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Klinik für Neonatologie und Pädiatrische Intensivmedizin, Eltern-Kind-Zentrum, des Universitätsklinikums Bonn
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Innovative Diagnostik und Therapie der kardialen Dysfunktion und Pulmonalen Hypertonie bei kritisch kranken Früh- und Neugeborenen

Habilitationsschrift
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Die folgenden aufgelisteten fünf Originalarbeiten liegen der kumulativen Habilitationsschrift zu Grunde, welche die wesentlichen Ergebnisse der Publikationen zusammenfasst und diskutiert.

1) **Schroeder L**, Kuelshammer M, Dolscheid-Pommerich R, Holdenrieder S, Mueller A, Kipfmueller F. NT-proBNP and Zlog-transformed NT-proBNP values predict extubation failure in critically ill neonates with pulmonary hypertension and ventricular dysfunction. Pediatr Pulmonol. 2023 Jan;58(1):253-261. doi: 10.1002/ppul.26193. Epub 2022 Oct 17. *(JIF 3.1).*
2) **Schroeder L**, Gries K, Ebach F, Mueller A, Kipfmueller F. Exploratory Assessment of Levosimendan in Infants with Congenital Diaphragmatic Hernia. Pediatr Crit Care Med 2021 Jul 1;22(7): e382-e390. doi: 10.1097/PCC.0000000000002665. *(JIF 3.9).*
3) **Schroeder L**, Monno P, Unger M, Ackerl J, Shatilova O, Schmitt J, Dresbach T, Mueller A, Kipfmueller F**.** Heart rate control with landiolol hydrochloride in infants with ventricular dysfunction and pulmonary hypertension. ESC Heart Fail. 2023 Feb;10(1):385-396. doi: 10.1002/ehf2.14202. Epub 2022 Oct 18. *(JIF 3.8).*
4) **Schroeder L**, Holcher S, Leyens J, Geipel A., Strizek B, Dresbach T, Mueller A, Kipfmueller F. Evaluation of levosimendan as treatment option in a large case-series of preterm infants with cardiac dysfunction and pulmonary hypertension. Eur J Pediatr. 2023; Jul;182(7):3165-3174. doi: 10.1007/s00431-023-04971-9. Epub 2023 Apr 27. *(JIF 3.6).*
5) **Schroeder L**, Monno P, Strizek B, Dresbach T, Mueller A, Kipfmueller F. Intravenous sildenafil for treatment of early pulmonary hypertension in preterm infants. Sci Rep. 2023 May 24;13(1):8405. doi: 10.1038/s41598-023-35387-y *(JIF 4.6).*

Inhaltsverzeichnis

Für meine Frau und unsere wundervollen Kinder

1. Abkürzungsverzeichnis

Bpm	Beats per minute (Schläge pro Minute)
BPD	Bronchopulmonale Dysplasie
BVD	Biventrikuläre Dysfunktion
CD	Cardiac Dysfunction (Kardiale Dysfunktion)
CDH	Congenital diaphragmatic hernia (kongenitale Zwerchfellhernie)
ELGAN	Extremely low gestational age newborns (Neugeborene mit sehr geringem Gestationsalter bei Geburt, <28 Schwangerschafts-Wochen)
FFTS	Feto-fetales Transfusionssyndrom
GA	Gestationsalter
LV	Linker Ventrikel
LVD	Links-ventrikuläre Dysfunktion
PDA	Persistierender Duktus arteriosus
PDE	Phosphodiesterase
PH	Pulmonaler Hypertonus
PVR	Pulmonal vaskulärer Widerstand
RV	Rechter Ventrikel
RVD	Rechts-ventrikuläre Dysfunktion
SSW	Schwangerschafts-Wochen
UKB	Universitätsklinikum Bonn
VLBW	Very low birth weight (sehr geringes Geburtsgewicht, <1500g)

2. Einleitung

Kritisch kranke Früh- und Neugeborene haben ein hohes Risiko eine kardiale Dysfunktion („cardiac dysfunction“, CD) nach der Geburt zu entwickeln sowie an einer frühen (<28. Lebenstag) oder späten (>28 Lebenstag) pulmonalen Hypertonie (PH) zu erkranken. Der Terminus CD kann mit der Bezeichnung akute Herzinsuffizienz gleichsinnig verwendet werden. Die CD ist gekennzeichnet durch eine ventrikuläre diastolische oder systolische Funktionsstörung, mit der Folge einer reduzierten Auswurfleistung des Herzens und einer Minderperfusion des Lungen- sowie des Körper-Kreislaufes. Die PH ihrerseits wird definiert als eine Erhöhung des mittleren pulmonal arteriellen Druckes (mPAP) >20mmHG (Apitz C. et al., 2020). Nach der WHO-Klassifizierung und des 6. Welt-Kongresses zur Diagnose und Therapie der PH wird diese bei Früh- und Neugeborenen weiter unterteilt in 1) die persistierende PH des Neugeborenen (PPHN), Klasse I, Gruppe 1.7 nach WHO), und 2) die PH bedingt durch eine strukturelle Lungenstörung (Klasse III nach WHO), meistens assoziiert mit einer bronchopulmonalen Dysplasie (BPD, BPD-PH) oder Erkrankungen wie eine angeborene Zwerchfellhernie („congenital diaphragmatic hernia“, CDH) (Rosenzweig et al., 2019).

Um die genauen Pathomechanismen so verstehen, welche zu einer CD oder PH bei Früh- und Neugeborenen führen, muss man sich den Grunderkrankungen nähern, die für eine CD oder PH prädisponieren. Zum einen sind dies die extreme Frühgeburtlichkeit, also Frühgeborene mit einem Gestationsalter (GA) <28 Schwangerschaftswochen (SSW), welche ein erhöhtes Risiko haben für die Entwicklung einer CD oder PH (Hilgendorff et al., 2016; Kluckow, 2018; Abman, 2021). Extreme Frühgeborene können weiter subklassifiziert werden in „very low birth weight infants“ (VLBW, Frühgeborene mit sehr geringem Geburtsgewicht, <1500g) und in „extremely low gestational age newborns“ (ELGANs, Neugeborene mit sehr geringem GA bei Geburt, <28 SSW). Bei VLBW-Frühgeborenen und ELGANs besteht per se durch das frühe GA und sehr geringe Geburtsgewicht ein erhöhtes Risiko für Störungen der Transition der intra- auf die extrauterine Kreislaufsituation (Kluckow, 2018). Offene intra-atriale Shunts wie das Foramen ovale oder der Duktus arteriosus, Volumen-Verschiebungen in das pulmonale Gefäßbett und Widerstands-Veränderungen der zentralen und peripheren Gefäße stellen Risikofaktoren für ein Pumpversagen des neonatalen Herzens dar. Zudem bestehen materno-fetale Risikofaktoren, welche bereits in der intrauterinen Umgebung das Risiko für eine CD

oder auch eine PH nach der Geburt bei Früh- und Neugeborenen erhöhen. Dies sind zum Beispiel maternale Erkrankungen wie eine Präeklampsie, ein HELLP-Syndrom oder eine diabetische Stoffwechsellage mit dem Vorliegen einer diabetischen Fetopathie (Levy et al., 2018; Youssef et al., 2020). Weitere Faktoren sind bedingt durch feto-plazentare Störungen wie eine intrauterine Wachstumsverzögerung („intrauterine growth retardation“, IUGR), eine intrauterine feto-maternale Transfusion oder eine Zwillingsschwangerschaft mit dem Vorliegen eines feto-fetalen Transfusionssyndroms (FFTS) (van Mieghem et al., 2009; Pérez-Cruz et al., 2015; Wohlmuth et al., 2018). Genauso können Störungen unmittelbar unter Geburt wie eine perinatale Asphyxie zu einer neonatalen CD oder PH führen (Levy et al., 2018).

Neben feto-plazentaren Störungen und der Frühgeburt gibt es weitere angeborene und postnatale Faktoren, die das Risiko für eine CD und eine PH deutlich erhöhen. Angeborene Herzfehler stellen die häufigste Ursache für eine neonatale CD dar (Hsu and Pearson, 2009). Als zweit häufigste Ursache für eine neonatale CD kommen angeborene und erworbene Kardiomyopathien in Betracht (Lipshultz et al., 2003). Als postnatale Risikofaktoren für eine CD müssen unter anderem eine Sepsis oder ein persistierender Duktus arteriosus (PDA) bei Frühgeborenen in Betracht gezogen werden (Saini et al., 2014; Philip et al., 2019). Genauso wurden die Sepsis und der PDA als Risikofaktor für eine neonatale PH identifiziert (Deshpande et al., 2022; Gentle et al., 2023).

Früh- und Neugeborene mit angeborenen Fehlbildungen der Lunge stellen ein besonderes Risikokollektiv für eine neonatale CD oder PH dar. Ein vulnerables Kollektiv mit einer angeborenen Lungenfehlbildung sind Neugeborene mit einer CDH. Für Neugeborene mit einer CDH wurde die Assoziation der Erkrankung mit der neonatalen CD und PH bereits beschrieben (Gupta and Harting, 2020b; Patel et al., 2020). Dies wird unter anderem bedingt durch die schwere einseitige Lungenhypoplasie, Veränderungen der intrauterinen kardialen Füllungsverhältnisse und mikro-anatomische Veränderungen der pulmonalen Gefäßarchitektur. Neugeborene mit einer CDH leiden häufig unter einer Kombination einer ventrikulären Funktionsstörung und einer schweren PH. Die medikamentöse Kreislauf- Therapie dieser Risikogruppe stellt eine große Herausforderung dar für das behandelnde Team.

2.1. Innovative Diagnostik der neonatalen CD und neonatalen PH

Da die neonatale CD und PH als Organ primär das Herz betrifft, kommt der neonatalen Echokardiographie in der Diagnostik der beiden Entitäten eine Schlüsselstellung zu. In Übersichtsarbeiten zur neonatalen Echokardiographie wurde ein Ansatz entwickelt, mit welchen Messmethoden die CD und die PH bettseitig ermittelt werden kann (Boode et al., 2018; Levy et al., 2018). Dieser Ansatz wird auch als „fokussierte neonatale Echokardiographie“ bezeichnet. Die neonatale CD teilt sich in ihrer Ausprägung in eine diastolische und systolische Funktionsstörung auf und man muss jeweils zwischen einer rechts-, einer links- und einer bi-ventrikulären Dysfunktion (RVD/ LVD/ BVD) differenzieren. Die diastolische Funktionsstörung des rechten Ventrikels (RV) kann mittels des Einstromprofils über der Trikuspidalklappe (E-Welle/A-Welle) unter Nutzung des PW (pulsed-wave)-Dopplers ermittelt werden. Weitere Messmethoden sind das sogenannte „speckle tracking“ und die ermittelte „diastolic strain rate“ oder die über Tissue (Gewebe)-Doppler ermittelte myokardiale Bewegung (E´-Welle/A´-Welle) (Boode et al., 2018; Levy et al., 2018). Die systolische Funktion des RV kann mittels der TAPSE („tricuspid annular plane systolic excursion“) ermittelt werden. Generell ist die Messung der diastolischen und systolischen Funktion des RV auf Grund seiner Geometrie deutlich schwerer als die des LV. Der RV besitzt eine halbmond-förmig Konfiguration und besitzt anders als der LV vorwiegend longitudinale Muskelfasern. Der LV hingegen besitzt vorwiegend radiäre Muskelfasern und kontrahiert sich zirkulär. Die diastolische Funktion des LV kann ebenso mittels PW-Doppler oder Tissue-Doppler Messung kalkuliert werden alternativ per „speckle tracking“. Zudem sind Messwerte- wie die „Fractional shortening“ (FS) oder die Ejektionsfraktion (EF) valide Parameter für die systolische Funktion des LV (Boode et al., 2018; Levy et al., 2018). Das sogenannte „Eyeballing“ oder „Eyeball Assessment“ ist ein quantitatives und valides Verfahren, um die RVD oder LVD optisch einzuteilen in normal oder dysfunktional (Unlüer et al., 2014; Tissot et al., 2018).

Die echokardiographische Messung der neonatalen PH basiert auf folgenden Parametern: 1) der Trikuspidalklappen-Regurgitation (TR), als indirektes Maß für den systolischen PAP; 2) der Stellung des intraventrikulären Septums (IVS), mit einem D-förmig positionierten Septum hin zum LV als Hinweis auf einen suprasystemischen PAP; 3) der Fluss über den PDA, mit einem rechts-links-Shunt als Hinweis auf einen suprasystemischen PAP; oder 4) der pulmonal arteriellen Akzelerationszeit (englisch „pulmonary artery acceleration time”, PAAT) und der rechtsventrikulären Ejektionszeit

(englisch „right ventricular ejection time“, RVET) als systolische Zeit-Intervalle des RV (Boode et al., 2018).

Um eine multimodale Diagnostik der neonatalen CD und PH zu erreichen, ist die Bestimmung von Blut-Plasma Markern (Biomarkern) mittlerweile ein etabliertes Verfahren. Es existieren verschiedene Biomarker, welche mittels Verfahren wie der ELISA („enzyme linked immunosorbend assay“) im Blut-Plasma bestimmt werden können. Ein validierter Biomarker ist das N-terminale pro B-Typ natriuretisches Peptid (NT-proBNP). Dieses Herzenzym wird von Kardiomyozyten unter Wandspannung in das Blut sezerniert und ist das biologisch inaktive Signalpeptid des B-Typ natriuretischen Peptides (BNP). NT-proBNP hat eine Plasma-Halbwertszeit von 120 Minuten und kann mittels ELISA zeitnah bestimmt werden. NT-proBNP korreliert signifikant mit der Schwere der neonatalen CD und auch der neonatalen PH (Baptista et al., 2008; Dasgupta et al., 2018; Heindel et al., 2020). Ein weiterer vielversprechender Biomarker, welcher signifikant mit der Schwere der CD und PH assoziiert ist, ist das Muzin bzw. der Tumormarker CA125 (Carbohaydrat Antigen 125) (Pektaş et al., 2017; Soler et al., 2020; Schroeder et al., 2023f). Weiterhin gelten sRAGE („soluble receptor of advanced glycation end products”) und die lösliche Form des ST2 (Interleukin-1 Rezeptor) als Biomarker für eine kardiale Belastung im Rahmen einer CD oder PH (Koyama et al., 2008; Tunc et al., 2014; Go et al., 2021; Savarimuthu et al., 2022).

2.2. Medikamentöse Therapie der neonatalen CD

Die medikamentöse Therapie der neonatalen CD basiert auf einem multimodalen Therapieansatz. Zum einen ist es essenziell die klinische Situation des Früh- und Neugeborenen zu stabilisieren, mittels Atemunterstützung, Beatmungsoptimierung und Flüssigkeits-Management. Als weitere Therapie kommt der Vor- und Nachlast-Optimierung eine besondere Rolle zu. Dies beinhaltet Wirkstoffgruppen wie ACE-Hemmer, Betarezeptorblocker, Diuretika und Mineralocorticoid-Rezeptor-Antagonisten (Michel-Behnke I. et al., 2020). Neben der Therapie mit oral applizierten Wirkstoffgruppen bedarf es gerade bei der Therapie der schweren neonatalen CD einer intravenösen Applikation. Verfügbare Medikamente können grob eingeteilt werden in Inotropika, Inodilatoren und Vasopressoren. Zu den Inotropika zählen unter anderem Dopamin, Dobutamin und Suprarenin. Der Phosphodiesterase (PDE)-III

Hemmer Milrinon und der Calciumsensetizer Levosimendan werden zu den sogenannten Inodilatoren gezählt und gelten als neuere Therapieansätze in der Therapie der neonatalen CD (Dempsey and Rabe, 2019). Jedoch gibt es bislang nur wenige Daten zum Einsatz von Milrinon bei einer neonatalen CD ohne Vorliegen eines angeborenen Herzfehlers und kaum Daten zum Einsatz von Levosimendan außerhalb von Früh- und Neugeborenen mit Notwendigkeit einer kardiochirurgischen Operation. Um den arteriellen Mitteldruck und die Nachlast zu stabilisieren sind Vasopressoren in der Therapie der neonatalen CD und PH unerlässlich. Vor allem kommen sie bei der Sepsis-assoziierten Form der CD zum Einsatz. Medikamente dieser Klasse sind unter anderem Noradrenalin, Vasopressin und auch Suprarenin (Zaveri et al., 2023). Ein weiterer neuer Therapie-Ansatz der neonatalen CD ist die Herzfrequenzkontrolle bei Sinustachykardie oder Vorhof-bzw. ventrikulären Tachykardien. Zwei Wirkstoffklassen stehen hierfür zur Verfügung. Zum einen sind dies I_f-Kanal Inhibitoren wie Ivabradin oder ultra-schnellwirksame ß-Blocker wie der Wirkstoff Landiolol, deren Wirksamkeit in pädiatrischen Studien nachgewiesen wurde im Rahmen einer Herzinsuffizienz-Therapie (Bonnet et al., 2017; Lipshultz et al., 2017; Yoneyama et al., 2018a).

2.3. Medikamentöse Therapie der neonatalen PH

Auch die Therapie der neonatalen PH gliedert sich in verschiedene Ansätze auf. Noch wichtiger als im Rahmen der CD-Therapie kommt der Verbesserung der Oxygenierung und Decarboxylierung zur Erhöhung des arteriellen Sauerstoff-Partialdruckes (paO_2) und Normalisierung des Kohlendioxid-Partialdruckes ($paCO_2$) eine wichtige Rolle zu. Um dies zu erreichen ist eine Sauerstoff-Therapie und auf Grund der sich schnell erschöpfenden Atemmuskulatur häufig eine Atem-Unterstützung via High-Flow Nasenbrille bzw. einer CPAP-Maske („continuous positive airway pressure“) oder eine maschinelle Beatmung bei Früh- und Neugeborenen notwendig. Das primäre Ziel der neonatalen PH-Therapie ist es den pulmonal vaskulären Widerstand (PVR) zu senken. Dies gelingt neben der Sauerstoff-Therapie auch mittels inhalativem Stickstoffmonoxid (iNO), jedoch wird die Datenlage trotz etlicher Studien bzgl. des Therapie-Effektes sehr kontrovers diskutiert (Chandrasekharan et al., 2021; Cookson et al., 2022). Neben der iNO-Therapie gibt es weitere verfügbare inhalative Therapeutika wie inhalatives Iloprost (Lakshminrusimha et al., 2016). Epoprostenol oder Treprostinil sind weitere Prostazyklin-Derivate, welche ihren therapeutischen Effekt mittels einer Erhöhung der

zyklischen Adenosin-Monophosphat (cAMP) Konzentration und damit einer Erweiterung der glatten Muskelzellen der Gefäße erzielen (Lakshminrusimha et al., 2016). Eine andere Wirkstoff-Klasse sind die Endothelin-1-Rezeptor Antagonisten, wie Bosentan, Macitentan und Ambrisentan, welche ihren Effekt über eine kombinierte oder selektive Inhibition der Endothelin$_{A/B}$-Rezeptoren entfalten und somit die Endothelin$_{A}$-Rezeptor vermittelte Vasokonstriktion verhindern (Lakshminrusimha et al., 2016). Als orale und intravenöse Therapie zur Senkung des PVR hat sich Sildenafil, ein PDE-V Hemmer, in der neonatalen PH-Therapie etabliert (Kelly et al., 2017; He et al., 2021). Sildenafil hemmt den PDE vermittelten Abbau von zyklischen Guanosin-Monophosphat (cGMP), welches für die endogene NO-Synthese essenziell ist. Viele Studien haben sich mit der oralen und intravenösen Anwendung von Sildenafil bei Spät-Frühgeborenen und Neugeborenen >34 SSW beschäftigt. Jedoch fehlen Daten bezüglich der Therapie bei Frühgeborenen <34 SSW und bei Frühgeborenen mit einer frühen neonatalen PH (<28 Lebenstag).

