Cardiology/CT Surgery (K Gist, Section Editor)

Non-invasive Cardiac Output Monitoring in Congenital Heart Disease

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Abstract

Purpose of review Cardiac output (CO) is a fundamental physiological parameter that measures the volume of blood that is pumped by the heart per unit of time, and helps define how oxygen is delivered to the tissues of the human body. In this paper, we discuss current methods of continuous CO monitoring while defining low CO syndrome (LCOS) and how analytical tools may help improve CO management in the subpopulation of patients with congenital heart disease (CHD).

Recent findings Non-invasive methods of measuring CO have become increasingly available in recent years. Advantages of non-invasive over invasive techniques include decreased risk of procedural complications, decreased exposure to sedative and/or anesthetic agents, and increased patient comfort. Pediatric patient populations are particularly sensitive to the risks and complications of invasive techniques given the relative size of current technologies to pediatric vascular and cardiac dimensions.

Summary Novel device technologies, combined with emerging analytical techniques, may help improve measurement of CO in children and those with CHD, and allow earlier detection of LCOS.

Introduction

Cardiac output (CO) is a fundamental physiological parameter that measures the volume of blood that is pumped by the heart per unit of time. It is an essential component of the cardiovascular system, as it ensures sufficient oxygen and nutrient delivery to the body's organs and tissues (Fig. 1). CO is typically measured in liters per minute (L/min) and is calculated by multiplying the heart rate (HR), measured in beats per minute (bpm), by the stroke volume (SV), measured in milliliters (mL) or liters (L), of blood that is ejected from the systemic ventricle during each heartbeat. The systemic ventricle is most commonly the morphologic left ventricle; however, in some severe forms of congenital heart disease (CHD), the right ventricle may serve as the systemic ventricle due to an absent or hypoplastic left ventricle. In pediatrics, cardiac index (CI) is often used instead of CO, as this can correct for anthropometric changes as a child grows. CI is calculated by dividing CO by the body surface area (BSA) and is measured in liters per minute per square meter (L/min/m^2). A normal CI is generally considered to be 3–4 L/min/m^2.

Non-invasive methods of measuring CO/CI have become increasingly available in recent years, as they
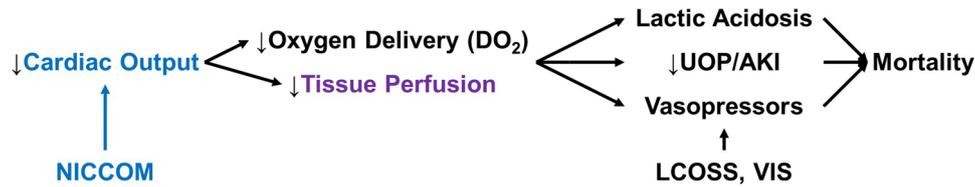
Fig. 1 Physiology of cardiac output. Decreased cardiac output (CO) can cause decreased oxygen delivery and tissue perfusion. These in turn can lead to anaerobic metabolism and lactic acidosis, end-organ injury including acute kidney injury (AKI), and the need for vasopressors for patient management. Ultimately, prolonged low cardiac output can lead to other morbidities and mortality. Non-invasive continuous cardiac output monitoring (NICCOM) technologies may help monitor this process at the most upstream end, because current methods of bedside monitoring use more downstream metrics, especially in children, including lactic acidosis (low cardiac output syndrome score, LCOSS) and vasopressor dosing (vasopressor-inotrope score, VIS).

offer several advantages over invasive techniques, such as decreased risk of procedural complications, decreased exposure to sedative and anesthetic agents, and increased patient comfort. In this paper, we discuss current methods of continuous CO/CI monitoring, low CO syndrome (LCOS), and how analytical tools may help improve CO/CI management in congenital heart disease (CHD).

