INVITED COMMENTARY

Diagnosis of Shock in Neonates: Need for Multimodal Monitoring

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Shock is a state of cellular energy failure resulting from the lack of adequate oxygen delivery. Shock can result from multiple pathogenic pathways including hypovolemia, poor myocardial contractility, and failure of the regulation of vascular tone. Shock, especially due to sepsis, has a high case fatality rate. Careful monitoring of at-risk neonates, early detection, and rapid initiation and titration of therapy can improve the outcome of neonates with shock. A number of clinical (heart rate, pulse volume, blood pressure, capillary refill time, core-peripheral temperature difference, urine output), non-invasive bedside (perfusion index (PI), plethysmography variability index (PVI), functional echocardiography measurements), and laboratory (blood pH, lactate levels, mixed venous oxygen saturation) measurement are used for the detection and management of shock. However, no single measure has been found to be sensitive and specific for detection of shock. Following questions drive the choice of an appropriate measure for detection of shock and titration of therapy:

- In neonates at risk of shock, which measure is an early and sensitive marker of tissue hypoperfusion so that the state of shock can be detected before decompensation?
- Once treatment of shock is initiated, which measure can be used for titration of therapy?
- For the given measure, what are the normative values or therapeutic targets for neonates born at different gestations and of different postnatal ages?
- What is the reference standard against which the candidate measures for detection of shock must be tested?

The PI and PVI measured by pulse oximeter have been suggested as an objective assessment of the pulsatile flow of blood in peripheral arteries and the flow variability during breathing [1]. A large study in healthy term neo-nates reported a median (IQR) value of 1.7 (1.18 to 2.50) for PI [2]. Preterm neonates have lower values. Presence of patent ductus arteriosus (PDA) or measurement in a prone position are associated with higher PI. In this issue of the journal, Sharma, et al. [3] present the utility of PI, PVI, and serum lactate levels in diagnosis of hypotension (invasive mean blood pressure <5th percentile). Authors have used fixed values of 0.455, 23.5, and 4.65, respectively to label the test as 'positive.' Correlation between these measures and mean blood pressure was found to be weak to moderate and the diagnostic test characteristics of the individual tests were less than optimal with highest positive predictive value being 51.7% for serum lactate [3]. This is not unexpected. Hypotension in neonates can result from varied causes including asphyxia, sepsis, extreme prematurity, PDA, and fluid deficit. These causes have overlapping pathophysiogical pathways and neonates may present with illness at different stages of shock and compensatory response [4]. Therefore, a single measure is unlikely to be superior to multi-modal monitoring for detection of tissue hypoperfusion.

Of the various measures, low blood pressure or hypotension is one of the commonest indication of initiation of therapy for shock. Hence, many studies have used hypotension as a reference standard to evaluate the performance of other measures. However, blood pressure alone is an inadequate marker of tissue perfusion [5]. Although, normative values have been suggested, evidence lacks about the threshold below which treatment should be started or the blood pressure values that should be targeted while titrating the treatment. There is a lack of agreement on the blood pressure levels below which cerebral auto-regulation fails or reduced end-organ perfusion occurs. Various therapeutic thresholds suggested include mean blood pressure lower than gestation at birth plus postnatal age, mean blood pressure lower than 30 mm Hg, and mean blood pressure lower than 5th percentile [6]. Uncertainty also prevails regarding the association between treatment of low blood pressure (especially in the first 24-48 hours) and adverse outcome. Non-invasive blood pressure level is dependent on cuff length and width, and the infant's level of alertness, resulting in large inter- and intra-patient varia-tion. Relying only on blood pressure can lead to under-treatment or over treatment.

Other measures suggested to measure tissue perfusion include cardiac output, superior vena cava (SVC) flow and tissue oxygen saturation or oxygen extraction (e.g., cerebral) measured by near infra-red spectroscopy (NIRS) [5,7,8]. However, each of these have their own challenges. Cardiac output in first few days after birth is influenced by presence of PDA and left ventricular output can overestimate the systemic blood flow by upto 200%. SVC flow is not affected by presence of PDA and has been shown to be a better predictor of the development of intraventricular hemorrhage and adverse neurodevelopment outcome [5,9]. However, its routine bedside application is challenged by need of technical expertise and large inter-operator variability. Direct measurement of tissue oxygenation status is promising but targeting therapy to achieve 'normal' tissue oxygenation has not led to improvement in clinical outcomes [10].

Given the current status of evidence, neonates at risk of shock should continue to monitored using multiple complementary measures. Abnormal values of more than one measure and trend over time are more important than any single measure.

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