2.4. Zielsetzung

Die folgenden Kapitel stellen die Arbeit von insgesamt fünf retrospektiven klinischen Studien dar. Die Zielsetzung der klinischen Studien war, innovative Diagnostik- und Therapie-Strategien für Früh- und Neugeborene mit einer neonatalen CD und PH zu evaluieren. Alle Früh- und Neugeborene wurden in der Klinik für Neonatologie und Pädiatrischen Intensivmedizin des Eltern-Kind-Zentrums am Universitätsklinikum Bonn (UKB) behandelt. In der ersten Studie wurde der Fokus auf die Diagnostik der neonatalen CD und PH gelegt, um den Biomarker NT-proBNP als kardiales Monitoring-Tool bei Früh- und Neugeborenen zu evaluieren und das Risiko eines Extubations-Versagens nach Beendigung der maschinellen Beatmung abschätzen zu können. Früh- und Neugeborene mit einer CD oder PH in der kurzzeitigen Anamnese haben ein deutlich erhöhtes Risiko ein Extubations-Versagen nach Beendigung der maschinellen Beatmung zu erleiden (Ödek et al., 2016; Schroeder et al., 2018). Daten zu dieser Thematik wurden bis dato wenig evaluiert. Der Hauptteil der klinischen Studien (Studien zwei bis fünf) beschäftigte sich mit Evaluation von innovativen medikamentösen Behandlungsstrategien bei Früh- und Neugeborenen mit einer neonatalen CD und PH. Die Behandlung von schwerstkranken Früh- und Neugeborenen (mit und ohne angeborenen Organ-Fehlbildungen) ist ein

Behandlungs-Schwerpunkt in der Klinik für Neonatologie und Pädiatrischen Intensivmedizin am UKB. Die medikamentöse Therapie mit innovativen Wirkstoffen wie Levosimendan, Sildenafil oder dem ß-Blocker Landiolol wird seit vielen Jahren als alternativer Heilversuch und als off-label Medikamente in unserer Klinik bei diesem Patienten-Kollektiv erfolgreich eingesetzt. Ebenso ist die neonatale Echokardiographie fest in die klinische Routine der Versorgung und Diagnostik der kritisch kranken Früh- und Neugeborenen in unserer Abteilung implementiert. Somit bot sich die Gelegenheit, retrospektive klinische Kohorten-Studien zur medikamentösen Therapie mit innovativen Wirkstoffen bei der neonatalen CD und PH durchzuführen. Zeitgleich konnten echokardiographische Untersuchungen retrospektiv ausgewertet werden, um Aussagen über das kardiale Assessment zu treffen. Aus dem adulten Bereich wurden viele Studien zu dem Inodilator Levosimendan im Rahmen einer CD oder chronischen Herzinsuffizienz sowie der PH durchgeführt, jedoch gibt es kaum Daten zur Levosimendan Therapie im neonatalen Bereich. Die wenigen Studien haben den Effekt von Levosimendan im Bereich vor oder nach einer Herzoperation untersucht und daher fehlen Daten zur Therapie bei Früh- und Neugeborenen, welche nicht an einem angeborenen Herzfehler erkrankt sind. Die Studien zwei und vier widmeten sich dieser Thematik. Ebenso fehlen Daten aus Kohortenstudien oder prospektiven Studien bezüglich der Therapie mit dem ultra-selektiven $ß_1$-Blocker Landiolol im Rahmen der neonatalen CD und PH, für dessen Evaluation bis dato nur Studien bei pädiatrischen Patienten vor und nach herzchirurgischen Eingriffen durchgeführt wurden. Die dritte Studie befasste sich daher mit der Evaluation der Landiolol-Therapie bei Früh- und Neugeborenen, welche in der Klinik für Neonatologie am UKB behandelt wurden. Gleiches gilt für Daten zur intravenösen Sildenafil-Therapie bei Frühgeborenen <37 SSW mit einer frühen PH (<28 Lebenstag). Die fünfte Studie widmete sich diesem Thema, um die Sildenafil-Therapie in diesem sehr vulnerablen Kollektiv kritisch zu evaluieren.

3. Ergebnisteil

3.1. NT-proBNP als Biomarker des Extubations-Versagens bei kritisch kranken Früh- und Neugeborenen mit einer CD und PH

Schroeder L, Kuelshammer M, Dolscheid-Pommerich R, Holdenrieder S, Mueller A, Kipfmueller F. NT-proBNP and Zlog-transformed NT-proBNP values predict extubation failure in critically ill neonates with pulmonary hypertension and ventricular dysfunction. Pediatr Pulmonol. 2023 Jan;58(1):253-261. doi: 10.1002/ppul.26193. Epub 2022 Oct 17. *(JIF 3.1).*

Zielsetzung der Studie: Kritisch kranke Früh- und Neugeborene, welche eine maschinelle Beatmung benötigen im Rahmen eines respiratorischen Versagens mit respiratorischer Partial- oder Globalinsuffizienz, haben ein erhöhtes Risiko für ein Extubations-Versagen nach Beendigung der maschinellen Beatmung. Eine neonatale CD oder neonatale PH in der kurzzeitigen Vorgeschichte und das Vorliegen einer persistierenden kardialen Funktionsstörung können den Erfolg der geplanten Extubation deutlich vermindern. Der Biomarker „N-terminales pro B-Typ natriuretischen Peptid“ (NT-proBNP) wird bei ventrikulärer Belastung freigesetzt und ins Plasma sezerniert. Es ist unklar, ob die Bestimmung von NT-proBNP unmittelbar vor und nach der Extubation dazu beiträgt, Patienten mit einem Extubations-Versagen frühzeitig zu identifizieren. Die Z_{log}-Transformation des NT-proBNP Wertes könnte als zusätzliches Tool die Interpretation der NT-proBNP Werte erleichtern.

Methoden und Ergebnisse: Es wurden retrospektiv Daten von 43 Früh- und Neugeborenen aus dem Studienzeitraum 01/2020 bis 12/2021 untersucht, welche in der Klinik für Neonatologie des UKB behandelt wurden. Als Einschlusskriterien wurden definiert: eine Langzeitbeatmung (<24 Stunden) mit mindestens einem Extubations-Versuch, eine echokardiographisch nachgewiesene kardiale Funktionsstörung (CD) und/ oder PH bei Aufnahme auf die neonatologische Intensivstation oder im Verlauf der intensivmedizinischen Behandlung vor der Extubation, eine NT-proBNP Messung im Zeitraum 24 Stunden vor dem Extubations-Versuch (Baseline) und 24 Stunden nach dem Extubations-Versuch (Follow-up). NT-proBNP wird in der klinischen Routine in unserer Abteilung durch das behandelnde Ärzteteam regelmäßig bestimmt und so waren ausreichend Daten zur retrospektiven Evaluation vorhanden. Das Extubations-Versagen innerhalb von 72 Stunden wurde als primärer Endpunkt definiert. Retrospektiv ausgewertet wurden zudem echokardiographische Daten vor und nach

der Extubation. Bei 21% der Neonaten kam es zu einem Extubations-Versagen nach Beendigung der maschinellen Beatmung. Die epidemiologischen Charakteristika der Patienten-Kohorte sind der Tabelle 1 der angefügten Originalpublikation zu entnehmen (Table 1, Schroeder et al., 2023b). Das mittlere NT-proBNP sowie das Z_{log}-transformierte NT-proBNP nach Beendigung der Beatmung zeigte sich signifikant erhöht bei Neonaten mit einem Exubations-Versagen (siehe Fig. 1 und Fig. 2., Schroeder et al., 2023b). Zudem korrelierten beide Werte signifikant mit der Schwere der PH und der ventrikulären Dysfunktion, jedoch zu unterschiedlichen Zeitpunkten vor und nach der Extubation. Die genauen Korrelationsanalysen und „Receiver Operating Characteristics“ (ROC) Analysen können der angefügten Originalarbeit entnommen werden (Table 2 und Fig. 2, Schroeder et al., 2023b).

Schlussfolgerung: Als wesentliche Ergebnisse der Studie konnten NT-proBNP und das Z_{log}-transformierte NT-proBNP als mögliche neue Biomarker für ein Extubations-Versagen bei kritisch kranken Neonaten identifiziert werden.

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ORIGINAL ARTICLE

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NT-proBNP and Zlog-transformed NT-proBNP values predict extubation failure in critically ill neonates with pulmonary hypertension and ventricular dysfunction

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Abstract

Objectives: Critically ill neonates with a history of pulmonary hypertension (PH) or ventricular dysfunction are at risk to experience an extubation failure (EF) after liberation from mechanical ventilation (MV). Due to insufficient data from neonatal cohorts, it remains unclear whether NT-proBNP is an appropriate biomarker to predict EF in this cohort. The Zlog-transformation of NT-proBNP (further named $NT\text{-}proBNP_{Zlog}$) is an additional tool to optimize the interpretation of NT-proBNP since absolute NT-proBNP values are varying with the age of these infants.

Patients and Methods: This was a retrospective single-center analysis at the University Children's Hospital, Bonn, Germany, during the study period from January 2020 until December 2021. Forty-three neonates met the inclusion criteria and were screened for study participation. Inclusion criteria: prolonged (>24 h) MV with at least one extubation attempt, with a history of PH and/or ventricular dysfunction in the echocardiographic assessment at admission to the neonatal intensive care unit or during the period of MV, NT-proBNP measurements before (max. 24 h, baseline) and after (max. 24 h, follow-up) the first extubation attempt. The primary clinical endpoint was defined as EF with need for reintubation (0–72 h). Neonates with an EF were allocated to group A and neonates with successful liberation from MV to group B.

Main Results: The primary clinical endpoint (EF) was reached in 21% (nine infants). Absolute mean NT-proBNP values ($NT\text{-}proBNP_{abs}$) at baseline did not differ significantly in infants of group A and B (6931 vs. 7136 pg/ml, $p = 0.227$). $NT\text{-}proBNP_{Zlog}$ values at baseline (2.35 vs. 1.57, $p = 0.073$) tended to higher values in group A. $NT\text{-}proBNP_{abs}$ values measured at follow-up were significantly higher in infants allocated to group A (11120 vs. 7570 pg/ml, $p = 0.027$). Likewise, $NT\text{-}proBNP_{Zlog}$ values at follow-up were significantly higher in infants allocated to group A (3.05 vs. 1.93, $p = 0.009$). $NT\text{-}proBNP_{abs}$ values at follow-up and $NT\text{-}proBNP_{Zlog}$ values at baseline correlated significantly with the severity of PH.

Regarding the receiver operating characteristic-analysis, a NT-proBNP$_{abs}$ value at follow-up of ≥4622 pg/ml was calculated as optimal cut-off value for the prediction of EF (area under the curve [AUC] 0.742, $p = 0.001$). A NT-proBNP$_{Zlog}$ value at baseline of ≥1.63 and at follow-up of ≥2.14 was calculated as optimal cut-off for the prediction of EF (AUC: 0.690/$p = 0.027$, and 0.781/$p = 0.000$, respectively).

Conclusion: NT-proBNP$_{abs}$ and NT-proBNP$_{Zlog}$ might be valuable biomarkers for the prediction of EF in critically ill neonates. The Zlog-transformation of NT-proBNP allows an age-independent interpretation of NT-proBNP and should be considered for clinical routine.

KEYWORDS

biomarker, extubation failure, neonates, NT-proBNP, Zlog-transformation

1 | INTRODUCTION

Neonates receiving prolonged mechanical ventilation (MV > 24 h) require a sufficient weaning period when liberation from MV is planned. The phase of extubation and initiation of spontaneous breathing, with or without noninvasive support, is vulnerable. Critically ill infants are at risk for extubation failure (EF) after liberation from MV. The transition of MV to spontaneous breathing induces important clinical and hemodynamic alterations: reduction of the intrathoracic pressure, increased venous return with increased right-ventricular preload, elevated pre- and afterload of the left ventricle, and elevated work of breathing. It is well known that extubation of critically ill patients might be associated with respiratory insufficiency and ventricular dysfunction with need for reintubation.[1] Pediatric patient with a history of ventricular dysfunction or pulmonary hypertension (PH) at admission to the neonatal intensive care unit (NICU) or during the period of MV are particularly at risk for EF.[2,3] Incorporating prediction tools during the weaning period on the ventilator might be useful to identify patients at high risk of EF early and to create an optimal setting for the extubation attempt. Biomarkers as the cardiac hormones B-type natriuretic peptide (BNP) and its aminoterminal peptide NT-proBNP provide useful prognostic information for extubation success in adult populations.[4–6] In this setting, NT-proBNP correlates with respiratory distress after extubation, and the relative change of BNP values during a spontaneous breathing trial (SBT) was predictive for the extubation success in adults. However, in a small prospective study, the baseline NT-proBNP was not associated with weaning failure.[7] Data for pediatric patients are scarce. In a study focusing on preterm infants (<32 weeks of gestational age), a high NT-proBNP was identified as an independent risk factor for weaning failure.[8] Although these results are promising, there is insufficient data on the role of natriuretic peptides during the weaning period in critically ill infants. On the other hand, more data are available on the association of natriuretic peptides with cardiac function and PH in preterm and term infants.[9–11]

The aim of this study was to evaluate absolute NT-proBNP (NT-proBNP$_{abs}$) and the Zlog-transformed NT-proBNP (NT-proBNP$_{Zlog}$) in a cohort of preterm and term infants with a history of PH and/or ventricular dysfunction following prolonged MV.

2 | MATERIALS AND METHODS

2.1 | Study population and ethical approval

Infants treated at the NICU of the University Children's Hospital of Bonn, Germany, during the study period from January 2020 until December 2021 were retrospectively identified for study participation. Inclusion criteria: prolonged (>24 h) MV with a weaning period and at least one extubation attempt, history of PH, and/or ventricular dysfunction on echocardiography, NT-proBNP measurements before (further named baseline) and after (further named follow-up) the first extubation attempt (max. 24 h). Exclusion criteria were as follows: primary palliative care, congenital heart defects requiring surgical repair, renal dysfunction (oliguria [<1 ml/kg/h] or anuria [<0.5 ml/kg/h] for the last 12–24 h, and acute kidney injury [AKI] stadium 2 or 3, according to the neonatal AKI KDIG criteria,[12] before extubation attempt), missing NT-proBNP values at both time points, no echocardiographic assessment at both time points. The study was approved by the local ethics committee of the Medical Center of the University of Bonn (local running number 492/21). Informed consent was waived due to the retrospective design of the study.

2.2 | Respiratory and cardiac support

Infants with acute respiratory failure and the need for MV were part of this retrospective analysis. The underlying primary diagnosis of ventilated infants are illustrated in Table 1. All infants were ventilated with a pressure-controlled synchronized intermittent mandatory ventilation (PC-SIMV). Ventilator settings were adjusted to target tidal

TABLE 1 Demographic and treatment data

	Overall cohort (*n* = 43)	Group A (*n* = 9)	Group B (*n* = 34)	*p* Level
Gestational age, w	38.2 (32.7/42.9)	39.2 (36.4/42.9)	38 (32.7/41.6)	0.311
Female sex, *n* (%)	18 (42)	4 (44)	14 (41)	0.860
Birth weight, kg	3.2 (1.8/4.9)	3.1 (2/4.3)	3.3 (1.8/4.9)	0.473
Primary diagnosis, *n* (%)				
CDH	24 (49)	7 (78)	17 (50)	
CPAM	3 (7)	0	3 (9)	
Meconium aspiration	3 (7)	1 (11)	2 (6)	
Perinatal asphyxia	3 (7)	0	4 (12)	
PPHN	7 (16)	1 (11)	5 (15)	
Omphalocele	2 (4)	0	2 (6)	
Congenital lymphangioma	1 (2)	0	1 (3)	
Mechanical ventilation, days	9.6 (0.5/60)	13 (0.5/28)	8.8 (0.5/60)	0.351
In-hospital mortality, *n* (%)	1 (3)	1 (11)	0	0.209
ECMO support, *n* (%)	13 (30)	5 (56)	8 (23)	0.102

Note: Data are demonstrated as absolute number with percentages or as median values with minimum/maximum.
Abbreviations: CDH, congenital diaphragmatic hernia; CPAM, congenital pulmonary airway malformation; ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension of the newborn.

volumes of 4–6 ml/kg with a maximum positive inspiratory pressure (PIP) of 28 mbar. The partial carbon dioxide pressure (pCO_2) was maintained within a range of 45–65 mmHg (normo- to permissive hypercapnia) and the fraction of inspired oxygen (FiO_2) was adjusted to achieve a pulse oximetry oxygen saturation (preterms: 88%–96% and terms: 92%–98%) or partial oxygen pressure (pO_2; 60–100 mmHg). In infants with treatment failure under conventional MV high-frequency oscillation (HFO) was optionally implemented in selective cases. For the reduction of pulmonary vascular resistance inhaled nitric oxide (iNO) was used when PH was present. Additionally, as second- and third-line medication, intravenous sildenafil or bosentan were used for PH treatment. Infants with the need for inotropic support were treated with dobutamine and with milrinone, when additional inodilative effect was necessary. Furthermore, levosimendan was administered in infants prone to high-dosed inotropic treatment. In cases of oxygenation failure, extracorporeal membrane oxygenation (ECMO) was implemented according to international guidelines and criteria.[13,14] In any case of ECMO therapy, canulation was performed venovenous.

Pharmacological support during MV consisted of analgosedation with midazolam and fentanyl or remifentanil. Additionally, clonidine or dexmedetomidine was administered in cases of prolonged use of opioid medication to handle opioid withdrawal symptoms. Dosage of medication was controlled using approved scoring systems (Hartwig score, Finnegan score and Neonatal Pain Agitation Sedation Scale [N-PASS]).

Infants with prolonged MV were weaned from the ventilator using SBT under intermittent spontaneous/assisted ventilation with the following criteria: lowering of inspiratory pressure support (ΔP) and a maximum PIP of <18 mbar, a positive end-expiratory pressure (PEEP) of 4–6 mbar, tidal volumes of 4–6 ml/kg, and oxygen demand of $F_iO_2 < 0.4$. The first extubation attempt was performed when infants were breathing comfortable, with normalized blood gases, without respiratory acidosis and echocardiographic exclusion of severe PH or presence of ventricular dysfunction. At last, readiness for extubation was defined by the NICU attending physician. After extubation infants were mainly placed on a noninvasive respiratory support, using continuous positive airway pressure (CPAP, via nasal mask or prong) or binasal high flow nasal cannulas (HFNC). In cases of respiratory insufficiency under CPAP with hypoxemia ($SpO_2 < 88\%$) and hypercapnia ($pH < 7.2$, $pCO_2 > 80$ mmHg) or signs of severe tachydyspnea noninvasive mask ventilation with pressure support was applied to avoid reintubation. Reintubation was performed according to the decision of the NICU attending physician in cases of respiratory failure despite maximum noninvasive support with persistent respiratory acidosis ($pH < 7.2$, $pCO_2 > 80$ mmHg) and oxygenation failure ($SpO_2 < 88\%$, $FiO_2 > 80\%$). EF was defined as reintubation to maximum 72 h after the first extubation attempt.

