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Afif EL-Khuffash and Eugene Dempsey

Advanced Hemodynamic Monitoring in the Neonatal Intensive Care Unit **423**

Willem-Pieter de Boode

Clinical assessment of cardiac output by interpretation of indirect parameters has proven to be inaccurate, irrespective of the level of experience of the clinician. Objective cardiac output monitoring is feasible in newborn infants in intensive care. The most promising methods include transthoracic echocardiography, transcutaneous Doppler, electrical biosensing technologies, transpulmonary ultrasound dilution, and arterial pulse contour analysis. Simultaneous assessment of blood pressure and cardiac output enables the identification of the earliest stage of shock. Comprehensive hemodynamic monitoring is pivotal for an individualized pathophysiology-based hemodynamic management.

Machine Learning to Support Hemodynamic Intervention in the Neonatal Intensive Care Unit **435**

David Van Laere, Marisse Meeus, Charlie Beirnaert, Victor Sonck, Kris Laukens, Ludo Mahieu, and Antonius Mulder

Hemodynamic support in neonatal intensive care is directed at maintaining cardiovascular wellbeing. At present, monitoring of vital signs plays an essential role in augmenting care in a reactive manner. By applying machine learning techniques, a model can be trained to learn patterns in time series data, allowing the detection of adverse outcomes before they become clinically apparent. In this review we provide an overview of the different machine learning techniques that have been used to develop models in hemodynamic care for newborn infants. We focus on their potential benefits, research pitfalls, and challenges related to their implementation in clinical care.

Cerebral Autoregulation in Sick Infants: Current Insights **449**

Elisabeth M.W. Kooi and Anne E. Richter

Cerebrovascular autoregulation is the ability to maintain stable cerebral blood flow within a range of cerebral perfusion pressures. When cerebral perfusion pressure is outside the limits of effective autoregulation, the brain is subjected to hypoperfusion or hyperperfusion, which may cause vascular injury, hemorrhage, and/or hypoxic white matter injury. Infants

born preterm, after fetal growth restriction, with congenital heart disease, or with hypoxic–ischemic encephalopathy are susceptible to a failure of cerebral autoregulation. Bedside assessment of cerebrovascular autoregulation would offer the opportunity to prevent brain injury. Clinicians need to know which patient populations and circumstances are associated with impaired/absent cerebral autoregulation.

Neonatal Blood Pressure Standards: What Is "Normal"? **469**

Beau Batton

Blood pressure (BP) is routinely measured in newborn infants. Published BP nomograms demonstrate a rise in BP following delivery in healthy infants at all gestational ages (GA) and evidence that BP values are higher with increasing birth weight and GA. However, the complex physiology that occurs in newborn infants and range of BP values observed at all GA make it difficult to identify "normal" BP for a specific infant at a specific time under specific conditions. As such, complete hemodynamic assessment should include the physical examination, perinatal history, other vital signs, and laboratory values in addition to BP values.

Simulation in Neonatal Echocardiography **487**

Michael Weidenbach and Christian Paech

There is a growing interest in neonatologists to train in echocardiography. Recommendations for training have been published by medical societies and working groups, but concerns exist on their feasibility in the face of limited resources. Simulators are increasingly used for training in medicine, including echocardiography. They have the potential to help overcome the shortage of training opportunities. We describe the currently available 2 echocardiography simulators designed for neonatology. Both systems are based on real 3-dimensional echocardiographic data and use an electromagnetic tracking system. Although limited data exist proving their effectiveness, deduction from other disciplines support this assumption.

The Future of Cardiac Ultrasound in the Neonatal Intensive Care Unit **499**

Alan Groves

Cardiac ultrasound is increasingly used to guide hemodynamic decision making in the neonatal intensive care unit (NICU). This article focuses on likely future progress in training, accreditation, digital connectivity, miniaturization, and modality development. Many documents have been published internationally to guide cardiac ultrasound training, accreditation, and implementation in the NICU, but challenges remain in providing assessments of hemodynamic status without risking missed structural diagnoses. Advances in simulation training and digital connectivity provide an opportunity to standardize approaches across institutions and continents. Development of machine learning and ultrasound modalities in turn provide huge scope for improving robustness and completeness of assessment.

Fluid Therapy: Friend or Foe? 515

Erin Grace and Amy K. Keir

Many questions surround fluid bolus therapy and subsequent fluid management in neonatal critical care as they do in pediatric and adult critical care. This review explores the known key clinical aspects of fluid bolus therapy and fluid balance in the first 7 days of life and provides suggestions for further work in this area. It draws on the pediatric and adult critical care literature to provide thought-provoking data around the potential harms of excessive intravenous fluids, which may prove relevant to neonatology. Current data suggest that fluid bolus therapy and early-life positive fluid balance in neonates may be associated with harm.

What Inotrope and Why? 529

Nilkant Phad and Koert de Waal

Primary function of cardiovascular system is to meet body's metabolic demands. The aim of inotrope therapy is to minimise adverse impact of cardiovascular compromise. Current use of inotropes is primarily guided by the pathophysiology of cardiovascular compromise and anticipated actions of inotropes. Lack of significant reduction in morbidity and mortality associated with cardiovascular compromise despite inotrope use, highlights major gaps in our understanding of circulatory targets, thresholds and choices of inotrope therapy. Thus far, prevention of cardiovascular compromise remains the most effective strategy to optimize outcomes. Studies of alternative design are needed for further advancement in cardiovascular therapy in neonates.