Cardiac output monitoring: current solutions

The ideal method of tracking changes in CO/CI would be non-invasive, continuous, accurate, actionable, and specifically designed for children and those with CHD. Existing CI/CO measurement methods have significant limitations in the CHD population, some of which are due to the unique physiology of those with CHD. For instance, patients with CHD span the age and size spectrum, meaning that device size is important. Many patients with CHD have intracardiac or extracardiac shunting (blood flowing outside the normal series circuit), meaning that some of the assumptions about thermodilution and/or dye methods are violated. For patients with either disease-based or surgical aortopulmonary shunt placement, and especially those with a single ventricle, the ventricle pumps to both the systemic and pulmonary vascular beds at once, so CO/CI may refer to systemic flow, pulmonary flow, or both. Aortopulmonary shunting also means that these patients are highly sensitive to changes in vascular resistance in the pulmonary and systemic vascular beds, which can lead to significant, rapid changes in CO/CI.

Currently used clinical metrics

The standard methods used most often in the post-operative period include calculating CO/CI using the Fick principle, which involves mixed venous oxygen saturation and arterial saturation, and assuming an oxygen consumption rate. Another surrogate method is the vasopressor-inotrope score (VIS), which measures the type and dose of vasoactive and inotropic medications a patient needs to maintain adequate blood pressure and organ perfusion, though this

really measures physician response to low CO/CI [1]. Additionally, the low cardiac output syndrome score (LCOSS) utilizes multiple parameters like heart rate and urine output for score calculation, but does not directly measure CO/CI (Fig. 2) [2••]. Cardiovascular magnetic resonance (CMR) imaging is the gold standard for CO measurement in children and those with CHD with high accuracy and excellent reproducibility [3], but is not feasible for continuous CO monitoring due to technical limitations, including needing to be performed in an MRI magnet, often with sedation and/or anesthesia, and cost.

Other tools are often used for adults. For instance, thermodilution-based pulmonary artery catheterization is relatively accurate, but is not commonly used in children due to the large size of catheters, the risk of vascular and arrhythmia complications, and inaccuracies in patients with shunts [4]. Transesophageal Doppler echocardiography is less invasive, but cannot often be used continuously, is angle-dependent and therefore less accurate, can be bulky, and requires a trained professional for interpretation [5•].

Wearable, non-invasive tools for CO/CI measurement

The development and use of wearable, non-invasive tools to monitor CO/CI has the potential to dramatically improve patient outcomes by enabling earlier diagnosis and treatment of cardiac diseases through less invasive and risky methods (Table 1). Wearable technology may allow for truly non-invasive, continuous cardiac output monitoring (NICCOM), both in hospital and ambulatory settings, providing clinicians with a more comprehensive view of a patient's health status. The progress in semiconductor technology, embedded computing, machine learning, and connectivity has made it possible to
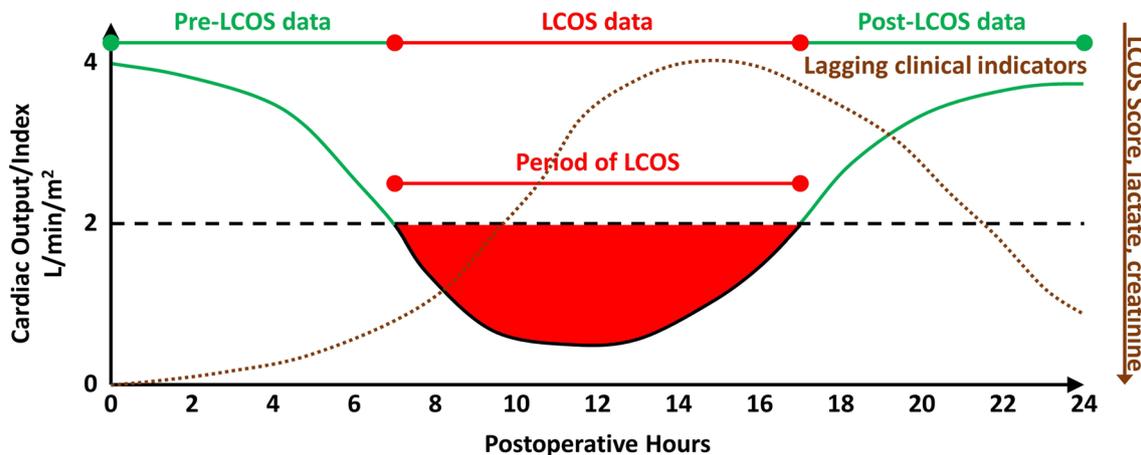

