Babies and Children at Last

Pediatric Cardiac Output Monitoring in the Twenty-first Century

Christine T. Trieu, M.D., Tiffany M. Williams, M.D., Ph.D., Maxime Cannesson, M.D., Ph.D., Jure Marijic, M.D.

In this issue of Anesthesiology, Sigurdsson *et al.* report on a new cardiac output monitoring system based on extracorporeal arteriovenous ultrasound measurement in small children.[1] While the technology they are describing is invasive, it is one of the first technologies to be meticulously tested in this important patient population. Specifically, the authors used the aortic flow probe—the physiologic gold standard for cardiac output monitoring—as a reference and they included children presenting with various congenital heart diseases. Rarely have clinical hemodynamic monitoring studies achieved such a level of scientific rigor not only in the pediatric setting, but also in the adult setting.

"Rarely have clinical hemodynamic monitoring studies achieved such a level of scientific rigor..."

Alfred Blalock, M.D., one of the great pioneers of pediatric congenital cardiac surgery, made a critical observation on the relationship between cardiac output and blood pressure during his shock experiments in the 1920s. He found that "the repeated removal of blood is usually associated with a decline in the cardiac output from 30 to 50% below the normal level *before* a marked diminution in the mean blood pressure occurs."[2] By Ohm's Law, blood pressure is related to cardiac output and systemic vascular resistance. Hence, blood pressure can remain relatively stable, despite a significant change in cardiac output due to compensatory changes in systemic vascular resistances. Although blood pressure is imperative for perfusion pressure, cardiac output is essential for oxygen delivery and cardiac output measurement is a vital part of hemodynamic monitoring and management of all critically ill patients, including pediatric patients of all ages and sizes.[3] Although almost a century has passed since Dr. Blalock illustrated the critical role of cardiac output in global cardiovascular circulation despite its shortcomings, blood pressure still remains the mainstay for hemodynamic monitoring of cardiovascular function in critically ill pediatric patients. Cardiac output is only rarely measured in this pediatric population, and the methods available for cardiac output monitoring in this population remain either poor surrogate, not validated, or inaccurate.

Today, the most common perioperative pediatric cardiac output monitoring only uses surrogates such as mixed venous oxygen saturation, lactate concentrations, regional venous oxygen saturation, toe-core temperature difference, and serial echocardiographic exams.[4] Invasive monitoring based on information from arterial and central venous pressures, such as pulse contour analysis methods, have been tested in pediatric patients. However, no study to date has ever tested these systems against a reference method such as the aortic flow probe and many of the devices that are commonly used in adult patients are not yet approved for children (vascular compliance evaluation used to calculate cardiac output with these systems has not been designed for children) by the U.S. Food and Drug Administration.[5] For these reasons, cardiac output monitoring use in pediatric clinical practice is more the exception than the rule. On the other side of the spectrum, newer noninvasive hemodynamic monitoring modalities such as electrical cardiometry, impedance cardiography, and bioreactance have been described and tested in pediatric populations but again, real life implementation has been scarce at best.[6–9] Overall, very few commercially available cardiac output monitoring devices are applicable in pediatric patients, and most of them present with incomplete validations and/or poor precision and accuracy.[9] So why has this important topic not made it to "prime time" in the pediatric anesthesia community?

There are a number of challenges to implementing translatable research regarding pediatric cardiac output monitoring. First from a clinical perspective, a subset of pediatric patients

Image: J. P. Rathmell.

This editorial accompanies the article on p. 712 and has a related Infographic on p. 19A.

Accepted for publication February 6, 2019. From the Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California Los Angeles Medical Center, Los Angeles, California.

