ORIGINAL CLINICAL RESEARCH REPORT

Administration of Milrinone Following Tetralogy of Fallot Repair Increases Postoperative Volume Administration Without Improving Cardiac Output

Kwannapas Saengsin, MD,*†‡ Francesca Sperotto, MD, PhD,*† Minmin Lu, MS,*† Julia Garcia Mancebo, MD,*† Elizabeth Sacco, RN,* Manasee Godsay, MS,* James A. DiNardo, MD,§‖ and John N. Kheir, MD*†

BACKGROUND: Phosphodiesterase inhibitors are known to relieve symptoms in the setting of heart failure, although their effects in restrictive ventricular physiology have been poorly characterized. We explored the association between the use of milrinone and volume administration during the first 72 hours following surgical repair of tetralogy of Fallot (TOF).

METHODS: We reviewed all cases of primary surgical repair of TOF with pulmonary stenosis or atresia at Boston Children's Hospital between 2011 and 2020. To adjust for baseline differences between patients who did and did not receive milrinone, we matched patients with similar propensity scores in a 1:1 ratio (use of milrinone versus not). We then compared the need for volume administration during the first 72 hours postoperatively, vital signs, and measures of cardiac output between the matched cohorts. Additionally, in the group of patients receiving milrinone, linear regression modeling was used to explore the relationship between total dose of milrinone and total volume administration.

RESULTS: Among 351 included patients, 134 received perioperative milrinone. A total of 212 patients (106 per group) were matched based on anatomic and surgical risks using a propensity score. After propensity matching, compared with nonmilrinone-treated patients, milrinone-treated patients were given postoperative volume more frequently (66% vs 52%; difference 14% [95% confidence interval, CI, 1%–27%]; $P = .036$). Milrinone-treated patients had a slower recovery of tachycardia during the first 12 hours (difference in slope 0.30 [95% CI, 0.14–0.47] beats per minute [BPM]/h; $P < .001$), and the intergroup difference peaked at 12 hours postoperatively (8 [95% CI, 5–12] BPM). Milrinone administration was not associated with improved cardiac output, including arteriovenous oxyhemoglobin saturation difference. In propensity-matched patients receiving milrinone, the total volume administered during the first 72 postoperative hours was significantly associated with the cumulative dose of postoperative milrinone ($r = 0.20$; 95% CI, 0.01–0.38; $P = .036$). Based on the slope of the regression line, for every 1000 μg/kg of milrinone (equivalent to ~0.25 μg/kg/min for 72 hours) administered in the first 72 postoperative hours, an estimated 11.0 (95% CI, 0.6–21.4) mL/kg additional volume was administered.

CONCLUSIONS: The use of milrinone within the first 72 hours following TOF repair is associated with more frequent administration of volume, a positive association between a higher total dose of postoperative milrinone and the amount of postoperative volume administered, a higher heart rate, and a lower blood pressure, but is not associated with improved cardiac output. (Anesth Analg 2023;XXX:00–00)

KEY POINTS

- **Question:** Does milrinone improve hemodynamics following tetralogy of Fallot (TOF) repair?
- **Findings:** Propensity-matched patients who received milrinone within the first 72 hours following TOF repair were given volume more frequently, had slower recovery of tachycardia, and lower blood pressure, without significant improvement in indices of cardiac output compared with those who did not; volume administration increased linearly with a dose of milrinone.
- **Meaning:** Milrinone administration following TOF repair may convert stressed volume to unstressed volume, increasing the likelihood of volume replacement, increasing heart rate, and decreasing blood pressure without improving cardiac output; the clinical impact of milrinone in this setting should be studied prospectively.

From the *Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts; †Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; ‡Department of Pediatrics, Chaing Mai University Hospital, Chaing Mai, Thailand; §Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts; and ‖Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts.

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Address correspondence to John N. Kheir, MD, Department of Cardiology, Division of Cardiovasular Intensive Care, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. Address e-mail to john.kheir@childrens.harvard.edu

GLOSSARY

ASD = absolute standard difference; **ATT** = average treatment effect on the treated; **AVO_2** = arteriovenous oxyhemoglobin saturation; **BH** = Benjamini-Hochberg; **BPM** = beats per minute; **cAMP** = 3′,5′-cyclic adenosine monophosphate; **CHD** = congenital heart disease; **CI** = confidence interval; **CPB** = cardiopulmonary bypass; **DBP** = diastolic blood pressure; **dP/dT** = change in pressure over change in time; **dP/dTmin** = most negative change in pressure over change in time; **ECMO** = extracorporeal membrane oxygenation; **EDV** = indicates end-diastolic volume; **fenestrated ASD** = fenestrated atrial septal defect; **GAM** = generalized additive modeling; **ICU** = intensive care unit; **LCOS** = low cardiac output syndrome; **LOS** = length of stay; **LVEDV** = left ventricular end diastolic volume; **MPA** = main pulmonary artery; **mVIS** = modified vasoactive-inotrope score; **PA** = pulmonary artery; **PDI** = phosphodiesterase inhibitors; **PRBC** = packed red blood cells; **PRIMACORP** = PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics; **PS** = pulmonary stenosis; **PSM** = propensity score matching; **PV** = pulmonary valve; **RV** = right ventricular; **RVEDV** = right ventricular end-diastolic volume; **SBP** = systolic blood pressure; **SD** = standard deviation; **SEM** = standard error of the mean; **TOF** = tetralogy of Fallot; **TV** = tricuspid valve; **VIS** = vasoactive-inotrope score; **VSD** = ventricular septal defect