Fig. 2 Theoretical low cardiac output syndrome (LCOS) timeline. After surgery for congenital heart disease, patients can develop low cardiac output syndrome (LCOS). Often, this manifests some hours after getting out of the operating room. Measured cardiac output and oxygen delivery decrease, and then lagging clinical indicators change, including low cardiac output syndrome score (LCOSS), lactate, and creatinine. An ideal monitoring system would provide data more continuously and earlier in the process of the development of LCOS.

Table 1. Non-invasive continuous cardiac output monitoring technologies. Selected references in the literature describing the method, the gold standard against which the technology was tested, and whether those technologies were tested in congenital heart disease (CHD) and in children

Author (year)	Method	Gold standard	No. of subjects	Correlation coefficient	Tested in CHD	Validated on children
Ganti et al. [6]	Seismocardiogram	Cardiac MRI	45	0.87	Yes	Yes
Mahajan et al. [7]	PiCCO system	Thermodilution	16	0.72	Yes	Yes
Taylor et al. [8]	Impedance cardiography	Direct Fick method	56	0.33	Yes	Yes
Yazdi et al. [9]	Bodyport Cardiac Scale	Direct Fick method	32	0.86	Yes	No
Dvir et al. [10•]	Photoplethysmogram	Thermodilution	7	0.91	No	No
Wang et al. [11]	Photoplethysmogram	Impedance cardiography	16	0.82	No	No
Bernstein et al. [12]	Trans-brachial impedance	Cardiac MRI	32	0.86	No	No
Godoy et al. [13]	Mobil-O-Graph monitor	Transthoracic echocardiogram	38	0.51	No	No
Saugel et al. [14]	Radial artery applanation tonometry	PiCCO system	22	0.30	No	No

integrate more features while consuming less power in small-sized circuits. These advances have led to wearable devices becoming increasingly reliable and accurate, to the extent that they may now be comparable to clinical devices. Wearable devices can also now incorporate multiple non-invasive techniques to measure biometric parameters, allowing for a comprehensive evaluation of human health through sophisticated data analysis. Lastly, the continuous advancement in manufacturing techniques and the development of novel materials for clinical use have created a distinctive prospect for wearables to offer comfortable, uninterrupted, and inconspicuous health monitoring. Though promising, much work remains to be done to bring these technologies to fruition.

Previous work by Wang et al. [11] has examined using photoplethysmography (PPG) to derive a metric that is closely correlated to CO/CI. PPG sensors are found in many commercial wearable devices, like smartwatches and smart rings, and is fundamentally a measure of blood volume pulse at the periphery (e.g., at a fingertip, toe, earlobe, or wrist). Thus, this approach can be easily deployed on a large scale. However, since this approach utilizes PPG waveform analysis, it is heavily affected by any kind of noise that might distort the waveform including motion noise, ambient light changes, skin tone variability, and sensor position. Moreover, the PPG waveform includes characteristics that reflect not only CO/CI but also other factors such as arterial compliance and perfusion index, a measure of peripheral perfusion [15]. A recent study used a combined PPG and finger cuff and showed reasonable correlation to upper arm arterial pressure in adults in the intensive care unit setting [16]. Seismocardiogram (SCG) signals have become popular due to improvements in micro-electromechanical systems (MEMS) technology that enables fabrication of small, high-resolution, low-noise accelerometers. SCG waveforms, a measure of the vibrations of the chest wall in response to the heartbeat, have been shown to be correlated to CO changes in healthy individuals after exercise [17]. A chest worn device incorporating dual-mode electrocardiography (ECG) and SCG has been used to assess CO in patients with CHD [6••]. Recent work on developing ultra-thin (<200 µm) thick, soft, chest-conformable non-invasive e-tattoos has the potential to improve the wearability and signal quality of mobile CO/CI sensors for children [18, 19]. Some of these technologies are capable of synchronous ECG and SCG recordings. As with PPG signals, SCG measurements contain information that is both pertinent to CO/CI but also relating to other factors such as valve timings and filing characteristics of the heart. Recently, wearable ultrasound patches have been designed, which can perform B-mode echocardiography on human subjects [20]. While the ultrasound beam forming and data processing require a wired device connection, this work represents a significant advancement in achieving comprehensive cardiac monitoring through wearable devices.

