Journal of Cardiothoracic and Vascular Anesthesia 000 (2020) 1–9

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Levosimendan Versus Milrinone for Inotropic Support in Pediatric Cardiac Surgery: Results From a Randomized Trial

Elin M. Thorlacius, MD[*,‡,1], Håkan Wåhlander, MD, PhD[†,‡], Tiina Ojala, MD, PhD[§], Kaisa Ylänen, MD, PhD[§], Juho Keski-Nisula, MD[¶], Mats Synnergren, MD, PhD[‖], Birgitta S. Romlin, MD, PhD[*,‡], Sven-Erik Ricksten, MD, PhD[*,‡], Albert Castellheim, MD, PhD[*,‡]

[*]*Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[†]*Department of Pediatric Cardiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[‡]*Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden*
[§]*Department of Pediatric Cardiology, Children's Hospital, Helsinki University Hospital, Helsinki University, Helsinki, Finland*
[¶]*Department of Anesthesia and Intensive Care, Children's Hospital, Helsinki University Hospital, Helsinki University, Helsinki, Finland*
[‖]*Department of Pediatric Thoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden*

Objective: The present study aimed to determine the differential effects of intraoperative administration of milrinone versus levosimendan on myocardial function after pediatric cardiac surgery. Transthoracic echocardiography was used for myocardial function evaluation using biventricular longitudinal strain with 2-dimensional speckle tracking echocardiography in addition to conventional echocardiographic variables.
Design: A secondary analysis of a randomized, prospective, double-blinded clinical drug trial.
Setting: Two pediatric tertiary university hospitals.
Participants: Infants between 1 and 12 months old diagnosed with ventricular septal defect, complete atrioventricular septal defect, or tetralogy of Fallot who were scheduled for corrective surgery with cardiopulmonary bypass.
Interventions: The patients were randomly assigned to receive an infusion of milrinone or levosimendan at the start of cardiopulmonary bypass and for 26 consecutive hours.
Measurements and Main Results: Biventricular longitudinal strain and conventional echocardiographic variables were measured preoperatively, on the first postoperative morning, and before hospital discharge. The association between perioperative parameters and postoperative myocardial function also was investigated. Images were analyzed for left ventricular (n = 67) and right ventricular (n = 44) function. The day after surgery, left ventricular longitudinal strain deteriorated in both the milrinone and levosimendan groups (33% and 39%, respectively). The difference was not significant. The corresponding deterioration in right ventricular longitudinal strain was 42% and 50% (nonsignificant difference). For both groups, biventricular longitudinal strain approached preoperative values at hospital discharge. Preoperative N-terminal pro-brain natriuretic peptide could predict the left ventricular strain on postoperative day 1 ($p = 0.014$).
Conclusions: Levosimendan was comparable with milrinone for left and right ventricular inotropic support in pediatric cardiac surgery.

Key Words: speckle tracking; longitudinal strain; congenital heart defect; cardiopulmonary bypass; randomized clinical trial; infant; milrinone; levosimendan

This work was supported by grants from the Swedish state under the agreement between the Swedish government and the country councils, the ALF agreement.
[1]*Address reprint requests to* Elin M. Thorlacius, MD, Sahlgrenska University Hospital, Rondvägen 10, 41650 Gothenburg, Sweden.
E-mail address: elin.thorlacius@gu.se (E.M. Thorlacius).

https://doi.org/10.1053/j.jvca.2020.02.027
1053-0770/

INODILATORS ARE widely used to reduce the risk of low cardiac output syndrome (LCOS) after cardiac surgery with cardiopulmonary bypass (CPB) in children. In this setting, milrinone is the drug of choice.[1] Levosimendan also is being used for preventing or treating LCOS after pediatric surgery in children.[2] It has been demonstrated that levosimendan is safe and at least as effective as milrinone in maintaining cardiac output in the pediatric postcardiac surgery setting.[3-5] To the authors' knowledge, no studies have compared the effect of these 2 inodilators on myocardial function in children as assessed with longitudinal strain (LS) using 2-dimensional speckle tracking echocardiography (2D STE). Speckle tracking echocardiography (STE) is a relatively new method, which is being used increasingly to detect left ventricular (LV) and right ventricular (RV) dysfunction. STE measures the relative movement of myocardial gray-scale alterations (speckle patterns) and thereby can quantify regional and global systolic deformation and strain, describing percentage changes in myocardial segment length. It is dimensionless and angle-independent with good feasibility and reproducibility. In the longitudinal axis of the heart the myocardium shortens during the contraction in systole, hence the negative value of strain (percentage shortening compared with diastole) demonstrates the myocardial function. Strain measured along the longitudinal axis is the most widely used and best-evaluated method.[6,7] The recently published pediatric reference values for left ventricular longitudinal strain (LV-LS) (GE Medical Systems) shows −17.5% to be the cutoff for normal.[8] LS has been demonstrated to be more sensitive to detect changes in myocardial function than traditional echocardiography parameters.[9] Furthermore, it has a good correlation with LV ejection fraction (LVEF) measured with magnetic resonance imaging.[6] Earlier studies have demonstrated that LS is impaired significantly on postoperative day (POD) 1 after cardiac surgery in children and that it does not completely recover by hospital discharge compared with preoperative values.[7,10]

In the present study, the potentially differential effect of levosimendan and milrinone on biventricular LS in the early postoperative period in infants undergoing corrective cardiac surgery was investigated, and the null hypothesis that these 2 inodilators exert comparable effects on LV and RV systolic function was tested.

