Cardiology in the Young

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Factors associated with renal oxygen extraction in mechanically ventilated children after the Norwood operation: insights from high fidelity haemodynamic data

Rohit S. Loomba[1,2], Enrique G. Villarreal[3], Juan S. Farias[4], Saul Flores[5] and Joshua Wong[1]

[1]Advocate Children's Hospital, Chicago, IL, USA; [2]Rosalind Franklin University of Medicine and Science, Chicago, IL, USA; [3]Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, NL, Mexico; [4]Children's Mercy Hospital, Kansas City, MO, USA and [5]Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

Original Article

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Corresponding author:
E. G. Villarreal;
Email: quique_villarreal93@hotmail.com

Abstract

Background: Maintaining the adequacy of systemic oxygen delivery is of utmost importance, particularly in critically ill children. Renal oxygen extraction can be utilised as metric of the balance between systemic oxygen delivery and oxygen consumption. The primary aim of this study was to determine what clinical factors are associated with renal oxygen extraction in children after Norwood procedure. *Methods:* Mechanically ventilated children who underwent Norwood procedure from 1 September, 2022 to 1 March, 2023 were identified as these patients had data collected and stored with high fidelity by the T3 software. Data regarding haemodynamic values, fluid balance, and airway pressure were collected and analysed using Bayesian regression to determine the association of the individual metrics with renal oxygen extraction. *Results:* A total of 27,270 datapoints were included in the final analyses. The resulting top two models explained had nearly 80% probability of being true and explained over 90% of the variance in renal oxygen extraction. The coefficients for each variable retained in the best were −1.70 for milrinone, −19.05 for epinephrine, 0.129 for mean airway pressure, −0.063 for mean arterial pressure, 0.111 for central venous pressure, 0.093 for arterial saturation, 0.006 for heart rate, −0.025 for respiratory rate, 0.366 for systemic vascular resistance, and −0.032 for systemic blood flow. *Conclusion:* Increased milrinone, epinephrine, mean arterial pressure, and systemic blood flow were associated with decreased (improved) renal oxygen extraction, while increased mean airway pressure, central venous pressure, arterial saturation, and systemic vascular resistance were associated with increased (worsened) renal oxygen extraction.

Parallel circulation represents a unique circulatory physiology in which the systemic saturation is dependent on a weighted average of the systemic and pulmonary venous saturations. The weights for this average depend on the relative proportion of blood flow going to the pulmonary and systemic circulations. This ratio of pulmonary and systemic blood flow is further dependent on the relative resistances in these two beds.[1–3]

Optimal management of children with parallel circulation, particularly after the Norwood operation, requires a thorough understanding of the nuances of the circulation and understanding of how the circulation is impacted by various clinical interventions. Data on the impact of clinical interventions on the physiology itself are limited. More detailed understanding of these impacts could better help improve the management of the children.

Oxygen extraction reflects the balance between oxygen delivery and oxygen consumption, or in other words, the adequacy of systemic oxygen delivery. Increased oxygen extraction has been demonstrated to increase morbidity and mortality, with oxygen extraction of 30–40 being as a period of increased risk of morbidity, such as impaired neurodevelopment, acute kidney injury, hepatic insufficiency, necrotising enterocolitis, and cardiac arrest increase.[4–22]

The primary aim of this study was to utilise high fidelity data to characterise the association of various clinical parameters and renal oxygen extraction in children with parallel circulation after the Norwood operation.

Methods

Study design

This study protocol was approved by the institutional review board. It is in concordance with the Helsinki Declaration. This study was a single-centre, retrospective study aimed to characterise the association between various clinical parameters and renal oxygen extraction. The resulting

model and the ability to predict the renal oxygen extraction were not necessarily the main aim of this study, but rather to demonstrate the relationship between the independent variables and renal oxygen extraction.

Variables of interest

The variables of interest collected were as follows: central venous pressure, heart rate, respiratory rate, mean arterial blood pressure, arterial saturation by pulse oximetry, renal near infrared spectroscopy, peak airway pressure, mean airway pressure, positive end expiratory pressure, body temperature, fluid balance, epinephrine dose, norepinephrine dose, dopamine dose, dobutamine dose, vasopressin dose, nitroprusside dose, and nicardipine dose. Patient weight and gestational age were also collected.

