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Levosimendan versus Milrinone for Inotropic Support in Pediatric Cardiac Surgery: Results from a Randomized Trial

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Highlights

We investigated the effect of two inodilators in infants post cardiac surgery.

The effect of levosimendan and milrinone on myocardial function was compared.

We used conventional and two-dimensional speckle tracking strain echocardiography.

Biventricular strain demonstrated deterioration initially and improvement later.

The two inodilators had comparable effect on cardiac function in this setting.

Levosimendan versus Milrinone for Inotropic Support in Pediatric Cardiac Surgery: Results from a Randomized Trial

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Declaration of interest

None.

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

Abstract

Objective: We aimed to determine the differential effects of intra-operative administration of milrinone versus levosimendan on myocardial function after pediatric cardiac surgery. Transthoracic echocardiography was employed for myocardial function evaluation, utilizing biventricular longitudinal strain with two-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 1-12 months of age 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 randomized 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 prior to hospital discharge. The association between perioperative parameters and postoperative myocardial function was also investigated. Images were analyzed for left ventricular (n=67) and right ventricular (n=44) function. The day after surgery, left ventricular longitudinal strain was 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% (non-significant difference). For both groups, biventricular longitudinal strain approached their preoperative values at hospital discharge. Preoperative N-terminal pro-brain natriuretic peptide could predict the left ventricular strain on postoperative day one (p=0.014).

Conclusions: Levosimendan was comparable to milrinone for left and right ventricular inotropic support in pediatric cardiac surgery.

Keywords

Speckle tracking, longitudinal strain, congenital heart defect, cardiopulmonary bypass, randomized clinical trial, infant, milrinone, levosimendan

Introduction

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 is also 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 post cardiac surgery setting [3-5]. To our knowledge, no studies are comparing the effect of these two inodilators on myocardial function in children assessed by longitudinal strain (LS) using two-dimensional speckle tracking echocardiography (2D STE). STE is a relatively new method, which is increasingly used to detect left ventricular (LV) and right ventricular (RV) dysfunction. STE measures the relative movement of myocardial gray-scale alterations (speckle patterns) and can thereby quantify regional and global systolic deformation, 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 to 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 LV longitudinal strain (GE Medical Systems), shows -17.5% to be the cut off 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 (EF) measured with magnetic resonance imaging [6]. Earlier studies have demonstrated that LS is significantly impaired on a postoperative day one (POD-1) after cardiac surgery in

children and that it has not completely recovered at discharge from the hospital compared to the preoperative values [7,10].

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

Material and methods

Study design and patients

The current 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, we included seventy-two infants aged one to 12 months and with three different congenital heart defect diagnoses, who were scheduled for elective corrective open-heart surgery with CPB. The patient diagnoses were non-restrictive ventricular septal defect (VSD), complete atrioventricular septal defect (AVSD) with non-restrictive VSD, and balanced ventricles, and Tetralogy of Fallot (ToF). The patients were recruited from October 2014 until April 2017 in two centers of congenital cardiac surgery (Sweden and Finland). A written informed consent was obtained from the parents prior to 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 prior to surgery, prematurity, preoperative need for mechanical ventilation and/or vasoactive drugs and/or extra corporeal membrane oxygenation. The medical staff and the cardiologist who analyzed the echocardiography images were blinded to the study drug. The patients were randomized to receive either milrinone or levosimendan. The drug infusion was initiated in the operating room immediately after the start of the 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 anesthetist in charge to administer an extra bolus dose (half the loading dose) at weaning of CPB if the myocardial function was reduced on the routine transesophageal echocardiogram performed after weaning from CPB. The infusion rate could also 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 two hours, where the infusion rate was reduced to 50% and thereafter it was stopped. Should the patient need further inotropic therapy after weaning, milrinone infusion was started.

There was a standardized operating procedure regarding the surveillance and treatment of the hemodynamic status with pre-defined target values. The target mean arterial pressure (MAP) 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 hours), at 2, 6, 12, 24 hours after CPB, and at the time of the echocardiography on the first postoperative morning (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. Inotropic score (IS) was calculated according to Wernovsky with a slight modification [15]. We added norepinephrine to the formula in line with Gaies's vasoactive inotropic score [16].