Other current solutions estimate CO/CI from models that use demographic information combined with either the impedance cardiogram or the finger arterial pressure waveform, obtained through bioimpedance and the vascular unloading technique, respectively [5, 21]. However, these approaches are obtrusive, require strict placement of multiple electrodes or cuff sizes, have diminished accuracy in critically ill patients, and are rarely tested in children,

so their practicality remains in doubt when used for monitoring CO/CI in patients with CHD [21]. Quain et al. [22] evaluated a thoracic impedance tool and found poor correlation with right heart catheter Fick CO/CI calculations in adults with Fontan palliation. CO/CI estimated by PRAM (Pressure Recording Analytical Method) after pediatric cardiac surgery was found to be reliably associated with clinical indicators of tissue perfusion, vasoactive and diuretic drug requirements, and predicted longer mechanical ventilation duration [23]. A study of pediatric CICU patients found that estimations of normal CO/CI via Pulse Index Contour Cardiac Output (PiCCO) were associated with shorter duration of mechanical ventilation and length of stay [24].

As shown, there are physiologic and technical limitations to many of the current methods for NICCOM in CHD. Improving these technologies to make them more accurate, accessible, and deployable in hospital and outpatient clinical settings remains a critical need in the field.

Low cardiac output syndrome

Low cardiac output syndrome (LCOS) physiology

The clinical significance of CO and CI lies in their ability to reflect the adequacy of tissue perfusion. Oxygen delivery to the tissues is calculated by multiplying the CO/CI by the oxygen content of the blood. Thus, low CO/CI can result in inadequate oxygen delivery to the tissues, leading to a state of tissue hypoxia. Tissue hypoxia leads to increased anaerobic metabolism, resulting in the production of lactic acid and metabolic acidosis. In severe and persistent cases, impaired oxygen delivery can lead to end-organ damage, cardiac arrest, and death (Fig. 1).

To describe this state of impaired oxygen delivery due to low CO/CI, the term Low Cardiac Output Syndrome (LCOS) has been used and best describes the altered ratio of oxygen delivery to consumption. LCOS is a common problem in patients with CHD following cardiac surgery, as their cardiac function is often compromised due to the structural defects in their heart and negative effects of cardiopulmonary bypass. Accurate and timely measurement of CO/CI is crucial in the management of these patients in the hospital and outpatient settings, as it helps clinicians to detect early signs of hemodynamic instability and to guide therapeutic interventions aimed at improving tissue perfusion.

Definitions of LCOS

Despite its clinical significance, there is no universally accepted definition of LCOS in the literature or in clinical practice. Various definitions of LCOS have been proposed in the literature, each with its own set of criteria. Wernovsky et al. [25••] defined LCOS as having a CI of <2 L/min/m^2, as determined by thermodilution catheter use. Other definitions focus on the clinical picture: Hoffman et al. [26] described LCOS as a clinical syndrome with manifestations such as tachycardia, oliguria, cold

extremities, and/or cardiac arrest, with or without a ≥30% difference in arterial-mixed venous oxygen saturation or metabolic acidosis (an increase in the base deficit of >4 or an increase in the lactate of >2 mg/dL) on 2 successive blood gas measurements. Other commonly used definitions use a combination of clinical findings, care team interventions, and lab values: Gaies et al. [27] used the Pediatric Cardiac Critical Care Consortium (PC4) definition of LCOS, which includes vasoactive-inotropic score (VIS) > 15; VIS tripled in 48 h to 10+; arterio-venous oxygen difference (AVO2 difference) > 40% with hemoglobin > 8; and LCOS described in the physician note. There are other varied examples in the literature as well [1, 2, 28–33].

