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Trajectory of physiologic indices in the cardiac intensive care unit after flow restrictor placement in functionally univentricular multidistributive circulation: hypothesis generation using high-fidelity data

Jeremy Fox
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Alan Nugent
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Conor P. O'Halloran
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Neil D. Patel
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Wesam Sourour
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Aadi Rao
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Aarnav Shah
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Daniel Critchfield
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Jordan Griffiths
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine
Rohit S. Loomba
loomba.rohit@gmail.com

Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine

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Table 1 is available in the Supplementary Files section.

Trajectory of physiologic indices in the cardiac intensive care unit after flow restrictor placement in functionally univentricular multidistributive circulation: hypothesis generation using high-fidelity data

Jeremy Fox, MD, Alan Nugent, MD, Conor P. O'Halloran, MD, Neil D. Patel, MD, Wesam Sourour, MD, Aadi Rao, BS, Aarnav Shah, BS, Daniel Critchfield, MD, Jordan Griffiths, MD, Rohit S. Loomba, MD

Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Background

Transcatheter pulmonary flow restrictors are increasingly used to limit pulmonary overcirculation in infants with functionally univentricular multidistributive circulation, but post-procedural physiology remains poorly characterized. This study evaluated cardiovascular and oximetric trajectories during the first 48 hours after cardiac intensive care unit admission following flow restrictor placement.

Methods

Eight patients were retrospectively studied using high-fidelity physiologic data. Fifteen measured and derived indices were evaluated, including heart rate, arterial pressures, central venous pressure, pulse oximetry saturation, cerebral and renal oxygen extraction, indexed systemic and pulmonary blood flow, pulmonary-to-systemic blood flow ratio, indexed systemic vascular resistance, mean circulatory filling pressure, and venous resistance. Mixed-effects models incorporated time as a natural cubic spline with 4 degrees of freedom, vasoactive-inotrope score, patient-level random intercepts, and autoregressive residual correlation. Sensitivity analyses separately adjusted for hemoglobin and body surface area.

Results

Heart rate increased significantly over 48 hours, from a modeled 132.6 to 155.5 beats/min ($p<0.01$). Central venous pressure increased from 8.74 to 11.39 mmHg ($p<0.01$), while indexed systemic vascular resistance decreased from 19.43 to 15.16 Wood units·m^2 ($p<0.01$). Cerebral oxygen extraction demonstrated a significant nonlinear trajectory in both sensitivity analyses, while mean circulatory filling pressure became significant after body surface area adjustment. Indexed systemic flow, indexed pulmonary flow, and pulmonary-to-systemic flow ratio did not significantly change.

Conclusion

Post-flow-restrictor physiology remained dynamic over 48 hours despite relative stability in pulmonary-systemic flow balance. Changes were most apparent in systemic vascular resistance, venous pressures, heart rate, and regional oxygen extraction, identifying candidate physiologic targets for future multicenter validation.

Introduction

Patients with functionally univentricular multidistributive circulation and excessive pulmonary blood flow represent a particularly challenging population in the cardiac intensive care unit. Preferential distribution of cardiac output toward the pulmonary circulation can limit systemic blood flow and consequently systemic oxygen delivery, contributing to end-organ dysfunction and clinical instability. Control of pulmonary blood flow is therefore an important component of initial palliation. While surgical pulmonary artery banding or more extensive surgical palliation may accomplish this goal, some patients have significant comorbidities, low body weight, prematurity, or other clinical features that increase the risk of early surgery. For these patients, a less invasive strategy capable of restricting pulmonary blood flow while allowing somatic growth and clinical stabilization may be advantageous.

Transcatheter pulmonary flow restrictors have emerged as an alternative means of controlling pulmonary blood flow in neonates and infants with congenital heart disease. Modified microvascular plugs and related devices can be positioned within the branch pulmonary arteries to increase resistance to pulmonary blood flow without surgical pulmonary artery banding [1–3]. Early pediatric experience has demonstrated reductions in systemic oxygen saturation and pulmonary-to-systemic blood flow ratio following placement, consistent with restriction of pulmonary blood flow [3–5]. Subsequent studies have demonstrated the feasibility of using this strategy as a bridge to later surgical palliation, repair, or transplantation, with persistence of pulmonary flow restriction at subsequent catheterization [4–7]. Complications of pulmonary flow restrictors have been reported, including inadequate or excessive restriction, device migration or embolization, and the need for repeat catheter-based or surgical intervention. Pulmonary artery injury, including residual stenosis requiring arterioplasty and rare aneurysmal dilation requiring urgent surgical repair, has also been described, underscoring the importance of appropriate device sizing, titration, and surveillance [4, 7–11].

