Acute effects of vasoactive medications in patients with parallel circulation awaiting hybrid or Norwood procedure

Emily Hendon[1], Jennifer Kane[1], Gina M. Golem[1], Amanda McBroom[1], Saul Flores[2,3], Joshua Wong[1], Enrique G. Villarreal[4], Rohit S. Loomba[1,5]

[1]Pediatric Cardiology, Advocate Children's Hospital, Chicago, IL, USA, [2]Section of Critical Care Medicine, Department of Pediatrics, Texas Children's Hospital, Houston, TX, USA, [3]Department of Pediatics, Baylor College of Medicine, Houston, TX, USA, [4]Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo Leon, Mexico, [5]Department of Pediatrics, Chicago Medical School/ Rosalind Franklin University of Medicine and Science, Chicago, IL, USA

ABSTRACT

Background	:	Vasoactive medications are frequently used in the preoperative stage to balance the pulmonary and systemic blood flow. However, not much is known about the effects of these agents during this stage.
Aims	:	The primary objective of this study was to characterize the acute effects of vasoactive medications in children with parallel circulation before either the hybrid or Norwood procedure.
Setting and Designs	:	This is a single-center, cross-sectional, retrospective study.
Methods	:	Hemodynamic and systemic oxygen delivery data were captured from patients' vital signs, arterial blood gases, near-infrared spectroscopy monitoring (NIRS). Data for each patient were collected before the initiation of a vasoactive medication and again 6 h after.
Statistical Analysis	:	Data were analyzed using paired *t*-tests, and analysis of covariance.
Results	:	A total of 139 patients were identified. After data extraction the following patients were included before the initial intervention: 7 were on milrinone, 22 were on dopamine, and 17 were on dobutamine. Dopamine and dobutamine were found to significantly increase systolic blood pressure. Only dopamine increased pH (mean difference 0.04), decreased paCO2 (mean difference −7.1), decreased lactate (mean difference −0.6 mmol/L), and decreased in bedside Qp: Qs (mean difference −7.5) after continuous infusion for 6 h. Milrinone was not associated with any significant hemodynamic change.

Access this article online

Quick Response Code:

Address for correspondence: Dr. Enrique G. Villarreal, Escuela de Medicina y Ciencias de la Salud, Tecnologico de Monterrey, Monterrey, Nuevo Leon, Mexico. E-mail: quique_villarreal93@hotmail.com

Conclusion	:	**In this study, dopamine was independently associated with improvement in markers of systemic oxygen delivery 6 h after initiation. Dobutamine and dopamine were associated with increased in blood pressure. Well-powered studies are required to detect changes in lactate and NIRS.**
Keywords	:	Hemodynamics, near-infrared spectroscopy, norwood procedures, pediatrics, vasoconstrictor agents

INTRODUCTION

The use of vasoactive medications after congenital heart surgery is one of the cornerstones of postoperative management. Although the postoperative hemodynamic effects of vasoactive medications in patients with congenital heart disease have been characterized, the hemodynamic regulation in patients with parallel circulation continues to be a challenge due to myocardial dysfunction.[1-4] Furthermore, the preoperative phase is a particularly vulnerable stage in patients with parallel circulation, characterized by evolving physiologies with dynamic vascular resistances, typically in the setting of limited monitoring.[5] Similar to the postoperative stage, providers rely on vasoactive medications in the preoperative stage to balance the pulmonary and systemic blood flow. However, not much is known about the effects of these agents during this stage. Therefore, the primary objective of this study was to characterize the acute effects of vasoactive medications (milrinone, dopamine, and/or dobutamine) on hemodynamic data, arterial blood gas (ABG) values, and markers of systemic oxygen delivery in children with parallel circulation awaiting initial palliation procedure.