Although there is no consensus on a single definition of LCOS, the criteria used in various definitions share some common features, such as signs and symptoms of inadequate tissue perfusion, metabolic acidosis, and low CO/CI. These criteria emphasize the importance of timely detection and management of LCOS, as it can lead to severe morbidity and mortality in patients with CHD, but also the challenge that a lack of objective measures poses in clinical management.

Incidence and sequelae of LCOS

LCOS is a common problem in the post-operative period for patients with CHD. The incidence of LCOS varies widely across studies. For example, Parr et al. [34] and Wernovsky et al. [25] both reported a cardiac index of <2 L/min/m^2 in 24% of patients. Butts et al. [30] found that 42% of neonates undergoing CHD surgery developed LCOS, while Gaies et al. [27] reported that 71% of patients had LCOS at some point in the post-operative period, with 38% having LCOS as the initial complication. Despite the widely varying incidence, LCOS is the leading cause of morbidity and death in the post-operative period for patients with CHD. Parr et al. [34] reported that 12% of post-surgical patients died of LCOS, representing 59% of post-operative deaths, and those with lower calculated cardiac index had higher mortality rates. Ma et al. [35] reported that LCOS was the cause of death in 52% of the last 100 patients who died, making it the leading cause of mortality. Gaies et al. [27] reported that systemic circulatory failure (51%) was the leading cause of death, with inadequate pulmonary blood flow (13%) and cardiac arrest (12%) being the next most common causes of death (which could also be related to LCOS). The development of LCOS is also associated with acute kidney injury, acute liver injury, prolonged hospital length of stay, and the need for mechanical circulatory support (such as extracorporeal membrane oxygenation, ECMO).

Although management strategies that mitigate the severity and duration of LCOS have not been clearly elucidated in the literature [29, 36], objective measurement of CO/CI may help bedside providers recognize and respond to LCOS early, which can lead to improved patient outcomes.

Mathematical modeling and machine learning in LCOS in CHD

Mathematical modeling is a valuable approach employed in scientific research to gain insights, make predictions, and address complex problems. In this section, we present a concise overview of the modeling process, condensed into five essential steps (Fig. 3). These steps encompass the entire modeling process, starting with problem identification, where researchers define the specific problem they aim to solve. Next, variables representing the system are selected, and assumptions are made to simplify the model. Mathematical equations are then formulated to describe the interactions between these variables. Parameter estimation follows, allowing researchers to determine the values of model parameters based on available data or literature. Model validation is crucial to assess the accuracy and reliability of the model's predictions by comparing them to independent data or experimental observations. Refinement of the model involves iterative adjustments based on feedback from validation and analysis. The model is then analyzed to gain insights into its behavior and properties. Once validated and refined, the model can be utilized for various purposes, such as prediction, optimization, or decision-making. Model verification ensures the correct implementation of
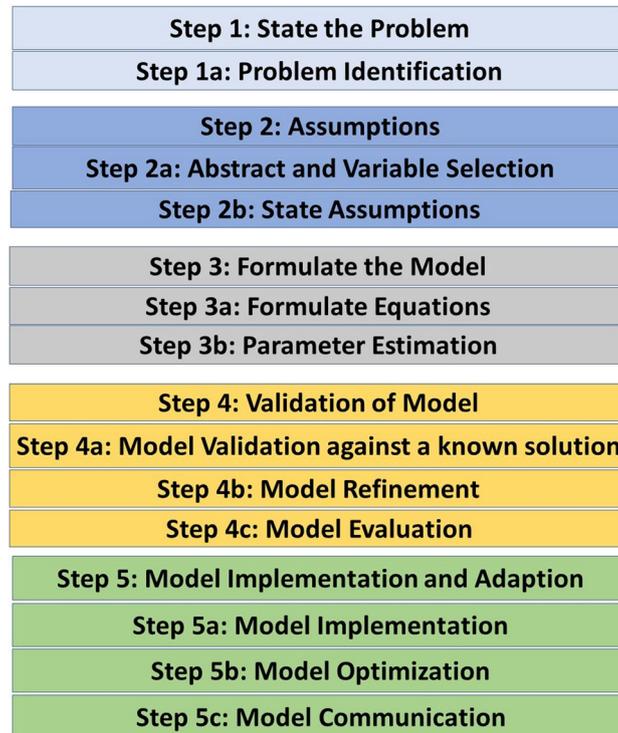
Step 1: State the Problem
Step 1a: Problem Identification