Available physiologic data, however, have focused predominantly on immediate procedural changes, isolated catheterization measurements, or averaged values before and after implantation. The evolution of cardiovascular physiology during the early post-procedural intensive care period remains incompletely characterized although a recent study did describe the immediate physiologic changes in the catheterization laboratory [12].

The present study sought to characterize physiologic changes during the first 48 hours following cardiac intensive care unit admission after pulmonary flow-restrictor placement in patients with functionally univentricular multidistributive circulation. High-fidelity physiologic data were used to evaluate continuous trajectories in arterial, oximetric, systemic and pulmonary flow, vascular resistance, and venous hemodynamic indices. This approach was intended to define the post-procedural physiologic state and identify patterns of cardiovascular adaptation that may not be apparent from conventional intermittent measurements.

Methods

Study design

This retrospective observational study evaluated physiologic trajectories during the first 48 hours following cardiac intensive care unit admission after catheter-based flow-restrictor placement in patients with functionally univentricular multidistributive circulation. High-fidelity physiologic data were obtained from Sickbay platform (Medical Informatics Corporation, Houston, Tx). This is a software platform that aggregates data from various bedside monitoring devices at their native resolution to facilitate centralized viewing and storage with high temporal resolution. Data are stored with 1-second resolution. Relative time zero was defined as arrival to the cardiac intensive care unit following flow-reducer placement in the cardiac catheterization laboratory. Accordingly, the analysis was designed to characterize the evolution and persistence of the post-intervention physiologic state rather than the immediate change from before to after flow-reducer placement.

The observation period extended continuously from cardiac intensive care unit admission through 48 hours. Raw physiologic signals were aggregated to patient-specific one-minute medians to standardize temporal resolution across patients and prevent differences in source sampling frequency from disproportionately weighting individual patients. Derived physiologic indices were calculated from these one-minute data. For inferential analyses, one-minute values were subsequently aggregated to hourly medians.

Institutional review board approval was obtained for the study. The investigation was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Identification

Patients with functionally univentricular multidistributive circulation who underwent catheter-based pulmonary flow-reducer placement and had high-fidelity physiologic data available following admission to the cardiac intensive care unit were retrospectively identified between January 1, 2022 and June 1, 2026. Patients supported with mechanical circulatory support at any point during the 48-hour observation period were excluded.

Missing physiologic data predominantly reflected absence of the corresponding monitoring modality rather than intermittent missing observations. When a specific monitoring modality was not clinically present for a patient, data for that physiologic index were absent throughout the observation period for that patient. Because these data were structurally missing and could not be reliably reconstructed from other measured variables, missing physiologic values were not imputed. Patients without available data for a given physiologic index were excluded only from analyses of that specific index and remained eligible for analyses of all other available physiologic variables.

Variables of Interest

Measured physiologic indices included heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, central venous pressure, and pulse oximetry saturation. Pulse pressure was calculated as systolic minus diastolic blood pressure.

Cerebral oxygen extraction ratio was calculated as (pulse oximetry saturation − cerebral near-infrared spectroscopy saturation) / pulse oximetry saturation, and renal oxygen extraction ratio was calculated as (pulse oximetry saturation − renal near-infrared spectroscopy saturation) / pulse oximetry saturation.

Indexed systemic and pulmonary blood flow were estimated using the Fick principle. Oxygen consumption index was estimated using the Seckeler equation incorporating age, weight, functionally univentricular circulation, and critical illness. Patient-specific hemoglobin concentration was used to calculate oxygen content. For systemic blood flow, pulse oximetry saturation was used as systemic arterial saturation and renal near-infrared spectroscopy saturation as a surrogate of systemic venous saturation. Indexed systemic blood flow was calculated by dividing estimated oxygen consumption index by the systemic arteriovenous oxygen-content difference.

For indexed pulmonary blood flow, pulmonary venous oxygen saturation was assumed to be 100%, while pulse oximetry saturation was used as pulmonary arterial saturation. Pulmonary-to-systemic blood flow ratio was calculated as indexed pulmonary blood flow divided by indexed systemic blood flow.

Indexed systemic vascular resistance was calculated as (mean arterial pressure − central venous pressure) / indexed systemic blood flow. Absolute systemic blood flow was calculated as indexed systemic blood flow multiplied by body surface area. Mean circulatory filling pressure was estimated as 0.96 × central venous pressure + 0.04 × mean arterial pressure + 0.02 × absolute systemic blood flow. Venous resistance was calculated as absolute systemic vascular resistance × mean circulatory filling pressure / mean arterial pressure.