Echocardiography

The echocardiographic images (Epiq 7, Philips, Andover, AM, USA and Vivid E95, General Electric, Horten, Norway) were recorded preoperatively, on the morning of POD-1 (whilst ongoing study drug infusion) and prior to the discharge from hospital. STE strain measurements, as well as automated 2D EF for LV and fractional area change for RV (RV-FAC) were analyzed from the apical 4-chamber view. The STE strain analyses were performed by one senior pediatric cardiologist (TO), using the VVI program (Syngo USWP 3.0, Siemens Healthineers, Erlangen, Germany) as earlier described [17,18]. Manual tracing of LV endocardial surface was performed in a single still frame in mid-systole. Tracing began at the septal edge of the mitral valve annulus, extended to the apex and returned to the lateral edge of the mitral valve annulus. In the case of RV, 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 were then automatically calculated for each frame of the cardiac cycle by the VVI algorithm. Tracings were accepted only when the endocardial border was correctly followed throughout the entire cardiac cycle. Individual regions of the border were adjusted until the border

was correctly tracked for each frame when necessary. The ventricular septal defect area or postoperatively the patch area were 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 sub-study, we performed a post-hoc power calculation based on the absolute values of LV-LS on POD-1, the primary end-point, in the whole study sample. We found that in order to detect a 30% difference in LV-LS on POD-1 between the two study groups, with a power of 80% and a level of significance of 0.05 and at a standard deviation of 4.1, we would need 19 patients in each group, and for a difference of 25% we would need 27 patients in each group.

For comparison between groups, Fisher's Exact test was used for dichotomous variables, Chi square test for non-ordered categorical variables, and Mann-Whitney U-test for continuous variables. We used mixed-model repeated measurements to investigate differences between and within the groups over time (group versus 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 NT-Pro-BNP, center, study drug, age-based Ross classification, the Comprehensive Aristotle score, and CPB-time. For evaluation of statistical significance, we chose *p*-values lower than 0.05. The data were analyzed using SAS v9.4 (Cary, NC) and IBM SPSS statistics for Windows, Version 25.0 (Armonk, NY). Figures were created in GraphPad Prism 8.0.0 for Windows, San Diego, California, USA.

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 one patient in the levosimendan group and two 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 two patients in each group. Concerning the vasoactive agents, none of the patients received dopamine, dobutamine or vasopressin, consequently the calculation of the inotropic score was based on norepinephrine and epinephrine.

The echocardiographic examination prior to hospital discharge was performed on day 7 (5;8) (median IQR) in the milrinone group and on day 7 (6;11) in the levosimendan group.

Hemodynamics and clinical outcome variables

Hemodynamic variables are depicted in Figures 2a and 2b. Early after weaning from CPB, heart rate and mean arterial pressure increased, while central venous pressure decreased. Central venous saturation and serum lactate decreased, while inotropic score 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 (Figure 2a and 2b), or at the time of echocardiographic examination on the POD-1 (data not shown). Additionally, there were no significant differences between the groups regarding the clinical outcome, in terms of time on the ventilator, hospital stay or mortality, and adverse advents, as demonstrated in Table 2.

Echocardiographic analyses

Biventricular LS in the study groups are 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 to 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 partially recovered to the preoperative level in both groups.

When compared over time, there was a significant difference between the two groups ($p=0.020$), probably reflecting slightly different patterns of changes in LV-LS. In post-hoc analyses of the three different measurement time points, LV-LS did not differ significantly between the treatment groups (preoperative, POD-1 and prior to 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 to the milrinone group on POD-1 and, vice versa, 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 to 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% vs. 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 (Figure 4), except for the low preoperative value of RV-LS in the 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 LV-EF and RV-FAC (p = 0.94 and 0.97 respectively).

Linear regression model demonstrated a significant relationship between preoperative NTproBNP and LV-LS on POD-1 (p = 0.014 and beta-score 0.9 with 95% CI 0.2;1.6), while other variables were not associated with LV-LS on POD-1. Additional information on the parameters in supplementary data as supplementary Table S1, and supplementary Figure S1 and S2.

