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ORIGINAL ARTICLE

Heart rate control with landiolol hydrochloride in infants with ventricular dysfunction and pulmonary hypertension

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Abstract

Aims Sinus tachycardia potentially leads to a deterioration of cardiac function in critically ill infants. The ultrashort-acting beta-blocker landiolol hydrochloride is a new pharmacological option for a selective heart rate (HR) control in patients with sinus tachycardia and heart failure.

Methods and results This study was a monocentric retrospective medical chart review study at the University Children's Hospital Bonn (Germany) from 01 January 2018 until 30 June 2020. This study included a cohort of 62 term and preterm infants with a diagnosis of ventricular dysfunction and/or pulmonary hypertension (PH), in combination with preexisting tachycardia and treatment with landiolol hydrochloride. Infants were allocated to subgroups according to weeks of gestational age (GA): born at <35 weeks of GA (Group A) and born at >35 weeks of GA (Group B). Tachycardia was defined depending on GA (<35 weeks of GA: >170 b.p.m.; ≥ 35 weeks of GA: >150 b.p.m.). The primary endpoint was defined as percentage of patients achieving HR normalization during the first 24 h of landiolol treatment. Twenty-nine infants were allocated to Group A and 33 infants to Group B. The overall median GA of the infants was 35.3 (23.3/41.3), with 53% female infants. The primary endpoint was achieved in 57 patients (91.9%). The median time to reach target HR was 1.8 (0.3–24) h. The median starting dose of landiolol was 8.8 (3.9–25.3) μk/kg/min, with a median dosing during the first 24 h of landiolol treatment of 9.9 (2.8–35.4) μk/kg/min. The median landiolol dose while achieving the target HR was 10 (2.4–44.4) μk/kg/min. The right ventricular dysfunction improved significantly in both groups 24 h after onset of landiolol infusion (P = 0.001 in Group A and P = 0.045 in Group B). The left ventricular and biventricular dysfunction improved significantly 24 h after onset of landiolol infusion in infants of Group B (P = 0.004 and P = 0.006, respectively). The severity of PH improved significantly after 24 h in infants of Group A (P < 0.001). During landiolol treatment, no severe drug-related adverse event was noted.

Conclusions The use of landiolol hydrochloride for HR control of non-arrhythmic tachycardia in critically ill infants is well tolerated. Reduction of HR can be guided quickly and landiolol treatment is associated with an improvement of ventricular dysfunction and PH.

Keywords Heart rate control; Landiolol hydrochloride; Cardiac dysfunction; Pulmonary hypertension

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Introduction

Critically ill term and preterm infants are at increased risk to present episodes of ventricular dysfunction and/or pulmonary hypertension (PH) during their initial neonatal intensive care unit (NICU) admission.[1,2] A broad variety of underlying aetiologies and triggers exist, and these episodes might be attributable to maternal, placental, fetal, and neonatal

pathologies. Affected infants typically present with sustained sinus tachycardia, as a consequence of heart failure with or without preserved ejection fraction, arterial hypotension, or preexisting inotropic support. Evidence exists that sinus tachycardia is associated with impaired diastolic and systolic ventricular function and might aggravate both acute and chronic heart failure.[3–6] However, data analysing this effect in a neonatal or paediatric setting are scarce and, to some extent, only experimental data are available.[3,7] Furthermore, the effect of sinus tachycardia on PH in this cohort is unknown.

A potential approach to improve tachycardia-induced ventricular impairment is a selective heart rate (HR) control. This can be achieved by drugs with predominant negative chronotropic effects [e.g. beta-blockers or funny-current (If) channel inhibitors]. Landiolol hydrochloride (further named landiolol) is an ultrashort-acting beta-blocker that is highly β1-selective (potency ratio β1/β2: 255) with a primarily negative chronotropic effect and a low risk for negative inotropic side effects. Landiolol reaches its maximum concentration within 5 min of application and has a short elimination half-life of 4 min.[8] Therefore, therapeutic effects can be guided quickly. Landiolol is authorized for the treatment of supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances and for non-compensatory sinus tachycardia. Additionally, landiolol was approved for the acute treatment of other malignant tachycardias in Japan.[9–11] Only a limited amount of studies are available investigating landiolol treatment in paediatric patients, mainly investigating the effect of landiolol for the control of junctional ectopic tachycardia or tachyarrhythmia following cardiac surgery.[12–15] The aim of the present study was to analyse the effects and safety of landiolol treatment in a cohort of term and preterm infants with ~~s~~inus tachycardia and concomitant ventricular dysfunction and/or PH.

Methods

Study population and ethical approval

This study included all patients with tachycardia treated with Rapibloc® (Landiolol Lyo®; active ingredient: landiolol hydrochloride) at the Department of Neonatology and Pediatric Critical Care Medicine at the University Children's Hospital Bonn between 01 January 2018 and 30 June 2020. Cases were identified by querying departments document hosting systems with Rapibloc®/landiolol treatment. Inclusion criteria included (i) male or female patients treated with landiolol and (ii) tachycardia at time of landiolol infusion start defined as >170 b.p.m. for preterm neonates [>150 b.p.m. for late-preterm and full-term neonates ≥ 35 + 0 weeks of gestational age (GA)]. This study has no exclusion criteria.

The study was approved by the Ethics Committee of the Medical Centre of the University of Bonn (Local Study Number 231/20), and informed consent was waived due to the retrospective design of the study in accordance with local law.