Material and Methods

Study Design and Patients

The present study was a secondary analysis of a randomized, prospective, double-blinded clinical drug trial called MiLe-1. The primary objective in MiLe-1 was to investigate the differential effects of milrinone and levosimendan on the incidence of acute kidney injury post-pediatric cardiac surgery. The details of MiLe-1 have been described elsewhere.[11] Briefly, that study included 72 infants ages 1 to 12 months old with 3 different congenital heart defect diagnoses who were scheduled for elective corrective open-heart surgery with CPB. The patient diagnoses were nonrestrictive ventricular septal defect (VSD); complete atrioventricular septal defect (AVSD) with nonrestrictive VSD and balanced ventricles; and Tetralogy of Fallot (ToF). The patients were recruited from October 2014 until April 2017 in 2 centers of congenital cardiac surgery (Sweden and Finland). Written informed consent was obtained from the parents before the surgery. The study was approved by the Swedish Medical Agency and the Regional Ethics Committees in both countries. Exclusion criteria included lack of written informed consent from parents, previous open-heart surgery, ongoing infection, renal disease, use of nephrotoxic drugs or contrast agents within 24 hours before surgery, prematurity, preoperative need for mechanical ventilation and/or vasoactive drugs, and/or extracorporeal membrane oxygenation. The medical staff and the cardiologist who analyzed the echocardiography images were blinded to the study drug. The patients were randomly assigned to receive either milrinone or levosimendan. The drug infusion was initiated in the operating room immediately after the start of CPB with a loading dose of 12 μg/kg of levosimendan or 48 μg/kg of milrinone, followed by a corresponding infusion of 0.1 μg/kg/min of levosimendan or 0.4 μg/kg/min of milrinone. The protocol allowed the anesthesiologist in charge to administer an extra bolus dose (half the loading dose) after weaning of CPB if the myocardial function was reduced on the routine transesophageal echocardiogram performed at weaning from CPB. The infusion rate also could be increased up to 0.16 μg/kg/min levosimendan or 0.67 μg/kg/min milrinone at any time after CPB weaning until the drug infusion was stopped. The drug was infused for 24 hours, followed by a weaning period of 2 hours, when the infusion rate was reduced to 50% and thereafter it was stopped. If the patient needed additional inotropic therapy after weaning, milrinone infusion was started.

There was a standardized operating procedure regarding the surveillance and treatment of the hemodynamic status with predefined target values. The target mean arterial pressure during and after CPB was 30 mmHg and 45 mmHg, respectively. The target levels of serum hemoglobin, serum lactate, and ionized calcium in serum were >100 g/L, < 2 mmol/L, and >1.2 mmol/L, respectively. Hemodynamic data were documented at the following time points: immediately after CPB weaning (0 h); at 2, 6, 12, and 24 hours after CPB; and at the time of the echocardiography on POD 1. The age-based Ross classification for heart failure in children[12] was used to grade the preoperative heart failure in the patients. The Comprehensive Aristotle score[13] and the risk adjustment for congenital heart surgery (RACHS-1) score[14] were used as risk assessment tools. The inotropic score (IS) was calculated according to Wernovsky with a slight modification.[15] Norepinephrine was added to the formula in line with Gaies's vasoactive IS.[16]

Echocardiography

The echocardiographic images (Epiq 7; Philips, Amsterdam, The Netherlands, and Vivid E95; GE Healthcare, Chicago, IL) were recorded preoperatively, on the morning of POD 1 (while ongoing study drug infusion) and before discharge from the hospital. STE strain measurements and automated 2D LVEF and fractional area change for the right ventricle (RV-FAC) were analyzed from the apical 4-chamber view. The STE strain

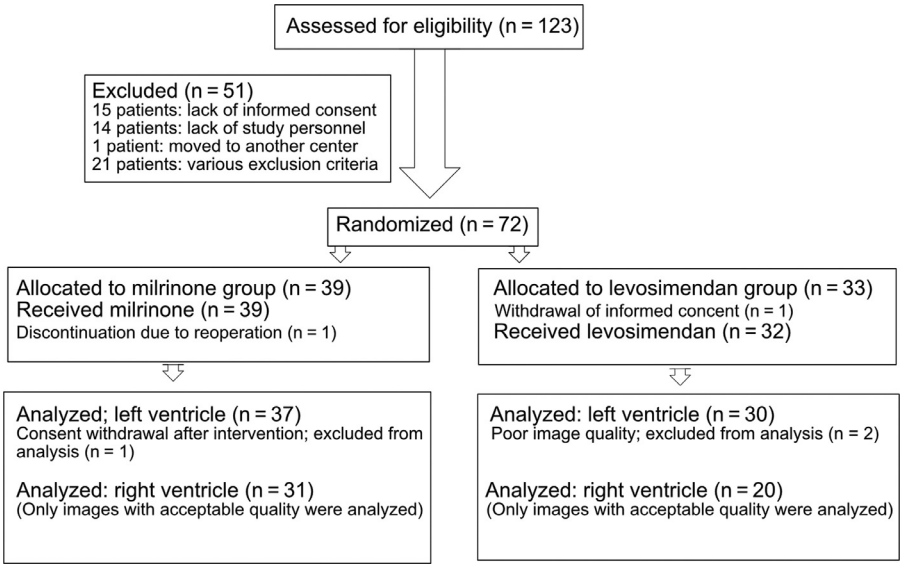

Fig 1. Study Consort flow chart. Additional details regarding the inclusion and exclusion of patients were published previously.[11]

