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Neonatal hypotension: Dopamine or dobutamine?

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SUMMARY

Controversy surrounds the assessment of perfusion and the methods currently utilised to define hypotension, especially blood pressure. There is growing agreement to assess heart function when selecting inotropic therapy and use bedside tools such as echocardiography for assessing at-risk infants. Both dopamine and dobutamine have comparative efficacy, and in certain disease states with immature myocardium there could be potential advantages in using dobutamine. The concomitant use of hydrocortisone has been shown to be beneficial when escalating doses of first-line inotropes are used. Other inotropes require further study through randomised trials for their safety and efficacy to be established.

1. Introduction

Neonatal hypotension is defined as a clinical condition of abnormally low arterial blood pressure affecting perfusion. There is little disagreement that inadequate perfusion or poor circulation should be treated. However, disagreement abounds as to what standards or thresholds should be utilised to trigger treatment of such infants, and which agent or agents should be used [1].

The definition of hypotension in newborn has a number of limitations. Unlike adults, newborn babies are delivered at different gestational ages and there is no single accepted value that defines low blood pressure. 'What to measure' has been a subject of debate and clinicians have used either systolic or mean blood pressure values in newborn infants to define hypotension [2]. For such a common problem, with an absence of a single standard, clinicians have adopted different approaches for managing hypotension in newborn infants. A wide gestational age range, different pathophysiologic states underlying poor perfusion, and the transition from fetal to adult circulation further complicate the question, and clinicians often find it difficult to utilise the available data to make informed choices for selecting the most appropriate inotrope [3].

Poor perfusion can result from persistence of fetal channels such as the ductus arteriosus, loss of blood, immature myocardium, or ischaemic damage after hypoxic injury, and as a manifestation of sepsis or underlying heart disease. It is not possible to treat all of the above utilizing the same approach, and hence the selection of specific inotrope requires more information than just a blood pressure reading to target the therapy to the underlying problem. With availability of bedside assessment tools such as echocardiography, it is becoming clear that we need to modify our approach and utilise more objective information before instituting treatment. However, because of the limited techniques and skills for this bedside assessment, blood pressure still remains the gold standard to initiate or titrate the drugs used for managing poor perfusion.

In this review we limit the discussion to the controversy of blood pressure, tools and techniques for non-invasive haemodynamic assessments, and the current evidence regarding the use of inotropes for managing neonatal hypotension. We suggest an approach to manage poor perfusion. The recommendations should be integrated with the advanced life support scheme (Neonatal Life Support/Neonatal Resuscitation Program) and be amalgamated with the stepwise approach of managing airway, breathing and circulation [4].

2. The blood pressure controversy

Blood pressure is given great attention, as hypotension in the newborn has been associated with impaired cerebral perfusion and ischaemic damage [5]. The arterial pressure is determined by two factors: the propulsion of blood from the heart (cardiac output) and the resistance to the flow of this blood through the blood vessels (arteriolar tone or vascular resistance). Thus flow = pressure ÷ resistance, or pressure = flow × resistance [6]. Low blood pressure could thus be caused by a decrease in flow (cardiac output), a fall in resistance, or both. Measurement of flow,

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however, requires advanced assessment techniques, and despite advances in technology, this tool is still not widely available. The resistance can only be calculated – not measured – but clinicians routinely rely on blood pressure determinations to gauge the adequacy of cardiac output and systemic perfusion. There could be increase in resistance with a drop in cardiac output or vice versa with minimal changes in blood pressure but considerable impairment of tissue perfusion. The issue becomes even more complicated when the fetal channels remain open during transitional circulation.

The 'gold standard' for determination of blood pressure is intra-arterial measurement using an umbilical arterial catheter or peripheral arterial line. However, in many situations the clinician has to rely on non-invasive blood pressure measurements. Often, too little attention is paid to the accuracy of these measurements. Although oscillometric methods of measuring blood pressure are widely used, neonatal readings are of limited accuracy, and the technique becomes least reliable when it needs to be most reliable – in babies with clinically significant hypotension. Fortunately, there is good agreement between intravascular and indirect Doppler measurements of systolic pressure, and between intravascular and pulse oximetry technique measurements throughout the blood pressure range [7,8].