Observation period of the study

The observation period was defined as the time from start of landiolol treatment (baseline) until 48 h after discontinuation of landiolol (follow-up). The observation period was subdivided into (i) baseline (24 to 0 h prior to start of landiolol infusion), (ii) early phase from 0 to 24 h after start of landiolol infusion, (iii) maintenance phase from 24 h to discontinuation of landiolol infusion, and (iv) maintenance phase from discontinuation of landiolol infusion to follow-up (48 h).

Haemodynamic and laboratory parameters

Sinus tachycardia was defined depending on GA and according to clinical practice in our department: (i) <35 weeks of GA: HR > 170 b.p.m. and (ii) ≥ 35 weeks of GA: HR > 150 b.p.m. As target range for optimum HR 150–170 b.p.m. (<35 weeks of GA) and 130–150 b.p.m. (≥ 35 weeks of GA) were determined. The following haemodynamic parameters were recorded from patients' charts and electronic database: HR (b.p.m.), systolic/diastolic blood pressure (mmHg), mean arterial pressure (MAP), pulse oximetric saturation (SpO_2), and body temperature (°C). Arterial hypotension was defined as MAP less than weeks of GA. Vital parameters were recorded at baseline and every 15 up until 210 min, and thereafter every 3 until 24 h, at 48 h, and before discontinuation of landiolol treatment. The vasoactive-inotropic score (VIS) was calculated at baseline and 24 and 48 h after start of treatment [dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10 000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min)].[16] A VIS of ≥25 is considered as a high score. Kinetics of N-terminal pro-brain natriuretic peptide (NT-proBNP, pg/mL), troponin I (μg/L), and arterial lactate (mmol/L) were evaluated when available.

Heart rate control

Landiolol was used for HR control in cases of sustained sinus tachycardia in combination with ventricular dysfunction and/or PH based on the decision of the attending NICU physician. Currently, landiolol is not approved for use in paediatric

patients. In this cohort, landiolol was administered as off-label therapy, after parental information and agreement.

Landiolol was administered continuously in a dose range of 1–40 μg/kg/min via central-line catheter in three standardized preparations (depending on body weight and infusion rate): 1000, 2000, and 6000 μg/mL. Treatment was started with 1–5 μg/kg/min and then stepwise up-titrated every 30 min according to HR monitoring in steps of 5–10 μg/kg/min. Infusion rates differed from minimum of 0.1 mL/h up to maximum of 2.5 mL/h. Landiolol was discontinued after haemodynamic stabilization with normalized HR and echocardiographic assessment of optimized cardiac function.

Echocardiographic assessment

Evaluation of echocardiographic measurements was done at the following timepoints (when available): at baseline, 24 h, and 48 h after start of landiolol therapy. Echocardiographic measurements were reviewed independently by two experienced neonatal echocardiographers, blinded to the clinical course of the individual patient.

Assessment of ventricular dysfunction was based on qualitative and quantitative measures according to international guidelines.[17,18] Ventricular dysfunction was graded as apparent or not apparent and was based on the subsequent quantitative parameters, if available: fraction shortening (FS), S' velocity on tissue Doppler imaging (TDI), mitral or tricuspid annular plane systolic excursion (MAPSE/TAPSE), tricuspid valve regurgitation (TR, Grades I–III), mitral valve regurgitation (MR, Grades I–III), or ventricular size and output. Additionally, the end-diastolic right ventricular to left ventricular (RV/LV) ratio was calculated as estimation of RV performance,[19] and laboratory parameters (NT-proBNP, troponin I, and arterial lactate) were evaluated as biomarkers for ventricular dysfunction.

PH estimation was influenced by the following parameters: (i) ductus arteriosus flow pattern, (ii) the intraventricular septum position, (iii) the TR, and (iv) flow pattern across the main pulmonary artery, measuring the time to peak velocity (TPV) and right ventricular ejection time (RVET). Severity of PH was classified as (i) *none*, (ii) *mild* (≤2/3 of systemic arterial pressure), (iii) *moderate* (≥2/3 to systemic arterial pressure), or (iv) *severe* (≥ systemic arterial pressure).

Vasoactive treatment

Dobutamine (2–20 μg/kg/min) was used as first-line inotropic support. Milrinone (0.3–0.7 μg/kg/min) was added when inodilatory effect was required. Levosimendan (0.2 μg/kg/min, without bolus infusion) was used as additional inodilatory therapy, when severe ventricular dysfunction was apparent despite high-dose inotropic support. In case of PH, inhaled nitric oxide (iNO) was implemented as first-line therapy, followed by sildenafil (intravenous) in cases of severe PH and bosentan, if necessary.

Definition and classification of adverse events

The following parameters were classified as adverse events (AEs): (i) cardiovascular events (including clinically significant hypotension and bradycardia), (ii) arrhythmias, (iii) drug–drug interaction, (iv) death, and (v) any event suspected to be related to the administration of landiolol. AEs were graded in intensity as mild, moderate, severe, or fatal. Furthermore, AEs were classified as related and unrelated to landiolol treatment. All collected AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0), tabulated, and provided for analysis. AEs and laboratory parameters were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0).

Group stratification and statistical analysis

Patients were allocated to one of two subgroups according to weeks of GA: preterm infants $<$ 35 weeks (Group A) and late-preterm infants and term infants $\geq$ 35 weeks of GA (Group B).