METHODS

Patient selection

In this retrospective study, we identified patients with the parallel circulation that underwent either hybrid procedure (placement of pulmonary artery band and arterial ductal stent) or Norwood procedure, at a pediatric tertiary care center, between January 1, 2011, and December 31, 2019. Clinical data before the hybrid or Norwood procedure was obtained by detailed chart review. Inclusion criteria were as follows: Arterial line access with ABGs obtained preoperatively, presence of renal near-infrared spectroscopy (rNIRS) monitoring, and infusion of one or more of the following vasoactive medications for a minimum of 6 h: Milrinone, dopamine, dobutamine, and/or epinephrine. Being as this was a retrospective study of preoperative patients that underwent Norwood or hybrid procedures, all of the included patients survived to intervention. Patients requiring a balloon atrial septostomy remained eligible for inclusion. Exclusion criteria included patients on extracorporeal membrane oxygenation and patients

transferred from outside hospitals while on vasoactive medications. Only rNIRS was utilized for NIRS data as previously published data and yet to be published data indicate that change in inferior caval vein saturations are a sensitive predictor of adverse events and that rNIRS are an accurate and continuous tool to noninvasively trend inferior caval vein saturations.[6]

The study protocol received approval from the institutional review board and is in compliance with the Helsinki declaration.

Data collection

Data were collected by review of patient charts. Demographic data included patient gender and birth date. Clinical data included primary cardiac diagnosis and the date of initial intervention. Hemodynamic data collected were as follows: Systolic blood pressure, heart rate, respiratory rate, and saturation by pulse oximetry. ABGs were used to collect pH, partial pressure of carbon dioxide (paCO2), partial pressure of oxygen (paO2), hemoglobin, and serum lactate levels. Markers of systemic oxygen delivery collected were as follows: rNIRS and serum lactate levels.

Collected data was used to calculate a bedside pulmonary blood flow (Qp) to systemic blood flow (Qs) ratio (Qp:Qs). Bedside Qp:Qs was calculated using the following simplified Fick equation: (Saturation by pulse oximetry – rNIRS)/ (100 – saturation by pulse oximetry). This equation has been simplified based on two assumptions: (1) The rNIRS value was used as a surrogate for systemic venous saturation (2) pulmonary venous saturation was assumed to be fully oxygen saturated at 100%. The authors acknowledge that pulmonary venous desaturation may be present in children with parallel circulation awaiting initial palliation procedures. This assumption may require further assessment given the occasional use of permissive hypercapnia and sub-ambient oxygen therapy in preoperative patients.

Data for each patient were collected immediately before initiation of a vasoactive medication and again 6 h after initiation. The 6-h period for re-evaluation was selected for the reason that the medications of interest have onset of effect by this point, with most reaching serum steady state in 6 h. In addition, the 6-h time frame was deemed clinically relevant for critically ill children by our intensive care team, as the acute effects of these

medications will influence further care and the need for escalation of care. The retrospective design of this study somewhat limits data collection as evidenced by the fact that not all patients had data at precisely 1 h and 6-h postinitiation of a vasoactive medication. For our analysis, data within 60 min before initiation of medication and within 60 min of the 6-h mark were deemed acceptable for collection and analysis. We acknowledge that there is a considerable amount of variability between medication onset and metabolism in critically ill patients including (but not limited to): Dose of medication used, patient age, patient gender, diagnoses, body mass, hepatic and renal function, and concomitant administration of medications.

Data analysis revealed that some patients were simultaneously maintained on multiple vasoactive medications before surgical intervention. To account for this, data collection for each vasoactive medication was done separately. Thus, if a patient was receiving two vasoactive medications simultaneously, a data set was collected with time zero specific to each vasoactive medication. This was to ensure that the effects of each specific vasoactive medication could most efficiently be characterized. There are patients who appear in multiple datasets. Data analysis also revealed that in some instances a vasoactive medication was initiated and subsequently discontinued only to be restarted later. In this situation, only data from the initial use of the specific vasoactive medication were eligible for inclusion.