Phosphodiesterase inhibitors (PDI; eg, milrinone) are commonly used after neonatal and pediatric cardiac surgery. PDIs inhibit the intracellular breakdown of 3′,5′-cyclic adenosine monophosphate (cAMP), enhancing intracellular Ca^{2+} transport. This is known to result in direct, dose-dependent vasodilatory effects on systemic and pulmonary veins,[1] and on peripheral[2] and cerebral[3] vasculature. Vasodilation, along with an inotropic effect, is thought to be responsible for clinical improvements in congestive pathologies. Numerous studies in patients with congestive heart failure describe an improvement in symptoms with milrinone administration (most commonly a bolus followed by intravenous infusion), including decreased pulmonary artery (PA) wedge pressure and systemic vascular resistance.[4–6] Milrinone's use following congenital heart surgery was rigorously examined in the PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics (PRIMACORP) study, a randomized controlled trial demonstrating that the administration of high dose milrinone (75 µg/kg loading dose followed by a 0.75 µg/kg/min) reduced the incidence of low cardiac output syndrome (LCOS) in pediatric patients following a variety of cardiac operations, including repair of tetralogy of Fallot (TOF).[7] The administration of milrinone to mitigate or treat LCOS after cardiopulmonary bypass (CPB) is now common following a number of congenital heart operations, though there remains insufficient evidence for the efficacy of milrinone to prevent death or LCOS following surgery.[8]

TOF is the most common cyanotic congenital heart disease (CHD), and children typically undergo surgical repair before 1 year of age. The corrective operation typically includes surgical relief of right ventricular (RV) outflow tract obstruction (via transannular myectomy, infundibulotomy, or transannular patch), closure of the ventricular septal defect (VSD), and restriction or closure of the interatrial shunt.[9] Outcomes following repair are excellent, and perioperative mortality is rare.[9,10]

The primary aim of this study was to explore the association between the administration of milrinone and volume administration during the first 72 postoperative hours following TOF repair. We hypothesized that in the setting of this prototypical restrictive ventricular physiology, milrinone may be associated with increased volume requirements, increased heart rate, and decreased blood pressure without significant improvement in cardiac output.

METHODS

This study was approved under the exemption from informed consent by the Institutional Review Board at Boston Children's Hospital (P00035450). We retrospectively identified all patients undergoing surgical repair of TOF with pulmonary stenosis or pulmonary atresia at Boston Children's Hospital between January 2011 and September 2020. We excluded patients with TOF with pulmonary atresia in whom there were major aortopulmonary collateral arteries, TOF and atrioventricular canal, and TOF with absent pulmonary valve. We also excluded patients undergoing a palliative procedure (eg, modified Blalock-Taussig shunt, central shunt), patients with a known genetic syndrome, and patients who required extracorporeal membrane oxygenation (ECMO) support within 72 hours of repair.

Demographic, clinical, and surgical details were collected from an internal surgical database and manually verified. Anatomic details, including pulmonary valve anatomy (atresia versus stenosis) and dimension, tricuspid valve *Z*-score, and main PA *Z*-score were collected from the most proximate preoperative study. Operative reports were reviewed to categorize the repair type as a transannular patch, pulmonary valvotomy, or RV to PA conduit, and to identify the presence of an atrial fenestration. Vital signs (collected every 5 seconds via direct data feed) and laboratory findings were extracted from a high-fidelity internal database (TWIST). Patients were divided into 2 groups based on the presence or absence of perioperative

milrinone administration (defined as intraoperative or within the first 72 postoperative hours). During the study period, the timing and dosing of milrinone administration was variable. Its use was directed exclusively by the practitioners caring for the patient and was not protocolized. The total dose of milrinone was computed as the sum of all intra- and postoperative loading doses plus cumulative infusion doses for the first 72 postoperative hours.

Our exposure of interest was postoperative use of milrinone. Our primary outcome measure was the administration of volume (yes/no) during the first 72 postoperative hours following TOF repair. This volume included blood products (packed red blood cells, whole blood, platelets, fresh frozen plasma, and cryoprecipitate), as well as albumin 5%. Volumes associated with medications, flushes, infusions, and nutritive fluids (eg, parenteral nutrition, intralipids, or dextrose-containing intravenous fluids) were excluded from analysis, as these fluids are not administered clinically as volume replacement. Our secondary outcome measures included vital signs (heart rate and blood pressure), as well as indices of cardiac output and oxygen delivery (eg, arteriovenous oxyhemoglobin saturation [AVO_2] difference) and serum lactic acid). To examine the association between milrinone and vasoconstrictor use, we compared vasoactive-inotrope score (VIS)[11] during the first 72 postoperative hours and a newly computed modified vasoactive-inotrope score (mVIS, which excluded dosing of milrinone). As a supplemental analysis, in the cohort receiving milrinone, we investigated the association between the total perioperative dose of milrinone and the total volume administered during the first 72 postoperative hours.

Statistical Analyses

Descriptive statistics included mean ± standard deviation (SD) and median with interquartile range (Q1–Q3) for continuous variables, as appropriate. Categorical variables were described as frequency and percentage. Differences between groups were compared using independent samples *t*-test, Wilcoxon rank sum test, or χ^2 test, as appropriate.

Given that differences in baseline characteristics may have affected the clinical choice to use milrinone, a propensity score was computed for each subject using a multivariable logistic regression model with milrinone exposure (yes/no) as the outcome. Baseline demographic, clinical and operative characteristics that could affect the type of surgical management, and the postoperative course were included in the model as independent variables, regardless of their *P* value at univariate analysis (see Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E479).

Subjects with and without milrinone were matched in a 1:1 ratio according to propensity score by optimal method, using a caliper width of 0.2 of the SD of the logit of the propensity score and without replacement.[12] Thereafter, a total of 212 patients (106 + 106) were matched. Density of propensity score distributions and absolute standard difference (ASD) were plotted to demonstrate adequacy of matching. Imbalance was defined as an ASD >1.962* sqrt($(n_1+n_2))/n_1n_2$ = 0.269 based on Austin's formula.[13] Since no imbalances in risk factors were identified following propensity matching, we compared outcomes without further adjusting for the effects of confounders. Propensity-matched cases who shared a similar value of the propensity score were treated as independent (ie, not paired) observations.

Primary Outcome

The relation between milrinone and the primary outcome—any bolus volume being administered (yes/no)—was assessed in the propensity-matched cohort by χ^2 test. Our propensity matching provided an estimation of the average treatment effect on the treated (ATT) because we matched patients who received milrinone to nonmilrinone users for comparative analysis. ATT was selected to allow for inferences on patients who are being considered for milrinone therapy following TOF repair. Further, we explored the relationship between total perioperative dose of milrinone and perioperative volume administration in patients who received milrinone using generalized additive modeling (GAM), a nonparametric method that does not assume linearity of the relationship between the outcome and the exposure. For example, if not linear, there may have been a threshold that stratifies patients into lower versus higher doses. Since the relationship was found to be linear, a linear regression model was used to assess the association.