The primary endpoint was defined as achievement of target HR within the first 24 h of treatment. The following parameters were identified as outcome measures: (i) percentage of infants achieving HR normalization during landiolol treatment, (ii) time from start of landiolol treatment until achievement of target HR, and (iii) time until $\geq$ 10% or $\geq$ 20% reduction of HR from baseline. Furthermore, the change in maximum VIS during landiolol treatment (iv), the incidence of AEs (v), the incidence of AEs requiring landiolol discontinuation (vi), the improvement of PH (vii), and the improvement of ventricular dysfunction (viii) served as outcome measures.

Demographic data and baseline characteristics are presented as mean or absolute number (*n*) with percentage. Haemodynamic parameters are presented as mean with standard deviation or median with minimum/maximum. For comparison of continuous variables, the Mann–Whitney *U* test was used. For categorical variables, the Fisher exact test and the χ^2 test were applied. Correlations between variables were evaluated by Pearson's correlation coefficients and were only applied if any two measurements were taken at the same point in time. A *P*-value $<$ 0.05 was considered significant. A regression analysis for outcome measures was not performed due to the small sample size of the cohort and the retrospective design of the study. The statistical analysis was performed using statistical software (IBM SPSS Statistics for Windows, Version 27.0, IBM Corp, Armonk, NY, USA; and

STATA software, Version 17.0, StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics and demographic data

Sixty-three infants were initially screened, and one infant was excluded from the analysis due to a screening failure and missing treatment with landiolol. Finally, 62 infants met inclusion criteria for the retrospective analysis. Twenty-nine infants were allocated to Group A and 33 infants to Group B. Baseline characteristics of the overall cohort and subgroups are demonstrated in *Table 1*. Sixty per cent of the infants were born prematurely (<37 weeks of GA). Treatment and outcome data [duration of hospital stay, extracorporeal membrane oxygenation (ECMO), and mortality] did not differ significantly between subgroups. Information on prenatal diagnosis and perinatal complications are presented in *Table 1*. Most infants required invasive (mechanical) ventilation during treatment on NICU (90% in Group A vs. 94% in Group B).

Evaluation of haemodynamic monitoring

At baseline, prior to start of landiolol infusion, all infants were tachycardic with all but one being in sinus rhythm (98%). The mean age at start of landiolol treatment was 2.6 days of life, with a mean GA of 34.7 weeks. Evaluation of HR response after start of landiolol treatment is demonstrated in *Table 2*. The primary endpoint, reaching target HR in the first 24 h, was achieved in 57 patients (91.9%), with similar findings in both subgroups. In most infants (80%), the target HR limits were reached within 3 h, with a median time of 1.8 h (0.3–24 h; see *Figure 1*). The median starting dose of landiolol was 8.8 (3.9–25.3) μk/kg/min, with a median dosing

Table 1 Baseline characteristics and demographic data

Variables	Overall cohort *n* = 62	Group A *n* = 29	Group B *n* = 33	*P*-value
Female sex, *n* (%)	33 (53)	14 (48)	19 (58)	0.611
Birth weight, kg	2.4 (0.6/5.4)	1.6 (0.6/3.2)	3.1 (1.7/5.4)	**<0.001**
Gestational age, weeks	35.3 (23.3/41.3)	31.4 (23.3/34.9)	38.1 (35.1/41.3)	**<0.001**
Caucasian ethnicity, *n* (%)	61 (98)	29 (100)	32 (97)	0.99
In-hospital stay, days	43 (1/162)	45.5 (1/162)	42.5 (4/143)	0.588
ECMO therapy, *n* (%)	16 (26)	7 (24)	9 (27)	0.494
Mortality during observation period, *n* (%)	2 (3)	2 (7)	0	0.230
Fetal diagnosis				
Congenital diaphragmatic hernia	30 (48)	9 (31)	21 (64)	**0.015**
Twin-to-twin transfusion syndrome	4 (6)	4 (14)	0 (0)	**0.030**
Fetal hydrops	2 (3)	2 (7)	0	0.215
Diabetic fetopathy	2 (3)	0	2 (6)	0.494
Genetic syndrome	2 (3)	0	2 (6)	0.494
Sacro-coccygeal teratoma	1 (2)	1 (3)	0	0.468
Congenital malformations	2 (3)	1 (3)	1 (3)	0.99
CHAOS		1 (3)	0	0.468
AV malformation		0	1 (3)	0.468
Reasons for preterm birth				
Intra-amniotic infection	6 (10)	6 (21)	0 (0)	0.317
Premature labour	18 (29)	14 (48)	4 (12)	0.99
Rupture of membranes	13 (21)	12 (41)	1 (3)	0.382
Fetal growth retardation	3 (5)	2 (7)	1 (3)	0.488
Pathological Doppler	17 (27)	14 (48)	3 (9)	0.99
Bleeding	3 (5)	3 (10)	0 (0)	0.99
Pre-eclampsia/eclampsia	3 (5)	3 (10)	0 (0)	0.99
Complications after birth				
Bronchopulmonary dysplasia	5 (8)	4 (14)	1 (3)	0.182
Intraventricular haemorrhage	8 (13)	8 (28)	0	**0.001**
Necrotizing enterocolitis	4 (6)	4 (14)	0	**0.046**
Retinopathy of prematurity	3 (5)	3 (10)	0	0.102
Sepsis	28 (45)	13 (45)	15 (45)	0.99
Renal failure	8 (13)	4 (14)	4 (12)	0.99