Corticosteroids for Neonatal Hypotension 549

Neha Kumbhat and Shahab Noori

Several limitations and controversies surround the definition of hypotension; however, it remains one of the most common problems faced by neonates. Approximately 15% to 30% of neonates with hypotension fail to respond to volume and/or vasopressor or inotropes. They are considered to have refractory hypotension. Although it is thought to have multiple causes, absolute and relative adrenal insufficiency is considered as the main reason for refractory hypotension. This article focuses on the role of adrenal insufficiency in causing refractory hypotension in preterm and term infants, the different options of corticosteroids available, and their risk/benefit profiles.

Intervention and Outcome for Neonatal Hypotension 563

Keith Barrington, Afif El-Khuffash, and Eugene Dempsey

Many observational studies have shown that infants with blood pressures (BPs) that are in the lower range for their gestational age tend to have increased complications such as an increased rate of significant intraventricular hemorrhage and adverse long-term outcome. This relationship does not prove causation nor should it create an indication for treatment. However, many continue to intervene with medication for low BP on the assumption that an increase in BP will result in improved outcome. Only

adequately powered prospective randomized controlled trials can answer the question of whether individual treatments of low BP are beneficial.

Hypothermia and Cardiovascular Instability 575

Eirik Nestaas and Brian H. Walsh

Severely asphyxiated neonates have acute heart failure as part of their multiorgan dysfunction syndrome during the first days of life. Supporting the cardiovascular system during this phase is part of contemporary treatment and regarded as vital for limiting the neurodevelopmental injury. The decision to treat cardiovascular instability should be based on evaluation of end-organ function. Neonatologist-performed echocardiography in combination with other diagnostic modalities enables comprehensive real-time assessment. This review discusses associations between hemodynamics and adverse outcome, modalities for evaluating the hemodynamic state of the infant, and therapeutic approaches during intensive care.

Updates on Management for Acute and Chronic Phenotypes of Neonatal Pulmonary Hypertension 593

Jessica Lauren Ruoss, Danielle R. Rios, and Philip T. Levy

Neonatal pulmonary hypertension is a heterogeneous disease in term and preterm neonates. It is characterized by persistent increase of pulmonary artery pressures after birth (acute) or an increase in pulmonary artery pressures after approximately 4 weeks of age (chronic); both phenotypes result in exposure of the right ventricle to sustained high afterload. In-depth clinical assessment plus echocardiographic measures evaluating pulmonary blood flow, pulmonary vascular resistance, pulmonary capillary wedge pressure, and myocardial contractility are needed to determine the cause and provide individualized targeted therapies. This article summarizes the causes, risk factors, hemodynamic assessment, and management of neonatal pulmonary hypertension.

Patent Ductus Arteriosus—Time for a Definitive Trial 617

Souvik Mitra and Patrick J. McNamara

More than 70 randomized controlled trials have been conducted on the management of patent ductus arteriosus (PDA) in preterm infants. Yet, clinicians are unsure if treating a PDA improves clinically important outcomes. Earlier clinical trials have primarily explored which pharmacotherapeutic agent effectively closes the PDA. Because many of these trials included older infants, had widely varying PDA definitions, and provided open-label treatment, it is difficult to draw inferences on clinical outcomes based on the results of these trials. These flaws in trial design might have contributed to the growing notion that “no treatment” is a feasible option irrespective of the clinical characteristics of the infant and the PDA shunt volume.

Clinical Trials in Hemodynamic Support: Past, Present, and Future 641

Eugene Dempsey and Afif EL-Khuffash

Managing low blood flow states in the preterm population remains a challenge in neonatal clinical care. The heterogeneity of the trials to date and

the relatively low number of infants enrolled, in addition to a desire to oversimplify the underlying pathophysiology, have contributed to an inability to draw meaningful conclusions to direct clinical care. This article reviews the current literature on this topic in the preterm population and outlines the challenges that have been encountered in performing such trials. Alternative studies are proposed, based on the lessons learned over the past number of years.

Hemodynamic Complications in Pregnancy: Preeclampsia and Beyond **653**

Anne Doherty, Kelsey McLaughlin, and John C. Kingdom

Normal pregnancy is a complex and dynamic process that requires significant adaptation from the maternal system. Failure of this adaptive process in pregnancy contributes to many pregnancy related disorders, including the hypertensive disorders of pregnancy. This article discusses placental development and how abnormalities in the process of vascular remodeling contribute to the multisystem maternal and fetal disease that is preeclampsia and fetal growth restriction. We review some of the consequences of this condition on the mother and fetus, aspects of the clinical management of preeclampsia and how it can influence both mother and infant in the postnatal period and beyond.

Extracorporeal Membrane Oxygenation for Hemodynamic Support **671**

Tobias Straube, Ira M. Cheifetz, and Kimberly W. Jackson

Extracorporeal membrane oxygenation was first successfully achieved in 1975 in a neonate with meconium aspiration. Neonatal extracorporeal membrane oxygenation has expanded to include hemodynamic support in cardiovascular collapse before and after cardiac surgery, medical heart disease, and rescue therapy for cardiac arrest. Advances in pump technology, circuit biocompatibility, and oxygenators efficiency have allowed extracorporeal membrane oxygenation to support neonates with increasingly complex pathophysiology. Contraindications include extreme prematurity, extremely low birth weight, lethal chromosomal abnormalities, uncontrollable hemorrhage, uncontrollable disseminated intravascular coagulopathy, and severe irreversible brain injury. The future will involve collaboration to guide and evolve evidence-based practices for this life-sustaining therapy.