Statistical analyses

Data for each vasoactive medication were analyzed separately. Paired *t*-tests were performed to compare data at the time of vasoactive initiation and 6-h after vasoactive initiation. All of the aforementioned hemodynamic data, ABG values and markers of systemic oxygen delivery including calculated bedside Qp:Qs were compared in univariate fashion.

Next, an analysis of covariance was conducted for the change (value at 6-h after initiation – value at the time of initiation) in each of the hemodynamic (systolic blood pressure, heart rate, respiratory rate, and saturation by pulse oximetry) and ABG values (pH, partial pressure of carbon dioxide [paCO2], partial pressure of oxygen [paO2], hemoglobin, and serum lactate). This analysis was completed for each specific vasoactive medication. The change in the specific hemodynamic or blood gas value was the dependent variable in the analysis while the change in vasoactive medication dose, change in the fraction of inspired oxygen, and change in hemoglobin were treated as independent variables. This allowed for the calculation of an adjusted mean difference.

As the main clinical aim in the management of this patient population is to increase systemic oxygen delivery, sample size calculations were calculated for the multivariate mean differences in rNIRS and lactate for each vasoactive. These were performed with the goal of achieving a power of 90% using paired *t*-test.

Categorical values are presented as absolute value and frequency while continuous variables are presented as mean and standard deviation. Mean differences are presented as mean and 95% confidence interval (CI). All statistical analyses were conducted using SPSS Version 23.0 (SPSS Inc., Chicago, IL, USA). A $P = 0.05$ was considered statistically significant. Any use of the word "significant" throughout the remainder of the manuscript will be referring to statically significant unless explicitly stated as "clinically significant."

RESULTS

Patient cohort

A total of 139 patients who underwent hybrid and/or Norwood procedures in the study period were identified. Of these, nine patients were on milrinone, 43 patients were on dopamine, 27 patients were on dobutamine, and seven patients were on epinephrine before initial intervention. After chart review and elimination based on study criteria, seven patients on milrinone, 22 patients on dopamine, and 17 patients on dobutamine were included in the final analyses. There were only three patients on epinephrine eligible for inclusion in the study, therefore epinephrine was excluded as a separate vasoactive of interest. Thirty-six unique patients were included in the analysis of which 15 (41%) were female and 21 (59%) were male. The mean weight of the patients is 3.3 ± 0.4 kg and mean age at the time of initiation of vasoactive medication is 1.7 days. Four patients (11%) in the cohort were premature. Baseline data are summarized in Table 1.

The most frequent cardiac diagnosis in the patient cohort was hypoplastic left heart syndrome followed by the interrupted aortic arch and double outlet right ventricle. Two patients with double inlet left ventricle were also included in the study.

Hemodynamic data, ABG values, and measures of systemic oxygen delivery including rNIRS and serum lactate levels at the time of each vasoactive medication initiation and 6-h after each vasoactive medication initiation are displayed in Figure 1.

Milrinone

Hemodynamic data, ABG values, and measures of systemic oxygen delivery including rNIRS and serum lactate levels at the time of milrinone initiation are displayed in Table 1. The dose of milrinone used at 6 h from initiation was 0.39 ± 0.17 (mcg/kg/min).
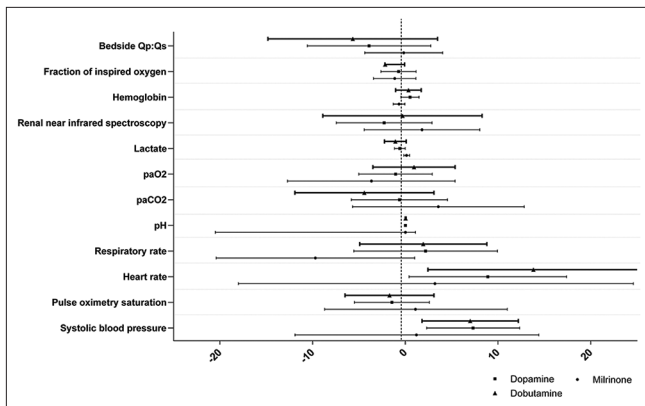
Univariate analyses demonstrate no significant change in these values after milrinone initiation.