The prespecified physiologic indices included heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, central venous pressure, pulse oximetry saturation, cerebral oxygen extraction ratio, renal oxygen extraction ratio, indexed systemic blood flow, indexed pulmonary blood flow, pulmonary-to-systemic blood flow ratio, indexed systemic vascular resistance, mean circulatory filling pressure, and venous resistance.

Statistical Analyses

Each physiologic index was modeled using a mixed-effects regression model in which time was represented by a natural cubic spline with 4 degrees of freedom and fixed boundaries at 0 and 48 hours. Absolute physiologic values were analyzed.

The primary model included spline-transformed time and vasoactive-inotrope score as fixed effects along with a patient-specific random intercept. Vasoactive-inotrope score and other patient-level covariates were centered and standardized prior to modeling. The primary inferential test was a joint 4-degree-of-freedom Wald test of the spline terms,

representing the global association between time and each variable across the 48-hour period. Individual spline coefficients were not interpreted.

Analyses were performed using all available data for each physiologic index. Because absence of a monitoring modality resulted in complete absence of that index for the affected patient, the number of patients contributing to individual models varied according to availability of the required source signals. No imputation was performed for these structurally missing data.

Four prespecified sensitivity analyses were performed. The first added hemoglobin concentration to the primary model, the second separately added body surface area, the third added sedation infusions, and the fourth added fluid balance in ml. Hemoglobin and body surface area were not entered simultaneously to reduce model complexity and collinearity. Model collinearity and numerical stability were assessed using patient-level predictor correlations, variance inflation factors where applicable, and design-matrix condition numbers.

Model-derived trajectories and 95% confidence intervals were generated across 0 to 48 hours. Modeled values at cardiac intensive care unit admission and 48 hours were reported to describe the direction and magnitude of change. Model outputs included regression coefficients, standard errors, confidence intervals, global time-effect p-values, likelihood-based fit statistics, residual error measures, and convergence diagnostics. Primary global time-effect p-values were corrected across the 15 prespecified physiologic indices using the Benjamini-Hochberg false discovery rate procedure. Statistical significance was defined as a two-sided p-value less than 0.05.

All data processing, physiologic calculations, visualization, and statistical analyses were performed using Python version 3.13.5. Principal libraries included pandas version 2.2.3 and NumPy version 2.3.5 for data manipulation and numerical computation, SciPy version 1.17.0 for statistical estimation and optimization, Patsy version 1.0.2 for construction of natural cubic spline design matrices, and Matplotlib version 3.10.8 for visualization.

Results

Cohort Characteristics

Eight patients with functionally univentricular multidistributive circulation underwent pulmonary flow-reducer placement and were included in the analysis. The median age at flow-reducer placement was 3.5 days (interquartile range, 2.0 to 4.8 days), with a range of 2 to 71 days. Median weight was 3.09 kg (interquartile range, 2.63 to 3.42 kg), median height was 47.3 cm (interquartile range, 45.8 to 49.3 cm), and median body surface area was 0.20 m^2 (interquartile range, 0.18 to 0.21 m^2). Median hemoglobin concentration was 14.7 g/dL (interquartile range, 12.9 to 15.3 g/dL), and median vasoactive-inotrope score was 4 (interquartile range, 0 to 5.2). Cardiac diagnoses included hypoplastic left heart syndrome in four patients, double outlet right ventricle in two, atrioventricular septal defect in one, and double inlet left ventricle in one.

Availability of individual physiologic signals varied according to the monitoring modalities present during the 48-hour observation period. All eight patients contributed heart rate, pulse oximetry, and blood pressure data, seven contributed central venous pressure data, and six contributed near infrared spectroscopy data.

Primary Analyses
Heart rate demonstrated a significant nonlinear trajectory over the 48-hour period (global $p<0.01$; false discovery rate-adjusted $q<0.01$). The modeled heart rate increased from 132.6 beats/min at cardiac intensive care unit admission to 155.5 beats/min at 48 hours, an increase of 22.9 beats/min or 17.3%. Heart rate reached a modeled maximum of 156.5 beats/min at approximately 25 hours and remained elevated through 48 hours.

Central venous pressure also demonstrated a significant trajectory over time (global $p<0.01$; $q=0.01$). Modeled central venous pressure increased from 8.74 mmHg at admission to 11.39 mmHg at 48 hours, corresponding to an increase of 2.65 mmHg or 30.3%. Central venous pressure reached a modeled maximum of 12.14 mmHg at approximately 29 hours before declining modestly thereafter.

Indexed systemic vascular resistance demonstrated a significant nonlinear trajectory (global $p<0.01$; $q=0.02$). The modeled value decreased from 19.43 Wood units·m^2 at admission to a nadir of 10.30 Wood units·m^2 at approximately 15 hours, followed by partial recovery to 15.16 Wood units·m^2 at 48 hours. The modeled 48-hour value remained 4.27 Wood units·m^2, or 22.0%, lower than the admission value.