analyses were performed by 1 senior pediatric cardiologist (T.O.) who used the VVI program (Syngo USWP 3.0; Siemens Healthineers, Erlangen, Germany), as described previously.[17,18] Manual tracing of the LV endocardial surface was performed in a single still frame in midsystole. Tracing began at the septal edge of the mitral valve annulus, was extended to the apex, and was returned to the lateral edge of the mitral valve annulus. For the right ventricle, the manual tracing of the endocardial surface began at the edge of the tricuspid valve annulus, extended to the apex of the ventricle without incorporation of the papillary muscle complex, and returned basally to the septal edge of the tricuspid valve annulus. Velocity vectors then were calculated automatically for each frame of the cardiac cycle with the VVI algorithm. Tracings were accepted only when the endocardial border was followed correctly throughout the entire cardiac cycle. Individual regions of the border were adjusted until the border was tracked correctly for each frame when necessary. The VSD area or postoperatively the patch area was rejected from the analysis.

Statistical Analysis

A power calculation was performed for the postoperative incidence of acute kidney injury in MiLe-1.[11] In order to evaluate the sample size for the current substudy, a post-hoc power calculation based on the absolute values of LV-LS on POD 1, the primary endpoint, in the whole study sample was performed. To detect a 30% difference in LV-LS on POD 1 between the 2 study groups, with a power of 80%, a level of significance of 0.05, and at a standard deviation of 4.1, 19 patients were needed in each group, and for a difference of 25%, 27 patients were needed in each group.

For comparison between groups, the Fisher exact test was used for dichotomous variables, the chi-square test was used for non-ordered categorical variables, and the Mann-Whitney *U* test was used for continuous variables. Mixed-model repeated measurements were used to investigate differences between and within the groups over time (group *v* time interaction) assuming unstructured covariance pattern. Linear regression analyses were performed to relate LV-LS on POD 1 to the following independent variables: congenital heart lesion, age, preoperative N-terminal pro-brain natriuretic peptide (NTproBNP), center, study drug, age-based Ross classification, Comprehensive Aristotle score, and CPB time. For evaluation of statistical

Table 1
Patient Demographic and Perioperative Data

	Levosimendan (n = 32)	Milrinone (n = 38)
Age at surgery (mo)	5.9 (2.9)	5.6 (2.7)
Gestational age (wk)	38.4 (2.3)	38.6 (2.2)
Preoperative weight (kg)	6.4 (2.0)	6.2 (1.5)
Male	16 (50.0%)	18 (47.4%)
Female	16 (50.0%)	20 (52.6%)
Nonrestrictive VSD	13 (40.6%)	14 (36.8%)
Complete AVSD	7 (21.9%)	8 (21.1%)
Tetralogy of Fallot	12 (37.5%)	16 (42.1%)
Preoperative fractional shortening (%)	36.4 (6.3)	39.2 (6.8)
Preoperative serum NT-proBNP (ng/L)	2,622 (6,276)	2,474 (4,539)
CPB duration (min)	90 (33)	93 (45)
ACC duration (min)	61 (23)	62 (33)
Lowest temperature during CPB (°C)	33.7 (1.8)	33.7 (1.4)
Age-based Ross classification	4.8 (3.4)	4.7 (3.4)
RACHS-1 score 2	25 (78.1%)	30 (78.9%)
RACHS-1 score 3	7 (21.9%)	8 (21.1%)
Comprehensive Aristotle score	9.0 (2.6)	8.3 (2.0)

NOTE. Values are presented as mean ± standard deviation or numbers (n, %). Data in this table were reported previously.[11] There were no significant differences among the variables.

Abbreviations: ACC, aortic cross-clamp time; AVSD, complete atrioventricular septal defect; CPB, cardiopulmonary bypass; NTproBNP, N-terminal pro-brain natriuretic peptide; RACHS-1, risk adjustment for congenital heart surgery; VSD, nonrestrictive ventricular septal defect.

significance, p values <0.05 were chosen. The data were analyzed using SAS, Version 9.4 (SAS Inc, Cary, NC) and IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY). Figures were created in GraphPad Prism 8.0.0 for Windows (GraphPad Software, San Diego, CA).

Results

Patient Demographics

The study Consort flow chart is illustrated in Figure 1. There were no significant differences in the demographic data between the treatment groups (Table 1). Regarding the study drug, only 1 patient in the levosimendan group and 2 patients in the milrinone group received an extra bolus of study drug during CPB weaning. The infusion rate of the study drug was increased in 2 patients in each group. Concerning the vasoactive agents, none of the patients received dopamine, dobutamine; or vasopressin; consequently, the calculation of the IS was based on norepinephrine and epinephrine.

The echocardiographic examination before hospital discharge was performed on day 7 (5-8) (median interquartile range) in the milrinone group and on day 7 (6-11) in the levosimendan group.