All the data except for vasoactive doses were collected from the T3 software. T3 is software designed to integrate multiple data streams in real time in clinical settings. The data from all the streams can then be displayed by the software in a user-defined fashion. Additionally, T3 also estimates the venous saturation and then displays the probability of the venous saturation being under 30, 40, or 50% in a metric known as the index of inadequate delivery of oxygen. The T3 software collects data from the available streams at an interval of 5 s, thus offering high temporal resolution.

Central venous pressures were obtained by use of femoral lines terminating in the inferior caval vein. Line placement was confirmed by radiographs.

Renal near infrared spectroscopy values were collected. Near infrared spectroscopy values were obtained using the Casmed ForeSight Elite tissue oximeter.

Vasoactive doses were collected manually through the electronic medical record as charted. It is local practice to document every time an infusion dose has been changed and at regular intervals. Doses of all vasoactive infusions were collected for each timepoint at which the data from T3 were collected.

Fluid balance was collected manually through the electronic medical record as charted. It is local practice to update fluid balance hourly. Fluid balance for each timepoint at which T3 data were collected was collected as the fluid balance for the hour prior to that timepoint.

Some values were also calculated. Renal oxygen extraction was calculated as ((arterial saturation by pulse oximetry – renal near infrared spectroscopy)/(arterial saturation by pulse oximetry)) × 100. Thus, if the arterial saturation were 80 and the renal near infrared spectroscopy value was 60, the renal oxygen extraction ratio would be 25. Oxygen consumption in ml/min was estimated using the LaFarge equation. Systemic blood flow was calculated by dividing the estimated oxygen consumption by the arteriovenous oxygen content difference. The renal near infrared spectroscopy value was used for this. Systemic vascular resistance was then calculated using the following equations: (mean arterial blood pressure – central venous pressure)/systemic blood flow.

Patient inclusion

Neonates with functionally univentricular hearts who underwent a Norwood operation were eligible for inclusion in this study. Data must have been collected and available for patients in T3 for patients to be included in this study. T3 was implemented locally on 1 September 1, 2022 and a final inclusion date of 1 March, 2023 was utilised. Only data while patients were intubated and mechanically ventilated were included as this allowed for airway pressures to be quantified. Data were available at five second intervals for patients with T3 data. Datapoints were included in the final analyses only if there was a central venous pressure and airway pressures available at that specific timepoint.

Statistical analyses

The primary statistical aim of the analyses was to model renal oxygen extraction ratio using the other collected data in order to quantitatively assess the association of the various parameters with renal oxygen extraction ratio. This was done utilising a Bayesian linear regression. Renal oxygen extraction ratio was the dependent variable, and the following independent variables were included: central venous pressure, heart rate, respiratory rate, mean arterial blood pressure, arterial saturation by pulse oximetry, mean airway pressure, body temperature, fluid balance, epinephrine dose, norepinephrine dose, dopamine dose, dobutamine dose, vasopressin dose, nitroprusside dose, nicardipine dose, estimated systemic blood flow, and estimated systemic vascular resistance. The Jeffreys–Zellner–Siow prior was utilised. The top 10 most likely models were evaluated.

Bayesian statistics were utilised rather than frequentist regressions for several reasons. The details of these are beyond the scope of this manuscript but in general Bayesian statistics allows for generating a distribution for all point estimates. This allows for the quantification of the probability of specific outcomes and models describing the outcomes. Bayesian models have also been demonstrated to be more well-fitted and reproducible.

Statistical analyses were conducted using JASP Version 0.16 (University of Amsterdam, Amsterdam, Netherlands). P-values are not presented as Bayesian statistical tools, and no frequentist statistical tools were utilised.

Results

Cohort information (*Table 1*)

A total of 27,270 datapoints were included in the final analyses. These were collected from nine patients over a total of 1,338 patient hours (55.7 days). As per the inclusion criteria for retaining datapoints in the final analyses, central venous pressure and airway pressures must have been available for the data for a timepoint to be included. It is important that the sample size here is 27,270 as the analyses are done on a datapoint level and not on an individual patient level.