No statistically significant overall trajectories were identified for systolic blood pressure ($p=0.28$), diastolic blood pressure ($p=0.31$), mean arterial pressure ($p=0.18$), pulse pressure ($p=0.12$), or pulse oximetry saturation ($p=0.13$). At 48 hours, modeled systolic blood pressure was 7.35 mmHg lower than at admission, pulse pressure was 5.23 mmHg lower, and pulse oximetry saturation was 2.87 percentage points lower; however, the overall nonlinear trajectories for these indices did not reach statistical significance.

Cerebral oxygen extraction demonstrated an early decrease, reaching a modeled nadir of 0.206 at approximately 23 hours from an admission value of 0.276, followed by an increase later in the observation period. The overall trajectory approached but did not reach statistical significance in the primary model ($p=0.07$; $q=0.23$). Renal oxygen extraction did not demonstrate a significant trajectory ($p=0.77$).

Neither indexed systemic blood flow nor indexed pulmonary blood flow demonstrated a significant overall trajectory ($p=0.82$ and $p=0.58$, respectively). Modeled indexed systemic blood flow decreased from 4.10 to 3.15 L/min/m^2 between admission and 48 hours, while indexed pulmonary blood flow decreased from 7.23 to 5.78 L/min/m^2. The pulmonary-to-systemic blood flow ratio decreased from a modeled value of 3.27 at admission to a nadir of approximately 2.22 at 36.5 hours, followed by partial recovery, but the overall trajectory

was not significant (p=0.65). Mean circulatory filling pressure increased from 13.72 to 15.81 mmHg and approached statistical significance (p=0.08), while venous resistance decreased from 22.31 to 18.81 Wood units without a significant overall trajectory (p=0.40).

Findings of the primary analyses are summarized in table 1. Modeled trajectories of heart rate, pulse oximetry, cerebral oxygen extraction, renal oxygen extraction, systemic blood flow, pulmonary to systemic blood flow ratio, indexed systemic vascular resistance, and mean circulatory filling pressure are demonstrated in figure 1.

Hemoglobin Sensitivity Analyses
Addition of hemoglobin concentration to the primary models did not materially alter the principal findings. Heart rate (p<0.01), central venous pressure (p<0.01), and indexed systemic vascular resistance (p<0.01) continued to demonstrate significant 48-hour trajectories. Systolic blood pressure (p=0.28), diastolic blood pressure (p=0.23), mean arterial pressure (p=0.13), pulse pressure (p=0.12), pulse oximetry saturation (p=0.13), renal oxygen extraction (p=0.75), indexed systemic blood flow (p=0.76), indexed pulmonary blood flow (p=0.58), pulmonary-to-systemic blood flow ratio (p=0.63), mean circulatory filling pressure (p=0.08), and venous resistance (p=0.38) remained nonsignificant.

The cerebral oxygen extraction trajectory reached statistical significance after adjustment for hemoglobin concentration (p=0.04), compared with p=0.07 in the primary analysis.

Body Surface Area Sensitivity Analyses
Addition of body surface area similarly preserved the principal findings. Significant trajectories remained present for heart rate (p<0.01), central venous pressure (p<0.01), and indexed systemic vascular resistance (p<0.01). Systolic blood pressure (p=0.28), diastolic blood pressure (p=0.23), mean arterial pressure (p=0.11), pulse pressure (p=0.12), pulse oximetry saturation (p=0.13), renal oxygen extraction (p=0.72), indexed systemic blood flow (p=0.75), indexed pulmonary blood flow (p=0.58), pulmonary-to-systemic blood flow ratio (p=0.65), and venous resistance (p=0.30) remained nonsignificant.

As in the hemoglobin sensitivity analysis, cerebral oxygen extraction demonstrated a significant trajectory after adjustment for body surface area (p=0.04). Mean circulatory filling pressure also reached statistical significance in the body surface area sensitivity model (p=0.04).

Sedation and fluid balance sensitivity analyses
Addition of sedation infusion doses or fluid balance similarly preserved the principal findings. Significant trajectories remained present for heart rate, central venous pressure, indexed systemic vascular resistance, and mean circulatory filling pressure.