Hemodynamics and Clinical Outcome Variables

Hemodynamic variables are depicted in Figure 2, *A* and *B*. Early after weaning from CPB, heart rate and mean arterial pressure increased, whereas central venous pressure decreased. Central venous saturation and serum lactate decreased, whereas the IS remained largely constant. These patterns were similar for both groups. In fact, there were no significant differences in the hemodynamic variables between the groups over time (see Fig 2, *A* and *B*) or at the time of echocardiographic examination on POD 1 (data not shown). In addition, there were no significant differences between the groups regarding the clinical outcome regarding time on the ventilator, hospital stay, or mortality and adverse advents (Table 2).

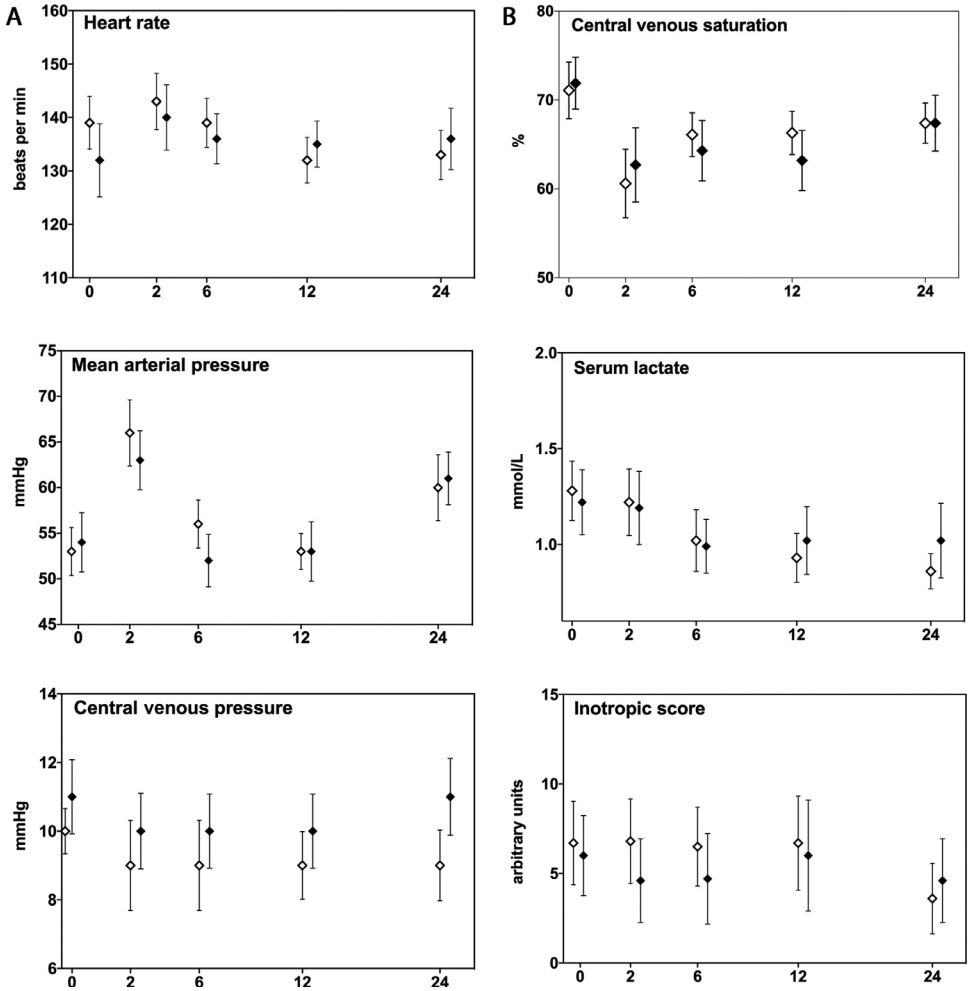

Fig 2. Hemodynamics over time in the 2 study groups. (A) Heart rate, mean arterial pressure,* and central venous pressure. (B) Central venous saturation,* serum lactate,* and inotropic score.* *Filled rhomboids* represent levosimendan and *non-filled rhomboids* milrinone. *Horizontal axes* show hours after cardiopulmonary bypass weaning and *vertical axes* measurement units. Data are presented as mean with 95% confidence interval. There were no significant differences between groups over time in any of the variables. *Data were published previously.[11]

Table 2
Clinical Outcome and Adverse Events

	Levosimendan n = 32	Milrinone n = 38	p Value
Hemodynamic support (POD 1)			
Active external atrioventricular pacing	4 (12.5%)	2 (5.3%)	0.40
Antiarrhythmic agents			
Amiodarone	4 (12.5%)	3 (8.1%)	0.83
Beta blocker	1 (3.1%)	0 (0%)	0.93
Others	0 (0%)	0 (0%)	1.00
Nitric oxide	4 (12.5%)	2 (5.3%)	0.54
Norepinephrine and/or epinephrine	15 (46.9%)	22 (57.9%)	0.47
Inotropic score	0 (0-10.5)	3 (0-8)	0.59
Adverse events*			
Junctional ectopic tachycardia	3 (9.4%)	7 (17.9%)	0.49
Atrioventricular block III	2 (6.3%)	0 (0.0%)	0.21
Sinus tachycardia (>180/min)	0 (0.0%)	0 (0.0%)	1.00
Other outcome parameters*			
Length of ventilator support (h)	30.0 (15.5-54.5)	21.0 (10.0-32.5)	0.21
PICU stay (d)	3.0 (2.0-5.5)	2.0 (2.0-3.0)	0.06
Hospital stay (d)	9.5 (8.0-14.5)	8.0 (7.0-11.0)	0.10
28-d mortality	0 (0.0%)	0 (0.0%)	1.00