Secondary Outcomes

Secondary outcomes were compared between the 2 propensity-matched cohorts using independent sample *t*-tests, Wilcoxon rank sum tests, χ^2 tests, or Fisher exact tests as appropriate. For comparisons of the volume of blood product components (eg, PRBC, albumin, etc), exposures were categorized as yes (transfused) or no (not transfused) given the left skew of the distribution in volumes administered. To protect against type I error in the setting of multiple comparisons (N = 25) between the 2 matched cohorts for the secondary outcomes, we used the Benjamini-Hochberg (BH) critical value for a false discovery rate of 0.05.

Using the BH method, we are limiting the proportion of significant findings that are false positives to

at most 5%. We first ordered the observed P values from smallest to largest and gave them ranks of 1 to 25. Then for each P value, we calculated X = rank/25 × 0.05. Finally, the BH critical value used to determine significance for all of the tests was chosen as the largest value of X for which the observed P value was smaller.

As demonstrated in Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E479, this value was 0.006. Therefore, all secondary outcomes with $P < .006$ were considered statistically significant.

As an additional exploratory analysis, linear mixed-effects models (fixed time, random subject) were performed to assess the association between cohort (ie, any milrinone exposure versus not) and vital signs over time during the first 72 postoperative hours. Time was included as a continuous variable in this model. This method was chosen to allow for assessment of a group-by-time interaction; following TOF repair, myocardial edema is thought to peak (and therefore diastolic capacitance nadirs) at 12–18 hours postoperatively,[7] which may dynamically alter the response of the circulation to milrinone over time. All statistical analyses were performed using Stata version 16.1 (StataCorp).

Sample Size Calculation

To date, there have been no studies addressing the effect of milrinone use on the volume administered postoperatively. Based on clinical experience, we hypothesized that 70% of the milrinone group will receive at least 1 bolus of volume postoperatively, vs 50% in the nonmilrinone group. Given these data, to detect this difference in the proportion of 20% between the 2 exposure groups (milrinone versus nonmilrinone) with a power of 0.8 and tolerating an α error of .05, we required 93 subjects per group (χ^2 test, 2-sided, using power.prop.test, R statistics).

RESULTS

Among 1061 patients diagnosed with TOF between January 2011 and September 2020, 351 fulfilled the study criteria and were included in the study (Figure 1). Median age at surgery was 92 (Q1–Q3 52–134) days. Among these, 134 (38%) patients received milrinone within 72 hours of the operation. Patients receiving milrinone were significantly younger, had lower weight, had smaller pulmonary valve, tricuspid valve, and main PA Z-scores (ie, number of SD from the mean based on age[14]), and more commonly received a transannular patch

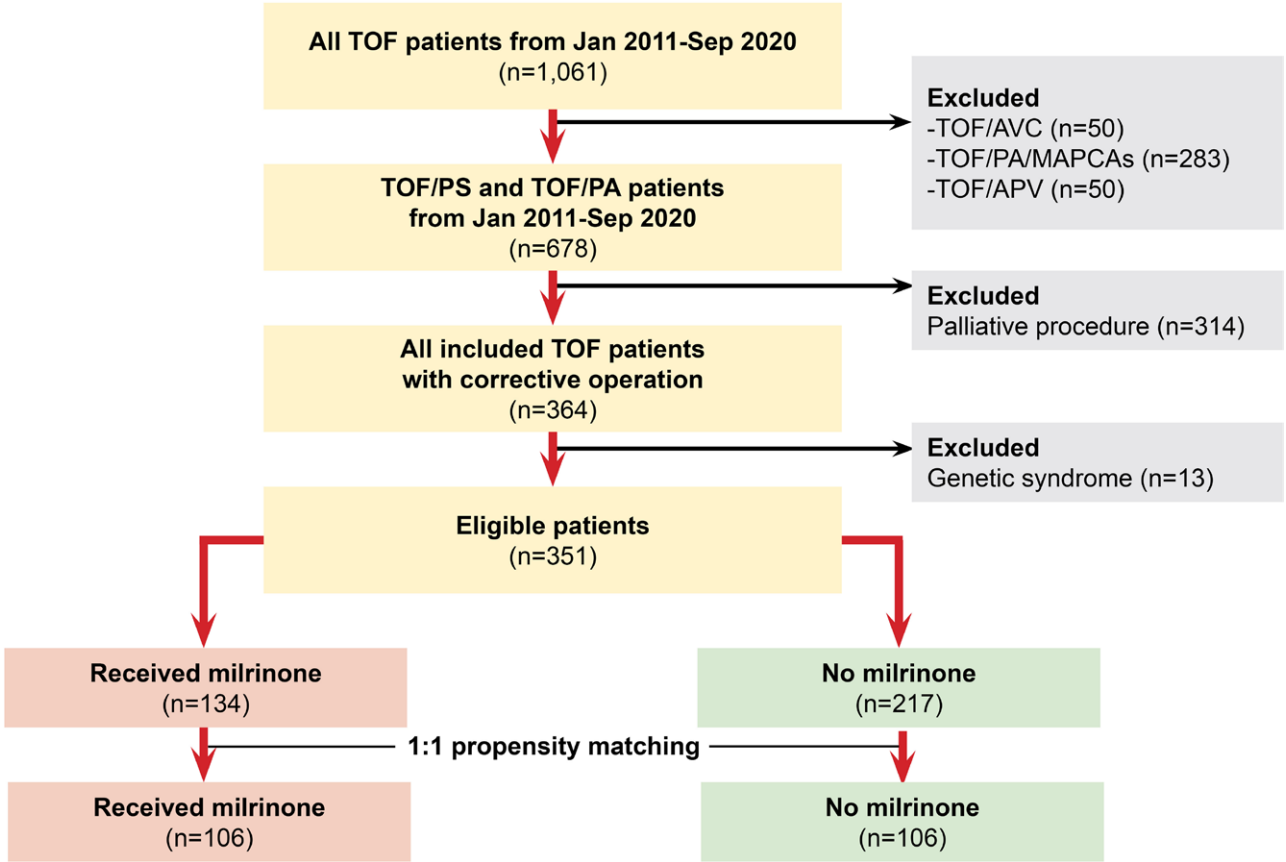

Figure 1. Subject flow chart. APV indicates absent pulmonic valve; AVC, atrioventricular canal defect; MAPCAs, multiple aortopulmonary collaterals; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.

repair (which is typically performed in the setting of a more restrictive native RV outflow tract) than those who did not (Table 1). These differences were controlled by propensity score matching with an absolute standardized difference for all <0.269 (Table 1). Additionally, the density of propensity score was not statistically significant in the propensity-matched cohorts (Supplemental Digital Content 2, Supplemental Figure 1, http://links.lww.com/AA/E480). Primary and secondary outcomes for the aggregate cohort are presented in Supplemental Digital Content 3, Supplemental Table 2, http://links.lww.com/AA/E481. The results presented below are analyses of the propensity-matched subset of patients.