Average gestational age was 38 weeks with 2 patients being premature. Average patient age at the time of the Norwood operation was 20 days. This was due to two patients getting their Norwood done closer to 2 months of life following a hybrid procedure. When these two patients are excluded, the mean age at time of Norwood was 2 days. Of the nine patients for whom data were collected, two had an identified genetic anomaly.

Regarding vasoactive agents, epinephrine was utilised during 91% of the timepoints at which data were collected, dopamine during 14.5%, milrinone during 24.8%, and nitroprusside during 3.8%, and vasopressin 0.3%. Norepinephrine, dobutamine, and nicardipine were not utilised in any of the patients during the study period.

Regression analyses (*Table 2*)

The most probable model had a probability of 71.5% and an R^2 value of 0.932. The R^2 value indicated that 93.2% of the variability

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Table 1. Descriptive data regarding cohort

Principle cardiac diagnosis (frequency)	
Hypoplastic left heart syndrome	5
Tricuspid atresia	2
Small left sided structures	2
Genetic anomaly (frequency)	2
Premature (frequency)	2
Age at Norwood (days)	20.5 ± 32.0
Weight at Norwood (kg)	3.3 ± 0.2

Table 2. Association of variables with change in renal oxygen extraction

Variable[a]	Beta-coefficient	Clinical interpretation
Milrinone (mcg/kg/min)	−1.700	An increase in milrinone of 0.5 is associated with a decrease in renal oxygen extraction by 0.85.
Epinephrine (mcg/kg/min)	−19.050	An increase in epinephrine by 0.02 is associated with a decrease in renal oxygen extraction by 0.38.
Mean airway pressure (cmH20)	0.129	An increase in mean airway pressure is associated with an increase in renal oxygen extraction by 0.12.
Mean arterial pressure (mmHg)	−0.063	An increase in mean arterial pressure of 10 mmHg is associated with a decrease in renal oxygen extraction by 0.63.
Central venous pressure (mmHg)	0.111	An increase in central venous pressure of 1 mmHg is associated with an increase in renal oxygen extraction by 0.11.
Arterial saturation by pulse oximetry (%)	0.093	An increase in arterial saturation by pulse oximetry of 5 is associated with an increase in renal oxygen extraction by 0.46.
Heart rate	0.006	An increase in heart rate by 10 is associated with an increase in renal oxygen extraction by 0.06.
Respiratory rate (breaths per minute)	−0.025	An increase in respiratory rate by 10 is associated with a decrease in renal oxygen extraction by 0.25.
Systemic vascular resistance (woods units)	0.366	An increase in systemic vascular resistance by 1 is association with an increase in renal oxygen extraction by 0.36.
Systemic blood flow (L/min)	−0.032	An increase in systemic blood flow by 1 is associated with a decrease in renal oxygen extraction by -0.03.

[a]Only variable with significant associations are included in the table.

in renal oxygen extraction ratio could be explained by the model and it's included variables.

The most probable model retained the following independent variables: milrinone, mean airway pressure, mean arterial pressure, central venous pressure, arterial saturation by pulse oximetry, heart rate, respiratory rate, systemic vascular resistance, and systemic blood flow.

The coefficients for each variable retained in the best were as follows: −1.70 for milrinone, −19.05 for epinephrine, 0.129 for mean airway pressure, −0.063 for mean arterial pressure, 0.111 for central venous pressure, 0.093 for arterial saturation by pulse oximetry, 0.006 for heart rate, −0.025 for respiratory rate, 0.366 for systemic vascular resistance, and −0.032 for systemic blood flow.

Correlation was present in this analysis between independent variables such as milrinone and systemic vascular resistance, milrinone and systemic blood flow.

To put the above in a more clinically relevant context, a 0.5 mcg/kg/min increase of milrinone is associated with a 0.85 decrease in renal oxygen extraction, a 0.01 mcg/kg/min increase of epinephrine is associated with a 0.19 decrease in renal oxygen extraction, a 1 cmH20 increase in mean airway pressure was associated with a 0.12 increase in renal oxygen extraction, a 5 mmHg increase in mean arterial pressure was associated with a 0.31 decrease in renal oxygen extraction, a 1 cmH20 increase in central venous pressure was associated with a 0.11 increase in renal oxygen extraction, a 5 increase in arterial saturation by pulse oximetry was associated with a 0.46 increase in renal oxygen extraction, a 10 beat per minute increase in heart rate was associated with a 0.06 increase in renal oxygen extraction, a 5 Woods units increase in systemic vascular resistance was associated with a 1.83 increase in renal oxygen extraction, and a 1 l/min increase in systemic blood flow was associated with a 0.03 decrease in renal oxygen extraction.