Multivariate analyses demonstrate that milrinone is not independently associated with a significant change in any of hemodynamic data, blood gas parameters, or measures of systemic oxygen delivery after continuous infusion for 6 h [Figure 1]. Adjustment for other covariates did not change any of these values [Figure 2].

Dopamine

Hemodynamic data, ABG values, and measures of systemic oxygen delivery including rNIRS and serum lactate levels at the time of dopamine initiation are displayed in Table 1. The dose of dopamine used at 6 h from initiation was 5.45 ± 2.34 (mcg/kg/min).

Univariate analyses demonstrate that there was a significant increase in systolic blood pressure (mean difference 7.3 mmHg, 95% CI 2.3–12.3), significant increase in heart rate (mean difference 8.9, 95% CI 0.4–17.4), and significant decrease in lactate (mean difference –0.5 mmol/L, 95% CI –1.1––0.01) 6 h after dopamine initiation [Figure 1].
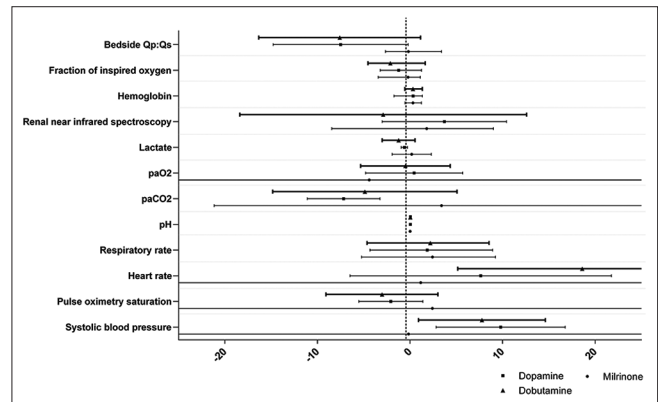
Multivariate analyses demonstrate that dopamine is independently associated with significant increase in systolic blood pressure (mean difference 9.8 mmHg, 95% CI 2.8-16.7), significant increase in pH (mean difference 0.04, 95% CI 0.01–0.07), significant decrease in $paCO_2$ (mean difference –7.1, 95% CI –11.1––3.2), significant decrease in lactate (mean difference –0.6 mmol/L, 95% CI –0.9––0.2) [Figure 2], and significant decrease in bedside Qp:Qs mean difference –7.5, 95% CI –14.7––0.2) after continuous infusion for 6 h [Figure 1].

Dobutamine

Hemodynamic data, ABG values, and measures of systemic oxygen delivery including rNIRS and serum lactate levels at the time of dobutamine initiation are displayed in Table 1. The dose of milrinone used at 6 h from initiation was 5.97 ± 2.45 (mcg/kg/min).

Univariate analyses demonstrate that there was a significant increase in systolic blood pressure (mean difference 7.0 mmHg, 95% CI 1.8-12.1) and significant

Figure 1: Univariate analysis of each vasoactive medication at the time of initiation and 6-h after to compare hemodynamic data, arterial blood gas values, and markers of systemic oxygen delivery

Figure 2: Multivariate analysis of each vasoactive medication at initiation and 6-h after, using the change in hemodynamic or blood gas value as dependent variable, while change in vasoactive medication dose, fraction of inspired oxygen, and hemoglobin as independent variables