Discussion
The present study characterizes cardiovascular physiology over the first 48 hours following cardiac intensive care unit admission after pulmonary flow-reducer placement in patients

with functionally univentricular multidistributive circulation. Heart rate increased significantly during this period, central venous pressure increased, and indexed systemic vascular resistance decreased. Cerebral oxygen extraction demonstrated a significant nonlinear trajectory in the hemoglobin- and body surface area-adjusted sensitivity analyses, characterized by an early decrease followed by recovery, while mean circulatory filling pressure increased significantly in the body surface area-adjusted sensitivity analysis. In contrast, indexed systemic blood flow, indexed pulmonary blood flow, and pulmonary-to-systemic blood flow ratio did not demonstrate significant trajectories. Thus, the principal finding is not continued redistribution of pulmonary and systemic blood flow during the 48 hours following cardiac intensive care unit admission, but rather continued evolution of systemic vascular and venous physiology within a relatively stable post-flow-restrictor circulatory state.

These findings are physiologically plausible in the context of functionally univentricular multidistributive circulation. Pulmonary flow restrictors increase pulmonary resistance to limit blood flow. Importantly, the present data begin after completion of the catheterization procedure. Any immediate redistribution of flow caused by device deployment therefore occurred before the first measurements included in this analysis. The absence of significant subsequent trajectories in indexed pulmonary blood flow, indexed systemic blood flow, or pulmonary-to-systemic blood flow ratio should not be interpreted as an absence of device effect. Rather, these findings suggest that the pulmonary-to-systemic flow relationship present upon arrival to the cardiac intensive care unit remained relatively stable throughout the subsequent 48 hours. The numerical decrease in pulmonary-to-systemic blood flow ratio from 3.2 at admission to 2.7 near the end of the observation period, with an intermediate nadir near 2.2, is consistent with persistence of pulmonary flow restriction without evidence of continued progressive redistribution.

The accompanying systemic and venous changes suggest that the circulation continues to adapt after the initial mechanical redistribution of flow. Indexed systemic vascular resistance decreased markedly early and, despite partial recovery, remained approximately 22% lower at 48 hours than at admission. Heart rate increased by approximately 17%, while central venous pressure increased by approximately 30%. This may have been the result of other clinical changes such as decreasing sedation and increasing diuresis. Mean circulatory filling pressure increased by approximately 15% and demonstrated a significant trajectory after adjustment for body surface area, whereas venous resistance did not significantly change. Together, the rise in central venous pressure and mean circulatory filling pressure without a corresponding increase in venous resistance may be more consistent with an increase in stressed venous volume or alteration in venous capacitance than with increasing resistance to venous return. Cerebral oxygen extraction demonstrated a different pattern, decreasing during the first approximately 23 hours before subsequently recovering. This may represent a transient improvement in the relationship between cerebral oxygen delivery and oxygen consumption rather than a sustained change in oxygen extraction. Prior high-fidelity studies in children after the Norwood operation have similarly demonstrated that regional

oxygen extraction reflects interactions among systemic blood flow, systemic vascular resistance, central venous pressure, and vasoactive support and cannot be inferred from arterial pressure alone [13–16].

The pediatric experience with catheter-based pulmonary flow restriction has evolved rapidly. Early reports demonstrated that pulmonary blood flow could be restricted using catheter-based devices or intraluminal techniques, while subsequent preclinical work established the modified microvascular plug as a low-profile, implantable and retrievable pulmonary artery flow restrictor [1, 17, 18]. This was followed by early clinical application of bilateral pulmonary flow restriction as part of a transcatheter stage I strategy for neonates with hypoplastic left heart syndrome and related lesions [2, 5, 19–22]. These initial experiences demonstrated feasibility but also considerable variability in the achieved physiologic effect. Nageotte and colleagues, for example, reported persistent pulmonary overcirculation in several patients despite apparently successful implantation, emphasizing that device deployment alone does not ensure adequate restriction [5]. In contrast, immediate improvement in systemic diastolic pressure has been described following effective restriction in selected patients, consistent with rapid redistribution of ventricular output away from the pulmonary circulation [21]. The absence of a significant diastolic or mean arterial pressure trajectory in the present study does not necessarily differ from these acute observations, as our analysis began only after patients had reached the cardiac intensive care unit. Flow-reducer technology has subsequently been applied across an increasingly broad pediatric population, including patients with existing systemic-to-pulmonary shunts, major aortopulmonary collateral arteries, cardiomyopathy, complex outflow tract anatomy, low birth weight, and patients being bridged to cardiac transplantation [23–35].