Volume Administration

Milrinone-treated patients received postoperative volume more frequently than nonmilrinone-treated patients (66% vs 52%; difference 14% [95% confidence interval, CI, 1%–27%]; $P = .036$, Table 2; component breakdown in Supplemental Digital Content 4, Supplemental Table 3, http://links.lww.com/AA/E482). Total volume administration decreased over the first postoperative 72 hours in both groups with no significant between-group differences (difference in slope −0.045 [95% CI, 0.095–0.005] mL/kg/h; $P = .077$; Figure 2A). Further, in patients receiving milrinone, the total volume administered during the first 72 postoperative hours was significantly associated with the total dose of postoperative milrinone ($r = 0.20$; 95% CI, 0.01–0.38; $P = .036$) (Figure 2B). Based on the slope of the regression line, for every 1000 µg/kg of milrinone (equivalent to ~0.25 µg/kg/min for 72 hours) administered in the first 72 postoperative hours, 11. 0 ± 5.2 mL/kg of additional volume was administered.

Vital Signs, Indices of Cardiac Output, and Oxygen Delivery

In the propensity-matched cohort analysis, the milrinone cohort was associated with a higher heart rate throughout the first 72 postoperative hours (5.6 [95% CI, 2.2–9.1] beats per minute [BPM]; $P = .001$, Figure 3; models presented in Supplemental Digital Content 5, Supplemental Figure 2, http://links.lww.com/AA/E483). Milrinone-treated patients had a slower recovery of tachycardia during the first 12 hours (−0.64 vs −0.94 BPM/h, difference in slope 0.30 [95% CI, 0.14–0.47] BPM/h, $P < .001$), such that the maximum difference occurred at 12 hours postoperatively (8 [95% CI, 5–12] BPM) and subsequently diminished (1.1 [95% CI, −2.2 to 4.4] BPM at 72 hours postoperatively).

Compared with the nonmilrinone-exposed cohort, the milrinone-exposed cohort was associated with a lower blood pressure on intensive care unit (ICU)

Table 1. Comparison of Milrinone Versus No-Milrinone Cohorts in Both Aggregate and Propensity-Matched Groups

		Aggregate cohort				Propensity-matched cohort			
Variable	All patients (N = 351)	With milrinone (n = 134)	Without milrinone (n =217)	*P* value	ASD[a]	With milrinone (n = 106)	Without milrinone (n = 106)	*P* value	ASD[a]
Age at first surgery(d), median (Q1–Q3)	92 (52,134)	71 (33,98)	105 (72,162)	**<.001**	0.33	86 ± 89	94 ± 36	.611	0.07
Sex, male, n (%)	197 (56)	77 (57)	120 (55)	.692	0.04	59 (56)	59 (56)	1.000	0.00
Weight (kg)	5. 77 ± 5.80	4. 32 ± 1.51	6. 67 ± 7.14	**.0002**	0.45	4. 63 ± 1.48	4. 62 ± 1.61	.972	0.005
TOF subtype, n (%)				.051	0.21			.417	0.11
Pulmonary stenosis	304 (87)	110 (82)	194 (89)			94 (89)	90 (85)		
Pulmonary atresia	47 (13)	24 (18)	23 (11)			12 (11)	16 (15)		
Pulmonic valve *Z*-score	−1.67 ± 1.11	−1.82 ± 1.11	−1.58 ± 1.10	.045	0.22	−1.80 ± 0.09	−1.81 ± 1.14	.916	0.01
Tricuspid valve *Z*-score	0.43 ± 1.01	0.20 ± 1.02	0.56 ± 0.99	**.002**	0.34	0.32 ± 1.05	0.22 ± 0.73	.439	0.11
MPA *Z*-score	−2.25 ± 1.97	−2.57 ± 1.69	−2.05 ± 2.11	.015	0.27	−2.42 ± 1.72	−2.65 ± 1.93	.357	0.13
Repair type, n (%)				.028	0.30			.748	0.11
Transannular patch	134 (38)	62 (46)	72 (33)			41 (39)	44 (42)		
Pulmonary valvotomy	194 (55)	62 (46)	132 (61)			58 (55)	53 (50)		
RV to PA conduit	23 (7)	10 (7)	13 (6)			7 (7)	9 (8)		
Fenestrated ASD, n (%)	233 (66)	96 (72)	137 (63)	.101	0.18	74 (70)	72 (68)	.767	0.04
Operative times (min)									
Total pump time	128 ± 44	134 ± 44	124 ± 44	.076	0.20	129 ± 44	136 ± 45	.283	0.15
Aortic cross-clamp time	89 ± 35	93 ± 38	87 ± 33	.108	0.17	91 ± 37	95 ± 33	.339	0.13
Circulatory arrest time	0.66 ± 3.86	1. 29 ± 5.91	0.26 ± 1.47	.015	0.24	0.67 ± 3.17	0.54 ± 2.08	.720	0.05

No missing data. *P* values are the result of independent sample *t*-test, Wilcoxon rank sum test, χ^2 test, or Fisher exact test as appropriate.

Abbreviations: Fenestrated ASD, fenestrated atrial septal defect; MPA, main pulmonary artery; PA, pulmonary artery; Q1–Q3, first quartile–third quartile; RV, right ventricular; TOF, tetralogy of Fallot.