 Anesthesiology 2019; 130:671–3

<zdoi;10.1097/ALN.0000000000002673>

for whom hemodynamic monitoring would be beneficial often have shunts and/or complex cardiac anatomy hampering accurate cardiac output measurement. Second, pediatric patients represent size limitations when developing either noninvasive or invasive cardiac output monitoring devices—the range of sizes and body habitus varies significantly from patient to patient and the relatively low cardiac output values in children significantly impacts accuracy of the measurements. Heightened regulations around clinical experimentation within nonadult populations coupled with perceived small market size further deters active industry involvement in development of novel cardiac output monitoring technologies. Furthermore, the accuracy and clinical utility of many of these cardiac output monitoring devices, though substantiated within the adult population, have not born out in pediatric population. The majority of these technologies are derivatives from innovations and studies in adult population.[9] In a recently published meta-analysis, our group actually found 20 studies testing cardiac output monitoring systems in children.[9] In this study, the main finding was that these studies presented with a very high interstudy heterogeneity and a lack of standardization in the way they were conducted regarding stratification by age, device, reference method, settings, invasiveness, and intracardiac shunt. Thus, further research is needed to validate the applicability of the adult algorithms and technologies to pediatric population. To this effort, Sigurdsson *et al.* conducted a "state of the art" validation of a relatively new technology (extracorporeal arteriovenous ultrasound) in a very challenging patient population[1]: small children undergoing corrective cardiac surgery. This study is remarkable for many reasons. The methodology follows all of the main criteria for methods comparison studies as emphasized by Riou *et al.* in an Editorial published in Anesthesiology in 2013[10]: a clear quantified hypothesis is tested (null hypothesis is that the methods are equivalent in precision and there is no bias in the cardiac output measurements); there is a unique primary endpoint (cardiac output absolute value); the type of the study is indicated (method comparison study); an *a priori* calculation of the number of patients needed is presented based on previous experiences; and the statistical plan was decided *a priori*. More impressive is the fact that the authors chose an almost indisputable but highly invasive reference method for cardiac output measurements: the periaortic flow probe, which remains the gold standard for cardiac output monitoring in the clinical setting.

Despite the encouraging results from this study, there are still many challenges in developing the ideal cardiac output monitor for pediatric patients. The perfect pediatric cardiac output monitor would have to be size unlimited, accurate, reproducible, continuous, have a rapid response time, noninvasive, user friendly, operator independent, cost effective, and have the ability to factor in simple and complex intra- and extracardiac shunts. No such device is in existence for either adult or pediatric patients yet. However, if we can overcome the other major factors, such as an unfavorable industrial interest and strict research constraints to conduct clinical validation, then innovation will surely drive the invention of such device in the future. Another equally important question that needs to be answered is whether the addition of cardiac output monitoring guided hemodynamic management would affect clinical outcomes the way it has potential to affect outcome in adult major surgery patients.[11] However, without reliable, practical, and widely adopted device, this debate is only academic. This is the reason why we welcome and applaud the study by Sigurdsson *et al.*; it offers possibility of a simple and reliable method that uses arterial line and central line to measure cardiac output in children of all sizes.

Research Support

Supported by grant Nos. R01GM117622, R01NR013012, U54HL119893, and 1R01HL144692 from the National Institutes of Health (Bethesda, Maryland; Dr. Cannesson).

Competing Interests

Dr. Cannesson is a consultant for Edwards Lifesciences (Irvine, California) and Masimo Corp. (Irvine, California) and has funded research from Edwards Lifesciences and Masimo Corp. He is also the founder of Sironis (Newport Beach, California) and owns patents for closed loop hemodynamic management that have been licensed to Edwards Lifesciences. The other authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Cannesson: mcannesson@mednet.ucla.edu