The larger pediatric series provide additional insight into the magnitude and persistence of pulmonary flow restriction. Haddad and colleagues demonstrated an immediate reduction in median pulmonary-to-systemic blood flow ratio from approximately 3.1 to 1.3, accompanied by a reduction in systemic oxygen saturation from approximately 97% to 84%, with systemic saturation remaining approximately 90% 48 hours later [36]. Subsequent evaluation of surgically explanted devices from this experience demonstrated that flow restrictors could be incorporated into the pulmonary arteries while generally permitting later surgical reconstruction, although device-related distortion and the technical consequences of prolonged implantation remain relevant [36]. Warren and colleagues similarly demonstrated an immediate reduction in systemic oxygen saturation from approximately 95% to 84% following pulmonary flow restriction, with subsequent catheterization generally demonstrating favorable pulmonary vascular resistance and transpulmonary gradients [4]. These immediate reductions in pulmonary blood flow and systemic oxygen saturation are compatible with the present finding that pulmonary-to-systemic blood flow ratio did not subsequently increase during the first 48 hours after cardiac intensive care unit admission. Sperotto and colleagues demonstrated persistence of this physiology at later catheterization, with a median pulmonary-to-systemic blood flow ratio of approximately 1.2 at a median of 2.3 months after implantation [6]. Experimental

and clinical investigations have nevertheless demonstrated that achieved restriction is sensitive to device geometry, fenestration size, vessel size, and device-vessel interaction, providing a mechanistic explanation for variation in pulmonary blood flow between patients [37]. More recent multicenter and larger institutional experiences have reinforced both the feasibility of this strategy and the variability in the degree of pulmonary restriction achieved [7]. The relatively elevated pulmonary-to-systemic blood flow ratios in the present cohort therefore do not necessarily indicate loss of device effect; importantly, these ratios remained relatively stable rather than progressively increasing over the subsequent 48 hours.

Recent pediatric studies examining physiology surrounding flow-reducer placement are particularly relevant to the present findings. Hussey and colleagues evaluated the sequential deployment of bilateral pulmonary flow restrictors in neonates and infants and demonstrated an immediate reduction in systemic oxygen saturation, an increase in mean arterial pressure, and a decrease in heart rate following implantation [38]. The direction of the heart-rate response differs from the subsequent increase observed in the present study, but the two analyses describe different phases of physiology. The former reflects the acute intraprocedural response to pulmonary flow restriction, while the present analysis begins after completion of the catheterization and follows subsequent adaptation over 48 hours. Reynolds and colleagues similarly demonstrated improvement in hemodynamic and metabolic indices after internal pulmonary flow restriction, supporting the concept that a substantial component of the desired physiologic redistribution occurs immediately following implantation [8]. Most directly comparable to the present study, Tran and colleagues examined systemic oxygen saturation and renal near-infrared spectroscopy during 48-hour periods before and after pulmonary flow-reducer implantation. Responses were heterogeneous, although systemic oxygen saturation frequently decreased while renal near-infrared spectroscopy increased, and higher renal near-infrared spectroscopy values were associated with survival to surgery [8]. The lack of a significant renal oxygen-extraction trajectory in the present study is consistent with this reported heterogeneity, while the early change in cerebral oxygen extraction suggests that regional responses may differ between organ beds. Published reviews of the evolving pediatric experience similarly emphasize that assessment of flow-reducer efficacy requires evaluation of physiology rather than technical implantation alone and that the optimal degree of restriction remains incompletely defined [39, 40]. Taken together, the existing literature and the present findings support a sequence in which pulmonary flow restrictors produce an immediate redistribution of pulmonary and systemic flow, followed by a period in which that flow relationship is relatively maintained while systemic vascular tone, venous loading conditions, heart rate, and regional oxygen extraction continue to evolve.

The present study adds several elements not addressed in previous pediatric pulmonary flow-restrictor studies. Most published reports have focused on procedural feasibility, immediate changes in systemic oxygen saturation or pulmonary-to-systemic blood flow ratio, discrete catheterization measurements, or clinical outcomes at subsequent surgery. The present analysis evaluates continuous 48-hour trajectories and, to our knowledge,

examines the broadest collection of physiologic indices reported following pulmonary flow-reducer placement. In addition to heart rate, arterial pressure, central venous pressure, and systemic oxygen saturation, the analysis incorporates cerebral and renal oxygen extraction, indexed systemic and pulmonary blood flow, pulmonary-to-systemic blood flow ratio, indexed systemic vascular resistance, mean circulatory filling pressure, and venous resistance. Importantly, this extends evaluation into the venous circulation, which has been largely absent from the published flow-reducer literature. Evaluating central venous pressure together with mean circulatory filling pressure and venous resistance allows changes in venous loading conditions to be distinguished, at least conceptually, from changes in resistance to venous return. The use of high-fidelity data also permits the shape and timing of physiologic change to be characterized rather than reducing the post-procedural period to isolated measurements or broad period averages. Previous high-fidelity studies in functionally univentricular circulation have demonstrated the value of this approach for characterizing oxygen extraction and organ-specific physiology across large numbers of longitudinal observations [13, 14, 41].