2.3 | Echocardiographic assessment

At our department, the echocardiographic assessment is implemented in the daily clinical routine in infants with clinical and echocardiographic diagnosis of PH and ventricular dysfunction. Infants with history of PH or ventricular dysfunction during their

NICU treatment and during the period of MV were routinely assessed by echocardiography at baseline and follow-up. For echocardiographic measurements, a Philips CX50 Compact Extreme Ultrasound system with an S12-4 sector array transducer (Philips Healthcare) was used. All echocardiographic data were retrospectively screened for analysis independently by two experienced neonatal echocardiographers. PH was graded as mild, moderate, or severe, using the following echocardiographic parameters: (a) flow pattern of the ductus arteriosus, (b) intraventricular septum position, (c) tricuspid valve regurgitation, and (d) time to peak velocity (TPV) and right ventricular ejection time (RVET), measured in the main pulmonary artery. Ventricular dysfunction was defined as (a) right-ventricular (RVD), b) left-ventricular (LVD), or (c) biventricular dysfunction (BVD) and classified as present or not present. For the assessment of ventricular dysfunction, a combined approach of quantitative and qualitative measurements was used, based on international guidelines.[15,16]

2.4 | NT-proBNP measurements

NT-proBNP plasma levels were measured using the electrochemiluminescence immunoassay Elecsys proBNP II on a cobas e801 analyzer (Roche Diagnostics). In infants with echocardiographic diagnosis of PH or ventricular dysfunction NT-proBNP plasma levels were measured initially with the laboratory assessment according to the local standard operating procedure. Repeated measurements were performed according to the NICU attending physician. When NT-proBNP plasma levels were available within 24 h before and 24 h after the first extubation attempt, infants met inclusion criteria for retrospective analysis.

In addition to the measurement of absolute values (pg/ml) NT-proBNP values were transformed into Zlog values (see formula below) for an age-independent interpretation, as described previously.[17,18]

$$\text{NT-proBNP Zlog} = \frac{\log x + 0.512 \times \log t - 3.417}{1.489 + 0.014 \times \log t} \times 3.92 \quad (x = \text{NT-proBNP in pg/ml}, \; t = \text{age in days}).$$

2.5 | Statistical analysis and outcome measures

The primary clinical endpoint was defined as EF with need for reintubation (0–72 h) after the first extubation attempt. These patients were allocated to group A. Group B consisted of infants with successful extubation.

Duration of MV, need for ECMO, and in-hospital mortality were defined as secondary clinical severity parameters. Data of baseline characteristics are shown as absolute number (with %), median (with range), or mean (minimum-maximum) as appropriate. For the comparison of continuous variables, the Mann–Whitney *U* test was used. For categorical variables, Fisher's exact test was applied. Correlations between variables were evaluated by Spearman correlation coefficients. Using receiver operating characteristic (ROC) analysis, an NT-proBNP cut-off value ($NTproBNP_{abs}$ and $NT\text{-}proBNP_{Zlog}$) was evaluated to predict the primary clinical endpoint (EF). A $p < 0.05$ was considered significant. The statistical analysis was performed using statistical software (IBM SPSS Statistics for Windows, Version 27.0., IBMCorp.).

3 | RESULTS

In the study period, 43 infants met the inclusion criteria for retrospective analysis. Baseline characteristics are shown in Table 1. The primary clinical endpoint (EF) was reached in 21% (nine infants). The baseline characteristics between both groups were equally distributed. Regarding the secondary clinical severity parameters, no significant differences were found between both groups.

The mean $NT\text{-}proBNP_{abs}$ value at baseline did not differ significantly in infants of groups A and B (6931 vs. 7136 pg/ml, $p = 0.227$, Figure 1). The mean $NT\text{-}proBNP_{Zlog}$ value at baseline (2.35 vs. 1.57, $p = 0.073$, Figure 1) was higher in group A, without reaching statistical significance. At follow-up, the mean $NT\text{-}proBNP_{abs}$ value was significantly higher in infants allocated to group A (11,120 vs. 7570 pg/ml, $p = 0.027$, Figure 1). Likewise, the mean $NT\text{-}proBNP_{Zlog}$ value at follow-up was significantly higher in infants allocated to group A (3.05 vs. 1.93, $p = 0.009$, Figure 1). Analyzing the absolute and relative change of the mean $NT\text{-}proBNP_{abs}$ value at baseline and follow-up, no difference was found for both parameters comparing groups A and B (4188 vs. 434 pg/ml, $p = 0.144$; 101% vs. 76%, $p = 0.170$). Nevertheless, the increment of the absolute and relative change in $NT\text{-}proBNP_{abs}$ values was higher in infants of group A.

The severity of PH and the presence of ventricular dysfunction (RVD/LVD/BVD) are displayed in Figure 2. The severity of PH, assessed at baseline and at follow-up, was significantly higher in infants with an EF (group A) at both time points ($p < 0.001$). Likewise, the incidence of RVD was significantly higher in infants of group A at both time points ($p = 0.026$, and $p < 0.001$, respectively). The incidence of BVD was higher at baseline in infants allocated to group A but not at follow-up ($p = 0.040$, and $p = 0.214$, respectively). At baseline and at follow-up, no statistical difference was found regarding LVD between subgroups.

The results of the correlation analysis are illustrated in Table 2. $NT\text{-}proBNP_{abs}$ values at follow-up and $NT\text{-}proBNP_{Zlog}$ values at baseline as well as follow-up correlated significantly with the severity of PH. Additionally, $NT\text{-}proBNP_{Zlog}$ values at follow-up correlated significantly with the presence of RVD. With focus on clinical severity parameters, $NT\text{-}proBNP_{Zlog}$ values at baseline and at follow-up correlated significantly with the need for ECMO. $NTproBNP_{abs}$ and $NT\text{-}proBNP_{Zlog}$ values were not correlated with gestational age and birth weight.

The results of the ROC analysis are shown in Figure 3. The area under the curve (AUC) with the corresponding sensitivity, specificity, and positive and negative predictive value (PPV, NPV) are illustrated in Table 3. A mean $NT\text{-}proBNP_{abs}$ value at baseline of ≥2232 pg/ml

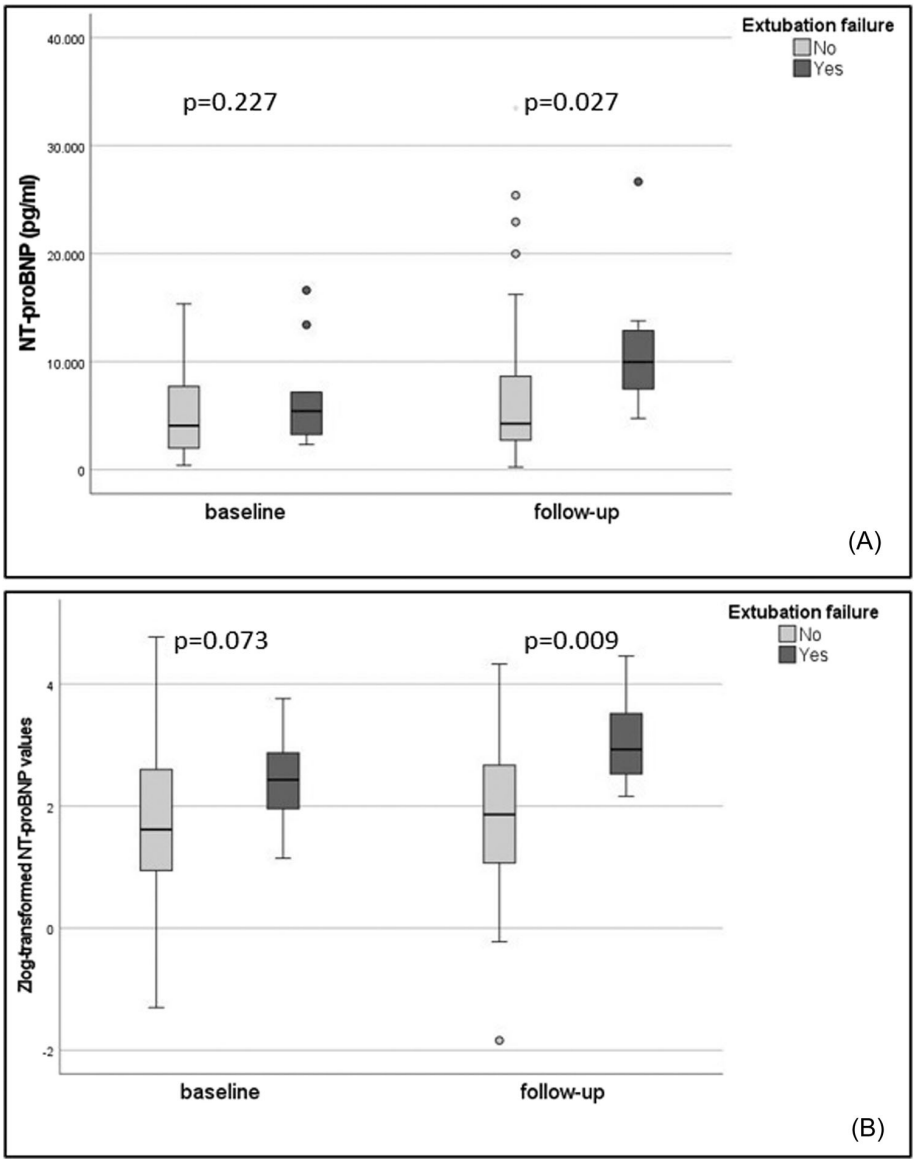

FIGURE 1 Mean NT-proBNP$_{abs}$ (A) and NT-proBNP$_{Zlog}$ values (B) at baseline (before the extubation) and at follow-up (after the extubation). Zlog-transformation was performed according to the equation formula described by Hoffmann et al.[18] NT-proBNP, N-terminal pro-brain natriuretic peptide.

and at follow-up of ≥4622 pg/ml was defined as the optimal cut-off value for the prediction of EF. A mean NT-proBNP$_{Zlog}$ value at baseline of ≥1.63 and at follow-up of ≥2.14 was defined as optimal cut-off for the prediction of EF, with almost equal values for sensitivity, specificity, PPV and NPV (see Table 3).

4 | DISCUSSION

The present study gives important insight about the role of NT-proBNP and Zlog-transformed NT-proBNP values as biomarkers for EF in critically ill preterm and term neonates with PH and/or ventricular dysfunction. One of our major findings was that mean NT-proBNP$_{abs}$ values at follow-up and mean NT-proBNP$_{Zlog}$ values at baseline as well as at follow-up were predictive for EF, with high sensitivity and NPV. Additionally, mean NT-proBNP$_{abs}$ values at follow-up and mean NT-proBNP$_{Zlog}$ values at baseline as well as at follow-up correlated significantly with the severity of PH of critically ill neonates. Furthermore, mean NT-proBNP$_{Zlog}$ values at follow-up correlated significantly with RVD. To our knowledge, this is the first study analyzing the association of Zlog-transformed NT-proBNP values with EF in neonates.

Only few studies are available analyzing NT-proBNP as a biomarker for extubation readiness in neonates. Zhang et al.[8]

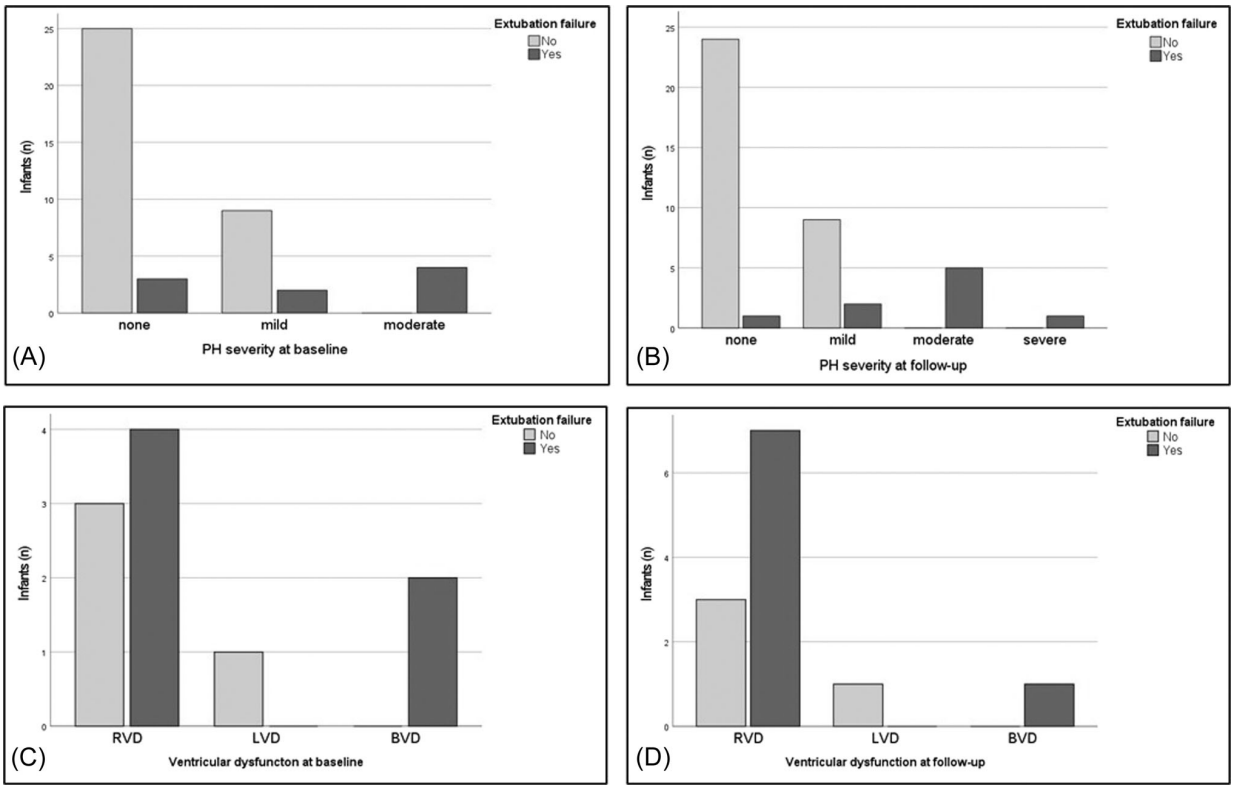

FIGURE 2 PH severity (A, B) and ventricular dysfunction (C, D) at baseline (before the extubation) and at follow-up (after the extubation). BVD, biventricular dysfunction; LVD, left-ventricular dysfunction; PH, pulmonary hypertension; RVD, right-ventricular dysfunction.

presented data on 88 preterm neonates with MV due to respiratory distress syndrome (RDS). NT-proBNP was identified as the only independent risk factor for weaning failure (including either failure of SBT or EF). A cut-off value of >18,500 pg/ml is highly predictive for weaning failure, with an AUC of 0.977 and a specificity of 94.2%. In their prospective study, the authors included only a single NT-proBNP value before the SBT and extubation attempt. According to these findings, we could demonstrate that NT-proBNP$_{abs}$ and NT-proBNP$_{Zlog}$ values are predictive for an EF in neonates, but contrarious to the before mentioned study our NT-proBNP values were measured after the extubation attempt. NT-proBNP$_{abs}$ values at baseline did not differ between subgroups in our cohort, but after Zlog-transformation of NT-proBNP values a trend to higher values in neonates suffering from EF was noticeable.

In a systematic review and meta-analysis on BNP and NT-proBNP as biomarker for EF no final recommendation on the use of BNP or NT-proBNP could be given due to insufficient data from pediatric cohorts.[6] However, more data are available from adult cohorts. In their final meta-analysis of 13 studies, Deschamps et al. conclude that the relative change of BNP or NT-proBNP (ΔBNP% or ΔNT-proBNP%) during an SBT is predictive for extubation success after cessation of MV. In our study, neither ΔNT-proBNP%$_{abs}$ nor ΔNT-proBNP%$_{Zlog}$ were significantly correlated with EF. Most of the studies analyzed BNP or NT-proBNP values before the extubation attempt. After cessation of MV important short- and long-term hemodynamic changes are induced, which might lead to changes in the release of NT-proBNP from cardiomyocytes (e.g., tachycardia, increased mean arterial pressure, increased right atrial pressure and mean pulmonary artery pressure).[19] Therefore, an additional NT-proBNP measurement should be performed also in the first hours after the extubation attempt. Our study adds additional information about the release of NT-proBNP after the extubation attempt, albeit the provided data are collected retrospectively and an evaluation in a larger cohort is warranted.

A limitation of pediatric studies is the interference of age with BNP and NT-proBNP values. Reference values for preterm and term neonates as well as older children are varying. Therefore, it remains unclear whether NT-proBNP is an appropriate biomarker in a group of individuals with widely differing age.[20] In a review on 690 children Nir et al. provided important data on the course of BNP and NT-proBNP and the age-dependent effect, as the values significantly decrease over time.[21] In a recent study, a new approach for an age-independent calculation of NT-proBNP values was elucidated.[17] Palm et al. introduced a Zlog-transformation of NT-proBNP values according to the formula provided by Hoffmann et al.[18] The advantage of NT-proBNP$_{Zlog}$ values is the age-independent interpretation and better identification of normal and increased values.[17] This study provides the first investigation of NT-proBNP$_{Zlog}$ values as a biomarker for EF in neonates.

It is discussible whether it is feasible to measure NT-proBNP values after the extubation attempt to predict EF. For the attending NICU

TABLE 2 Correlation analysis of NT-proBNP values

	NT-proBNP before extubation correlation (*p* level)	NT-proBNP after extubation correlation (*p* level)	Zlog NT-proBNP before extubation correlation (*p* level)	Zlog NT-proBNP after extubation correlation (*p* level)
Outcome parameter				
Length of MV	0.000 (0.998)	−0.027 (0.864)	0.267 (0.087)	0.251 (0.109)
ECMO treatment	−0.010 (0.950)	0.212 (0.201)	**0.424 (0.005)**	**0.388 (0.010)**
In-hospital mortality	−0.012 (0.947)	0.112 (0.537)	0.187 (0.231)	0.199 (0.201)
Baseline characteristics				
Gestational age	−0.247 (0.115)	0.070 (0.658)	−0.020 (0.899)	0.014 (0.931)
Birth weight	−0.052 (0.739)	0.132 (0.398)	−0.084 (0.593)	−0.052 (0.740)
Cardiac assessment				
PH				
Before extubation	0.069 (0.661)	**0.445 (0.003)**	**0.453 (0.002)**	**0.489 (<0.001)**
After extubation	0.172 (0.277)	**0.427 (0.005)**	**0.425 (0.005)**	**0.549 (<0.001)**
RVD				
Before extubation	−0.014 (0.927)	0.093 (0.553)	0.182 (0.242)	0.147 (0.348)
After extubation	−0.023 (0.886)	0.136 (0.392)	0.234 (0.135)	**0.317 (0.041)**
LVD				
Before extubation	0.064 (0.686)	0.163 (0.298)	0.206 (0.185)	0.209 (0.178)
After extubation	0.063 (0.692)	0.162 (0.205)	0.207 (0.187)	0.211 (0.180)
BVD				
Before extubation	−0.039 (0.806)	0.056 (0.723)	0.115 (0.462)	0.193 (0.152)
After extubation	0.000 (0.997)	0.094 (0.556)	0.135 (0.392)	0.173 (0.273)

Note: Pearson correlation was performed for the calculation of the correlation coefficient. *p* levels < 0.05 are highlighted in bold.