Table 1: Baseline data for each of the vasoactive agents

	Milrinone (*n*=7)[a]	Dopamine (*n*=22)[a]	Dobutamine (*n*=17)[a]
Age at initiation (days)	2.7±0.7	1.5±0.4	1.7±0.5
Dose at 6 h (mcg/kg/min)	0.39±0.17	5.45±2.34	5.97±2.45
Systolic blood pressure (mmHg)	65.5±13.2[a]	56.3±12.0	60.1±11.1
Pulse oximetry saturation (%)	86.7±10.0	87.7±8.0	90.3±6.7
Heart rate (beats per min)	150.4±18.7	144.4±16.4	142.6±15.0
Respiratory rate (breaths per min)	45.5±28.5	38.6±12.1	41.2±14.2
pH	7.34±0.07	7.36±0.07	7.31±0.06
$paCO_2$ (mmHg)	41.5±4.3	40.6±10.5	46.0±13.2
paO_2 (mmHg)	45.5±5.7	42.3±8.8	39.8±8.8
Lactate (mg/dl)	1.4±0.4	2.5±1.6	3.2±2.5
Renal near infrared spectroscopy (%)	59.4±8.4	58.1±18.0	58.0±15.7
Hemoglobin (g/dl)	14.8±2.6	13.8±3.0	14.5±3.1
Fraction of inspired oxygen (%)	19.1±2.1	21.6±9.3	22.4±11.3
Bedside Qp:Qs	2.8±2.0	8.4±4.8	9.9±4.2

[a]Data represented in mean+SD. mmHg: Millimeters of mercury, $paCO_2$: Partial pressure of carbon dioxide, paO_2: Partial pressure of oxygen, Bedside Qp:Qs: Bedside pulmonary blood flow (Qp) to systemic blood flow (Qs) ratio, SD: Standard deviation

increase in heart rate (mean difference 13.8 beats per min, 95% CI 2.4–25.2) 6 h after dobutamine initiation [Figure 1].

Multivariate analyses demonstrate that dobutamine is independently associated with significant increase in systolic blood pressure (mean difference 7.77 mmHg, 95% CI 0.92–14.62) and significant increase in heart rate (mean difference 18.6, 95% CI 5.1–32.0) after continuous infusion for 6 h [Figure 1].

Sample size calculations

Milrinone

to detect a significant difference in the rNIRS of 1.8 with 90% power, a sample size of 11 would be required. The sample size for milrinone was seven. Mean serum lactate levels remained normal both before and after milrinone initiation, therefore a power calculation was not done.

Dopamine

to detect a significant difference in the rNIRS of 3.7 with 90% power, a sample size of 11 would be required. To detect a significant difference in the lactate of 0.6 with 90% power a sample size of 2 would be required.

Dobutamine

to detect a significant difference in the rNIRS of 2.8 with 90% power, a sample size of 13 would be required. To detect a significant difference in the lactate of 1.2 with 90% power a sample size of 8 would be required.

DISCUSSION

The use of vasoactive medications in children with parallel circulation awaiting initial palliation is highly physician and center dependent. Data regarding the actual effects of these agents on hemodynamics and markers of systemic oxygen delivery are anecdotal and is often extrapolated from understanding of the effects of these vasoactive medications in biventricular, series circulation.[7,8] Thus, to our knowledge, this current study provides the first objective data regarding the effects of these agents in this unique circulation.

This study demonstrates the acute effects of vasoactive medications on hemodynamic data, ABG values, and measures of systemic oxygen delivery including rNIRS and serum lactate levels in patients with parallel circulation awaiting their initial palliation procedure. The vasoactive medications included in these analyses were milrinone, dopamine, and dobutamine. There were too few patients receiving epinephrine to provide meaningful analyses for this vasoactive, and it was therefore excluded from the study.