Step 2: Assumptions
Step 2a: Abstract and Variable Selection
Step 2b: State Assumptions

Step 3: Formulate the Model
Step 3a: Formulate Equations
Step 3b: Parameter Estimation

Step 4: Validation of Model
Step 4a: Model Validation against a known solution
Step 4b: Model Refinement
Step 4c: Model Evaluation

Step 5: Model Implementation and Adaption
Step 5a: Model Implementation
Step 5b: Model Optimization
Step 5c: Model Communication

Fig. 3 Summarized steps of mathematical modeling process. Caption: The steps involved in the modeling process, highlighting problem identification, assumptions and variable selection, equation formulation, parameter estimation, model validation, refinement, analysis, verification, implementation, and effective communication. These steps enable researchers to leverage mathematical modeling to tackle complex scientific challenges

the model, while effective communication of the model's results, findings, and limitations to stakeholders is crucial for understanding and application. Through this comprehensive modeling process, researchers can leverage the power of mathematical modeling to tackle complex scientific challenges effectively.

As described above, another potential tool for estimating CO/CI is mechanistic mathematical modeling, which leverages advanced computational techniques to simulate the complex cardiovascular system. By incorporating physiological data and mathematical equations describing the balance between tissue oxygen supply and tissue oxygen demand, these models may predict cardiac output and other important clinical parameters such as urine output [37]. This approach can be particularly beneficial for individualized patient care, as it allows for the consideration of unique patient characteristics and the effects of various interventions. Mathematical models can also facilitate a deeper understanding of the underlying mechanisms driving cardiac function, supporting the development of more targeted therapies and treatment strategies. Mechanistic mathematical models can provide fundamental insight into pathophysiology, potentially leading to the discovery of new therapeutic or prophylactic clinical management strategies. Also, the increasing rate of development of computational technology allows for more intricate and faster simulations in real time. However, the scale of the model is critical for its clinical applicability. Larger, more complex models can be challenging for clinicians to understand and use at the bedside.

To address this challenge, machine learning techniques, such as neural networks, have been used to process large amounts of data and produce good predictive results. However, neural networks are often considered a black box, providing little insight into pathophysiology and thus hindering their acceptance among clinicians. A new approach is to combine mechanistic mathematical modeling and neural networks, known as physically and biologically informed neural networks (PINNs and BINNs, respectively) [38]. This hybrid approach has the potential to combine the understandability and transparency of mechanistic mathematical models with the power of neural networks to discover unknown variables and parameter estimation, making them a promising tool for clinical applications. Both mechanistic mathematical modeling and BINNs have the potential to be useful tools in understanding LCOS pathophysiology and management of patients with LCOS due to ever increasing computational capacity and the further application of these methods in data science.

Conclusion

Among critically ill children and adults with CHD, maintaining CO/CI is fundamental to ensuring sufficient oxygen delivery to tissues, as evidenced by the potentially devastating consequences of LCOS. Methods exist to measure CO/CI, but there is a critical need in the field to make the technologies non-invasive, more accurate, and useful and to test them in children and those with CHD. Mathematical modeling provides another approach to using physiologic data to detect LCOS. We believe that multi-disciplinary teams of physicians, biomedical engineers, and mathematicians can solve the need for improved CO/CI monitoring through collaborative efforts.

Author contribution

All authors conceived of this manuscript, provided content, and revised it. All authors agree with the submitted version.

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Declarations

Conflict of interest

Dr. Animesh Tandon is a consultant for Synergen Technology Labs LLC and Siemens Healthineers. Dr. Omer Inan is a co-founder and board member for Cardiosense, Inc. Sarnab Bhattacharya, Ayse Morca, Daniel S Munther, Shawn D Ryan, Samir Q Latifi, Nanshu Lu, Javier J. Lasa, Bradley S Marino, and Orkun Baloglu report no competing interests.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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