Abbreviations: BVD, biventricular dysfunction; ECMO, extracorporeal membrane oxygenation; LVD, left ventricular dysfunction; MV, mechanical ventilation; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; RVD, right ventricular dysfunction; Zlog, Zlog transformation of NT-proBNP values.

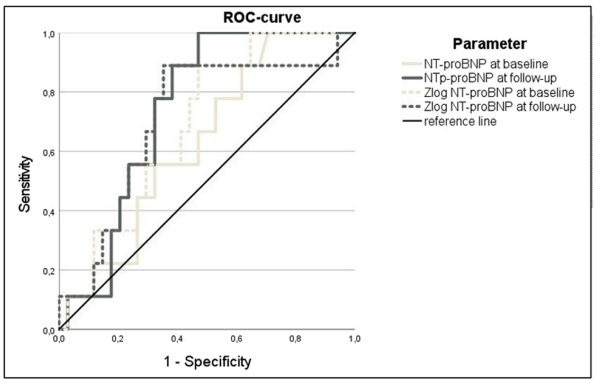

FIGURE 3 Receiver operating characteristic-curve analysis of mean NT-proBNP$_{abs}$ and mean NT-proBNP$_{Zlog}$ values at baseline (before the extubation) and at follow-up (after the extubation). Zlog-transformation was performed according to the equation formula described by Hoffmann et al.[18] NT-proBNP, N-terminal pro-brain natriuretic peptide.

team, it is necessary to guide therapy as quick as possible and, therefore, rapid measurement of NT-proBNP values after the extubation is essential. NT-proBNP values were measured in the median at 2.5 (1–24) h. With a half-life of 120 min of NT-proBNP, a median of 2.5 h in our cohort seems adequate as sample time point. Measuring NT-proBNP immediately after the extubation (0–60 min) certainly will lead to an underestimation of NT-proBNP release by cardiomyocytes, which will be induced due to changes in atrial/ventricular pressures.

We could demonstrate that NT-proBNP$_{abs}$ and NT-proBNP$_{Zlog}$ values were significantly correlated with the severity of PH in critically ill neonates. This is in line with previous findings, as described in neonatal studies on infants suffering from congenital diaphragmatic hernia (CDH) or preterm infants at risk/or suffering from bronchopulmonary dysplasia (BPD).[9,10,22,23] Additionally, NT-proBNP$_{Zlog}$ values after the extubation significantly correlated with RVD and LVD. Recent studies in neonates and pediatric cardiological patients confirmed the association of RVD and elevated NT-proBNP values.[24,25]

TABLE 3 ROC-analysis for outcome parameter extubation failure

	NT-proBNP before extubation	NT-proBNP after extubation	Zlog NT-proBNP before extubation	Zlog NT-proBNP after extubation
Outcome parameter				
Extubation failure, AUC (*p* level)	0.632 (0.152)	**0.742 (0.001)**	**0.690 (0.027)**	**0.781 (0.000)**
Cut-off value, pg/ml	2232	4622	1.63	2.14
Sensitivity, %	100	100	89	100
Specificity, %	30	53	53	65
PPV, %	28	36	34	43
NPV, %	100	100	95	100

Note: Receiver operating characteristic analysis was performed for the calculation of the AUC. *p* levels < 0.05 are highlighted in bold.

Abbreviations: AUC, area under the curve; NPV, negative predictive value; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPV, positive predictive value; Zlog, Zlog transformation of NT-proBNP values.

The evaluation of PH severity and ventricular dysfunction by echocardiography in combination with the NT-proBNP measurement before (and after) extubation might optimize clinical decision-making. Future prospective analysis of $NT\text{-}proBNP_{abs}$ and $NT\text{-}proBNP_{Zlog}$ and the association with EF is essential to further evaluate our findings. An approach and flowchart for the attending physicians with prospectively evaluated cut-off values and an echocardiographic assessment to determine the extubation readiness of infants could be the target of future studies.

In patients with AKI NT-proBNP values should be used carefully as biomarker for EF, because renal dysfunction potentially leads to biased NT-proBNP values and overestimation of the results. This was anew illustrated in a recent post-hoc analysis of data from a randomized trial on NT-proBNP guided therapy in adults.[26]

5 | LIMITATION

The small size of the cohort and the retrospective design of the study could have influenced the power of the results and statistic effects could have been biased or probably remained undetected. The measurement of NT-proBNP was at the decision of the attending NICU physician and therefore time points of blood samples differed between individuals. This might have an impact on the interpretation of intra- and interindividual NT-proBNP values. It is important to mention, that the determined cut-off values for NT-proBNP values as well as Zlog-transformed NT-proBNP values are specific for the utilized assay in our institution (Elecsys proBNP II on a cobas e801 analyzer; Roche Diagnostics). NT-proBNP cut-off values obtained with another assay need to be interpreted carefully. The echocardiographic assessment of PH and ventricular dysfunction was based to some extent on a qualitative grading, with the risk of observer-related bias. We tried to minimize this bias, by reviewing the echocardiographic data independently by two neonatal echocardiographers, blinded to the clinical course of the respective subject.

6 | CONCLUSION

This study demonstrates the role of NT-proBNP and Zlog-transformed NT-proBNP as biomarker for EF in critically ill neonates. Zlog-transformation of NT-proBNP allows the age-independent interpretation of NT-proBNP values in a subset of patients with a widely varying range of age and NT-proBNP values.

AUTHOR CONTRIBUTIONS

Lukas Schroeder: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; visualization; software; data curation, formal analysis; project administration, resources. **Manuel Kuelshammer**: Investigation; writing – review and editing; conceptualization; resources. **Ramona Dolscheid-Pommerich**: Investigation; validation; methodology; writing – review and editing; formal analysis; resources. **Stefan Holdenrieder**: Writing – review and editing; methodology; validation; conceptualization; formal analysis; supervision. **Andreas Mueller**: Writing – review and editing; methodology; conceptualization; resources; supervision; validation. **Florian Kipfmueller**: Writing – review and editing; methodology; validation; visualization; investigation; conceptualization; writing – original draft; data curation; formal analysis; project administration; resources; supervision.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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3.2. Levosimendan-Therapie bei Neonaten mit einer angeborenen Zwerchfellhernie

Schroeder L, Gries K, Ebach F, Mueller A, Kipfmueller F. Exploratory Assessment of Levosimendan in Infants with Congenital Diaphragmatic Hernia. Pediatr Crit Care Med 2021 Jul 1;22(7): e382-e390. doi: 10.1097/PCC.0000000000002665. *(JIF 3.9).*

Zielsetzung der Studie: Neugeborene mit einer angeborenen Zwerchfellhernie („congenital diaphragmatic hernia“, CDH) stellen ein besonderes Risikokollektiv für die Entwicklung einer schweren CD und einer schweren PH dar. Der Inodilator und Calciumsensitizer Levosimendan könnte eine Therapie-Alternative durch das vielversprechendes pharmakologisches Wirkprofil sein. Jedoch fehlten bis dato Daten zur Therapie mit Levosimendan in der Gruppe der Neugeborenen mit einer CDH.

Methoden und Ergebnisse: Es wurden Daten zu 24 Neugeborenen mit einer CDH aus dem Zeitraum 01/2017-12/2018 retrospektiv ausgewertet, welche in der Klinik für Neonatologie des UKB behandelt wurden. Eingeschlossen wurden alle Neugeborenen mit einer CDH, welche mindestens eine intravenöse Levosimendan-Therapie (0.2µg/kg/min über 24 Stunden) erhalten haben. Es wurden neben epidemiologischen Daten zusätzlich echokardiographische Analysen, welche vor und nach der Levosimendan-Therapie erstellt wurden (Baseline, Tag 1, Tag 7), sowie hämodynamische Parameter retrospektiv evaluiert. Die Patienten-Charakteristika sowie die Behandlungsdaten können der angefügten Originalpublikation entnommen werden (siehe Table 1, Schroeder et al., 2021) Die Levosimendan-Therapie war mit einer signifikanten Reduktion der Schwere der PH sowie der RVD und LVD assoziiert (siehe Fig. 3, Schroeder et al., 2021). Relevante Medikamenten-assoziierten Nebenwirkungen konnten nicht festgestellt werden.

Schlussfolgerungen: Die Studie beschreibt als erste Arbeit die Anwendung des Inodilators Levosimendan in einer Kohorte von Neugeborenen mit einer CDH. Die Levosimendan-Therapie ist mit einer signifikanten Verbesserung der CD und PH-Schwere assoziiert und könnte ein neuer Ansatz im Rahmen der vasoaktiven Therapie dieser Patientengruppe sein.

ONLINE CLINICAL INVESTIGATION

Exploratory Assessment of Levosimendan in Infants With Congenital Diaphragmatic Hernia

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OBJECTIVES: Infants with congenital diaphragmatic hernia frequently suffer from cardiac dysfunction and pulmonary hypertension during the postnatal course. With the use of the inodilator levosimendan, a therapeutic approach is available in situations with catecholamine-refractory low-cardiac-output failure and severe pulmonary hypertension.

DESIGN: Retrospective single-center cohort study.

SETTING: University-based, tertiary-care children's hospital neonatal ICU.

PATIENTS: Cohort of 24 infants with congenital diaphragmatic hernia and levosimendan therapy, without underlying major cardiac defect, treated at the University Children´s Hospital Bonn, Germany, between January 2017 and December 2018.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Twenty-four infants with congenital diaphragmatic hernia were treated with levosimendan (41% of hospitalized congenital diaphragmatic hernia infants in the study period). In 88%, the congenital diaphragmatic hernia was left-sided. The median observed-to-expected lung-to-head ratio was 36%. About 60% of the infants were supported with venovenous extracorporeal membrane oxygenation and the mortality was 38% (9/24 infants). Levosimendan administration was associated with improvement of pulmonary hypertension severity ($p = 0.013$ and $p = 0.000$) and right ventricular dysfunction ($p = 0.011$ and $p = 0.000$) at 24 hours and 7 days after treatment. Similarly, the prevalence of left ventricular dysfunction decreased from 50% at baseline to 10% after 7 days ($p = 0.026$). A significant reduction in the peak inspiratory pressure was observed after drug application ($p = 0.038$) and a significant decrease of the Vasoactive-Inotropic Score was apparent ($p = 0.022$). A relevant arterial hypotension as a drug-related adverse event occurred in one patient.

CONCLUSIONS: This is the first study exploring clinical and hemodynamic changes after levosimendan treatment in a cohort of infants with congenital diaphragmatic hernia. An association of levosimendan application and an improvement in pulmonary hypertension, right ventricular, and left ventricular dysfunction were observed within 7 days after drug infusion. However, due to the retrospective design of this study, the results should be interpreted carefully.

KEY WORDS: calcium-sensitizer; cardiac dysfunction; congenital diaphragmatic hernia; echocardiography; inodilator; neonates

The impact of pulmonary hypertension (PH) and lung hypoplasia on morbidity and mortality in infants with congenital diaphragmatic hernia (CDH) has been recognized for decades (1). Recently, cardiac

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dysfunction has been identified as a third key determiner for outcome in this population (2). Therefore, studies investigating therapeutic strategies to improve cardiac dysfunction in infants with CDH are still limited and the management remains challenging. Abnormal development of the fetal lung and the pulmonary vasculature causes pulmonary vascular disease that is fundamental for the development of PH and cardiac dysfunction during postnatal transition (3). Several studies highlighted the importance of an appropriate cardiovascular therapy for cardiac dysfunction in CDH infants (3–5).

Levosimendan is a calcium-sensitizing drug with positive inotropic, lusitropic, and vasodilating effects mainly investigated in adults and infants with acute and chronic heart failure. The pharmacological effects of levosimendan are manifold: first, levosimendan improves cardiac contractility by increasing the affinity of myocardial troponin C to calcium. An advantage over other inotropic agents is the absence of an increasing oxygen demand during levosimendan administration (6). A vasodilating effect is induced by opening of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells. Additionally, levosimendan acts as a selective inhibitor of phosphodiesterase type 3 (7). The active metabolite odds ratio-1896 has an elimination half-life of 70–80 hours, which explains the long-lasting effect of levosimendan after a 24-hour infusion. Hemodynamically, levosimendan improves right ventricular (RV) contractility, reduces RV afterload, and leads to a reduction in PH (8–10). Levosimendan furthermore improves left ventricular (LV) contractility and low cardiac output syndrome (11). Besides these positive effects, levosimendan infusion has been associated with the side effect of arterial hypotension (12).

The use of levosimendan in infants with CDH who are prone to cardiac dysfunction has not been described. The aim of the present study was to describe the hemodynamic effects of levosimendan on cardiac dysfunction and PH in infants with CDH.

MATERIALS AND METHODS

Study Population and Ethical Approval

Infants with CDH and levosimendan therapy treated at the University Children´s Hospital of Bonn between January 2017 and December 2018 were included in the analysis and assembled as convenience sample. Infants without levosimendan treatment or with underlying congenital heart defects were not included (**Fig. 1**). The study was approved by the local ethics committee of the Medical Center of the University of Bonn and informed consent was waived due to the retrospective design of the study.

Data Collection

Treatment data and vital signs were recorded for a period of 24 hours before and after the administration of levosimendan. Baseline values were defined as values at the closest time point before levosimendan administration. Echocardiographic assessment was obtained at the following three time points: 1) within 24 hours before, 2) 12–24 hours after, and 3) 7–10 days after levosimendan administration.

Clinical Data and Cardiovascular Therapy

From each infant, the following monitoring and laboratory data were recorded: mean arterial blood pressure,

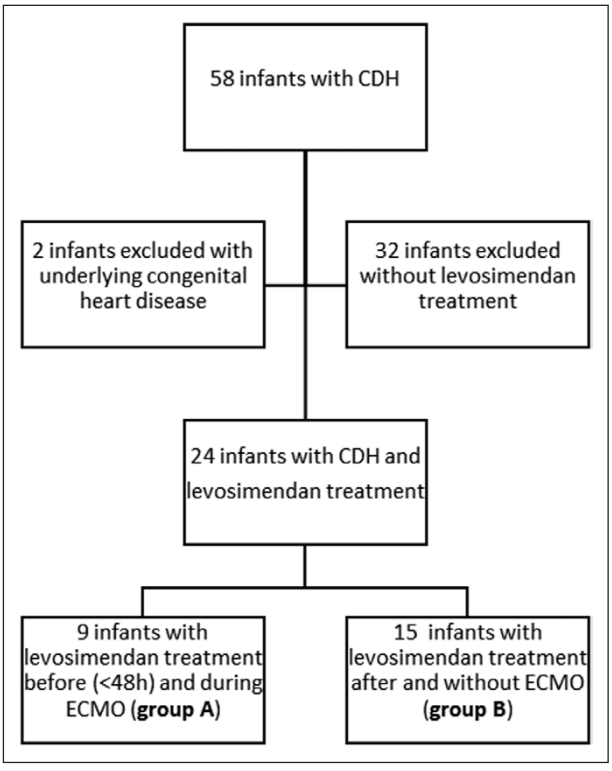

Figure 1. Flow diagram of congenital diaphragmatic hernia (CDH) cohort. ECMO = extracorporeal membrane oxygenation.

heart rate, oxygen saturation (postductal), fraction of inspired oxygen (FIO_2), the oxygenation index, and arterial lactate levels as well as levels of n-terminal pro-brain natriuretic peptide (NT-BNP). For calculation of vasoactive medication, we used a modified Vasoactive-Inotropic Score (VIS) (exclusion of dopamine in the calculation) (13).

As first-line inotropic support, dobutamine and milrinone were used. Vasopressor therapy consisted of norepinephrine and vasopressin. PH was treated with inhaled nitric oxide (iNO) and IV sildenafil according to the severity on echocardiography. Levosimendan (0.2 µg/kg/min for 24 hr, with or without a preceding bolus of 12 µg/kg/min in 10 min) therapy was initiated based on the decision of two neonatologist following echocardiographic assessment. Infants were qualified for levosimendan treatment in the case of moderate-to-severe PH, right ventricular dysfunction (RVD), or left ventricular dysfunction (LVD), despite the first-line inotropic support (dobutamine and milrinone). As meeting criteria for the indication of venovenous extracorporeal membrane oxygenation (ECMO) therapy, we used the recommendations for ECMO therapy as described by the CDH Euro Consortium group (5).

Echocardiographic Data

Echocardiography was performed using a Philips CX50 Compact Extreme Ultrasound system with an S12-4 sector array transducer (Philips Healthcare, Best, The Netherlands). All echocardiographic data were retrospectively reviewed independently by two neonatal echocardiographers blinded to the clinical course of the respective infants.

PH was graded in three categories: 1) less than 2/3 systemic pressure (mild), 2) 2/3 to systemic systolic pressure (moderate), and 3) suprasystemic systolic pressure (severe PH) (14). Grading of PH included: 1) ductus arteriosus flow pattern, 2) the intraventricular septum position, and 3) the tricuspid valve regurgitation. At the time point of the echocardiographic assessment (during levosimendan treatment), 76% of the infants presented with a patent ductus arteriosus.

RVD and LVD (graded as mild, moderate, or severe) were defined using a combination of qualitative and quantitative measures based on international guidelines (15, 16). In addition to a qualitative analysis, we used the following quantitative values as a guideline of LV systolic function: normal function: fractional shortening (FS) 26–45%; mild dysfunction: FS 20–25%; moderate dysfunction: FS 15–19%; severe dysfunction: FS less than 15% (15). RV systolic function was graded based on the subsequent quantitative information, if available: S' velocity on tissue Doppler imaging (TDI), tricuspid annular plane systolic excursion, or RV size and output. Diastolic function was assessed with pulsed-wave (PW) Doppler measurements of the tricuspid and mitral waves, examining the early (E) and late (A) waves of the inflow pattern in either ventricle, if available.

Statistical Analysis

Data are presented as median with interquartile range or absolute number (n) with percentage. Comparison between the time points of levosimendan administration was performed with a student *t* test analysis or Wilcoxon test for continuous variables and chi-square test for categorical variables. 95% CIs were calculated and a Bonferroni-correction for repeated measurements was applied to longitudinal data. A *p* value of less than 0.05 was considered significant. The statistical analysis was performed using statistical software (IBM SPSS Statistics for Windows, Version 22.0., IBM Corp, Armonk, NY).