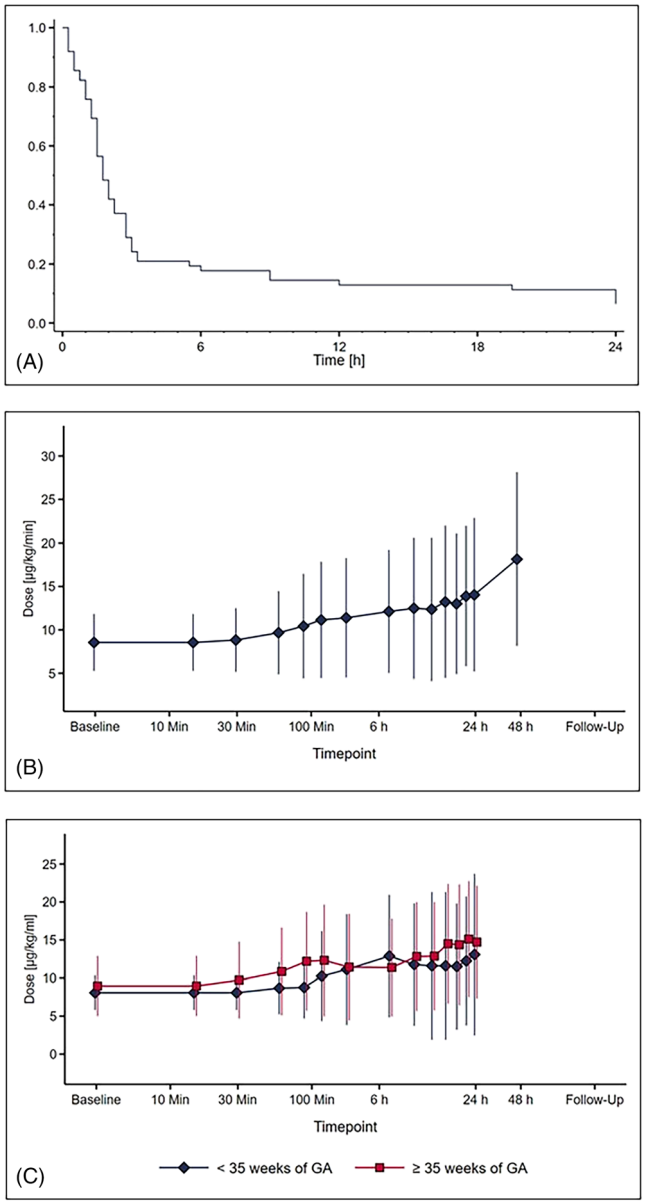
AV, arteriovenous; CHAOS, congenital high airway obstruction syndrome.
Data are presented as median (with minimum/maximum) or absolute number with %. A *P*-value < 0.05 was considered as statistically significant, and values are highlighted in bold. Sepsis was defined as clinical and laboratory signs of invasive infection and antibiotic therapy for at least 5 days or clinical signs of sepsis and detection of pathogenic agent via blood culture or PCR. Renal failure is defined as a stadium II or higher according to the pRIFLE criteria (paediatric Risk of kidney dysfunction, renal Injury, Failure or Loss of kidney function, and End-stage renal disease). The observation period is defined as time from baseline (24 h prior to start of landiolol hydrochloride infusion) until 48 h after discontinuation of landiolol hydrochloride infusion.

Table 2 Effectiveness of landiolol hydrochloride on heart rate monitoring

Variable	Overall cohort $n = 62$	Group A $n = 29$	Group B $n = 33$	*P*-value
Infants achieving target HR during the first 24 h of landiolol treatment, *n* (%)	57 (91.9)	27 (93.1)	30 (90.9)	0.752
Time until achievement of target HR from baseline, h	1.8 (0.3–24)	1.8 (0.5–24)	2 (0.3–24)	0.702
Current dose while achieving target heart rate, μg/kg/min	10 (2.4–44.4)	9.4 (3–44.4)	10.6 (2.4–28)	0.603
Time until ≥10% reduction of HR from baseline, h	1.3 (0.3–180)	1.8 (0.3–24)	1.3 (0.3–180)	0.094
Current dose while achieving 10% reduction, μg/kg/min	10 (2.4–44.4)	9.4 (3–44.4)	11.6 (2.4–32.9)	0.322
Time until ≥20% reduction of HR from baseline, h	2.9 (0.3–260.5)	6 (0.3–79.5)	2.4 (0.3–260.5)	**0.028**
Current dose while achieving 20% reduction, μg/kg/min	11 (2.4–32)	9.70 (3.5–21.5)	12.2 (2.4–32)	0.151

HR, heart rate.
Data are presented as median (minimum–maximum) or absolute number with %. A *P*-value < 0.05 was considered as statistically significant and is highlighted in bold.

Figure 1 All data are presented as arithmetic mean ± SD or absolute number. The baseline value is the last available value prior to the first administration of landiolol. (A) The Kaplan–Meier plot for achievement of normal heart rate. (B) Landiolol dose (μg/kg/min) over time. (C) Subgroup analysis of landiolol dose (μg/kg/min) over time. GA, gestational age.