[a]Absolute standardized differences are depicted in Supplemental Digital Content 2, Supplemental Figure 1, http://links.lww.com/AA/E480. Fenestrated ASD denotes that there was a patent communication between the right and left atria postoperatively, commonly via restricting the patent foramen ovale. This is of clinical relevance because the atrial fenestration permits maintenance of cardiac output in the setting of severe restrictive RV physiology via atrial shunting.

Table 2. Incidence of Postoperative Volume Administration (Primary Outcome) Over the First 72 Postoperative Hours in Propensity-Matched Patients By χ^2 Test

Variable	Overall (N = 212)	With milrinone (n = 106)	Without milrinone (n = 106)	Difference (95% CI)	*P* Value
Primary outcome: any postoperative bolus volume administered					.036
Yes	125 (59.0%)	70 (66.0%)	55 (51.9%)		
No	87 (41.0%)	36 (34.0%)	51 (48.1%)		
Secondary outcomes					
Sao_2	97. 26 ± 3.91 (n = 195)	97. 01 ± 4.64	97. 52 ± 2.99	–0.51 (–1.61, 0.59)	.366
SvO2	63. 62 ± 12.78 (n = 162)	62. 47 ± 12.01	64. 99 ± 13.59	–2.51 (–6.49, 1.46)	.213
AVO_2 difference	40. 51 ± 12.46 (n = 154)	41. 59 ± 13.03	39. 13 ± 11.62	2.46 (–1.54, 6.45)	.226
Serum lactic acid (mmol/L)	1. 69 ± 0.84 (n = 211)	1. 65 ± 0.77	1. 75 ± 0.93	–0.10 (–0.33, 0.13)	.391
Cumulative thoracic tube drainage (mL/kg)	52. 4 ± 38.7 (n = 212)	52. 7 ± 34.1	52. 0 ± 42.9	0.70 (–9.80, 11.20)	.895

Breakdown of volume components is provided in Supplemental Digital Content 1, Supplemental Table 2, http://links.lww.com/AA/E479. Comparison of postoperative cardiac output and oxygen delivery indices (secondary outcomes) between propensity score matching groups by 2-sample *t*-test. Statistical significance for the primary outcome was set at $P = .05$. For secondary outcomes, to protect against a type I error in the setting of multiple comparisons, a test with *P* value equals to .006 or lower was considered statistically significant according to the Benjamini-Hochberg critical value for a false discovery rate of .05.
Abbreviations: AVO_2, arteriovenous oxyhemoglobin saturation; Sao_2, arterial oxyhemoglobin saturation; SvO2, venous oxyhemoglobin saturation.

admission (time 0) and the difference diminished over time. The difference in SBP at time 0 was −3.3 (95% CI, 6.4 to −0.3) mm Hg ($P = .033$), and the difference at 72 postoperative hours was −1.2 (95% CI, −4.2 to 1.9) mm Hg ($P = .46$). The difference in DBP at time 0 was −4.3 (95% CI, −6.2 to −2.6) mm Hg ($P < .001$), and at 72 postoperative hours was −1.1 (95% CI, −2.9 to 0.6) mm Hg ($P = .219$).

No significant differences were observed between groups in values of markers of oxygenation or perfusion, including arterial oxyhemoglobin saturation, venous oxyhemoglobin saturation, arteriovenous oxyhemoglobin saturation (AVO_2) difference, serum lactic acid, or chest tube drainage in the same timeframe (Table 2).

No differences were observed in cumulative 72-hour dosing of vasoactive drugs (Supplemental Digital Content 6, Supplemental Table 4, http://links.lww.com/AA/E484) nor in milrinone-absent VIS scores at 0, 12, 24, 48, and 72 hours postoperatively (Supplemental Digital Content 7, Supplemental Table 5, http://links.lww.com/AA/E485) between the 2 groups.

Clinical Outcomes

In the propensity-matched cohort analysis, no differences were observed between groups in ICU length of stay and hospital length of stay between patients who received milrinone and patients who did not (ICU length of stay 3 days [Q1–Q3 2, 6] versus 3 days [Q1–Q3 2, 6], $P = .486$; hospital length of stay 7 days [Q1–Q3 6, 13] versus 7 days [Q1–Q3 5, 13], $P = .597$, respectively). No deaths occurred before hospital discharge in either group.

DISCUSSION

We found that in a propensity-matched cohort, milrinone-treated patients received postoperative bolus volume more frequently than nonmilrinone-treated ones (66% vs 52%). Further, the total volume administered during the first 72 postoperative hours was significantly associated with the cumulative dose of postoperative milrinone. Further, we found that milrinone-treated patients had a significantly higher heart rate for the first 72 postoperative hours, and a slower recovery rate of postoperative tachycardia in the early postoperative period. The maximal difference between groups (8 BPM) occurred at 12 hours, corresponding to the known peak of myocardial edema and LCOS as described in the PRIMACORP study.[7] There was also a clinically insignificant lower blood pressure in milrinone-treated patients; this, combined with a higher heart rate and increased likelihood of volume administration may be explained by the vasodilatory effect of milrinone with a compensatory chronotropic response. However, this cannot be stated with certainty given the retrospective nature of this study and its inherent biases (including selection bias). Of note, milrinone-treated patients did not have evidence of improved oxygen delivery compared with nonmilrinone-treated ones.

In contrast with congestive heart failure, the predominant clinical phenotype following TOF repair is a restrictive ventricular physiology. The hypertrophied right ventricle, ventricular incision, infundibular patch, VSD patch, and myocardial edema all combine to diminish RV capacitance. In this setting, LCOS is most commonly a manifestation of diminished right ventricular end-diastolic volume (RVEDV; ie, preload) as a proximate cause for diminished stroke volume and cardiac output. Sans the effect of atrial shunting, maximizing cardiac output in this setting requires maximizing RVEDV (colloquially, filling the "stiff" right ventricle); when present, systolic ventricular dysfunction in this setting is more likely a manifestation of diminished preload. Targeting RVEDV in this setting requires the centralization of blood volume and the optimization of stressed volume (Figure 4).[15] Interventions that venodilate (eg, vasodilator therapy,