RESULTS

Study Cohort

The final convenience sample consisted of 24 infants (Fig. 1). Demographic data are demonstrated in **Table 1**. All but one patient presented with moderate (46%) or severe (50%) PH at the onset of levosimendan administration. RVD was observed on echocardiography in 100% of patients and 50% suffered from LVD. The incidences of PH, RVD, and LVD at admission on the ICU of CDH infants without levosimendan treatment in the study period are presented in Table 1.

Levosimendan Administration

In 38%, levosimendan was started with a bolus infusion prior to the continuous drug infusion. In one infant, the bolus infusion was discontinued due to arterial hypotension. In 42% of the infants, levosimendan was started on the first day of life (DOL) (median 9 hr) and in 37% between DOL 2 and DOL 14 (median

TABLE 1.
Demographic Data

Variables	With Levosimendan Treatment (*n* = 24)	No Levosimendan Treatment (*n* = 32)
Gestational age, wk	38.7 (38–40)	38.8 (37–39)
Birth weight, kg	3.2 (2.4–3.6)	3.2 (2.8–3.5)
Female sex, *n* (%)	14 (58)	15 (44)
CDH left-sided, *n* (%)	21 (88)	29 (85)
Observed to expected lung-to-head ratio, %	36 (30–50)	37 (30–49)
Liver herniation, *n* (%)	10 (42)	19 (55)
ECMO, *n* (%)	14 (58)	8 (23)
Duration of ECMO, d	7 (5–22)	6 (4–10)
Length of hospital stay, d	37 (12–67)	26 (16–49)
Mortality, *n* (%)		
Before CDH repair	4 (17)	5 (14)
Overall inhospital	9 (38)	9 (27)
Cardiac status first day of life, *n* (%)		
Pulmonary hypertension (any severity)	24 (100)	33 (97)
Right ventricular dysfunction	24 (100)	21 (62)
Left ventricular dysfunction	12 (50)	12 (35)

CDH = congenital diaphragmatic hernia, ECMO = extracorporeal membrane oxygenation.

DOL 2). Five infants (19%) received levosimendan between DOL 25 and DOL 80. ECMO therapy was initiated in 14 infants, reflecting 70% of all ECMO runs in CDH infants during the study period.

Hemodynamic and Clinical Changes After Levosimendan Administration

All infants were on iNO and sildenafil treatment at the onset of levosimendan therapy. The course of mean arterial pressure, heart rate, FIO_2, and oxygen saturation in association with levosimendan treatment is illustrated in **Figure 2**. Changes in parameters of volume load, mechanical ventilation, oxygenation status, and laboratory values are demonstrated in **Table 2**. The peak inspiratory pressure (PIP) and the modified VIS decreased significantly after application of levosimendan ($p = 0.038$ and $p = 0.022$, respectively).

Echocardiographic Analysis After Levosimendan Administration

PH severity significantly decreased from baseline to follow-up at day 1 and day 7 after levosimendan administration (**Fig. 3**) ($p = 0.013$ and $p = 0.000$, respectively). The severity of the RVD decreased significantly after levosimendan administration at days 1 and 7 (Fig. 3) ($p = 0.011$ and $p = 0.000$, respectively). The LVD remained almost similar at day 1 ($p = 0.721$) but was significantly lower at day 7 after levosimendan administration ($p = 0.026$). The course of PH, RVD, and LVD after group stratification (A or B) according to the time of levosimendan administration in association with the use of ECMO support is demonstrated in **Supplemental Table 1** (http://links.lww.com/PCC/B669). PW-Doppler measurements of the tricuspid and mitral valves are presented in **Table 3**.

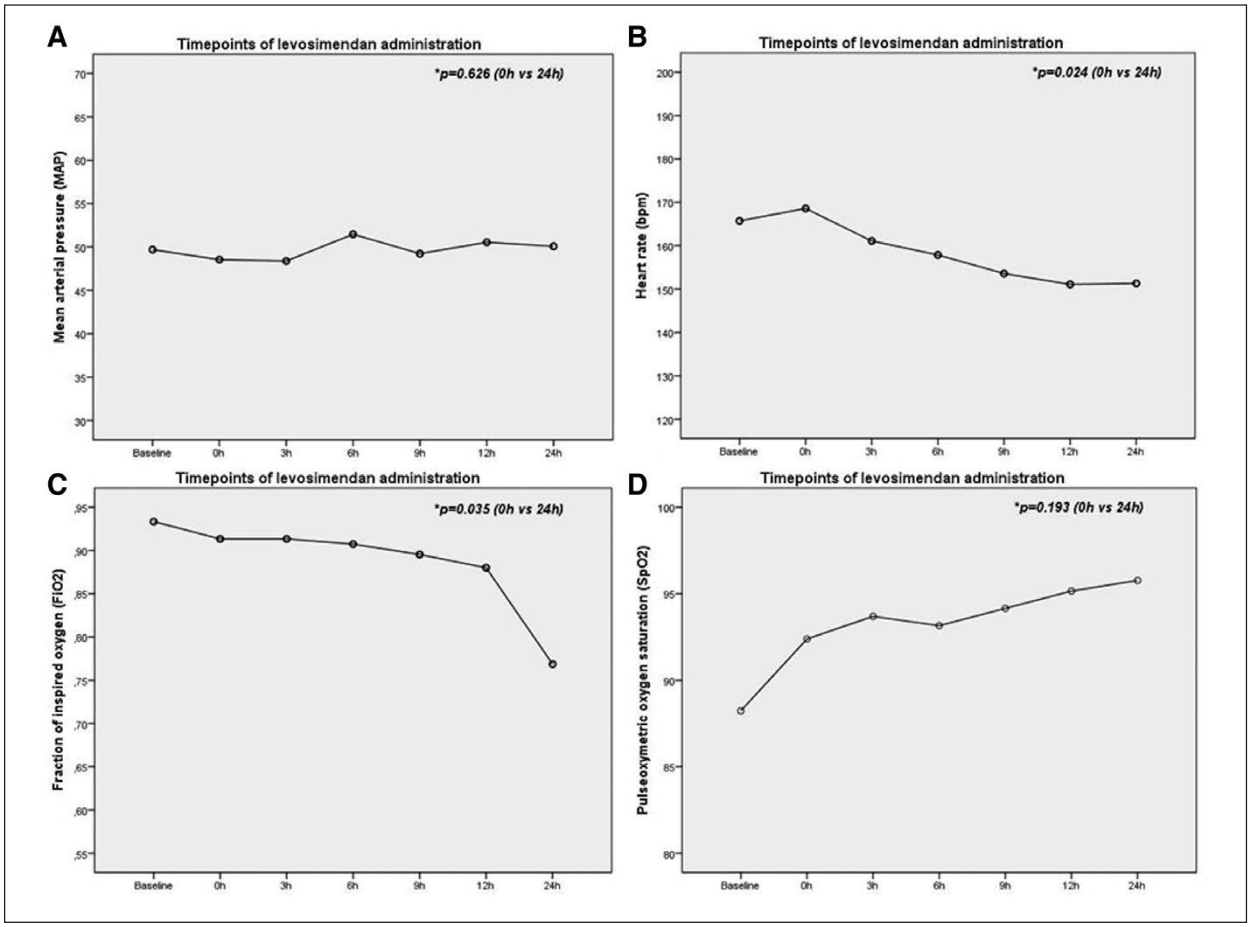

Figure 2. Trends of hemodynamic variables (**A–D**) in response to levosimendan treatment.

DISCUSSION

To our knowledge, this is the first study investigating the course of PH and cardiac dysfunction in levosimendan-treated infants with CDH. Our data demonstrate a reduction in PH severity and improvement in RVD and LVD within the first 7 days after levosimendan administration. The prevalence of moderate-to-severe PH decreased from 96% at baseline to 71% after 24 hours and to 19% 7 days after treatment. RVD was diagnosed in 100% of infants before levosimendan treatment and resolved in 25% at 24 hours and 73% at 7 days. LVD dropped from 50% at baseline to 38% and 10% at 24 hours and 7 days, respectively. Furthermore, an improvement in ventilation and oxygenation parameters (i.e., PIP and F_{IO_2}) was observed after commencing levosimendan. The VIS, as a measure of vasoactive support, decreased significantly over time.

PH plays a major role in the complexity of the CDH pathophysiology (17). Despite decades of investigation and the availability of several pulmonary vasodilators, a significant proportion of CDH infants suffer from persistent PH during the initial hospital course (17, 18). Based on current data, moderate or severe PH is still present in 65% and 37% of CDH infants at 2 and 4 weeks, respectively (18). As previously described, levosimendan is associated with improvement in PH and RV performance, which is consistent with our findings (8, 19). However, a thorough investigation of therapeutic effects of levosimendan in CDH infants is needed.

In addition to PH, cardiac dysfunction is an independent contributor to mortality in this population, and therefore, improvement in systolic and diastolic ventricular dysfunction might be an important target in postnatal CDH therapy (1–4). In a recent registry-based study including 1173 CDH infants, Patel et al

TABLE 2.
Analysis of Volume Status, Ventilation Data, Laboratory Data, and Oxygenation Index/ Vasoactive-Inotropic Scores

Variables	*n* = 24	Mean Difference (CI 95%)	*p*
Volume status			
Bolus volume, mL/kg (crystalloid/ colloidal)			
Baseline	38	5.3 (−18.9 to 25.5)	0.649
0–24 hr	33		
Fluid balance, mL ± (crystalloid/colloidal)			
Baseline	+70	−11.2 (−222 to 199)	0.907
+24 hr	+80		
Urine output, mL/kg/hr			
Baseline	6.3	−1.7 (−6.4 to 3.0)	0.443
+24 hr	8.0		
Mechanical ventilation			
Peak inspiratory pressure, cm H_2O			
Baseline	22	2.2 (0.1–4.3)	**0.038**
+24 hr	20		
Positive end-exspiratory pressure, cm H_2O			
Baseline	4.4	−0.5 (−1.4 to 0.4)	0.251
+24 hr	4.9		
Mean airway pressure, cm H_2O			
Baseline	9.5	0.6 (−1.1 to 2.2)	0.436
+24 hr	9.0		
Laboratory data			
NT pro-brain natriuretic peptide, pg/mL			
Baseline	24,912	3,658 (−3,530 to 10,846)	0.287
0–48 hr	21,254		
Lactate, mmol/L			
Baseline	2.6	0.51 (−0.44 to 1.5)	0.237
+24 hr	2.1		
Scores			
Oxygenation index			
Baseline	18	7.5 (−2.6 to 17.6)	0.133
+24 hr	11		
Vasopressor-Inotropic Score			
Baseline	66	17 (2.8 to 31.3)	**0.022**
+24 hr	50		

Data are presented as mean values. 95% CI presents the CI around the mean difference. Time points were defined as follows: 24 hr prior to levosimendan administration until onset of levosimendan administration (baseline) and 24 hr after levosimendan administration (+24 hr) N terminal pro-brain natriuretic peptide levels were obtained within 48 hr prior (baseline) and after levosimendan administration. Significant *p* levels ($p < 0.05$) are indicated in boldface font.

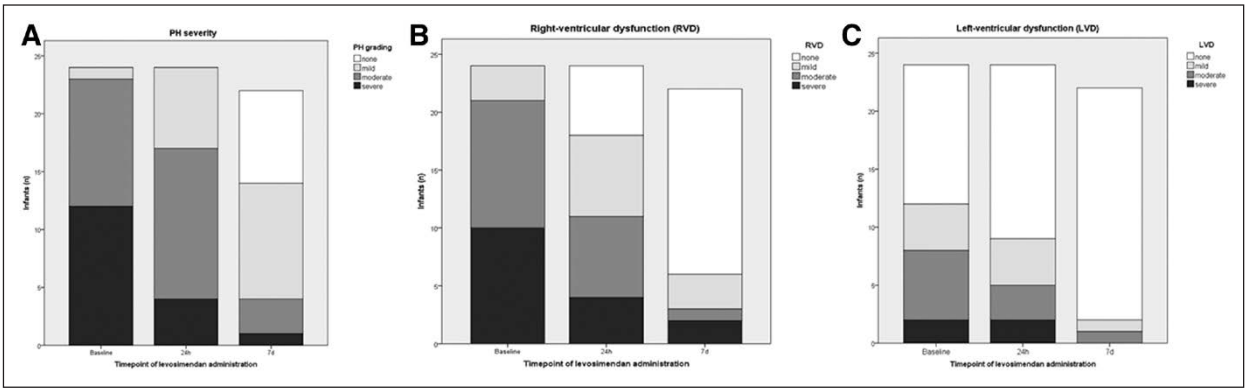

Figure 3. Changes in severity of pulmonary hypertension (PH) (**A**), right ventricular dysfunction (RVD) (**B**), and left ventricular dysfunction (LVD) (**C**) in association to levosimendan treatment.

(2) reported a 39% incidence of cardiac dysfunction diagnosed by echocardiography within the first 2 days. Additionally, on follow-up, echo at a median age of 5 days cardiac dysfunction was still present in 22%. Among all infants treated at our institution within the study period ($n = 56$), the incidence of any ventricular dysfunction dropped from 80% after birth to 11% at 7 days. However, a comparison of different CDH cohorts is difficult, and although there was a large decrease in PH and cardiac dysfunction within the first week in our study, the absence of a control group is a weakness of our study. An early assessment and treatment of RVD and LVD in CDH infants might be crucial, given the impact of both, early and persistent, cardiac dysfunctions on mortality. Therefore, levosimendan might be a candidate for hemodynamic stabilization of CDH infants. In the pediatric population, numerous studies have been published, demonstrating a positive effect of levosimendan on low cardiac output syndrome in patients undergoing cardiac surgery (9, 20). However, due to the design of these studies, evidence is still limited (21).

Diastolic and systolic cardiac dysfunctions in infants with CDH can be assessed by PW-Doppler or TDI (4, 22). In our cohort, we observed a significant improvement in the E-wave velocity of the mitral valve after levosimendan administration, probably indicating an improvement in the impaired LV diastolic-relaxation. In contrast, an increased E-wave velocity could potentially be secondary to a reduction in pulmonary vascular resistance and increased pulmonary blood flow, causing higher inflow velocities of the left ventricle. Due to limited data on PW measurements in our cohort, these data need to be interpreted carefully.

The administration of levosimendan was associated with a significant reduction in vasoactive medication, which is in line with previous findings in children undergoing cardiac surgery (20). In contrast to recently published data, NT-proBNP and lactate levels did not change significantly after levosimendan administration in our study cohort (19, 23). Whether NT-proBNP is an appropriate monitoring tool in CDH infants is still under discussion (24, 25).

The mean arterial pressure remained stable during levosimendan administration in our study (Fig. 2). Of note, arterial hypotension considered relevant to discontinue levosimendan infusion occurred only in one infant. In this infant, arterial hypotension was observed following a bolus-infusion at starting levosimendan. Based on our experience, withholding an initial bolus-infusion results in a similar effect on cardiac dysfunction and improvement of oxygenation. Based on these findings, levosimendan seems safe and well tolerable during pre- and postoperative stabilizations in CDH infants. Ventricular or arterial dysrhythmias during levosimendan administration were not observed, which makes levosimendan a favorable vasoactive drug in children at risk for atrial or ventricular arrhythmia (26).

The retrospective design and the small sample size are certainly limitations of our study. A study design with a comparator cohort would facilitate the analysis of statistical effects and the interpretation of results. However, this study was conducted to analyze the effects of levosimendan in CDH infants and might serve to design further prospective trials. Echocardiographic assessment of cardiac dysfunction was based to some extent on qualitative grading. This

TABLE 3.
Diastolic Echocardiographic Analysis

Variables	*n* = 9 (Valid Data)	Mean Difference (95% CI)	*p*
Tricuspid-valve measurements by PW-Doppler			
E-wave, cm/s			
Baseline	61.3	1.3 (−24.6 to 27.1)	0.912
+24 hr	60.0		
A-wave, cm/s			
Baseline	40.0	−8.8 (−37.2 to 19.7)	0.490
+24 hr	48.8		
E/A ratio, cm/s			
Baseline	2.1	0.7 (−0.8 to 2.1)	0.322
+24 hr	1.5		
Mitral-valve measurements by PW-Doppler			
E-wave, cm/s			
Baseline	60.0	−10.6 (−20.8 to −0.3)	**0.045**
+24 hr	70.6		
A-wave, cm/s			
Baseline	53.8	6 (−10.1 to 21.3)	0.425
+24 hr	48.1		
E/A ratio, cm/s			
Baseline	1.2	−0.16 (−0.60 to 0.29)	0.412
+24 hr	1.4		

A-wave = late wave pattern of the transvalvular pulsed wave-Doppler caused by the atrial contraction, E-wave = early wave pattern of the transvalvular pulsed wave-Doppler caused by the ventricular relaxation and passive ventricular filling, PW = pulsed wave.
Data are presented as mean. 95% CI presents the CI around the mean difference. Time points were defined as follows: within 24 hr prior to levosimendan administration until onset of levosimendan administration (baseline) and 24 hr after levosimendan administration (+24 hr). All *p* levels are referenced to baseline values. Significant *p* levels ($p < 0.05$) are indicated in boldface font.

incorporates a certain bias that we tried to minimize by retrospective, blinded reviewing of echocardiographic studies. Additionally, echocardiographic assessment of diastolic function was not available in all patients, bearing the risk of underestimation of LVD incidence in our cohort.

CONCLUSIONS

This is the first study analyzing the effect of levosimendan in a cohort of infants with CDH. Documented improvement in PH severity, cardiac dysfunction, and oxygenation status was observed within 7 days of treatment with levosimendan. Our study adds information on a new promising vasoactive drug in situations of limited therapeutic strategies. However, more research is required in this study population.

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The authors disclosed off-label product use of levosimendan.

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3.3. Herzfrequenzkontrolle mittels Landiolol bei Neonaten mit einer CD und PH

Schroeder L, Monno P, Unger M, Ackerl J, Shatilova O, Schmitt J, Dresbach T, Mueller A, Kipfmueller F**.** Heart rate control with landiolol hydrochloride in infants with ventricular dysfunction and pulmonary hypertension. ESC Heart Fail. 2023 Feb;10(1):385-396. doi: 10.1002/ehf2.14202. Epub 2022 Oct 18. *(JIF 3.8).*

Zielsetzung der Studie: Die Sinustachykardie kann eine CD und PH bei Früh- und Neugeborenen verschlechtern und sich negativ auf das Outcome auswirken. Mittels ultra-kurz wirksamen ß-Blockern wie dem Wirkstoff Landiolol ist es möglich eine hoch-selektive Herzfrequenzkontrolle zu erreichen und die Schwere der CD sowie der PH zu verbessern. Daten zum Einsatz von Landiolol bei Früh- und Neugeborenen (ohne angeborene Herzfehler und die Notwendigkeit für einen kardiochirurgischen Eingriff) sind bis dato nicht vorhanden und wurden in dieser Studie retrospektiv evaluiert.