Discussion

In the present study, we evaluated the potentially differential effect of levosimendan and milrinone on biventricular systolic function, assessed by strain echocardiography, early after pediatric cardiac surgery. 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, none of the inodilators could prevent a substantial fall 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 our knowledge, this is the first study which evaluates and compares the effects of two inotropic agents on LV and RV systolic function by 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 having EF < 55% and fractional shortening (FS) < 28% on the POD-1 and found no significant difference between the two 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 two groups. However, the patients in the levosimendan group had an increase in cardiac index over time while 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] compared the effect of levosimendan and milrinone on early postoperative LV-LS. The study drug infusion was initiated after arrival to the ICU, and the strain measurements were performed during three hours while the inotrope was administered in a step-up fashion. During this period preload, afterload and heart rate were maintained constant. Both drugs induced a dose-dependent improvement in LV-LS and cardiac index, but there was no significant difference between the effect of these two inodilators on either LV-LS or cardiac index. Our 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 our study, several new aspects provide valuable information regarding the effect of these two inotropes on the myocardial function in this young patient group undergoing cardiac surgery. Firstly, our study is to our knowledge the first randomised study in patients with ToF, VSD, and AVSD, aged one to 12 months, investigating cardiac function in connection with a perioperative infusion of milrinone

or levosimendan. Secondly, we used STE and strain, a relatively new technique in echocardiography, which is more sensitive to detect changes in myocardial function than traditional echocardiography parameters [9]. Thirdly, we examined biventricular function, and lastly, we gave a loading dose of the inotropic agent at the initiation of CPB aiming for obtaining an early effect of the drug. In our units, it is routine practice to initiate the inotropic infusion around the time of CPB initiation, with or without 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 stay in hospital was similar to what has been reported earlier [20].

In the present study, preoperative NTproBNP predicted worse LV-LS on POD-1. Although 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 has, to our knowledge, not been studied earlier. The correlation of age, age-based Ross classification, the Comprehensive Aristotle score, and CPB-time with LV-LS on POD-1 in our study were weak. This was probably due to the fairly homogenous study population. Perdreau *et al* found a correlation between aortic cross-clamp time (ACC) > 30 minutes and worse postoperative LV-LS [7]. De Boer *et al* investigated postoperative LS, in a more heterogenous pediatric population, compared with our study, and found a correlation between CPB- and ACC-time with RV-LS but not LV-LS [10].

There was no association between the type of heart defect and LV-LS post-operatively. This was despite the fact that the hemodynamics in VSD, AVSD, and ToF result in different types of load on the left ventricle. In our patient population, there was a variation in LV-LS pre-operatively, 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 pre-operative LV-LS was not due to a systematic variation between patients with different heart defects, but rather a variation across the entire cohort.

Our study has several limitations. The patient population was restricted to merely three diagnoses with an age span of one 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 our centers, 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, there was some missing data on right ventricular function due to the fact that the evaluations of RV-LS is technically more challenging compared with the LV-LS [22], especially on POD-1 when the acoustic window often is poor.

The strengths of this study were the following: firstly, it was a double-blinded randomized clinical trial, performed in two centers. Secondly, 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. Thirdly, all the strain analyses were performed merely by a single cardiologist blinded to the study groups. Fourthly, to have a fairly homogenous study population, we only included patients aged one to 12 months, with VSD, AVSD, or ToF undergoing-corrective surgery.

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

Figure Legends

Figure 1. Study CONSORT flow chart. Further details regarding the inclusion and exclusion of patients are provided in reference [11]