NOTE. Data are presented as numbers (n, %) or median (interquartile range).
Abbreviations: PICU, pediatric intensive care unit; POD 1, postoperative day 1.
* Values were reported previously.[11]

Echocardiographic Analyses

Biventricular LS in the study groups is demonstrated in Figure 3, and all echocardiographic variables are shown in Table 3. Cardiac surgery induced a significant deterioration in LV-LS (less negative LS) measured at POD 1 compared with the preoperative value both in the milrinone group (33% deterioration; $p < 0.0001$) and in the levosimendan group (39% deterioration; $p < 0.0001$). At hospital discharge, LV-LS had recovered partially to the preoperative level in both groups.

When compared over time, there was a significant difference between the 2 groups ($p = 0.020$), probably reflecting slightly different patterns of changes in LV-LS. In post-hoc analyses of the 3 different measurement time points, LV-LS did not differ significantly between the treatment groups (preoperative, POD 1, and before discharge from hospital [$p = 0.57$, 0.12, and 0.14, respectively]). Thus, although not significant, there was a trend for more impaired LV-LS in the levosimendan group compared with the milrinone group on POD 1, whereas at discharge from the hospital, there was a trend for more impaired LV-LS in the milrinone group.

RV-LS also decreased on POD 1 compared with the preoperative value both in the milrinone group (42% deterioration; $p < 0.0001$) and in the levosimendan group (50% deterioration; $p < 0.0001$) with only partial recovery at hospital discharge in both groups. Postoperative changes in RV-LS, LVEF, and RV-FAC did not differ between the groups over time. There was a trend for a lower LVEF on POD 1 in the levosimendan group (31% *v* 36%; $p = 0.065$), with no difference at hospital discharge.

When the biventricular LS measurements in the whole study population were divided by the type of cardiac lesion, the changes in strain measurements over time looked quite similar (Fig 4), except for the low preoperative value of RV-LS in patients with VSD. In fact, there was no significant difference between the type of heart defects over time for LV-LS and RV-LS ($p = 0.84$ and 0.16, respectively) and LVEF and RV-FAC ($p = 0.94$ and 0.97, respectively).

The linear regression model demonstrated a significant relationship between preoperative NTproBNP and LV-LS on POD 1 ($p = 0.014$; beta-score 0.9 [95% confidence interval 0.2-1.6]), whereas other variables were not associated with LV-LS on POD-1. Additional information on the parameters can be found in Supplementary Table S1 and Supplementary Figs S1 and S2.

Discussion

In the present study, the potentially different effects of levosimendan and milrinone on biventricular systolic function, assessed by strain echocardiography, early after pediatric cardiac surgery were evaluated. The main finding was that there were no significant differences between the groups with respect to early (POD 1) or late (hospital discharge) LV-LS or RV-LS. Furthermore, neither of the inodilators could prevent a substantial decrease in LV-LS (30%-40%) or RV-LS (40%-50%) the day after surgery. In addition, biventricular LS was only partially restored at the time of hospital discharge. Finally, there was a significant correlation between preoperative NTproBNP and LV-LS on POD 1.

To the authors' knowledge, this is the first study to evaluate and compare the effects of these 2 inotropic agents on LV and RV systolic function with the use of 2D STE in pediatric cardiac surgery. In a blinded, randomized clinical trial, Pellicer et al. compared the effect of levosimendan and milrinone on 20 neonates undergoing open-heart surgery. They reported the number of patients experiencing ejection fraction <55% and fractional shortening (FS) <28% on POD 1 and found no significant difference between the 2 groups.[3] Lechner et al. compared the effects of levosimendan and milrinone on FS and on the cardiac index (measured with transesophageal Doppler technique) in 40 infants after cardiac surgery. They found no significant difference in postoperative FS measured up to 48 hours after CPB or in the cardiac index between the 2 groups. However, the patients in the levosimendan group had an increase in cardiac index over time, whereas it remained stable over time in the milrinone group.[4] In neither of these studies was a bolus dose of the inotropic agent administered during CPB.

In a recent blinded randomized study on 31 adult patients with normal preoperative myocardial function undergoing aortic valve replacement for aortic stenosis, Fredholm et al.[19]