Thus, increased milrinone, epinephrine, mean arterial pressure, and systemic blood flow were associated with decreased (improved) renal oxygen extraction, while increased mean airway pressure, central venous pressure, arterial saturation by pulse oximetry, and systemic vascular resistance were associated with increased (worsened) renal oxygen extraction.

The second most probable model had a probability of 10.9% and an R^2 value of 0.931. Thus, the two most probable models had a total probability of 82.4%; thus, these two models were able to explain a majority of the data, accounting for 93% of the variance in renal oxygen extraction. The second most probable model was similar to the most probable model except for the addition of temperature as a retained variable.

Discussion

The current study demonstrates factors that were statistically significantly associated with renal oxygen extraction in mechanically ventilated children with parallel circulation after the Norwood operation. Renal oxygen extraction improved with increases in milrinone, epinephrine, mean arterial pressure, and systemic blood flow while renal oxygen worsened with increasing mean airway pressure, arterial saturation by pulse oximetry, and systemic vascular resistance. Of equal note is that other vasoactive agents such as dopamine, vasopressin, and nicardipine did not demonstrate any statistically significant effect on renal oxygen extraction.

While statistical significance was demonstrated for the above-mentioned variables, milrinone and systemic vascular resistance seemed to be the most clinically significant. The subjective review of the change in the variable needed to modify renal oxygen extraction was most clinically possible. For instance, a 1 change in renal oxygen extraction would require a 15 mmHg change in mean arterial pressure which in a neonate is an unlikely clinical change to experience.

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Oxygen extraction can be evaluated regionally using near infrared spectroscopy as a surrogate for venous saturation. The correlation between near infrared spectroscopy and underlying venous saturations has been demonstrated.[23] More importantly, an independent association between regional near infrared spectroscopy values and morbidity and mortality has been demonstrated.[24–28] Use of superior or inferior caval vein saturations, or analogously, cerebral or renal near infrared spectroscopy seems reasonable according to findings of published data, despite anecdotally perpetuated superiority of the superior caval vein saturation or cerebral near infrared spectroscopy.[27,28]

Parallel circulation is a unique circulation in which the systemic venous blood and pulmonary venous blood mix. Thus, the systemic arterial saturation becomes a weighted average of the systemic venous and pulmonary venous saturation with the weights of each being dictated by the relative amount of pulmonary and systemic blood flow. The systemic and pulmonary blood flow have a unique relationship in that cardiac output is the sum of these two individual flows and a change in either must be met by a change of equal magnitude but opposite direction in the other circulation if total cardiac output remains constant. This delicate balance of saturations and flows between the pulmonary and systemic circulations puts children with parallel circulation at greater risk of experiencing inadequacy of systemic oxygen delivery.[1] The findings of this study seem to demonstrate that increased systemic oxygen delivery seems to largely be mediated by increase in systemic blood flow and decreased systemic vascular resistance.

A growing body of data has helped lend valuable insight into the factors that help mediate this balance and subsequently decrease the risk of morbidity and mortality, particularly in parallel circulation.[14,29–70] The current data add to the present data with the benefit of high temporal resolution of collected data. This is particularly beneficial in characterising the associations with changes in vasoactive medication doses. Data regarding dose-dependent changes in haemodynamics in the setting of CHD is lacking, nonetheless in the setting of parallel circulation.[46,71,72] Characterisation of vasoactive support has largely been done based on the vasoactive-inotrope score which assigns relatively arbitrary coefficients to the dosage of vasoactive medications to result in a score which has subsequently been demonstrated to correlate with morbidity and mortality. This more vasoactive support worse outcome approach doesn't directly reflect haemodynamic changes. A scoring system in which coefficients are based on haemodynamic changes associated with vasoactive medications could be much more telling and have a more pragmatic impact on bedside vasoactive titration.