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during the first 24 h of landiolol treatment of 9.9 (2.8–35.4) µk/kg/min. The median landiolol dose administered to infants (n = 48) from 24 h onwards until drug discontinuation was 15.7 (1.7–35) µg/kg/min. The median landiolol dose while achieving the target HR was 10 (2.4–44.4) µk/kg/min. The mean landiolol dose over time is shown in *Figure 1*. In cumulation, the median exposure to landiolol over time was 82.5 (2–759.3) h, with a median overall drug exposure of 50 (0.5–1434.3) mg/kg. Landiolol was administered at a mean infusion rate of 0.3 mL/h (±0.2). Two selective case examples of a preterm and a term infant and the respective landiolol infusion over time with the according haemodynamic changes are illustrated in *Figure 2*.

Changes in HR during landiolol infusion are displayed in *Figure 3*. At baseline, the mean HR was 185.6 b.p.m. (±14.7). Significant ($P \leq 0.001$) decreases in HR since baseline were observed at each measurement stage from baseline to follow-up.

The systolic pressure, diastolic pressure, and MAP remained stable during landiolol treatment, with an increasing trend over time (see *Figure 3*). This trend was found in both subgroups. During landiolol treatment, no significant variation of body temperature was noticed over time, both in term and in preterm infants. The fraction of inspired oxygen (FiO_2) first decreased significantly after onset of landiolol infusion at the timepoint 210 min (0.8 vs. 0.7, P = 0.045), with a further decrease at later timepoints.

The median VIS prior to landiolol treatment was 42 (0–135) in infants of Group A und 42 (12–93) in Group B. In Group A, the median VIS increased to 45 (0–126) at 24 h after onset of landiolol infusion and then decreased to 41 (0–98) from 24 h onwards until landiolol discontinuation. In Group B, the median VIS initially increased to 72 (20–117) at 24 h after onset of landiolol infusion and subsequently decreased to 60 (12–103) from 24 h onwards until landiolol discontinuation.

Echocardiographic assessment

At echo assessment, 85% of the infants presented a persistent ductus arteriosus. Severity of TR decreased significantly from baseline to 24 h after onset of landiolol treatment ($P < 0.001$); severity of MR decreased at both timepoints after onset of landiolol treatment ($P < 0.001$ at 24 h and P = 0.041 at 48 h).

At baseline, PH was diagnosed in 82% (n = 51), with 48% classified as severe, 22% as moderate, and 30% as mild or no PH. Severity of PH was significantly higher in infants allocated to Group B (P = 0.007). On baseline echocardiography, right ventricular dysfunction (RVD), left ventricular dysfunction (LVD), and biventricular dysfunction (BVD) were present in 87%, 64%, and 57%, respectively. LVD was more common in patients in Group A (P = 0.039), but RVD and BVD were similarly distributed between groups. The changes in PH severity, RVD, LVD, and BVD during landiolol treatment are displayed in *Figures 4* and *5*. The end-diastolic RV/LV ratio decreased significantly during landiolol treatment (see *Figure 5*), with similar findings after separating into subgroups.

Drug-related adverse events and long-term outcome

In the overall cohort, in one infant (1.6%), a sinus bradycardia during landiolol treatment was considered as a drug-related

Figure 2 (A) A selected case example of a term infant with landiolol treatment is illustrated. The targeted heart rate limits were 130–150 b.p.m. The vital parameters (heart rate and systolic and diastolic blood pressure) are displayed in the upper row. The heart rate measurements and dose range of landiolol infusion are displayed in the lower row of the figure. (B) A selected case example of a preterm infant with landiolol treatment is illustrated. The targeted heart rate limits were 150–170 b.p.m. The vital parameters (heart rate and systolic and diastolic blood pressure) are displayed in the upper row. The heart rate measurements and dose range of landiolol infusion are displayed in the lower row of the figure. MAP, mean arterial pressure.