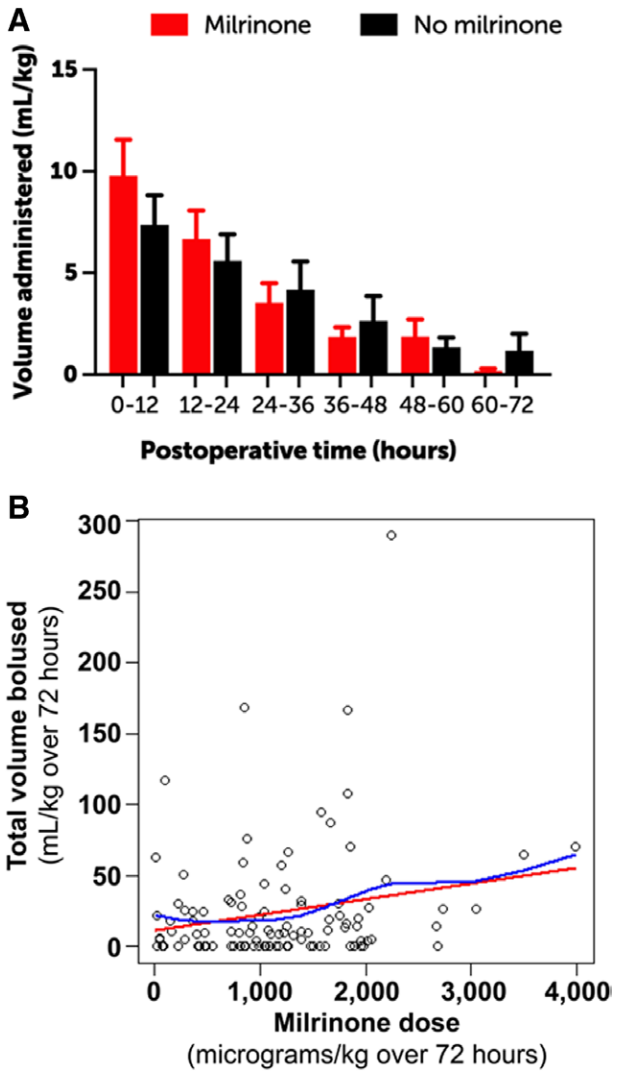

Figure 2. Volume administration. A, Volume administration over time within the first 72 postoperative hours by 12-h bins, separated by treatment group. Data are means and error is SEM. Red indicates milrinone-treated and black indicates nonmilrinone-treated. B, Total volume administered in the first 72 postoperative hours increased with total milrinone dose during the same time (P = .036). The flexible fit between these 2 variables estimated by generalized additive modeling (blue line) suggests that the relationship is linear. The red line depicts the results of the linear regression model. SEM indicates standard error of the mean.

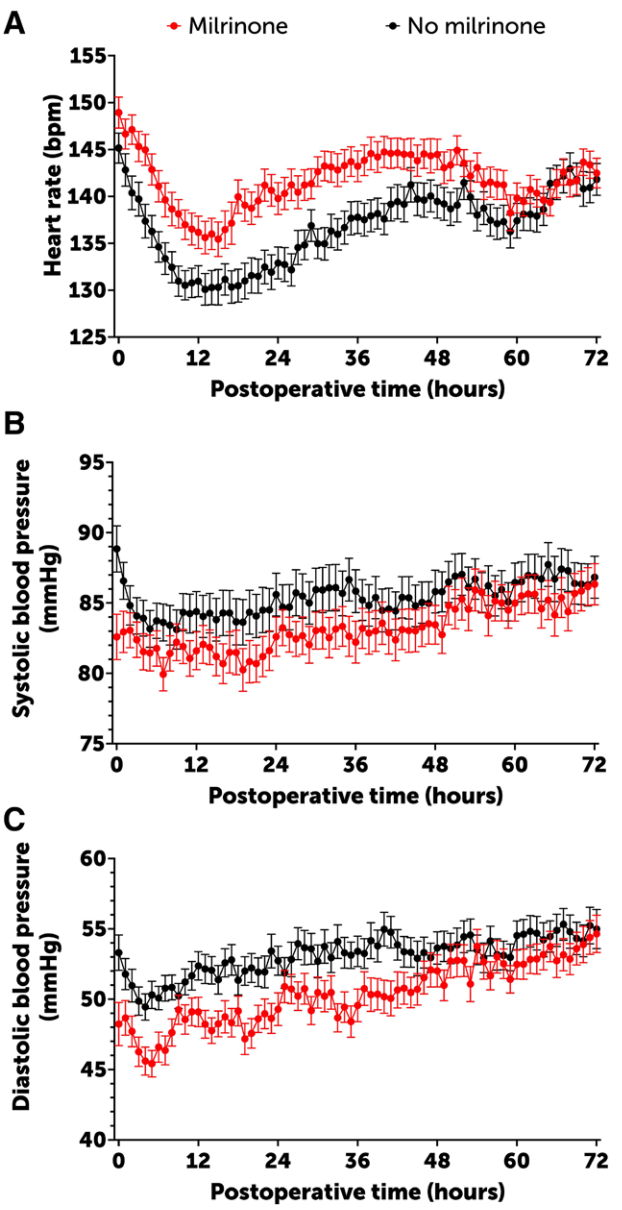

Figure 3. Hemodynamic differences between cohorts. A, Among PSM-matched patients, heart rate was higher in milrinone-treated than in nonmilrinone-treated patients during the first 72 postoperative hours (P = .001). During the first 12 postoperative hours, heart rate decreased more slowly in milrinone-treated patients (slope −0. 64 ± 0.06 BPM/h) than nonmilrinone-treated patients (slope −0. 94 ± 0.06 BPM/h, difference in slope is 0.30 [95% CI, 0.14 to 0.47] BPM/h, P < .001). Systolic (B) and diastolic (C) blood pressure were significantly lower over time between groups. Based on the models of these data (depicted in Supplemental Digital Content 5, Supplemental Figure 2, http://links.lww.com/AA/E483), the initial difference in SBP was −3.3 (95% CI, −6.4 to −0.3) mm Hg (P = .033) and the difference at 72 postoperative hours was −1.2 (95% CI, −4.2 to 1.9) mm Hg (P = .46); in DBP, the initial difference was −4.3 (95% CI, −6.2 to −2.6) mm Hg (P < .001) and difference at 72 postoperative hours was −1.1 (95% CI, −2.9 to 0.6) mm Hg (P = .219). A–C, Red indicates milrinone-treated and black indicates nonmilrinone-treated. Data are means and error is SEM. BPM indicates beats per minute; CI, confidence interval; DBP, diastolic blood pressure; PSM, propensity score matching; SBP, systolic blood pressure; SEM, standard error of the mean.

fever) increase systemic venous capacitance and therefore unstressed volume, diminishing RVEDV, stroke volume, and cardiac output. When restrictive physiology is severe, diminished stroke volume may cause a compensatory tachycardia, hypotension, and the need for volume administration to recruit end-diastolic volume and stroke work in the vasodilated state.