The adequacy of systemic oxygen delivery represents the relative balance between oxygen delivery and oxygen consumption.[73] Systemic oxygen delivery is the product of cardiac output and oxygen content. Cardiac output further breaks down into the quotient of oxygen consumption and the arteriovenous oxygen content difference, while oxygen content is a function of haemoglobin, arterial saturation, and partial pressure of oxygen.[74,75] With this in mind, it becomes apparent why conventionally monitored haemodynamic parameters may not reflect systemic oxygen delivery as they do not actually directly influence them.[9,20] Additionally, monitored pressures are a product of flow and resistance and resistance cannot be quantified in any meaningful way, nonetheless on a second-to-second base. Thus, whether a change in arterial pressure, for instance, is due to an increase in cardiac output or system vascular resistance cannot be easily delineated. This, however, is of utmost importance if arterial pressure is to be used to guide clinical care as increased blood pressure driven by increased cardiac output may help improve systemic oxygen delivery while increased blood pressure driven by increased systemic vascular resistance may actually decrease systemic oxygen delivery.

The current data serve as a proof of concept that high fidelity haemodynamic monitoring tools such as T3 can be used to help more clearly characterise the effects of various clinical factors, including vasoactive medications in vivo. This is important as much of the current understanding of such effects vastly originates from ex vivo studies or animal studies. Ex vivo studies lack the ability to replicate in vivo feedback mechanism while animal studies may not be generalisable to humans due to differences between species. Even human in vivo data from specific subsets of patients may not be generalisable to all humans. But leveraging large, high fidelity sets from multiple institutions in a manner done in the current study may help characterise in vivo effects of vasoactive medications in specific patient populations.

The novel application of high-fidelity haemodynamic data is one strength of this study. Additionally, factors such as vasoactive medication doses and fluid balance which aren't captured by the T3 system were manually collected in high fidelity to be combined with the T3 dataset, allowing for additional insight. The characterisation of effects was done at a time point level, which led to a robust sample size of underlying data. Additionally, the use of baseline values with subsequent time points allowed for some characterisation of the effect of time with the principles of causal-mediated analysis. Additionally, the high temporal resolution of data further sides to this. The incorporation of fluid balance, airway pressures, multiple haemodynamic variables, and multiple vasoactive medications help make the variable specific effect estimates more convincing. The use of Bayesian statistics is also a strength of this study as it allowed for quantifying the probabilities of the dependent and independent variables as well as allowed for comparison of multiple models to help determine which model was most helpful. The high probability of the data being explained by the top two models and the high degree of similarity between these two models (second most probable model included all the same instrument variables as the most likely and included the addition of only a single variable) speak to the strength of the resulting models. The selection of a very specific patient population may have also contributed to the ability for models to be quite predictive.

The study is not without its limitations. Some vasoactive medications, specifically nicardipine, could not be well characterised due to the relatively short duration they were utilised during the study period. As this is a single centre study generalisability may be limited. For instance, centres who utilise routine postoperative alpha blockade or differing cardiopulmonary bypass strategies may see slightly different effects of specific vasoactive medications. The overall physiologic implications should be less variable. The local practice of using specific vasoactive medications also affects the generalisation of this data. For instance, the institution in the current study does not utilise norepinephrine or nicardipine as much as other centres may and may utilise dopamine more often than other centres may. Additionally, cerebral near infrared spectroscopy data were not available during this monitoring period for technical reasons.

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Conclusion

In children with parallel circulation immediately following the Norwood operation, increased milrinone, increased epinephrine, mean arterial pressure, and systemic blood flow were associated with decreased (improved) renal oxygen extraction, while increased mean airway pressure, central venous pressure, arterial saturation by pulse oximetry, and systemic vascular resistance were associated with increased (worsened) renal oxygen extraction.

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Author contribution. RSL, SF and EGV contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JW and RSL. The first draft of the manuscript was written by JSF and JW. SF and EGV commented on previous versions of the manuscript. All authors read and approved the final manuscript. Reviewing and editing was done by EGV.

Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of human rights. The study have been approved by the appropriate institutional ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Data transparency. All data and materials, as well as software application, support our published claims and comply with field standards.

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