While the sample size for each vasoactive medication is low, this study offers the first objective insight into how hemodynamics and blood gas values change with specific vasoactive medications, in patients with parallel circulation, before initial palliation. Dopamine was found to significantly increase systolic blood pressure, increase pH, decrease lactate, and improved Qp:Qs 6 h after initiation. Dobutamine was found to significantly increase systolic blood pressure and heart rate 6 h after initiation. Milrinone was found to have no significant effect on hemodynamics or blood gas values 6 h after initiation. It is important to mention that the hemodynamic and metabolic effects of vasopressors are dose dependent, particularly the dose-dependent effects of dopamine.[9-11]

Markers of systemic oxygen delivery were significantly improved in patients on dopamine in this cohort of patients. Those on dopamine had a significant decrease in lactate. A significant increase in rNIRS was not noted. However, this could be due to the low sample size and lack of power to detect a statistically significant change in rNIRS. The mechanism by which dopamine increases systemic oxygen delivery in this circulation cannot be entirely delineated by this study. It is possible that the inotropic effect of dopamine leads to increased cardiac output. The increase in systolic blood pressure would be consistent with this hypothesis, however, the lack of a significant increase in rNIRS would not. It is also possible that systemic oxygen delivery improved by the reduction in Qp, meaning that systemic cardiac output increased. The increase in systolic blood pressure would be consistent with this hypothesis, although the lack of a significant increase in rNIRS would not.

With multivariate analyses, dobutamine demonstrated no significant change in markers of systemic oxygen delivery (lactate or rNIRS). While not a significant change, the mean effect of dobutamine decreased rNIRS. This comes in the setting of a significant increase in heart rate leading to increase in myocardial oxygen demand at the expense of systemic oxygen delivery (albeit statistically insignificant). This would be consistent with previous studies of the effects of dobutamine in biventricular circulation.

With multivariate analyses, milrinone also demonstrated no significant change in markers of systemic oxygen delivery (lactate or rNIRS). While the mean effect of milrinone showed a decrease in Qp:Qs and increase in rNIRS, these were both insignificant changes. Interestingly, the mean effect of milrinone was to increased lactate, although this was insignificant. It should be noted that the baseline lactate in patients receiving milrinone was lower than those receiving dopamine or dobutamine. Thus, the modest increase in lactate implied by the multivariate analyses actually keeps the lactate within normal limits. These findings were in part not expected based on previous studies.[12,13] To further demonstrate this point, considering the baseline lactate and the mean

effect from the multivariate analyses, the postmilrinone lactate for the milrinone cohort would be estimated to be 1.6 mmol/L while the postdopamine lactate for the dopamine cohort would be estimated to be 1.9 mmol/L.

While this study offers novel, objective data regarding the effects of various vasoactive medications in those with parallel circulation awaiting initial palliation, it is not without its limitations. There is a relative lack of sample size. In fact, due to such a low number of patients on epinephrine, there were no primary analyses done for epinephrine, although epinephrine dose was controlled for in multivariate analyses. The sample size in the current study was adequate for detecting significant changes in lactate and rNIRS for dopamine and dobutamine but not for milrinone. The current sample size also does not allow for adequate exploration of the effect of the dose of specific vasoactive medications on the various endpoints. Sample size calculations based on the markers of systemic oxygen delivery are delineated in the results and can help guide future studies. Another limitation of this study is that it is a single-center study. Local practice patterns may lead to selection bias inherent to the selection of vasoactive medications. For instance, the relative use of vasoactive medications implies institutional bias favoring specific vasoactive medications. Additionally, the large difference in the lactate and Qp:Qs at the time of initiation further highlights institution-specific bias, with patients with higher lactate seemingly initiated on dopamine or dobutamine. Furthermore, most of vasoactives are generally started with low dose and the dose is gradually increased to reach the optimal dosing and effect. Therefore, the effect may not stabilize in 6 h from the initiation of the vasoactive medications. Finally, the lack of clinical monitoring to help truly quantify pulmonary and systemic blood flow, as it is not clinically feasible to quantify the pulmonary and systemic blood flows in clinical practice at this time. The same applies for the quantification of pulmonary and systemic vascular resistances in routine clinical care. With these limitations in mind, it is important to interpret these data with caution. These findings do not provide head-to-head data comparing the three vasoactive medications, they simply characterize the acute effects of these agents before and after initiation in individual patients. These data highlight the need for multicenter collaboration to pool retrospective data and improve sample size in a similar designed set of analyses to further characterize the acute effects of these medications. While a prospective study would be ideal, the time it would take for patient accrual could make such a study difficult. A retrospective multicenter effort could be done efficiently with low resource utilization. This could be facilitated via one of the existing collaborative efforts in pediatric cardiology.