The impact of milrinone on restrictive physiologies has not been directly studied. The potent vasodilating properties of PDIs confound the rigorous assessment of changes in lusitropy or contractility, likely explaining the inconsistent findings of an independent

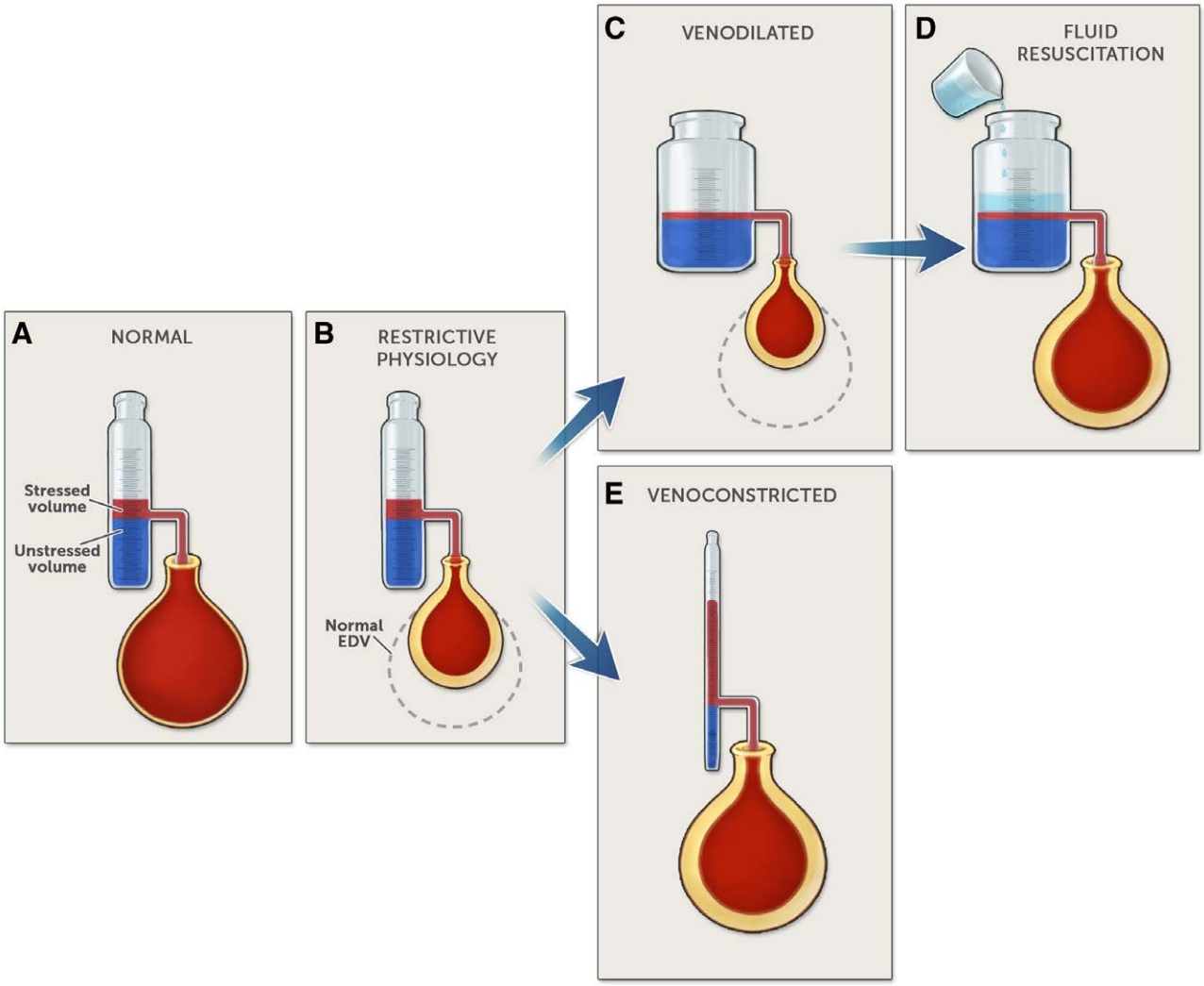

Figure 4. Intravascular volume, depicted by the column, can be subdivided into unstressed volume (blue) and stressed volume (red); only stressed volume generates the pressure head for ventricular filling. Unstressed volume represents the volume that must be filled before stressed volume is achieved. In the healthy state (A), a low-stressed volume (and atrial pressure) is required to achieve a normal EDV because ventricular compliance is normal. In restrictive ventricular physiology (B), this same low central venous pressure results in a lower EDV and stroke volume; such patients require a higher atrial pressure to maintain normal preload. In this circulation, vasodilators increase venous capacitance, reducing the fraction of the circulation devoted to stressed volume (C), lowering atrial pressure, EDV and stroke volume; this physiology, particularly when combined with arteriolar dilation, can result in hypotension. The recruitment of stroke work in this situation can be achieved through the administration of volume (D) or by the reduction in venodilated state (eg, reducing venodilation or inducing venoconstriction). In contrast, venoconstrictors decrease venous capacitance, raise stressed volume, centralize blood volume and increase stroke volume for a given intravascular volume (E). EDV indicates end-diastolic volume. Image credit: KaiOu Tang, MS.