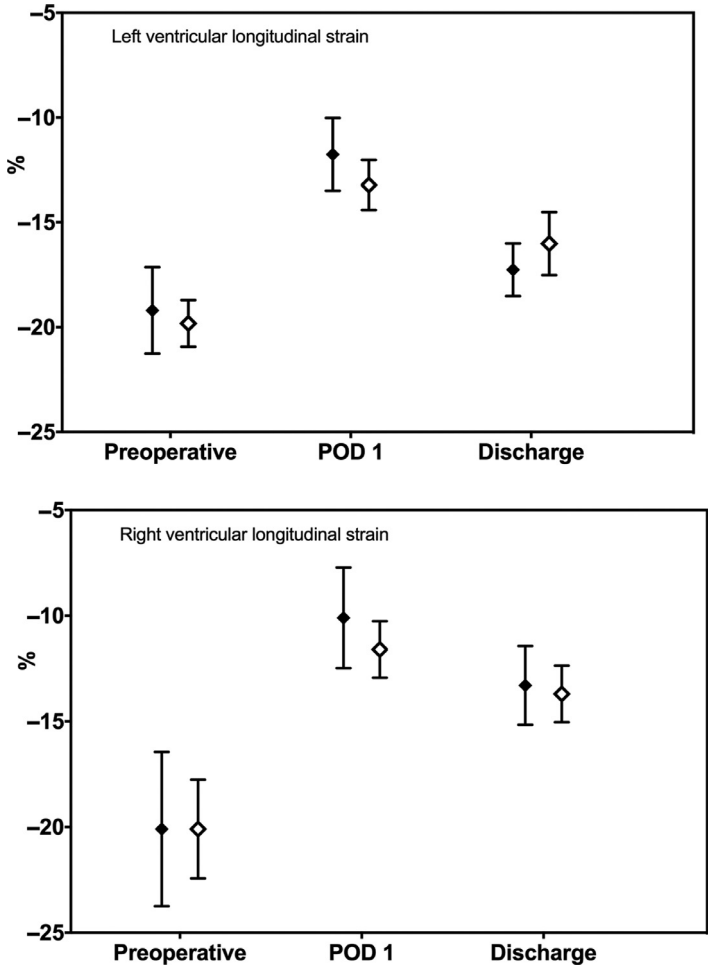

Fig 3. Left ventricular and right ventricular longitudinal strain in the 2 study groups. Longitudinal strain represents the shortening of the myocardium in systole compared with diastole in the longitudinal plane, hence the unit of negative percent on the y-axis. Data are presented as mean values with 95% confidence interval. *Filled rhomboids* resemble the levosimendan group and *non-filled rhomboids* the milrinone group. The 3 time points of the strain measurements were preoperative, on postoperative day 1, and at discharge from the hospital. Left ventricular and right ventricular longitudinal strain were impaired in both groups on postoperative day 1 compared with the preoperative values, and they had only partially recovered at hospital discharge. POD, postoperative day.

compared the effect of levosimendan and milrinone on early postoperative LV-LS. The study drug infusion was initiated after arrival to the intensive care unit, and the strain measurements were performed during 3 hours, whereas the inotrope was administered in a step-up fashion. During this period, preload, afterload, and heart rate were maintained at a constant level. Both drugs induced a dose-dependent improvement in LV-LS and cardiac index, but there was no significant difference between the effect of these 2 inodilators on either LV-LS or cardiac index. The present study confirms the results of these prior studies that levosimendan and milrinone exert comparable LV inotropic effects in the early postoperative period after cardiac surgery.

In the present study, several new aspects provide valuable information regarding the effect of these 2 inotropes on the myocardial function in this young patient group undergoing cardiac surgery. First, the present study is, to the authors' knowledge, the first randomized study in patients with ToF, VSD, and AVSD, in patients 1 to 12 months old that investigated cardiac function in connection with a perioperative infusion of milrinone or levosimendan. Second, STE and strain, a relatively new technique in echocardiography that is more sensitive to detect changes in myocardial function than traditional echocardiography parameters, were used.[9] Third, biventricular function was examined and finally, a loading dose of the inotropic agent was administered at the initiation of CPB, aiming for obtaining an early effect of the drug. In the authors' institutions, it is routine practice to initiate the inotropic infusion around the time of CPB initiation, with or without a loading dose, with the purpose of reducing the risk of LCOS.

The pattern of reduction of myocardial function early after cardiac surgery with partial restoration of function during the hospital stay was similar to what has been reported earlier.[20] In the present study, preoperative NTproBNP predicted worse LV-LS on POD 1. Even though Carmona et al. found a correlation between preoperative NTproBNP and clinical parameters of LCOS,[21] the association between preoperative NTproBNP on LV-LS after cardiac surgery in children, to the authors' knowledge, has not been studied. The correlation of age, age-

Table 3
Echocardiographic Parameters

	LV-LS (%)				LVEF (%)			
	Levosimendan	Milrinone	p Value		Levosimendan	Milrinone	p Value	
			Between Groups	Interaction			Between Groups	Interaction
Preoperative	−19.2 (5.5)	−19.8 (3.3)	0.57		52 (7)	51 (9)	0.77	
POD 1	−11.8 (4.6)	−13.2 (3.6)	0.12		31 (11)	36 (7)	0.065	
At discharge	−17.3 (3.3)	−15.7 (3.8)	0.14	0.020	43 (9)	42 (7)	0.77	0.096
$P_{\text{within groups}}$ Preop/POD 1	<0.0001	<0.0001			< 0.0001	<0.0001		
$P_{\text{within groups}}$ Preop/discharge	0.051	<0.0001			0.0002	<0.0001		
	RV-LS (%)				R-FAC (%)			
	Levosimendan	Milrinone	p Value		Levosimendan	Milrinone	p Value	
			Between Groups	Interaction			Between Groups	Interaction
Preoperative	−20.1 (6.6)	−20.1 (5.9)	0.96		30 (9)	28 (8)	0.49	
POD 1	−10.1 (4.3)	−11.6 (3.4)	0.23		23 (11)	27 (8)	0.13	
At discharge	−13.3 (3.5)	−13.7 (3.1)	0.69	0.69	31 (9)	29 (9)	0.56	0.15
$P_{\text{within groups}}$ Preop/POD-1	<0.0001	<0.0001			0.021	0.76		
$P_{\text{within groups}}$ Preop/discharge	<0.0001	<0.0001			0.77	0.59		