These findings should be interpreted as hypothesis generating. The principal limitation is the small number of patients, particularly for derived indices requiring simultaneous availability of several monitoring modalities. Dense longitudinal sampling provides a very large number of physiologic observations and consequently allows within-patient trajectories to be well characterized and provides substantial statistical power for identifying temporal change. This does not, however, increase the number of independent patients, and the small cohort therefore remains the principal limitation to clinical generalizability. Missing data were predominantly structural because individual monitoring modalities were not present in all patients, resulting in complete absence of those indices for affected patients rather than sporadic missing measurements. Time zero represented cardiac intensive care unit admission rather than device deployment, precluding assessment of the immediate pre- to post-procedural response and limiting causal attribution of subsequent changes specifically to the flow restrictors. A prospective multicenter study incorporating standardized monitoring, measurements before and immediately after device deployment, serial high-fidelity data, device and fenestration characteristics, and invasive hemodynamic validation would therefore be valuable. The present findings can help inform such a study by identifying heart rate, systemic vascular resistance, central venous pressure, mean circulatory filling pressure, and regional oxygen extraction as candidate physiologic signals and by demonstrating that pulmonary-to-systemic flow balance should be evaluated separately from the systemic and venous adaptations occurring during the subsequent 48 hours.

Conclusion

Pulmonary flow restrictor placement was followed by continued changes in systemic vascular resistance and venous physiology over the first 48 hours after cardiac intensive care unit admission. In contrast, indexed systemic blood flow, indexed pulmonary blood flow, and pulmonary-to-systemic blood flow ratio did not significantly change during this period. These findings suggest that the principal effects of flow restrictors on pulmonary

and systemic blood flow occur shortly after placement, with subsequent physiologic adaptation occurring predominantly in the systemic vascular and venous circulations.

Figure legends

Figure 1. Modeled trajectories over time for key physiologic indices. Median and 95% confidence interval are demonstrated in each plot.

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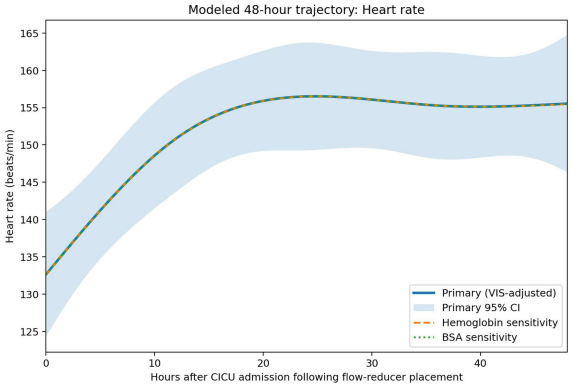
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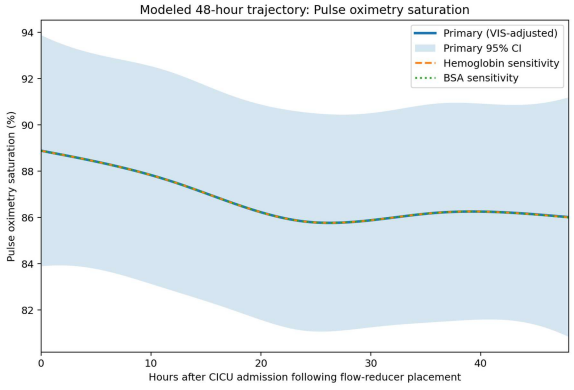
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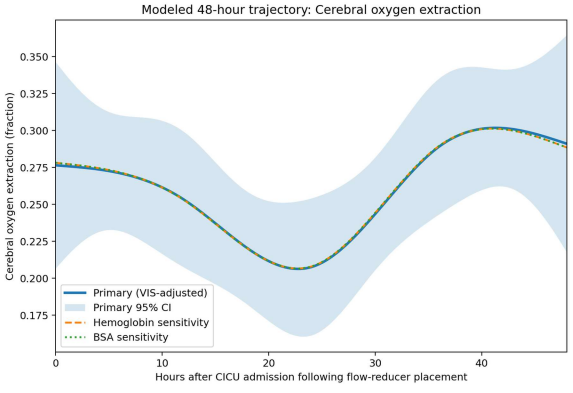
A


Modeled 48-hour trajectory: Heart rate
Heart rate (beats/min)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

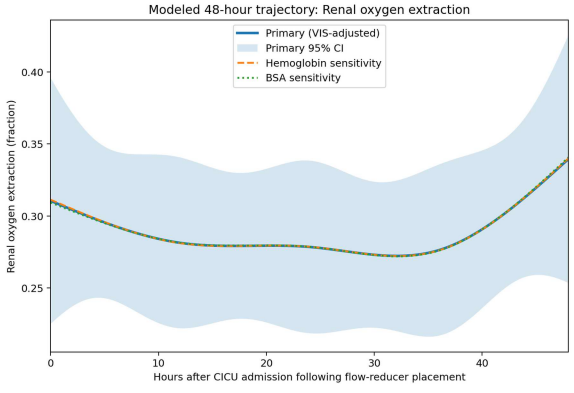
B


Modeled 48-hour trajectory: Pulse oximetry saturation
Pulse oximetry saturation (%)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