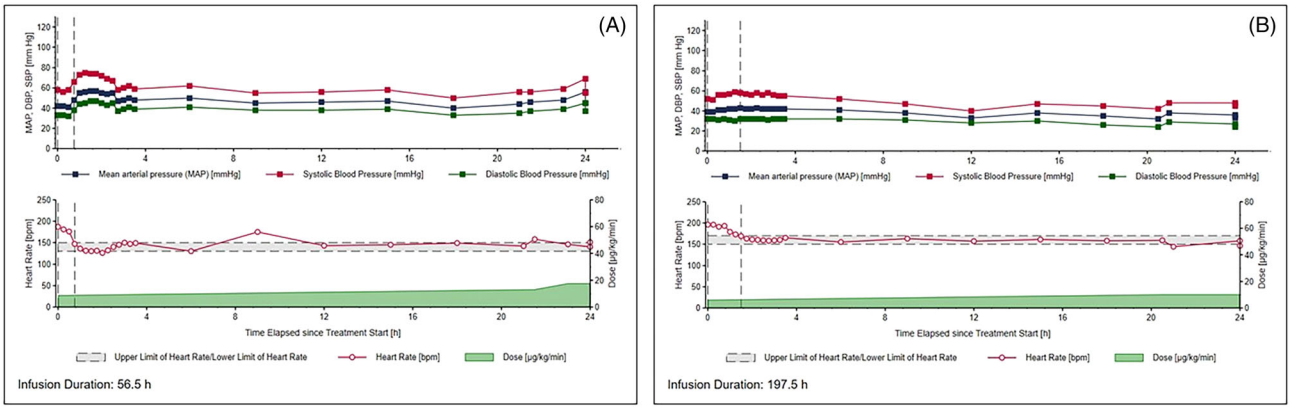
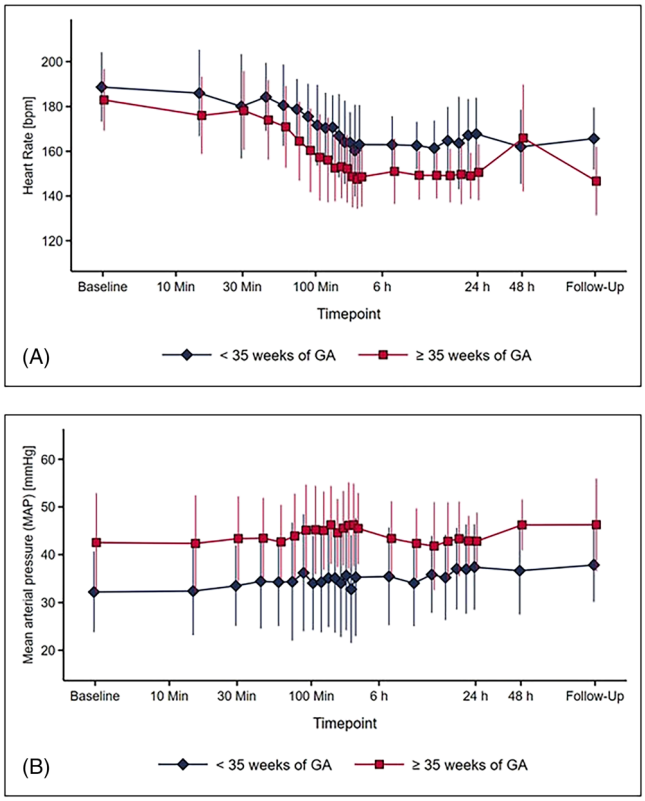


Figure 3 All data are presented as arithmetic mean ± SD. The baseline value is the last available value prior to the first administration of landiolol. (A) Heart rate (b.p.m.) over time during landiolol treatment. (B) Mean arterial pressure (MAP) (mmHg) over time during landiolol treatment. GA, gestational age.



AE. In this case, landiolol infusion was interrupted. Otherwise, no relevant drug-related AEs were noted. After discontinuation of landiolol infusion, no rebound tachycardia (increase of HR $>$ 10% of baseline) was observed (mean HR prior to landiolol discontinuation 162 b.p.m. vs. mean HR at follow-up after landiolol discontinuation 155 b.p.m.). Two infants died during the observation period. One infant died due to cardiac failure with arterial hypotension and one infant died due to cardiac and respiratory failure during ECMO treatment. Both events were unrelated to landiolol treatment.

The overall mortality not related to the observational period of landiolol treatment until discharge was 29% (18 infants: 11 infants allocated to Group A and 7 infants allocated to Group B; $P = 0.200$). All these infants had a severe clinical course, signs of severe PH or severe ventricular dysfunction, and a priori a poor predicted outcome.

Laboratory parameters

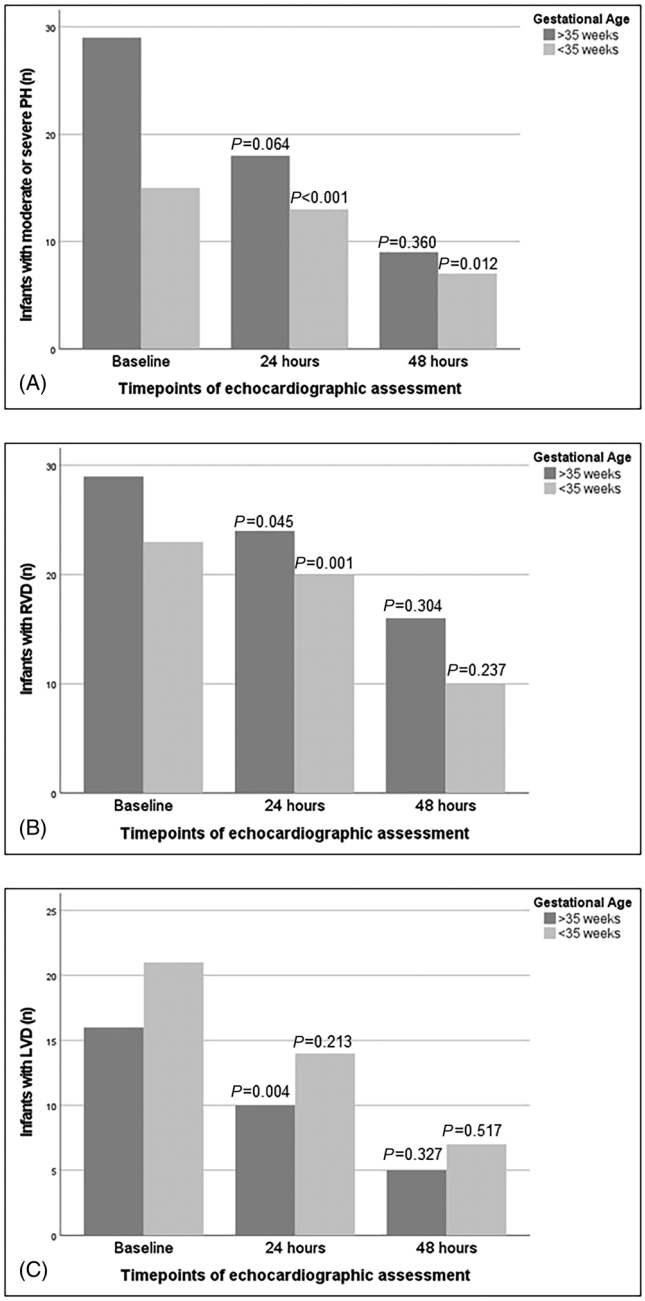
Mean NT-proBNP values decreased from baseline (22 746.1 pg/mL) to 24 h after onset of landiolol infusion (14 762.9 pg/mL, $P = 0.08$) and to timepoint 24 h until discontinuation of landiolol infusion (14 267.5 pg/mL, $P = 0.109$). On the other hand, mean troponin I values initially increased from baseline (69 μg/L) to timepoint 24 h (379 μg/L, $P = 0.465$) and decreased to timepoint 48 h (213 μg/L, $P = 0.317$). The mean arterial lactate decreased significantly from baseline (3.56 mmol/L) to 24 h (3.03 mmol/L, $P = 0.026$) and to 48 h (2.51 mmol/L, $P = 0.003$).