positive inotropic action.[16] It has been suggested that the prevention of LCOS associated with milrinone administration can be entirely explained, in the absence of significant inotropic or lusitropic effects, by its potent afterload-reducing effects in the setting of depressed contractility.[17] One study demonstrated that a nitroprusside infusion (a pure vasodilator) resulted in equivalent improvements in pulmonary capillary wedge pressure and myocardial oxygen consumption as a milrinone infusion in patients with congestive heart failure.[18] When studied in the setting of an isolated heart preparation in which preload and afterload were held constant, milrinone's effect on contractility (vis-a-vis dP/dT, stroke work) and lusitropy (vis-a-vis dP/dT_{min}, tau, LVEDV) were similar to placebo.[19] This leaves milrinone's vasodilating properties uncompensated by an increase in EDV, which may be detrimental in a number of physiologies. Particularly in restrictive physiologies in which EDV is largely fixed, a reduction in afterload precipitates hypotension with negligible change in stroke volume[17]; when the effects of preload are considered, stroke volume likely decreases due to the dominant effects of venodilation. This physiology may explain why milrinone loading following coronary artery bypass grafting has been associated with hypotension,[20] and why its use in ischemia-related heart failure resulted in increased mortality and rehospitalization.[4] Similarly, despite

transient improvements in clinical signs of LCOS (eg, cool extremities), the PRIMACORP study described a mean 10% reduction in systolic blood pressure from baseline in the hours following milrinone loading, findings that were absent in patients receiving placebo.[7] Therefore, the use of milrinone to avert LCOS must be critically reconsidered in restrictive ventricular physiologies, which are common following congenital heart surgery.

There are several limitations to this study. First, intrinsic to this work as a retrospective cohort study is the possibility of selection bias. While we used propensity scoring to identify 2 groups that were equivalent in known risk factors, it is possible that our findings in part reflect unaccounted-for confounding variables, though none are apparent to us. The association between the use of milrinone and postoperative hemodynamics in restrictive physiologies could be more rigorously studied prospectively. Second, we examined changes in absolute blood pressures rather than those normalized to age (eg, Z-scores); however, given that the age distributions in the propensity-matched analysis were comparable, and that blood pressure *Z*-scores do not change substantively during the relevant timeframes, we believe this weakness to be of negligible impact. Third, inclusion in the milrinone cohort was categorical, and given the absence of a protocol guiding its use, the timing and dosing was variable amongst patients within the group. Finally, clinical practice surrounding transfusions, including platelet transfusions and albumin administration, was not protocolized and therefore may have differed between groups.

CONCLUSIONS

Milrinone use following TOF repair is associated with more frequent administration of volume, a positive association between higher total dose of postoperative milrinone and more postoperative volume administered, a higher heart rate, and a lower blood pressure. Milrinone use is not associated with improved cardiac output, including AVO_2 difference.

DISCLOSURES

Name: Kwannapas Saengsin, MD.
Contribution: This author collected the data, verified their accuracy, analyzed the data, wrote a first draft of the paper, and reviewed the final paper.
Name: Francesca Sperotto, MD.
Contribution: This author conceptualized the study, analyzed the data, and revised the final paper.
Name: Minmin Lu, MS.
Contribution: This author analyzed the data and revised the final paper.
Name: Julia Garcia Mancebo, MD.
Contribution: This author analyzed the data, responded to reviewers, and edited the final paper.
Name: Elizabeth Sacco, RN.
Contribution: This author collected and verified the data, and reviewed the final paper.
Name: Manasee Godsay, MS.
Contribution: This author collected and verified the data, and reviewed the final paper.
Name: James A. DiNardo, MD.
Contribution: This author conceptualized the study and edited the final paper.
Name: John N. Kheir, MD.
Contribution: This author conceptualized the study, supervised data collection, and wrote the final paper.
This manuscript was handled by: Nikolaos J. Skubas, MD, DSc, FACC, FASE.

REFERENCES

1. Rieg AD, Suleiman S, Perez-Bouza A, et al. Milrinone relaxes pulmonary veins in guinea pigs and humans. *PLoS One*. 2014;9:1–11.
2. Cody RJ, Müller FB, Kubo SH, Rutman H, Leonard D. Identification of the direct vasodilator effect of milrinone with an isolated limb preparation in patients with chronic congestive heart failure. *Circulation*. 1986;73:124–129.
3. Abulhasan YB, Ortiz Jimenez J, Teitelbaum J, Simoneau G, Angle MR. Milrinone for refractory cerebral vasospasm with delayed cerebral ischemia. *J Neurosurg*. 2020;134:971–982.
4. Felker GM, Benza RL, Chandler AB, et al; OPTIME-CHF Investigators. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol*. 2003;41:997–1003.
5. Biddle TL, Benotti JR, Creager MA, et al. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. *Am J Cardiol*. 1987;59:1345–1350.
6. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation*. 1986;73:III175–III183.
7. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation*. 2003;107:996–1002.
8. Burkhardt BEU, Rücker G, Stiller B. Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. *Cochrane Database Syst Rev*. 2015:CD009515. doi:10.1002/14651858.CD009515.pub2.
9. Donato RMD, Jonas RA, Lang P, Rome JJ, Mayer JEJ, Castaneda AR. Neonatal repair of tetralogy of Fallot with and without pulmonary atresia. *J Thorac Cardiovasc Surg*. 1991;101:126–137.
10. Pigula FA, Khalil PN, Mayer JE, Nido PJ, Jonas RA. Repair of tetralogy of Fallot in neonates and young infants. *Circulation*. 1999;100:II157–II161.
11. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11:234–238.
12. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161.
13. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.

14. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr*. 2008;21:922–934.
15. Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care*. 2016;20:1–11.
16. Sonnenblick EH, Grose R, Strain J, Zelcer AA, LeJemtel TH. Effects of milrinone on left ventricular performance and myocardial contractility in patients with severe heart failure. *Circulation*. 1986;73:III162–III167.
17. DiNardo JA, Nasr VG. Milrinone administration and pediatric cardiac surgery: beloved but sadly misunderstood. *J Cardiothorac Vasc Anesth*. 2021;35:2079–2081.
18. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation*. 1986;73:III168–III174.
19. DeWitt ES, Black KJ, Thiagarajan RR, et al. Effects of commonly used inotropes on myocardial function and oxygen consumption under constant ventricular loading conditions. *J Appl Physiol*. 2016;121:7–14.
20. Jeon Y, Ryu JH, Lim YJ, et al. Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. *Eur J Cardiothorac Surg*. 2006;29:952–956.