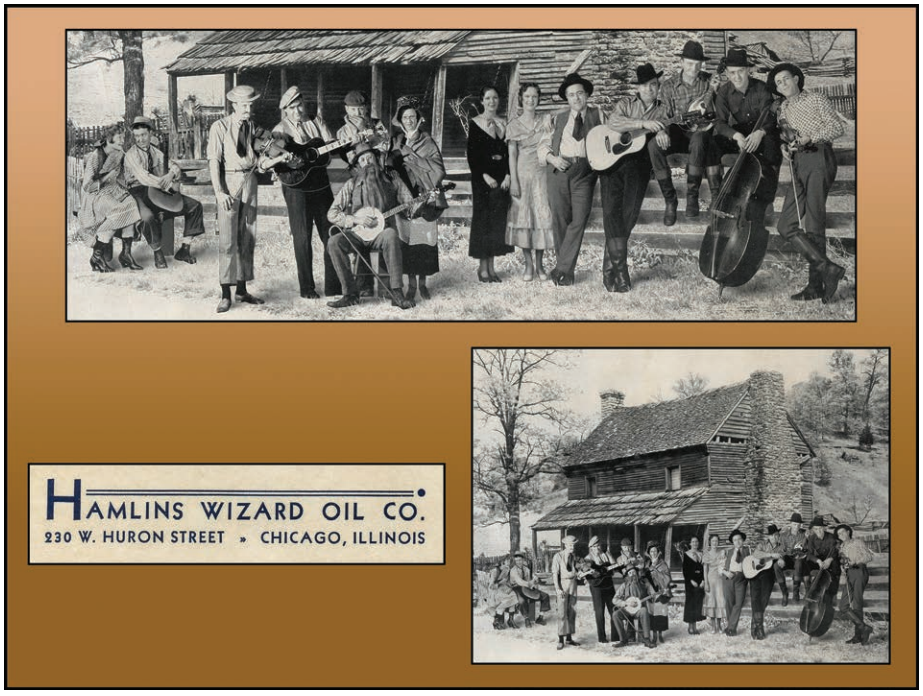
References

1. Sigurdsson TS, Aronsson A, Lindberg L: Extracorporeal arteriovenous ultrasound measurement of cardiac output in small children. Anesthesiology 2019; 130:712–8
2. Blalock A: Mechanism and treatment of experimental shock I. Shock following hemorrhage. Arch Surg 1927; 15: 762–98
3. Guyton AH, Hall JE: Overview of the circulation: Medical physics of pressure, flow, and resistance, Textbook of medical physiology, 11th edition. Edited by Elsevier S. Philadelphia, Elsevier, Inc., 2006, pp 161–70
4. Roeleveld PP, de Klerk JCA: The perspective of the intensivist on inotropes and postoperative care following pediatric heart surgery: An international survey and systematic review of the literature. World J Pediatr Congenit Heart Surg 2018; 9:10–21
5. Yang F, Iacobelli R, Wang JM, Iorio FS: Assessment of cardiac function in infants with transposition of the

great arteries after surgery: Comparison of two methods. World J Pediatr 2018; 14:373–7
6. Tirotta CF, Lagueruela RG, Madril D, Velis E, Ojito J, Monroe D, Aguero D, Irizarry M, McBride J, Hannan RL, Burke RP: Non-invasive cardiac output monitor validation study in pediatric cardiac surgery patients. J Clin Anesth 2017; 38:129–32
7. Beck R, Milella L, Labellarte C: Continuous non-invasive measurement of stroke volume and cardiac index in infants and children: Comparison of Impedance Cardiography NICaS® vs CardioQ® method. Clin Ter 2018; 169:e110–3
8. Fathi EM, Narchi H, Chedid F: Noninvasive hemodynamic monitoring of septic shock in children. World J Methodol 2018; 8:1–8
9. Suehiro K, Joosten A, Murphy LS, Desebbe O, Alexander B, Kim SH, Cannesson M: Accuracy and precision of minimally-invasive cardiac output monitoring in children: A systematic review and meta-analysis. J Clin Monit Comput 2016; 30:603–20
10. Riou B: Continuous measurement of hemoglobin: Methodological approach and lessons for the future. Anesthesiology 2013; 118:497–9
11. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K; OPTIMISE Study Group: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA 2014; 311:2181–90

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Renfro Valley Sells a Mountain of Hamlins Wizard Oil: A Chloroform Elixir Cure?



A charmed (?) source for pharmaceuticals, ex-magician John A. Hamlin added the botanicals sassafras and cloves to a chloroform elixir that also contained turpentine, ammonia, and camphor. He then bottled it in Chicago (*bottom left*) as "Hamlins Wizard Oil." This magical medicine was peddled as an external liniment and topical remedy for toothache and earache. Unfortunately, Hamlin also began encouraging internal use of his panacea as a cure for headache, diphtheria, pneumonia, rabies, and cancer. (Granted, the roughly 60% alcohol content may have provided imbibers with transient relief from their aches and pains.) Among many entertainers advertising Hamlins Wizard Oil in the mid-1930s, the Renfro Valley Folks (*top* and *bottom right*) broadcast their country music by radio from Kentucky to most of the United States. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.