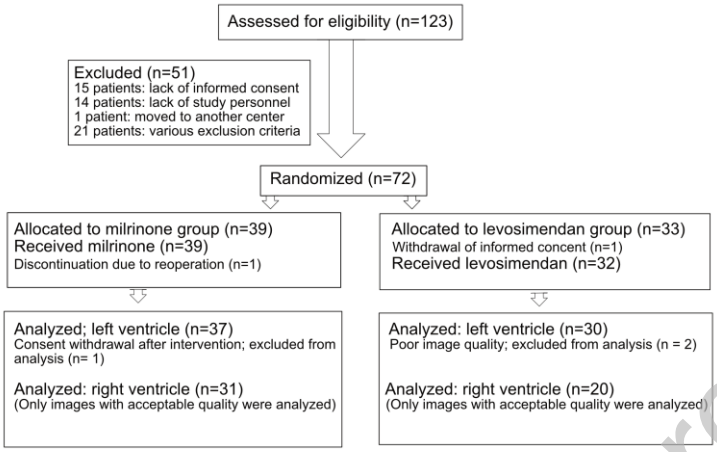
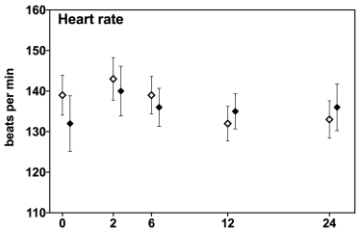
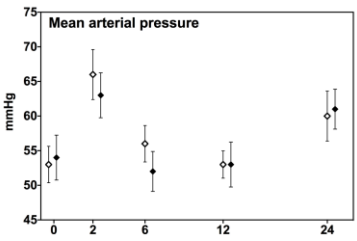
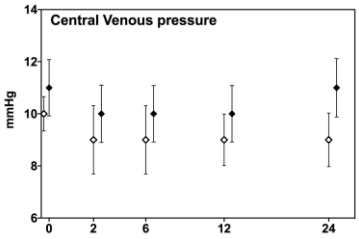


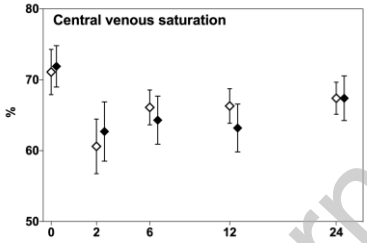
Figure 2 Hemodynamics over time in the two study groups**;** a) heart rate, mean arterial pressure[a] and central venous pressure, and b) central venous saturation[a], serum lactate[a,] and inotropic score[a]. Filled rhomboids represent levosimendan, non-filled rhomboids milrinone. Horizontal axes show hours after CPB-weaning and vertical axes measurement units. Data are shown as mean with 95% confidence interval. There were no significant differences between groups over time in any of the variables.

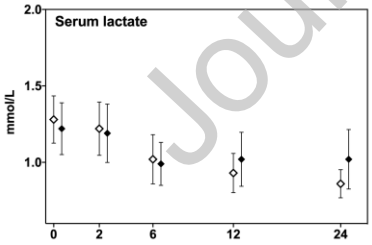
[a] Data previously reported in reference [11].











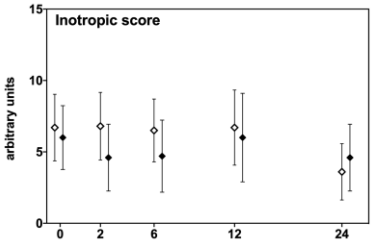


Figure 3. Left and right longitudinal strain (LV-LS and RV-LS) in the two study groups. Longitudinal strain represents the shortening of the myocardium in systole compared to diastole in the longitudinal plane, hence the unit of negative percent on the y-axis. Data are shown as mean values with 95% confidence interval. Filled rhomboids resemble the levosimendan group, empty rhomboids the milrinone group. The three time points of the strain measurements were preoperative, on the first postoperative morning (POD-1), and at discharge from the hospital. LV-LS and RV-LS were impaired in both groups on POD-1 compared to the preoperative values, and they had only partially recovered at the discharge from the hospital.

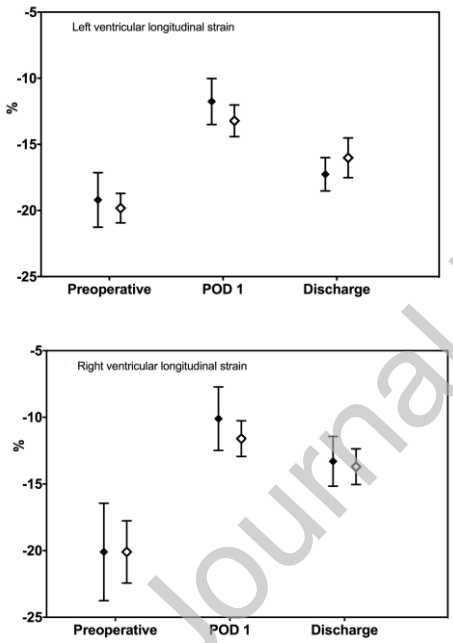


Figure 4. Left and right longitudinal strain (LV-LS and RV-LS) in the whole study population differentiated by the type of congenital heart defect. Longitudinal strain represents the shortening of the myocardium in systole compared to diastole in the longitudinal plane, hence the unit of negative percent on the y-axis. Data are shown as mean values with 95% confidence interval. Empty circles resemble VSD, filled circles AVSD, and filled triangles ToF. The three time points of the strain measurements were preoperative, on the first postoperative morning (POD-1), and at discharge from the hospital. The changes in strain over time were quite similar for these three types of heart lesions, except for the preoperative RV-LS of the patients with VSD.