Discussion

This is the first study evaluating landiolol hydrochloride for HR control in a cohort of preterm and term neonates, suffering from ventricular dysfunction and/or PH. Landiolol might be an ideal agent for HR control in neonates due to its high β1-selectivity, the potent negative chronotropic effect, a limited negative inotropic potential, and an ultrashort elimination half-life (4 min).[20] Landiolol seems to be superior to other short-acting and selective beta-blockers such as esmolol, when comparing its chronotropic and inotropic effect.[21–23]

Recently, several studies evaluated landiolol in the paediatric population, mainly focusing on its effect on tachyarrhyth-

Figure 4 (A) Changes of the severity of the pulmonary hypertension (PH) during landiolol treatment. (B) Changes of the incidence of the right ventricular dysfunction (RVD) during landiolol treatment. (C) Changes of the incidence of the left ventricular dysfunction (LVD) during landiolol treatment. At baseline, the severity of PH differed significantly between subgroups ($P < 0.001$), but not at later timepoints. The *P*-values in the figure indicate the Fisher exact test in relation to the baseline of the selective subgroup.



mias in children with congenital heart defects or following cardiac surgery.[12,13,24] In this context, landiolol was highly effective in converting tachyarrhythmias to sinus rhythm and improving cardiac function. To our knowledge, this is the first study describing the use of landiolol in a large cohort of term and preterm neonates with non-arrhythmic sinus tachycardia. Our data demonstrate that landiolol is highly effective in HR control with a similar response rate in term and preterm infants. The response to landiolol in the present cohort was identical across the infants, irrespective of the GA, birth weight, and primary diagnosis. The median time to reach the target HR of 1.8 (0.3–24) h was comparable with previously published studies in older children.[13,25] In adults, landiolol can be administered with a loading dose (40–100 μg/kg/

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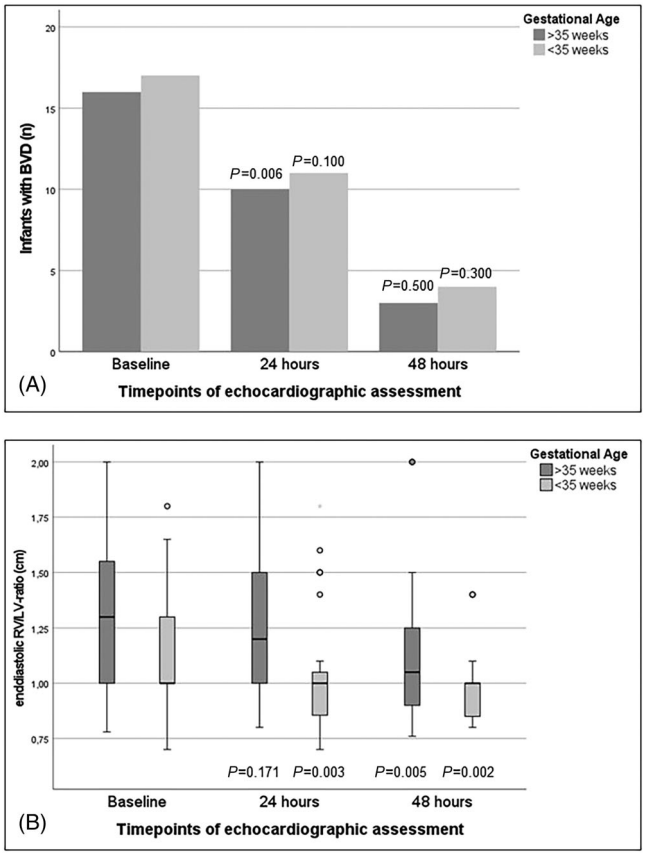
Figure 5 (A) Changes of the incidence of the biventricular dysfunction (BVD) during landiolol treatment. (B) Changes of the end-diastolic right ventricular to left ventricular (RV/LV, cm) ratio during landiolol treatment. The RV/LV ratio differed significantly between subgroups at all timepoints (P = 0.026, P = 0.006, and P = 0.040, respectively). The P-values in the figure indicate the Fisher exact test or the Mann–Whitney U test in relation to the baseline of the selective subgroup.