Methoden und Ergebnisse:

Es wurde eine retrospektive Kohorten-Analyse an 62 Früh- und Neugeborenen durchgeführt, welche im Zeitraum vom 01/2018 bis 06/2020 in der Klinik für Neonatologie am UKB behandelt wurden. Als Einschlusskriterien wurden definiert: die Diagnose einer CD und/ oder PH, das Vorhandensein einer Sinustachykardie (Frühgeborene <35 SSW: >170 bpm, Früh- und Neugeborene ≥35 SSW: >150 bpm) sowie die dokumentierte Behandlung mit dem ß-Blocker Landiolol. Als primärer Endpunkt wurde die Herzfrequenznormalisierung innerhalb von 24 Stunden definiert. Die epidemiologischen Charakteristika und Subgruppen-Aufteilung (nach primärem Endpunkt) sind der beiliegenden Originalpublikation zu entnehmen (siehe Table 1, Schroeder et al., 2023d). Der primäre Endpunkt wurde in 92% der Patienten innerhalb von 24 Stunden erreicht. Der mediane Zeitpunkt bis zum Erreichen des angestrebten Herzfrequenzbereichs (<35 SSW: 150-170bpm; ≥35 SSW: 130-150bpm) betrug im Median 1.8 Stunden (0.3-24), mit einer medianen Dosierung von 8.8 µg/kg/min (3.9-35.4) über die ersten 24 Stunden. Sowohl die RVD, die LVD, die biventrikuläre Dysfunktion (BVD) als auch die Schwere der PH zeigten sich signifikant verbessert 24 Stunden nach Beginn der Herzfrequenzkontrolle mit Landiolol. Über den Beobachtungszeitraum der Landiolol-Behandlung (definiert als: 24 Stunden vor Behandlung bis 48 Stunden nach Beendigung der Behandlung) zeigten sich keine Landiolol-assoziierten Nebenwirkungen (arterielle Hypotension, schwere

Bradykardie). In den Fig. 1-3 der beiliegenden Originalpublikation (Schroeder et al., 2023d) kann der Verlauf der hämodynamischen Parameter (Blutdruck, Herzfrequenz) sowie die Dosierungs-Verläufe der Landiolol-Therapie nachvollzogen werden. Die Auswertung der echokardiographischen Analysen sind der Fig. 4 und 5 der Originalpublikation zu entnehmen (Schroeder et al., 2023d).

Schlussfolgerungen: Es konnte erstmals die erfolgreiche und sichere Anwendung mittels Landiolol zur Herzfrequenzkontrolle in einer Früh- und Neugeborenen-Kohorte beschrieben werden. Die Senkung der Herzfrequenz wurde in einem kurzen Zeitraum erreicht. Die Landiolol-Therapie scheint mit einer signifikanten Verbesserung der CD und PH in diesem Kollektiv assoziiert zu sein.

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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 sinus 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

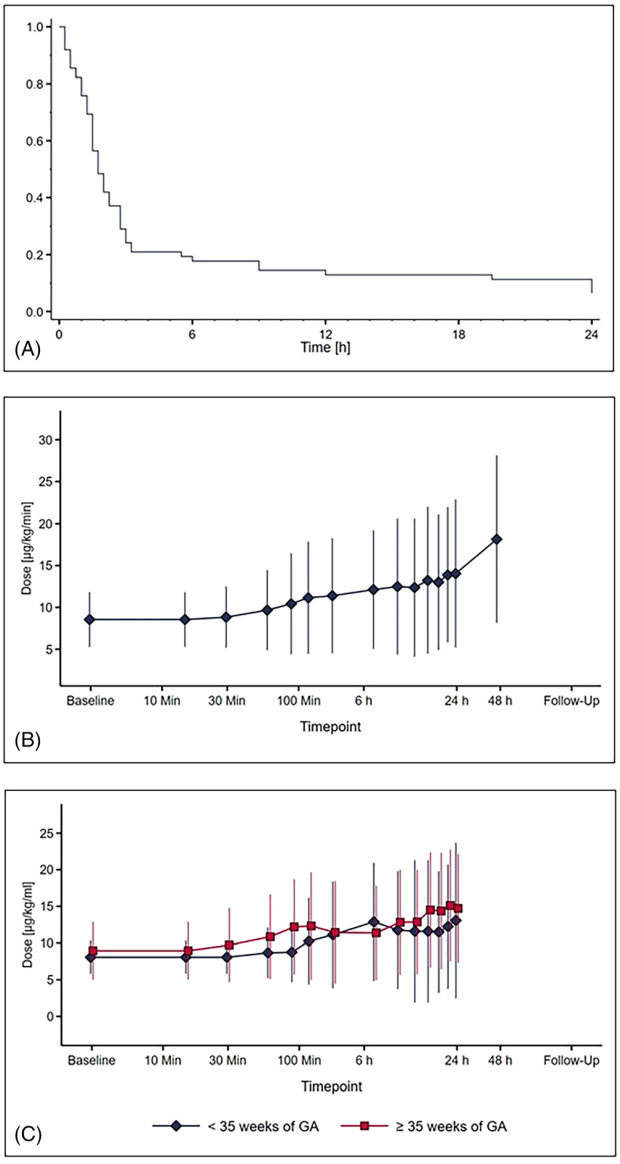
AV, arteriovenous; CHAOS, congenital high airway obstruction syndrome.
Data are presented as median (with minimum/maximum) or absolute number with %. A *P*-value < 0.05 was considered as statistically significant, and values are highlighted in bold. Sepsis was defined as clinical and laboratory signs 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.



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.

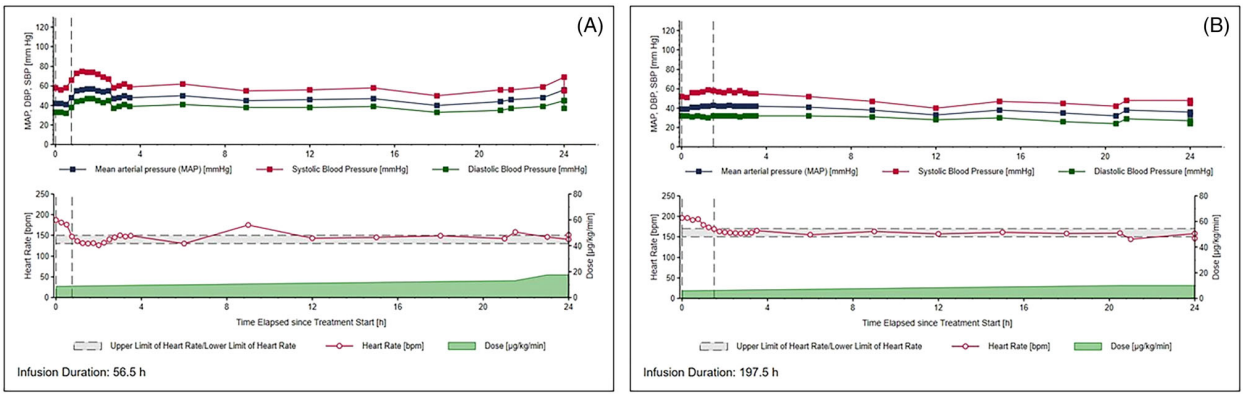
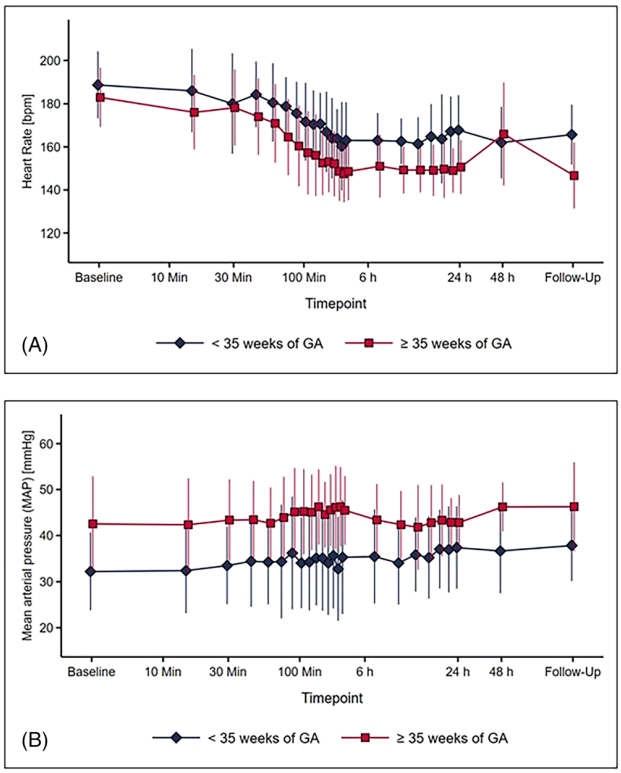


Figure 3 All data are presented as arithmetic mean ± SD. The baseline value is the last available value prior to the first administration of landiolol. (A) Heart rate (b.p.m.) over time during landiolol treatment. (B) Mean arterial pressure (MAP) (mmHg) over time during landiolol treatment. GA, gestational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

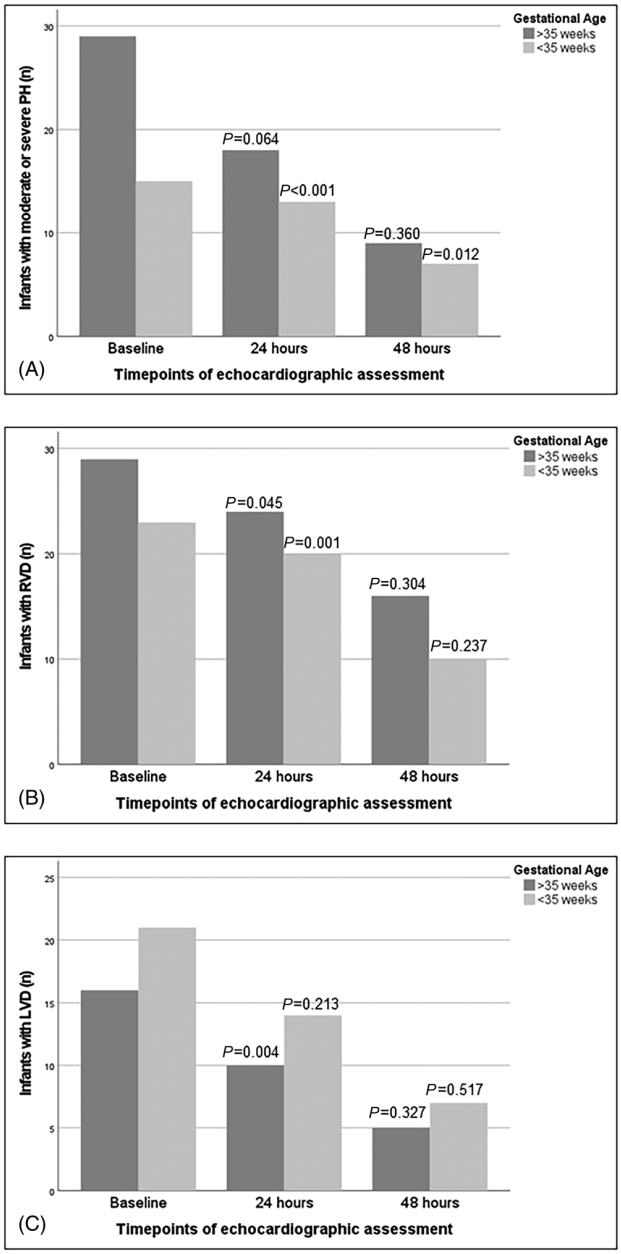
Mean NT-proBNP values decreased from baseline (22 746.1 pg/mL) to 24 h after onset of landiolol infusion (14 762.9 pg/mL, $P = 0.08$) and to timepoint 24 h until discontinuation of landiolol infusion (14 267.5 pg/mL, $P = 0.109$). On the other hand, mean troponin I values initially increased from baseline (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]

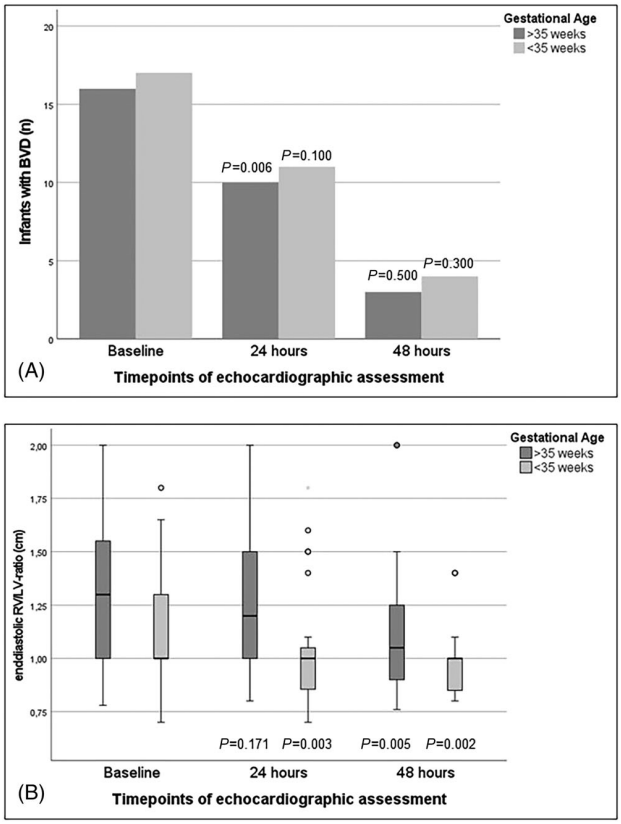
Recently, several studies evaluated landiolol in the paediatric population, mainly focusing on its effect on tachyarrhyth-

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/

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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3.4. Levosimendan-Therapie bei Frühgeborenen mit einer CD und PH

Schroeder L, Holcher S, Leyens J, Geipel A., Strizek B, Dresbach T, Mueller A, Kipfmueller F. Evaluation of levosimendan as treatment option in a large case-series of preterm infants with cardiac dysfunction and pulmonary hypertension. Eur J Pediatr. 2023; Jul;182(7):3165-3174. doi: 10.1007/s00431-023-04971-9. Epub 2023 Apr 27. *(JIF 3.6).*

Zielsetzung der Studie: Nach aktueller Datenlage scheint der Calciumsensitizer und Inodilator Levosimendan eine vielversprechende Therapie-Option im Rahmen der Behandlung einer CD und PH zu sein. Jedoch fehlen bis dato Daten zur Therapie bei Frühgeborenen <37 SSW und Frühgeborenen ohne angeborene Herzfehler, denn die bisherige Datenlage beschränkt sich auf pädiatrische Patienten vor und nach herzchirurgischen Eingriffen.

Methoden und Ergebnisse: Es erfolgte die retrospektive Kohorten-Analyse von Frühgeborenen (<37 SSW), welche im Zeitraum von 01/2018 bis zum 06/2021 in der Klinik für Neonatologie und Pädiatrischen Intensivmedizin des UKB behandelt wurden. Insgesamt wurden 105 Frühgeborene in die Studie eingeschlossen, welche die Einschlusskriterien erfüllten. Als Einschlusskriterien wurden folgende Parameter definiert: echokardiographisch nachgewiesene CD und/ oder PH, mindestens eine dokumentierte intravenöse Behandlung mit Levosimendan (0.2 µg/kg/min über 24 Stunden). Als primärer Endpunkt wurde die „Response“ auf die Levosimendan-Therapie gewertet. Als Response wurde die Verbesserung der CD (RVD, LVD, BVD; vorhanden-nicht vorhanden) oder des PH-Schweregrades (Verbesserung mindestens eines Grades; mild-moderart-schwer) 24 Stunden nach Beginn der Levosimendan-Therapie gewertet. Es wurden hämodynamische Parameter (Blutdruck), Laborparametern (arterielles Laktat), Oxygenierungs-Scores („Oxygenation Saturation Index“ [OSI]; „Saturation Oxygenation Pressure Index“ [SOPI]), der „Vasoacitve-Inotropic Score“ (VIS) und alle zur Verfügung stehenden echokardiographischen Analysen der Patienten retrospektiv ausgewertet zu den Zeitpunkten a) Baseline (vor Beginn der Therapie und b) Follow-up (24 Stunden nach Beginn der Therapie). Die epidemiologischen Charakteristika und Subgruppen-Einteilungen (Responder vs. Nicht-Responder) sind der beiliegenden Originalpublikation zu entnehmen (siehe Table 1, Schroeder et al., 2023a). In 71% zeigte sich eine Response auf die Levosimendan-Therapie. 48% der Kohorte wurden als ELGANs und 73% als VLBW-Frühgeborene klassifiziert. Bei Respondern zeigte sich eine signifikante Reduktion der

PH-Schwere sowie der LVD und BVD. Zudem zeigte sich in der gesamten Kohorte eine signifikante Reduktion des arteriellen Laktat-Wertes (vergleiche hierzu Fig. 2 (A-D) und Fig. 3 (A-D)) der Originalpublikation (Schroeder et al., 2023a). Unter der Therapie zeigte sich eine Stabilisierung des arteriellen Mitteldruckes. Medikamenten-assoziierte Nebenwirkungen, wie eine schwere arterielle Hypotension, konnten in der Dokumentation retrospektiv nicht festgestellt werden.

Schlussfolgerungen: Die Levosimendan-Therapie scheint mit einer signifikanten Verbesserung der CD und PH bei Frühgeborenen assoziiert zu sein. Dies konnte vor allem auch bei ELGANs und VLBW-Frühgeborenen zum ersten Mal beschrieben werden. Die Levosimendan-Therapie scheint sich stabilisierend auf den mittleren arteriellen Blutdruck auszuwirken und die Therapie-Effekte konnten anhand des sinkenden arteriellen Laktates gemessen werden.

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RESEARCH

Evaluation of levosimendan as treatment option in a large case-series of preterm infants with cardiac dysfunction and pulmonary hypertension

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Abstract

Levosimendan as a calcium-sensitizer is a promising innovative therapeutical option for the treatment of severe cardiac dysfunction (CD) and pulmonary hypertension (PH) in preterm infants, but no data are available analyzing levosimendan in cohorts of preterm infants. The design/setting of the evaluation is in a large case-series of preterm infants with CD and PH. Data of all preterm infants (gestational age (GA) < 37 weeks) with levosimendan treatment and CD and/or PH in the echocardiographic assessment between 01/2018 and 06/2021 were screened for analysis. The primary clinical endpoint was defined as echocardiographic response to levosimendan. Preterm infants (105) were finally enrolled for further analysis. The preterm infants (48%) were classified as extremely low GA newborns (ELGANs, < 28 weeks of GA) and 73% as very low birth weight infants (< 1500 g, VLBW). The primary endpoint was reached in 71%, without difference regarding GA or BW. The incidence of moderate or severe PH decreased from baseline to follow-up (24 h) in about 30%, with a significant decrease in the responder group ($p < 0.001$). The incidence of left ventricular dysfunction and bi-ventricular dysfunction decreased significantly from baseline to follow-up (24 h) in the responder-group ($p = 0.007$, and $p < 0.001$, respectively). The arterial lactate level decreased significantly from baseline (4.7 mmol/l) to 12 h (3.6 mmol/l, $p < 0.05$), and 24 h (3.1 mmol/l, $p < 0.01$).