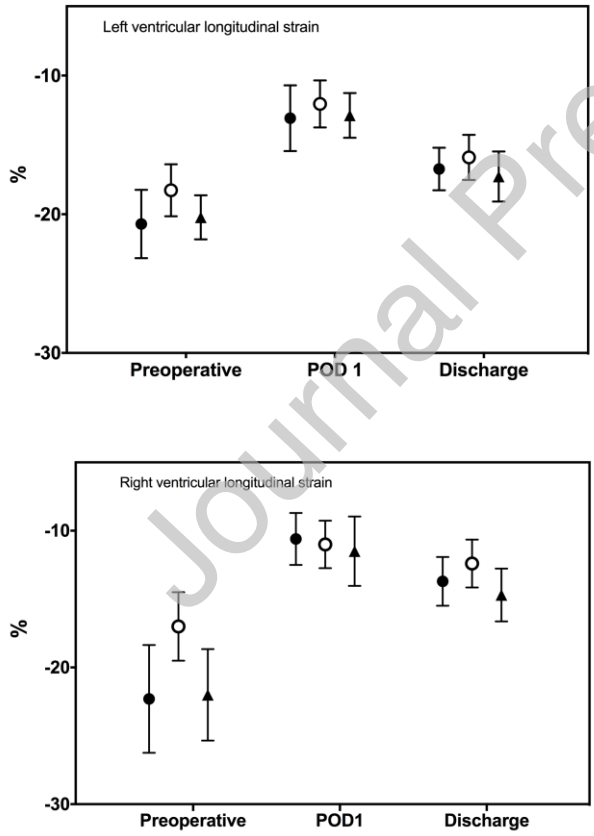


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Table 1: Patient demographic and perioperative data

	Levosimendan (n = 32)	Milrinone (n = 38)
Age at operation (months)	5.9 (2.9)	5.6 (2.7)
Gestational age (weeks)	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%)
Non-restrictive 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)	2622 (6276)	2474 (4539)
CPB-duration (minutes)	90 (33)	93 (45)
ACC-duration (minutes)	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)

Values are mean +SD or numbers, n (%). Data in this table have been previously reported11. There were no significant differences among the variables. ACC = aortic cross-clamp time; AVSD = complete atrioventricular septal defect; CPB = cardiopulmonary bypass; NT-proBNP = N-terminal pro-brain natriuretic peptide; RACHS-1 = risk adjustment for congenital heart surgery; VSD = non-restrictive ventricular septal defect.

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
Betablocker	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 [a]			
Junctional ectopic tachycardia	3 (9.4%)	3 (7.9%)	1.00
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 [a]			
Length of ventilator support (hours)	30.0 (15.5; 54.5)	21.0 (10.0; 32.5)	0.21
PICU stay (days)	3.0 (2.0; 5.5)	2.0 (2.0; 3.0)	0.06
Hospital stay (days)	9.5 (8.0; 14.5)	8.0 (7.0; 11.0)	0.10
28-day mortality	0 (0.0%)	0 (0.0%)	1.00

Data are shown as numbers, n (%) or median (interquartile range). [a] values previously reported in ref [11].

POD-1 = first postoperative morning; PICU = pediatric intensive care unit.

Table 3: Echocardiographic parameters

	LV-LS (%)					LVEF (%)			
				P value				*P* value	
	Levosimendan	Milrinone		Between groups	Interaction	Levosimendan	Milrinone	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 mean (standard deviation)

Abbreviations: EF = ejection fraction; FAC = fractional area change; LS = longitudinal strain, LV = left ventricle; $P_{\text{Interaction}}$ = *P* value between groups over time; Preop = preoperative; POD-1 = postoperative day one;

RV = right ventricle