NOTE. Values are presented as mean (standard deviation).
Abbreviations: FAC, fractional area change; LS, longitudinal strain, LV, left ventricle; LVEF, left ventricular ejection fraction; $P_{Interaction}$, P interaction is between groups; POD 1, postoperative day 1; Preop, preoperative; RV, right ventricle.

based Ross classification, the Comprehensive Aristotle score, and CPB time with LV-LS on POD 1 in the present study was weak. This probably was because of the fairly homogenous study population. Perdreau et al. found a correlation between aortic cross-clamp time >30 minutes and worse postoperative LV-LS.[7] De Boer et al. investigated postoperative LS in a more heterogenous pediatric population compared with that of the present study and found a correlation between CPB time and aortic cross-clamp time with RV-LS but not LV-LS.[10]

There was no association between the type of heart defect and LV-LS postoperatively. This was despite the fact that the hemodynamics in VSD, AVSD, and ToF result in different types of load on the left ventricle. In the present study's patient population, there was a variation in LV-LS preoperatively, and patients with more affected preoperative LV-LS seemed to exhibit worse LV function in terms of LV-LS on POD 1. However, the variation in preoperative LV-LS was not a result of a systematic variation between patients with different heart defects, but rather a variation across the entire cohort.

The present study has several limitations. The patient population was restricted to merely 3 diagnoses with an age span of 1 to 12 months, which makes it difficult to generalize the results to more complex diagnoses and other age groups. Another limitation was the lack of a placebo group. However, in the authors' institutions, milrinone is used routinely to reduce the risk of LCOS postoperatively, and in this setting, including a placebo group and withholding patients from active treatment would have been ethically unjustified. Finally, some data on RV function were missing because the evaluations of RV-LS are technically more challenging compared with those for LV-LS,[22] especially on POD 1 when the acoustic window often is poor.

The strengths of this study included it being a double-blinded, randomized clinical trial performed in 2 centers. Second, the responsible physicians followed a study protocol to maintain the hemodynamic status of the patients as similar as possible. In fact, there were no significant differences between the study groups over time regarding hemodynamic variables. Third, all the strain analyses were performed by a single cardiologist blinded to the study groups. Fourth, to have a fairly homogenous study population, only patients ages 1 to 12 months old with VSD, AVSD, or ToF undergoing corrective surgery were included.

In conclusion, there were no significant differences between the groups with respect to early or late LV or RV systolic function assessed with STE after corrective heart surgery for ToF, AVSD, or VSD.

Acknowledgment

The authors would like to devote a few words to the memory of their colleague Pertti Suominen. To the authors' great sorrow, Suominen passed away in January 2018. He was a great friend and the main investigator for the trial in Helsinki.