What should be measured: systolic or mean pressures? The systolic pressure is the amount of pressure that blood exerts on arteries and vessels while the heart is beating, whereas the mean pressure is the average arterial pressure during a single cardiac cycle. Mean blood pressure is derived using systolic and diastolic pressure values [(diastolic pressure $\times$ 2) + (systolic pressure) $\div$ 3]. The measurement of mean blood pressure was suggested because it was thought to be free of the artefacts caused by resonance, thrombi, and air bubbles, when measured intravascularly, but this may not always be true. The correlation between systolic pressure measurements in nearly 400 preterm babies in the first 10 days and their long-term outcomes at age 2 years in non-disabled children suggest that values below the third percentile of systolic blood pressure in the first 4–24 h of life approximates the gestational age (in weeks), and that these are associated with impairment in long-term outcome [7]. Zubrow et al. [9] also observed similar findings, with the lower 95% confidence limits equal to gestational age, but with a narrow range. Yet, the majority of clinicians target a mean blood pressure greater than the gestational age. Dempsey and Barrington [10] criticised this notion, suggesting that the recommendation was made without supporting data. Other studies have reported a cut-off for acceptable mean blood pressure at 30 mmHg based on the findings that the lower limit of the cerebral blood flow autoregulation was near 30 mmHg [11]. This hypothesis is, however, not supported by any substantial longitudinal long-term outcome data. Additionally, there is a progressive rise in blood pressure during the first week of life in very preterm babies. This uncertainty of 'what to measure' is presently weighted by the ease of use rather than the evidence, and a majority of clinicians still seem to use the gestational age as the cut-off value of mean blood pressure for the reasons described above.

Table 1
Methods for haemodynamic assessment.

	Clinical	Non-invasive	Invasive
Heart (pump)	Heart rate	Echocardiogram Electrocardiogram Non-invasive cardiac output monitoring	Intracardiac catheterization
Artery (after-load)	Pulse volume	Non-invasive blood pressure	Intra-arterial blood pressure
Capillary	Capillary refill	Pulse-oximetry Transcutaneous oximetry	–
End-organ (perfusion)	Urine output Skin colour Core–peripheral temperature difference Lactate	Near infra-red spectroscopy	Arterial blood gas Mixed venous saturation
Veins (pre-load)	Jugular venous pressure	Echocardiography	Central venous pressure

3. Blood flow and systemic venous return

The adult cardiac physiology of systemic flow equals left ventricular output does not hold true for newborn babies with open fetal channels [12]. In these infants, the patent ductus arteriosus (PDA), an extracardiac shunt, causes additional volume loading of the left ventricle. Thus, left ventricular output (LVO) reflects the volume of blood perfusing the lungs and is the summation of right ventricular output and the volume of blood shunting across the PDA. In these situations the right ventricular output (RVO) measured at the pulmonary valve equals the systemic flow, as it is comprised of blood returning from the superior and inferior venae cavae. However, in the presence of a patent foramen ovale (PFO), an inter-atrial shunt, this RVO is overestimated depending on the volume of shunt across the PFO [13]. These estimations of cardiac output in preterm infants with open fetal channels should thus be interpreted cautiously, keeping in mind the aforesaid physiologic considerations.

Clinicians have been interested in the estimations of superior vena cava (SVC) flow over the last decade. Fetal channels do not affect SVC flow measurement and reflect the venous return from the upper body and brain [14]. The bedside measurements of SVC flow using echocardiography correlated well with intraventricular haemorrhage and poor outcome [14,15]. Clinicians adopted this approach and started estimating the ventricular function and the SVC flow to identify those babies who would benefit from inotropic support. A cut-off value of 40 ml/kg/min was suggested as a threshold, and values below this in the first 24 h were interpreted as abnormal [14].

When the SVC flow measurements and simultaneous recording of blood pressure were compared, the results pointed out the limitations of blood pressure for making informed decisions for treatment of hypotension. There was a group of babies in whom the blood pressure was reported to be normal (mean BP >30 mmHg) but their SVC flows were <40 ml/kg/min, suggesting poor cardiac output with normal or increased vascular tone [16,17]. Such babies benefit from inotropic support early (rather than vasopressor support), such as extreme preterm babies with poor myocardial reserves and function. There was another group of babies with low blood pressure but with normal SVC flow, suggesting normal or high cardiac output with poor vascular tone. These babies are usually identified clinically using vital signs and they benefit from inotropic support that improves vascular tone. Thus, isolated assessment of blood pressure or measurement of SVC flow would not help targeting the therapy to the underlying problem, but, when combined, could help in selecting the appropriate drug and institute the therapy directed to the pathology (problem-based therapy).

Recently, Groves et al. [17] challenged the measurement of SVC flow. They compared the SVC diameters computed using echocardiography and magnetic resonance imaging (MRI). It was suggested that SVC flow is not reproducible as the vessel's cross-sectional area is not circular but crescentic, indented by the adjacent aorta. Thus, the physics of measurement introduces error in calculation.

How to assess perfusion to measure the effects of therapy is another subject of debate. One can divide the methods for