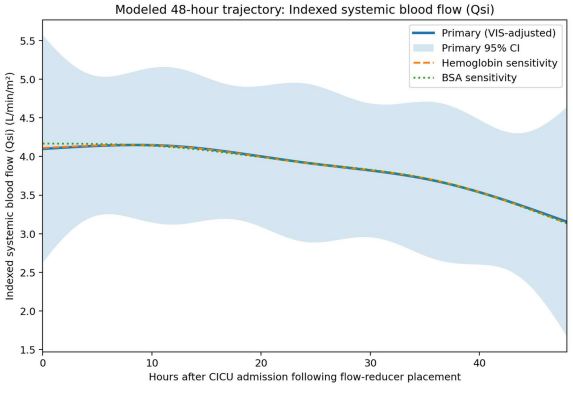
C


Modeled 48-hour trajectory: Cerebral oxygen extraction
Cerebral oxygen extraction (fraction)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

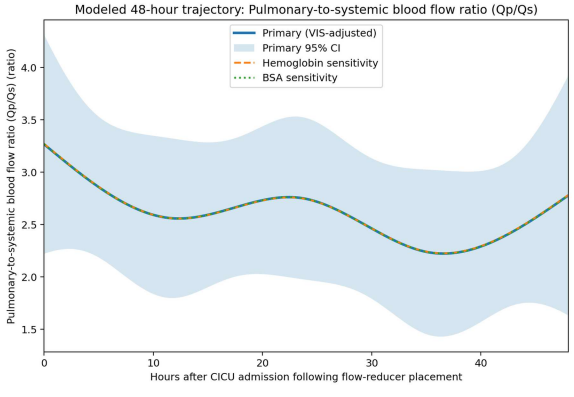
D


Modeled 48-hour trajectory: Renal oxygen extraction
Renal oxygen extraction (fraction)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

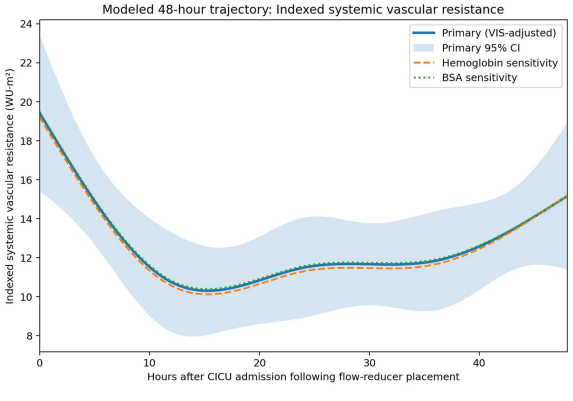
E


Modeled 48-hour trajectory: Indexed systemic blood flow (Qsi)
Indexed systemic blood flow (Qsi) (L/min/m²)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

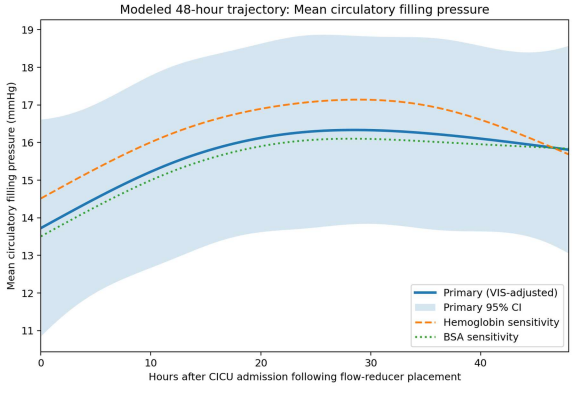
F


Modeled 48-hour trajectory: Pulmonary-to-systemic blood flow ratio (Qp/Qs)
Pulmonary-to-systemic blood flow ratio (Qp/Qs) (ratio)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

G


Modeled 48-hour trajectory: Indexed systemic vascular resistance
Indexed systemic vascular resistance (WU·m²)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

H


Modeled 48-hour trajectory: Mean circulatory filling pressure
Mean circulatory filling pressure (mmHg)
Hours after CICU admission following flow-reducer placement
Primary (VIS-adjusted)
Primary 95% CI
Hemoglobin sensitivity
BSA sensitivity

Supplementary Files

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- table1.docx