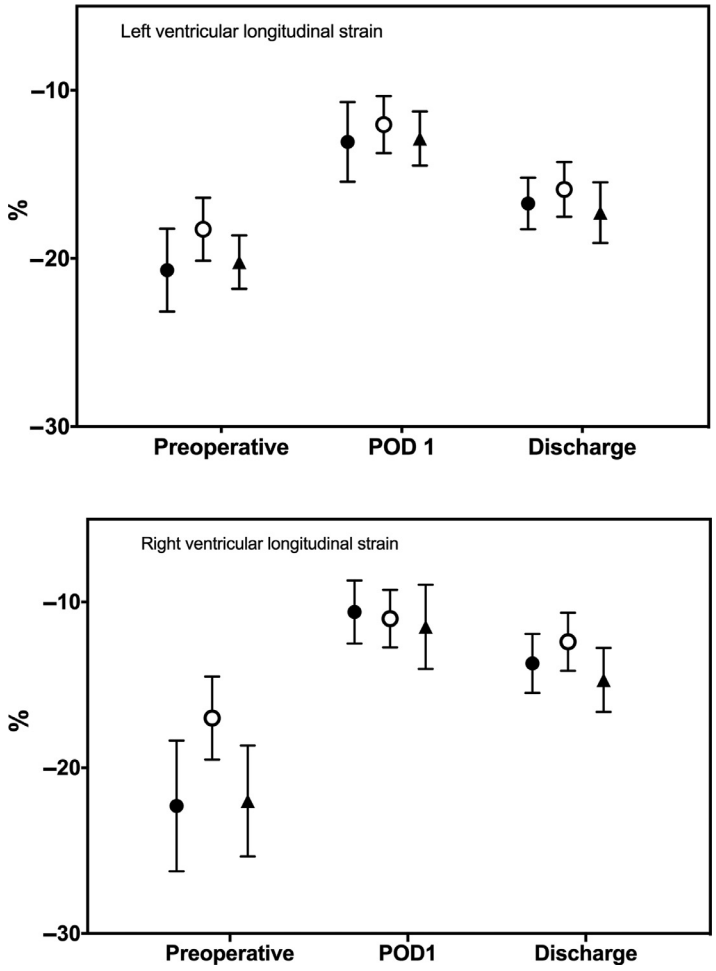

Fig 4. Left ventricular and right ventricular longitudinal strain in the whole study population differentiated by the type of congenital heart defect. Longitudinal strain represents the shortening of the myocardium in systole compared with diastole in the longitudinal plane, hence the unit of negative percent on the y-axis. Data are presented as mean values with 95% confidence interval. *Empty circles resemble* ventricular septal defect, *filled circles* atrioventricular septal defect, and *filled triangles* tetralogy of Fallot. The 3 time points of the strain measurements were preoperative, on postoperative day 1, and at discharge from the hospital. The changes in strain over time were quite similar for the 3 types of heart lesions, except for the preoperative right ventricular longitudinal strain of the patients with ventricular septal defect. POD, postoperative day.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.02.027.

References

1 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.
2 Amiet V, Perez MH, Longchamp D, et al. Use of levosimendan in postoperative setting after surgical repair of congenital heart disease in children. Pediatr Cardiol 2018;39:19–25.
3 Pellicer A, Riera J, Lopez-Ortego P, et al. Phase 1 study of two inodilators in neonates undergoing cardiovascular surgery. Pediatr Res 2013;73:95–103.
4 Lechner E, Hofer A, Leitner-Peneder G, et al. Levosimendan versus milrinone in neonates and infants after corrective open-heart surgery: A pilot study. Pediatr Crit Care Med 2012;13:542–8.
5 Momeni M, Rubay J, Matta A, et al. Levosimendan in congenital cardiac surgery: A randomized, double-blind clinical trial. J Cardiothorac Vasc Anesth 2011;25:419–24.
6 Colquitt JL, Pignatelli RH. Strain Imaging: The emergence of speckle tracking echocardiography into clinical pediatric cardiology. Congenit Heart Dis 2016;11:199–207.
7 Perdreau E, Seguela PE, Jalal Z, et al. Postoperative assessment of left ventricular function by two-dimensional strain (speckle tracking) after paediatric cardiac surgery. Arch Cardiovasc Dis 2016;109:599–606.
8 Dallaire F, Slorach C, Bradley T, et al. Pediatric reference values and Z score equations for left ventricular systolic strain measured by two-dimensional speckle-tracking echocardiography. J American Soc Echocardiog 2016;29:786–93.
9 Van der Ende J, Vazquez Antona CA, Erdmenger Orellana J, et al. Left ventricular longitudinal strain measured by speckle tracking as a predictor of the decrease in left ventricular deformation in children with congenital stenosis of the aorta or coarctation of the aorta. Ultrasound Med Biol 2013;39:1207–14.
10 de Boer JM, Kuipers IM, Klitsie LM, et al. Decreased biventricular longitudinal strain shortly after congenital heart defect surgery. Echocardiography 2017;34:446–52.

11 Thorlacius EM, Suominen PK, Wåhlander H, et al. The effect of levosimendan versus milrinone on the occurrence rate of acute kidney injury following congenital heart surgery in infants: A randomized clinical trial. Pediatr Crit Care Med 2019;20:947–56.

12 Ross RD. The Ross classification for heart failure in children after 25 years: A review and an age-stratified revision. Pediatr Cardiol 2012;33:1295–300.

13 Lacour-Gayet F, Clarke D, Jacobs J, et al. The Aristotle score: A complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg 2004;25:911–24.

14 Jenkins KJ, Gauvreau K. Center-specific differences in mortality: Preliminary analyses using the Risk Adjustment in Congenital Heart Surgery (RACHS-1) method. J Thorac Cardiovasc Surg 2002;124:97–104.

15 Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92:2226–35.

16 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;11:234–8.

17 Suominen PK, Keski-Nisula J, Ojala T, et al. Stress-dose corticosteroid versus placebo in neonatal cardiac operations: A randomized controlled trial. Ann Thorac Surg 2017;104:1378–85.

18 Suursalmi P, Ojala T, Poutanen T, et al. Velocity vector imaging shows normal cardiac systolic function in survivors of severe bronchopulmonary dysplasia at six to 16 years of age. Acta Paediatr 2017;106:1136–41.

19 Fredholm M, Jorgensen K, Houltz E, et al. Inotropic and lusitropic effects of levosimendan and milrinone assessed by strain echocardiography - a randomised trial. Acta Anaesthesiol Scand 2018;62:1246–54.

20 Hammer S, Loeff M, Reichenspurner H, et al. Effect of cardiopulmonary bypass on myocardial function, damage and inflammation after cardiac surgery in newborns and children. Thorac Cardiovasc Surg 2001;49:349–54.

21 Carmona F, Manso PH, Vicente WV, et al. Risk stratification in neonates and infants submitted to cardiac surgery with cardiopulmonary bypass: A multimarker approach combining inflammatory mediators, N-terminal pro-B-type natriuretic peptide and troponin I. Cytokine 2008;42:317–24.

22 Karsenty C, Hadeed K, Dulac Y, et al. Two-dimensional right ventricular strain by speckle tracking for assessment of longitudinal right ventricular function after paediatric congenital heart disease surgery. Arch Cardiovasc Dis 2017;110:157–66.