Conclusion: Levosimendan treatment is associated with an improvement of both CD and PH in preterm infants, with a stabilization of the mean arterial pressure during the treatment and a significant decrease of arterial lactate levels. Future prospective trials are highly warranted.

What is Known:

- *Levosimendan as a calcium-sensitizer and inodilator is known to improve the low cardiac output syndrome (LCOS), and improves ventricular dysfunction, and PH, both in pediatric as well as in adult populations. Data related to critically ill neonates without major cardiac surgery and preterm infants are not available.*

What is New:

- *This study evaluated the effect of levosimendan on hemodynamics, clinical scores, echocardiographic severity parameters, and arterial lactate levels in a case-series of 105 preterm infants for the first time. Levosimendan treatment in preterm infants is associated with a rapid improvement of CD and PH, an increase of the mean arterial pressure, and a significant decrease in arterial lactate levels, as surrogate marker for a LCOS.*
- *How this study might affect research, practice, or policy. As no data are available regarding the use of levosimendan in this population, our results hopefully animate the research community to conduct future prospective trails analyzing levosimendan in randomized controlled trials (RCT) and observational control studies. Additionally, our results potentially motivate clinicians to introduce levosimendan as second second-linetherapy in cases of severe CD and PH in preterm infants without improvement using standard treatment strategies.*

Keywords Case-series · Levosimendan · Preterms · Cardiac dysfunction · Pulmonary hypertension

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Introduction

Today's challenges in the treatment of critically ill preterm infants are mainly raised by extremely low gestation age newborns (ELGANs), very low birth weight (VLBW), immaturity of lungs, and the acute respiratory distress syndrome (RDS). Putting the neonatal heart in focus, major

targets of intensive care treatment are the treatment of an early (< 28 days of life) or late (> 28 days of life) pulmonary hypertension (PH) as well as a cardiac dysfunction (CD) in preterm infants.

Known risk factors for PH or CD in preterm infants are to be found in prenatal and postnatal factors. Prenatal risk factors or conditions putting preterm infants at risk for CD are intrauterine growth restriction (IUGR), discordant twin pregnancies with known complications such as the twin-to-twin transfusion syndrome (TTTS) or selective IUGR (sIUGR), preeclampsia, intrauterine transfusions, or an amniotic infection syndrome [7, 18, 26, 28, 29]. Focusing on PH, major underlying risk factors in VLBW infants comprise RDS, intrauterine conditions with fetal hypoxia (IUGR, TTTS, preeclampsia), and lung disorders leading to lung hypoplasia or vascular remodeling [2, 8, 19].

A new promising drug for the treatment of CD and PH is the inodilator levosimendan. Levosimendan is a calcium-sensitizing drug with positive inotropic, lusitropic, and vasodilating effects, and a lot of research was done in recent years in adults and infants with CD or chronic heart failure. Levosimendan has manifold pharmacological effects: it improves myocardial contractility by increasing the affinity of myocardial troponin C to calcium, induces vasodilation in the smooth muscle cells of the vasculature by opening ATP-dependent potassium channels, and a selective PDE-3 inhibition was described, similar to the effect of PDE-inhibitors such as milrinone [5, 15, 17, 24]. Levosimendan improves both right and left ventricular contractility and is a candidate drug for PH treatment [3, 6, 13].

There are no data analyzing the use of levosimendan in larger cohorts or case-series of preterm infants, apart from case reports [10]. Our study aimed to analyze levosimendan as treatment option for CD and PH in critically ill preterm infants.

Material and methods

Patient information

Preterm infants (< 37 weeks of GA) treated at the neonatal intensive care unit (NICU) of the University Children's Hospital of Bonn, Germany, during the study period of 01/2018–06/2021 were retrospectively screened for inclusion in the case-series. Inclusion criteria include documented use of levosimendan, echocardiographic diagnosis of CD, or PH at baseline and available echocardiographic data at baseline and 24 h after onset of levosimendan administration. Exclusion criteria include congenital heart defect with need for operative correction, severe syndromic disorder or chromosomal anomalies, palliative care after birth, and infants with a congenital diaphragmatic hernia (CDH), as levosimendan treatment was already evaluated recently in a subgroup of preterm and term infants with CDH [20]. Of 136 preterm infants (< 37 weeks of GA) detected in the preliminary screening, 105 infants were included in the final analysis, after exclusion of 12 infants due to incorrect data and 19 infants due to missing echo data (see Fig. 1). Baseline characteristics of the study population are displayed in Table 1. The preterm infants (48%) were classified as ELGANs (< 28 weeks of GA) and 73% as very low birth weight (VLBW) infants (< 1500 g).

Patient's consent and ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review of the Medical Center of the University of Bonn (local running number 476/22). Informed consent of participants or their parent/ legal guardian was waived due to the retrospective design of the study, as a decision of the local Ethical Committee of the Medical Center of the University of Bonn (running number 476/22).

Clinical findings

Diagnosis and treatment of CD/PH

Diagnosis of CD was based on clinical findings and echocardiographic assessment. A low cardiac output syndrome (LCOS) and CD was suspected in the presence of sinus tachycardia (> 180 bpm), arterial hypotension, low urine output, prolonged capillary refill time, and elevated lactate. Echocardiographic assessment and verification of CD was

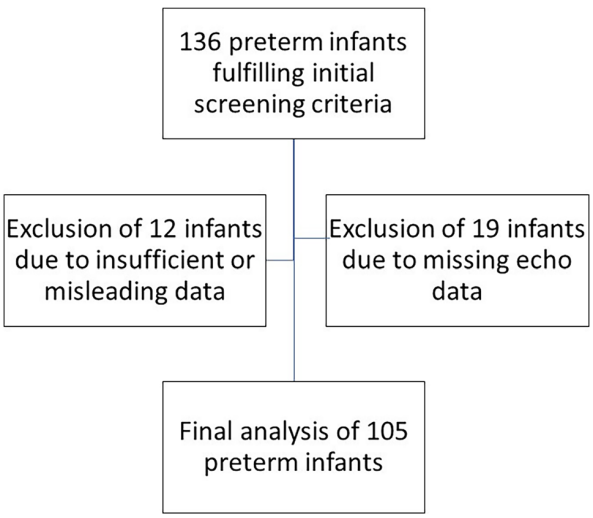

Fig. 1 Flow-chart of patient inclusion for the final cohort

Table 1 Demographic and treatment data

Variables	**Overall cohort** $n = 105$	**Responder** $n = 75$	**Non-responder** $n = 30$	***p*-level**
Gestational age, w	28.5 (25.5/32.4)	27.9 (25/32)	29.5 (26/32)	0.382
Female sex, n (%)	40 (38)	29 (39)	11 (37)	0.99
Birth weight, kg	0.98 (0.7/1.8)	0.9 (0.7/1.8)	0.98 (0.6/1.6)	0.771
pH umbilical artery	7.35 (7.3/7.4)	7.35 (7.3/7.4)	7.38 (7.3/7.4)	0.348
Lowest FiO_2 in the first 24 h	0.43 (0.3/0.9)	0.42 (0.3/0.8)	0.55 (0.3/1.0)	0.602
Apgar 5	8 (7/9)	8 (7/9)	7 (6/9)	0.362
Apgar 10	9 (8/9)	9 (8/9)	9 (7/10)	0.796
CRIP-score	8 (3/11)	8 (3/11)	9 (3/14)	0.537
Primary diagnosis, n (%)	16 (15)	11 (15)	5 (17)	0.771
a) TTTS or sIUGR, n (%)	6 (6)	6 (8)	0	0.179
b) Fetal hydrops, n (%)	6 (6)	6 (8)	0	0.179
c) IUGR, n (%)	23 (22)	14 (19)	9 (30)	0.295
d) AIS, n (%)	8 (8)	7 (9)	1 (3)	0.435
e) Congenital lung disorder	9 (9)	4 (5)	5 (17)	0.115
f) Syndromic disorder	6 (6)	5 (7)	1 (3)	0.671
g) Minor malformations				
Complications after birth				
Respiratory distress syndrome, grade 3 or 4	52 (50)	37 (49)	15 (50)	0.703
Bronchopulmonary dysplasia	23 (22)	16 (23)	7 (26)	0.791
Intraventricular hemorrhage, grade 2 or 3	26 (25)	18 (24)	8 (27)	0.075
Necrotizing enterocolitis	7 (7)	5 (7)	2 (7)	0.99
Sepsis	36 (34)	28 (38)	8 (27)	0.364
Interventional or operative PDA closure	4 (4)	3 (4)	1 (3)	0.99
Mechanical ventilation, d	6 (3/12)	6 (3/11)	6 (1/22)	0.956
Oxygen supplementation, d	11 (4/54)	11 (5/57)	7 (2/28)	0.304
In-hospital mortality, n (%)	26 (25)	16 (21)	10 (33)	0.218

Data are demonstrated as absolute number with percentage or as median values with IQR. Infants with an improvement in right ventricular, left ventricular, or biventricular dysfunction and/ or in PH-severity (min. 1 grade) were defined as responder to levosimendan. A p-value of <0.05 was considered as statistically significant

AIS amniotic infection syndrome, *CRIP* clinical risk index for babies, *d* days, *IUGR* selective intrauterine growth retardation, *n* number, *PDA* persistent ductus arteriosus, *TTTS* twin-to-twin-transfusion syndrome, *sIUGR* selective intrauterine growth retardation, *w* week

performed by the attending physician with experience in neonatal echocardiography. The echocardiographic assessment is described below in more detail. When CD was apparent, dobutamine or milrinone were used as first-line inotropes for improvement of ventricular function. In case of arterial hypotension and need for increased afterload, vasopressors (norepinephrine and vasopressin) were added to the inotropic therapy. In infants with missing improvement with the standard drug therapy and severe CD, levosimendan was implemented as a second-line therapy due to the decision of the attending senior physician.

Likewise, the diagnosis of PH consisted of clinical signs of PH and the echocardiographic assessment. Possible clinical signs of PH and oxygen impairment were $FiO_2 > 0.4$, pre- and post-ductal SpO_2-difference > 5%, $paO_2 < 60$ mmHg despite oxygen therapy and ventilation support, low mean arterial pressure (MAP), and sinus tachycardia. The echocardiographic PH assessment is described more detailed below. For the reduction of the pulmonary vascular resistance, iNO was used as primary drug therapy when PH was present. In preterm infants with moderate to severe PH, intravenous continuous sildenafil was added as a second-line therapy, followed by bosentan as third-line therapy.

Diagnostic assessment

Echocardiographic measurements

For echocardiographic measurements, a Philips CX50 Compact Extreme Ultrasound system with a S12-4 sector array transducer (Philips Healthcare, Best, the Netherlands) was used. All available echocardiographic data at baseline (prior to start of levosimendan administration) and at follow-up (24 h after onset of levosimendan administration) were retrospectively evaluated offline for analysis independently by two experienced neonatal echocardiographers blinded for the course of the respective infant. Ventricular dysfunction was defined as (a) right ventricular dysfunction (RVD), (b)

left ventricular dysfunction (LVD), and (c) biventricular dysfunction (BVD) and classified as: present or not present. For the assessment of ventricular dysfunction, a combined approach of quantitative and qualitative measurements was used, based on international guidelines for neonatal echocardiography [12, 14, 23]. In all patients, stored loops (3–5 s) visualizing the ventricular function (both 4-chamber view and parasternal long-axis) were interpreted via eyeballing assessment [23, 25]. Additionally, fractional shortening (FS; normal: 26–45%, abnormal ≤ 25%) or ejection fraction (EF; normal ≥ 55%, abnormal < 55%) were analyzed when available. The end-diastolic right ventricular to left ventricular (RV/LV) ratio was calculated in a standard four chamber view directly distal to the tricuspid and mitral annulus as a horizontal line from the endocardium of the RV and LV free wall to the endocardium of the interventricular septum. RV dysfunction was assumed when RV/LV-ratio was > 1.0 [23]. Tricuspid and mitral valve regurgitation was further analyzed and graded as I°, II°, or III°. PH was graded as mild, moderate, or severe, using the following echocardiographic parameters: (a) ductus arteriosus (DA) flow pattern, (b) intraventricular septum (IVS) position, and (c) tricuspid valve regurgitation (TVR). Mild PH was diagnosed when DA shunt-flow was left-to-right, IVS was flattened, and TVR was I–II°. Moderate PH was diagnosed when DA shunt-flow was alternating (left-to-right/right-to-left), IVS was flattened, and TRV was II–III°. Severe PH was diagnosed when DA shunt-flow was right-to-left, IVS was D-shaped (towards left ventricular cavity), and TRV was III°.

Assessment of monitoring data

The following hemodynamic parameters were documented at baseline and at follow-up (3, 6, 9,12, 24, and 48 h after onset of levosimendan drug infusion): systolic and diastolic blood pressure, MAP, heart rate, pre- and post-ductal peripheral oxygen saturation (SpO_2), and fraction of inspired oxygen (FiO_2). Arterial blood gas measurements with pH, arterial oxygen partial pressure (paO2), arterial carbon dioxide partial pressure (paCO2), and arterial lactate were documented when available at baseline, and at follow-up (3, 6, 9, 12, 24, and 48 h). For stratification of the oxygenation impairment and for infants with mechanical ventilation (MV), the Oxygenation Saturation Index (OSI; $\frac{\text{FiO2xMAPx100}}{\text{SpO2}}$) was calculated at baseline and follow-up (12, 24, and 48 h), for infants without MV the Saturation Oxygenation Pressure Index (SOPI; $\frac{\text{CPAPpressureorPEEPxFiO2}}{\text{SpO2}}$) [22] was calculated at the respective timepoints. The vasoactive-inotropic score (VIS) was calculated at the same timepoints according to the formula described elsewhere for estimation of cardiovascular drug support [4].

Statistical analysis and outcome measures

Infants were divided into subgroups according to the primary outcome: response to levosimendan therapy (responder vs. non-responder). A response to levosimendan treatment was defined as echocardiographic improvement of RVD, LVD, or BVD after 24 h, and/or decrease of PH severity (≥ 1 grade) after 24 h. The following parameters were defined as secondary endpoints or outcome measures: decrease in arterial lactate ≥ 20% after 24 h of levosimendan administration, duration of MV, days of oxygen supply, VIS at 24 h and 48 h, and in-hospital mortality.

For data analysis, SPSS version 27 (IBM Corp., Armonk, NY) was used. Continuous variables were described using median and interquartile range (IQR), and categorical variables were summarized as absolute number (*n*) with percentage. For comparison of continuous and non-normally distributed variables, a Wilcoxon-test or Mann–Whitney *U* test was performed to compare continuous variables between timepoints and subgroups (responder vs non-responder), as appropriate. For categorical variables, the Pearson's chi^2 test and Fisher's exact test were applied, as appropriate. Correlations between variables were evaluated by Spearman correlation coefficients. A *p*-value of < 0.05 was considered significant.

Results of the therapeutic intervention

Levosimendan treatment data and oxygenation scores

The primary endpoint (response to levosimendan) was reached in 71%, without difference between VLBW infants/ELGANs (75%, and 66%) and non-VLBW infants/non-ELGANs (70%, and 78%). The summary of the treatment data is displayed in Table 2. Levosimendan was administered with a continuous infusion over 24 h with a dose of 0.2 µg/kg/min. Only in three preterm infants (3%), a bolus was administered at the start of the infusion (12 µg/kg over 10 min), and in most of the infants (97%), a bolus infusion was waived to avoid an arterial hypotension. In 6 (6%) infants, levosimendan was administered for a second time with a minimum treatment interval of 7 days. No difference was found regarding the concomitant vasoactive treatment and allocation to subgroups (see Table 2).

The MAP remained stable after the onset of levosimendan administration over the first 24 h and increased significantly within 48 h ($p = 0.05$; see Fig. 2a). Regarding the use of vasoactive treatment, no difference was found analyzing the VIS at baseline and at the follow-up timepoints in the overall cohort and between subgroups (see Fig. 2b). The analysis of oxygenation indices (OSI and SOPI) and VIS is displayed in Fig. 2c–d. The arterial lactate

Table 2 Levosimendan treatment data and concomitant cardiac drugs

Variables	**Overall cohort** ***n*** **= 105**	**Responder** ***n*** **= 75**	**Non-Responder** ***n*** **= 30**	***p*-level**
Levosimendan treatment data				
Start of i.v. levo, DOL	2 (1/3)	2 (1/3)	2 (2/3)	0.484
Levo Bolus at start of infusion (12 µg/kg, 10 min)	3 (3)	2 (3)	1 (3)	0.99
Concomitant treatment data				
iNO treatment at start of levo therapy, n (%)	65 (62)	45 (60)	20 (67)	0.657
Dobutamine dose at start of levo treatment, µg/kg/min	7 (5/10)	6 (5/10)	9 (5/10)	0.738
Dobutamine dose at 24 h of levo treatment, µg/kg/min	8 (5/10)	8 (5/10)	7 (5/11)	0.79
Milrinone dose at start of levo treatment, µg/kg/min	0.7 (0.5/0.7)	0.7 (0.5/0.7)	0.7 (0.5/0.7)	0.929
Milrinone dose at 24 h of levo treatment, µg/kg/min	0.7 (0.7/0.7)	0.7 (0.7/0.7)	0.7 (0.7/0.7)	0.952
Norepinephrine dose at start of levo treatment, µg/kg/min	0.25 (0.1/0.5)	0.25 (0.1/0.5)	0.3 (0.1/0.5)	0.893
Norepinephrine dose at 24 h of levo treatment, µg/kg/min	0.3 (0.1/0.5)	0.2 (0.1/0.5)	0.3 (0.1/0.5)	0.946
Vasopressin dose at start of levo treatment, mU/kg/min	0.6 (0.2/1.8)	0.5 (0.2/2.4)	0.6 (0.6/1.7)	0.63
Vasopressin dose at 24 h of levo treatment, mU/kg/min	1.2 (0.5/1.8)	1.0 (0.4/1.9)	1.4 (0.6/1.8)	0.789
Outcome measures				
Mechanical ventilation at start of levo treatment, n (%)	42 (40)	32 (43)	10 (33)	0.509
Discharge with oxygen supplementation, n (%)	29 (28)	21 (28)	8 (27)	0.99

Data are presented as median with IQR or absolute number with %. A p-value < 0.05 was considered as statistically significant

d days, *CPAP* continuous positive airway pressure, *DOL* day of life, *h* hours, *iNO* inhaled nitric oxide, *i.v.* intravenous, *levo* levosimendan, *n* number, *NICU* neonatal intensive care unit

decreased significantly from baseline (4.7 mmol/l) to 12 h (3.6 mmol/l, $p < 0.05$), and 24 h (3.1 mmol/l, $p < 0.01$) after the onset of levosimendan administration in the overall cohort. No difference was found between responder and non-responder.

Echocardiographic assessment

The echocardiographic data are illustrated in Figs. 3a–d and Fig. 4. Moderate or severe PH was present in 77% of the infants. Mild PH was diagnosed in 16% of the infants, and in 8%, no PH was present at baseline. The overall incidence of RVD was 40%, of LVD 21%, and of BVD 31% at baseline. The end-diastolic RV/LV ratio decreased significantly from baseline to follow-up (1.05 vs 0.96, $p < 0.001$), without statistical significance between subgroups (see Fig. 4).