CONCLUSION

Multivariate analyses demonstrate dopamine is independently associated with improvement in markers of systemic oxygen delivery 6 h after initiation. Dobutamine and milrinone were not independently associated with improvements in systemic oxygen delivery in this patient population. Although this study lacks statistical power to detect significant change in lactate and rNIRS for milrinone, it does highlight the need to objectively characterize the effects of these vasoactive medications in this unique clinical setting rather than relying on anecdotal evidence.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kwapisz MM, Neuhäuser C, Scholz S, Welters ID, Löhr T, Koch T, *et al.* Hemodynamic effects of dobutamine and dopexamine after cardiopulmonary bypass in pediatric cardiac surgery. Paediatr Anaesth 2009;19:862-71.

2. Cavigelli-Brunner A, Hug MI, Dave H, Baenziger O, Buerki C, Bettex D, *et al.* Prevention of low cardiac output syndrome after pediatric cardiac surgery: A double-blind randomized clinical pilot study comparing dobutamine and milrinone. Pediatr Crit Care Med 2018;19:619-25.

3. Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, *et al.* Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: Lessons learned from 115 consecutive patients. Circulation 2002;106:I82-9.

4. White PA, Chaturvedi RR, Shore D, Lincoln C, Szwarc RS, Bishop AJ, *et al.* Left ventricular parallel conductance during cardiac cycle in children with congenital heart disease. Am J Physiol 1997;273:H295-302.

5. Wik G, Jortveit J, Sitras V, Døhlen G, Rønnestad AE, Holmstrøm H. Severe congenital heart defects: Incidence, causes and time trends of preoperative mortality in Norway. Arch Dis Child 2020;105:738-43.

6. Dabal RJ, Rhodes LA, Borasino S, Law MA, Robert SM, Alten JA. Inferior vena cava oxygen saturation monitoring after the Norwood procedure. Ann Thorac Surg 2013;95:2114-20.

7. Duggal B, Pratap U, Slavik Z, Kaplanova J, Macrae D. Milrinone and low cardiac output following cardiac surgery in infants: Is there a direct myocardial effect? Pediatr Cardiol 2005;26:642-5.

8. Hyldebrandt JA, Agger P, Siven E, Wemmelund KB, Heiberg J, Frederiksen CA, *et al.* Effects of milrinone and epinephrine or dopamine on biventricular function and hemodynamics in right heart failure after pulmonary regurgitation. Am J Physiol Heart Circ Physiol 2015;309:H860-6.

9. Nachar RA, Booth EA, Friedlich P, Borzage M, Soleymani S, Wider MD, *et al.* Dose-dependent hemodynamic and metabolic effects of vasoactive medications in normotensive, anesthetized neonatal piglets. Pediatr Res 2011;70:473-9.

10. Wen L, Xu L. The efficacy of dopamine versus epinephrine for pediatric or neonatal septic shock: A meta-analysis of randomized controlled studies. Ital J Pediatr 2020;46:6.

11. Seri I, Rudas G, Bors Z, Kanyicska B, Tulassay T. Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates. Pediatr Res 1993;34:742-9.

12. Loomba RS, Dorsey V, Villarreal EG, Flores S. The effect of milrinone on hemodynamic and gas exchange parameters in children. Cardiol Young 2020;30:55-61.

13. Loomba RS, Flores S. Use of vasoactive agents in postoperative pediatric cardiac patients: Insights from a national database. Congenit Heart Dis 2019;14:1176-84.