by 50% and, at the same time, vascular resistance doubles. Thus, the significant limitation of relying on BP alone in assessing the adequacy of blood flow is clear. Therefore, information about both perfusion pressure and blood flow is required for us to be able to appropriately assess the circulation and gauge the hemodynamic response to treatment.

The major function of the circulation is to deliver oxygen and nutrients to the tissue to meet metabolic demands. The interaction between systemic flow and systemic resistance, in the form of maintaining a driving pressure, ensures adequate oxygen delivery. These two relatively independent factors are regulated and controlled by autonomic, endocrine and paracrine factors and affected by a host of other physiologic and pathologic events [18]. Beyond the interaction between systemic flow and SVR in determining perfusion pressure, if compensatory mechanisms start failing to maintain adequate oxygen delivery, capillary recruitment and an increase in oxygen extraction will match oxygen demand with availability for a period. Since we can now continuously assess changes in oxygen extraction using near-infrared spectroscopy (NIRS), we can indirectly follow the progression of shock and/or the response to treatment even if we cannot continuously monitor changes in cardiac output. Although ensuring adequacy of blood flow is our goal, our routinely available clinical and laboratory assessment tools of low blood flow state, such as capillary refill time (CRT) and serum lactate level, respectively have either very limited sensitivity and specificity or have a significant time-lag. These shortcomings render them less helpful in timely recognition of shock [19]. Therefore, more recently many centers have started assessing systemic blood flow by using bedside echocardiography and, less frequently, by electrical impedance velocimetry (EV) along with the information routinely available on systemic BP to better assess cardiovascular function. Of note is that the methods used for the assessment of systemic and organ blood flow and their changes at the bedside (echocardiography, EV and NIRS) all have their own significant limitations as well [18,19].

4. Evidence-based versus pathophysiology-based approach

As is the case with any other conditions, when managing a patient with shock, we should strive to incorporate high-level evidence in our approach to diagnosis and treatment. Unfortunately, high-level evidence is lacking in this area of neonatology. Furthermore, the outlook for establishing treatment strategies and defining the most appropriate subpopulations that would benefit from a given treatment based on findings of RCTs is, at best, grim in the near future. The only study to date that specifically attempted to investigate the effect of untreated hypotension in a randomized fashion found that such a trial was not feasible [20]. In seven neonatal intensive care units (NICUs) and out of 336 eligible extremely preterm infants (23–26 weeks' gestational age), only 10 patients ended up being enrolled and studied during a trial period of one year. The main reason for failure to effectively conduct the study was the inability of the researchers to obtain parental consents in a timely fashion. However, the lack of equipoise by the participating clinicians has also played a significant role. Among patients meeting enrollment criteria but without the parents having been approached for consent, in 65% of these cases the physicians believed that the patients were too sick for enrollment.