min), when a rapid bradycardic effect is desired, followed by a continuous infusion rate of 1–40 μg/kg/min. There are no data supporting a bolus infusion of landiolol in paediatric patients, and a higher loading dose seems to be dispensable, due to its fast-acting pharmacokinetics and quick titration. In a pilot study of landiolol treatment in patients with atrial fibrillation or atrial flutter, the administration of a preceding bolus of landiolol seems not necessary.[26] In a paediatric study, evaluating landiolol for control of junctional ectopic tachycardia, a loading dose was waived due to a severe bradycardia seen in one infant.[13]

Our data support previously published results that cardiac function can be restored during HR control of sinus tachycardia. On the basis of the echocardiographic assessment, we could demonstrate that the improvement of cardiac function is associated with a normalization of the HR. It is known that tachycardia can lead to ventricular dysfunction by decreasing ventricular filling and increasing myocardial oxygen demand, imbalance of diastolic calcium concentrations, and calcium release from the sarcoplasmic reticulum.[27–29] There are few studies analysing the effect of HR control in children. Bonnet *et al*. demonstrated that an HR control with ivabradine improved LV function in children with dilated cardiomyopathy.[30] In a piglet study, HR was shown to be negatively correlated with the invasively measured diastolic function.[3] In adults, more insight could be given into the relationship between HR control and heart failure, as shown in large prospective trials analysing landiolol and ivabradine.[31,32] To date, the effect of landiolol on PH severity has not been described elsewhere. But the positive effect of HR reduction on PH was demonstrated in an animal model using carvedilol and ivabradine.[33] The authors showed that the reduction of HR led to an improvement of RV relaxation and an improvement of early diastolic LV filling, due to the improvement of the interventricular interaction and improved timing. According to the before mentioned data, our data demonstrate a beneficial effect of landiolol on PH severity, an optimized RV unloading, and better filling of the LV, illustrated by a decreasing RV/LV ratio. A decrease in HR potentially leads to higher filling pressures of the RV, with an optimized RV stroke volume and increased lung perfusion with decreasing right-to-left intrapulmonary shunts.

Few studies have focused on the question, whether it is feasible to add beta-blockers during vasoactive treatment with inotropes such as dobutamine or milrinone. In a retrospective cohort study, the use of landiolol was beneficial during catecholamine treatment in patients following cardiovascular surgery, as shown by an improvement of ventricular function due to an increasing stroke volume.[34] Similar results were found for the combination of landiolol and milrinone in patients with heart failure and rapid atrial fibrillation.[35] Our data support the observation that, despite continuous β1-blockade during landiolol infusion, positive inotropy is maintained. One possible explanation is that β1- and β2-receptors of ventricular myocardiocytes are linked to an inotropic effect of β-adrenergic stimulation. Whereas landiolol counteracts β1-stimulation, inotropy is possibly maintained via β2-receptor mediation.[34] Another potential explanation is that, during a combination of landiolol treatment and high-dose β1-stimulating inotropes such as dobutamine, there is a partial inhibition and stimulation of β1-receptors, leading to negative chronotropy and positive inotropy. However, authors speculate that very high doses of inotropes might be necessary to overcome the β-blockade.[36] Therefore, the combination of phosphodiesterase inhibitors as milrinone and β-blockade has advantages and seems reasonable, due to the fully preserved mechanism of phosphodiesterase inhibition during β-blockade.[35] Additionally, a similar approach was described for the combination of levosimendan and landiolol.[37] As many infants in our cohort were treated with a combination of high-dose inotropes (dobutamine, milrinone, and, in some cases, levosimendan), it is challenging to identify the principal mechanism leading to landiolol effectivity when treating with inotropes.

According to our data, landiolol treatment and the HR normalization led to a reduction of biomarkers of ventricular dysfunction (NT-proBNP and arterial lactate levels). To our knowledge, no data are available analysing cardiac biomarkers during landiolol treatment in infants, but NT-proBNP was shown to be a valuable cardiac biomarker in a cohort of infants with ventricular dysfunction and PH.[38] In adults, decrease of BNP and troponin I levels correlated significantly with landiolol treatment for prevention of atrial fibrillation in patients after cardiac surgery.[39]

Limitations

Due to the retrospective design of this study, certain limitations need to be stated. No comparator cohort was analysed, making it challenging to identify statistical effects and interpretation of study results. Nevertheless, the findings of this study are relevant and important as preliminary data to design prospective randomized-controlled trials. Echocardiographic assessment of cardiac function was to some extent based on qualitative measures, which can bias validation of these data. Furthermore, the echocardiographic estimation of ventricular dysfunction in infants with tachycardia can be inaccurate. The analysis of biomarkers for ventricular dysfunction helps to minimize this interference.

Conclusions

This is the first study analysing the ultra-selective beta-blocker landiolol for HR control of sinus tachycardia in term and preterm infants with ventricular dysfunction and PH. During landiolol treatment, HR control can be achieved quickly, and landiolol administration is well tolerated and safe. Landiolol treatment is associated with an improvement of ventricular dysfunction and PH severity in critically ill infants. This study provides important preliminary data for future prospective trials using landiolol in neonatal populations.

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Conflicts of interest

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The submission is a truthful, original work without fabrication, fraud, or plagiarism and contains no libellous or unlawful statements. The manuscript is not under consideration for publication, nor will it be submitted for publication, elsewhere until a final decision has been made by this journal. As the author I certify that each author has participated sufficiently in the work to take responsibility for its truthfulness and validity, has read the complete manuscript, and concurs with its content.

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