Safety profile

During the observation period (from baseline to follow-up, max. 48 h), we did not identify a drug-related severe arterial hypotension after starting the levosimendan infusion in the electronic patient's charts and vital parameter documentation. A severe arterial hypotension was defined as a MAP 5 mmHg < weeks of GA for > 10 min. Additionally, there were no documented cardiac arrhythmias in the retrospective chart review during levosimendan treatment.

Discussion

The major findings of the present case-series are as follows: over two-thirds of the preterm infants with CD and PH responded to levosimendan treatment. The use of levosimendan is associated with an improvement of both LVD and BVD as well as PH. The response rate to levosimendan is similar in both VLBW infants/ ELGANs, and preterm infants > 28 weeks of GA and with a BW > 1500 g. During levosimendan treatment, the MAP increased significantly from baseline to follow-up (48 h). Additionally, the arterial lactate as surrogate parameter of LCOS decreased significantly after the onset of levosimendan treatment in the first 24 h. However, response to levosimendan was not associated with a reduction in in-hospital mortality.

To our knowledge, only a single case report of levosimendan treatment in a preterm infant is available. Lechner et al. described the successful treatment with levosimendan of a LCOS in a preterm infant of 32 weeks of GA at birth with a transposition of the great arteries [10]. The first experiences of levosimendan treatment in infants were published in the context of pediatric cardiac surgery in 2009 [16], and since several more studies have been published, but research data outside the scope of pediatric cardiac surgery remain scarce [26–28]. Meta-analysis of levosimendan treatment in this population concluded that levosimendan led to an improvement of LCOS, overall hemodynamic stabilization,

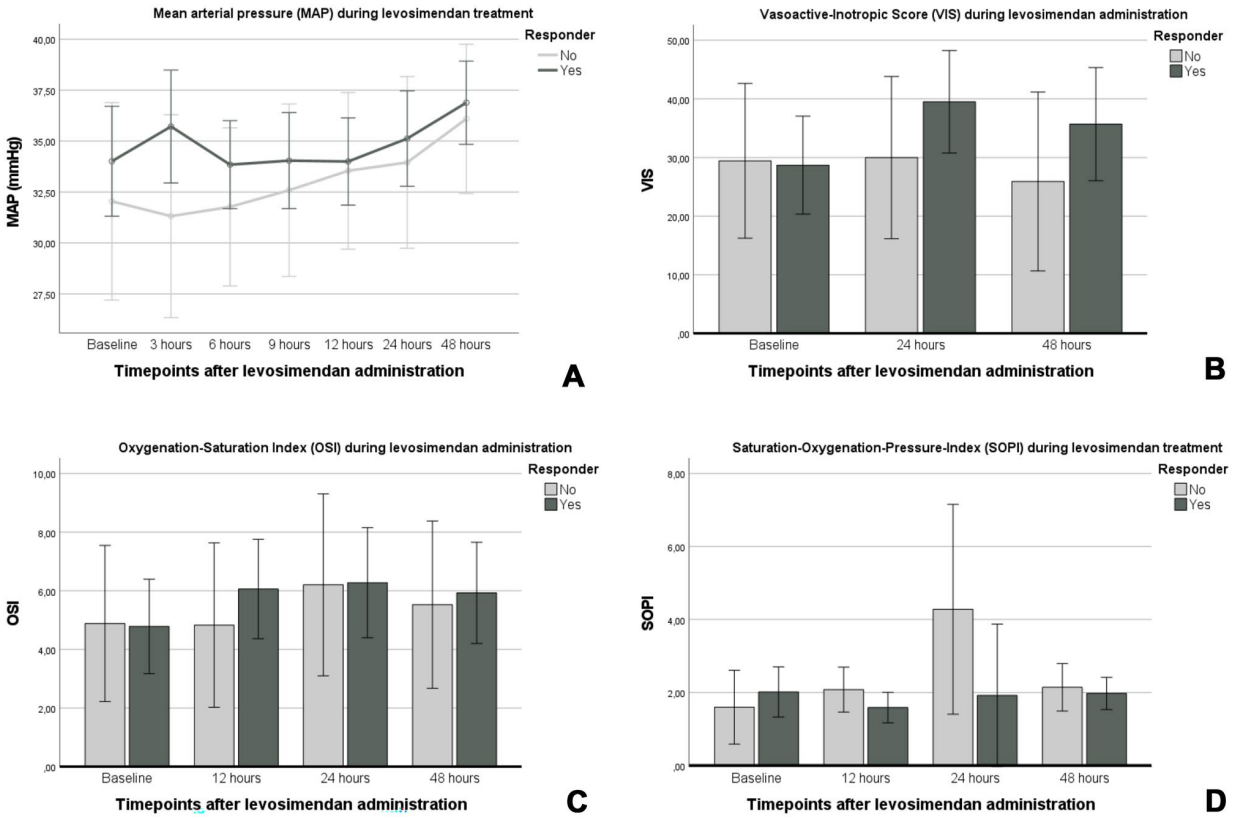

Fig. 2 The course of the mean arterial pressure (MAP) during the levosimendan treatment (**A**), the course of the Vasoacitve-Inotropic Score (VIS) during the levosimendan treatment (**B**), the course of the Oxygenation-Saturation Index (OSI), and the Saturation Oxygenation Pressure Index (SOPI) during the levosimendan treatment (**C** and **D**) are displayed for responder and non-responder infants. Data are presented as mean with 95%CI

and reduction of arterial lactate levels, but failed to decrease mortality rates, or the incidence of an acute kidney injury in this population [21, 27]. Nevertheless, the authors stated that levosimendan treatment in the post cardiac-surgery neonatal population is safe and relevant drug-related side effects extremely rare. Similarly, we did not observe drug-related arterial hypotension or arrhythmias during levosimendan administration.

Levosimendan treatment is associated with a significant improvement in RVD and LVD, markers of systolic and diastolic ventricular function, and PH, as previously described in adult populations [6, 9, 11]. Our results are in line with these findings, and levosimendan seems to have a prompt and beneficial effect on myocardial contractility and PH in preterm infants, as a hemodynamic stabilization with higher MAP and lower arterial lactate levels could be observed.

No data are available regarding the effect of levosimendan on oxygenation impairment and the improvement of oxygenation indices. Our data reveal that levosimendan has no effect on the oxygenation impairment in preterm infants, as indicated by the course of the OSI and SOPI after onset of levosimendan treatment (see Fig. 2). As levosimendan is known to improve PH severity in both infants and adults [6, 20], levosimendan can have a positive impact on the oxygenation impairment in critically ill patients. Furthermore, research data show that levosimendan can also improve cerebral oxygenation and peripheral tissue oxygenation in newborns [1].

Underlying prenatal and perinatal complications such as IUGR, TTTS, preeclampsia, or PROM elevate the risk of CD and early PH in preterm infants, with the presence of both comorbidities in many preterm infants. In our cohort, 72% of all infants had a diagnosis of CD in combination with PH. The pharmacologic profile of levosimendan with beneficial effects on the right and left ventricle and the potential to decrease the pulmonary as well as the systemic vascular resistance make levosimendan a promising candidate as an inodilating treatment option in preterm infants.

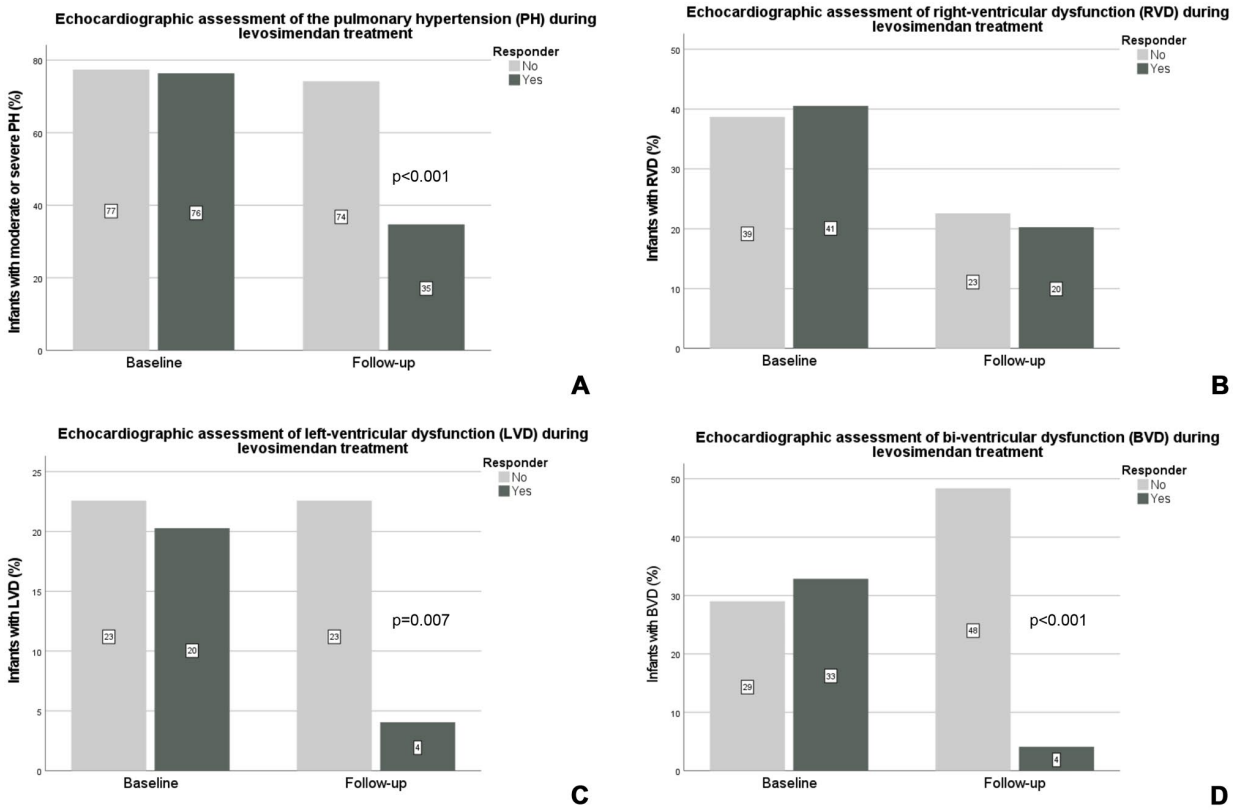

Fig. 3 The course of PH (**A**), RVD (**B**), LVD (**C**), and BVD (**D**) during levosimendan treatment at the timepoints baseline and follow-up (24 h) are displayed for responder and non-responder infants. Data are presented as percentage of the respective subgroup. *P*-levels illustrated in figure are related to the difference between subgroups for the related timepoint

Preterm infants with an acute or chronic TTTS suffer frequently from a severe dilated cardiomyopathy (DCM, donating cotwin) or hypertrophic (± obstructive) cardiomyopathy (HOCM, recipient cotwin) immediately after birth, with the need in part for multiple cardiac drug therapy [28]. In our case-series, 15% of the infants had a diagnosis of TTTS/sIUGR (see Table 2). Especially in infants with HOCM, there are limited treatment options in the presence of ventricular dysfunction because classic inotropes such as dopamine/dobutamine further increase the myocardial oxygen demand, increase ventricular muscle-mass, and can therefore worsen HOCM and the patients' outcome. In infants with DCM, the systolic as well as diastolic function is strongly impaired, and a reduction of afterload is warranted. Levosimendan does not increase myocardial oxygen demand, restores ventricular diastolic function, and reduces right and left ventricular afterload [24]. Therefore, levosimendan can expand pharmacologic treatment options for these infants and should be considered as a first-line inotropic agent. The beneficial effects and its safety profile regarding drug-related side effects make levosimendan a promising drug for cardiac therapy in neonatal population. We hypothesize that levosimendan can be used without preoccupation of arterial hypotension in preterm infants and neonates, but a bolus infusion should be avoided [20].

Limitations

Retrospective analysis bears the risk of overestimation or underestimation of statistical effects. A comparator cohort is missing, and a prospective randomized trial analyzing the effects of levosimendan as treatment option for CD and PH in preterm infants is highly warranted. Furthermore, the interpretation of the echocardiographic data is at risk for bias because echocardiographic assessment is to some extent operator-dependent, subjective, and based on qualitative grading (eyeball-assessment). By the inclusion of two experienced neonatal echocardiographers for the interpretation of the offline echocardiographic measurements, we tried to reduce potential subjective interpretation.

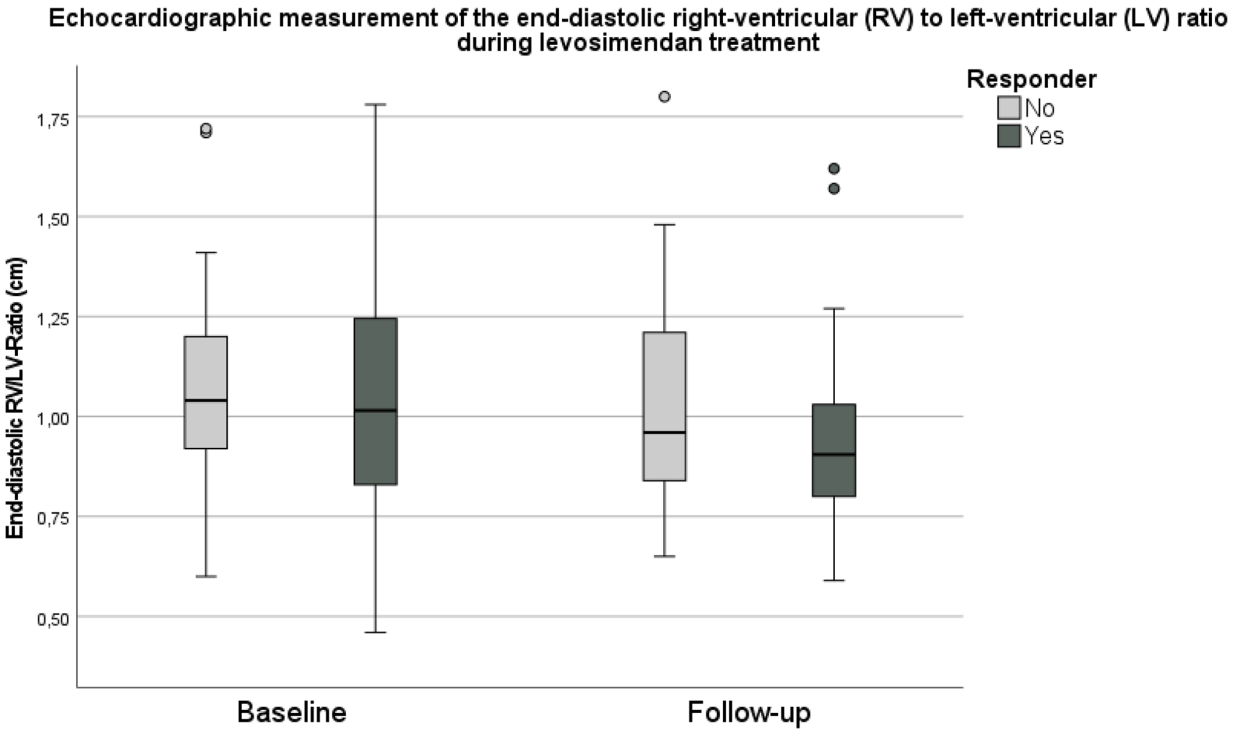

Fig. 4 The course of the end-diastolic right ventricular to left ventricular (RV/LV) ratio during the levosimendan treatment is displayed for responder and non-responder infants. Data are presented as boxplots with minimum/maximum, 25/75 quartiles and median

Conclusion

Levosimendan treatment is associated with an improvement of both CD and PH in preterm infants, with similar results when adjusting to GA and BW. Furthermore, levosimendan treatment led to a stabilization of the MAP and a significant decrease of arterial lactate levels. The retrospective results need to be interpreted carefully, and future prospective trials are needed.

Author's contributions Conceptualization: Schroeder L., Holcher S., and Kipfmueller F.; methodology: Schroeder L., Holcher S., Leyens J., Kipfmueller F., and Mueller A.; software: Schroeder L., and Holcher S.; Validation: Schroeder L., and Kipfmueller F.; formal analysis: Schroeder L., and Holcher S.; investigation: Schroeder L., and Holcher S.; writing – original draft preparation: Schroeder L., and Kipfmueller F.; writing – review and editing: Schroeder L., Holcher S., Leyens J., Geipel A., Stritzek B., Dresbach T., Mueller A., and Kipfmueller F.; visualization: Schroeder L.; supervision: none; project administration: none; funding acquisition: none.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Statement of ethics and consent to participate The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review of the Medical Center of the University of Bonn (local running number 476/22). Informed consent of participants or their parent/ legal guardian was waived due to the retrospective design of the study, as a decision of the local Ethical Committee of the Medical Center of the University of Bonn (running number 476/22).

Competing interests The authors declare no competing interests.

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3.5. Intravenöse Sildenafil-Therapie bei Frühgeborenen mit der Diagnose einer frühen PH (<28 Tage)

Schroeder L, Monno P, Strizek B, Dresbach T, Mueller A, Kipfmueller F. Intravenous sildenafil for treatment of early pulmonary hypertension in preterm infants. Sci Rep. 2023 May 24;13(1):8405. doi: 10.1038/s41598-023-35387-y *(JIF 4.6).*

Zielsetzung der Studie: Bisher gibt es keine größeren retro- oder prospektiven Kohorten-Studien zur intravenösen Sildenafil-Therapie bei Frühgeborenen <34 SSW, obwohl der Effekt der Sildenafil-Therapie auf die PH mittlerweile bei late-preterm (späte Frühgeborene) und Termin-gerecht geborenen Neugeborenen gut beschrieben ist. Das Ziel dieser Studie war die Evaluation der Behandlungsdaten aus der Klinik für Neonatologie am UKB, um einen besseren Einblick in das Kollektiv der Frühgeborenen mit einer notwendigen Sildenafil-Therapie zu erhalten und Effekte abschätzen zu können.

Methoden und Ergebnisse: Es erfolgte eine retrospektive Kohorten-Studie an Frühgeborenen <37 SSW, welche im Zeitraum von 01/2012 bis 12/2021 in der Klinik für Neonatologie des UKB behandelt wurden, mit der Notwendigkeit für eine intravenöse Sildenafil-Therapie (1.6µg/kg/d, kontinuierlich intravenös) im Rahmen einer früh diagnostizierten PH (<28 Lebenstag). Insgesamt wurden 58 Frühgeborene identifiziert und in die Studie eingeschlossen. Es wurden hämodynamische Daten, Behandlungsdaten zu allen vasoaktiven Medikamenten, echokardiographische Analysen sowie Beatmungsparameter und Daten der durchgeführten Blutgasanalysen zur Kalkulation der Oxygenierungs-Indices retrospektiv ausgewertet. Der primäre Endpunkt wurde als die „Response“ auf die Sildenafil-Therapie definiert und die Response wurde definiert als die Score-Reduzierung um ≥20% der Oxygenierungs-Indices a) „Oxygenation Index“ (OI) und b) „Oxygenation Saturation Index“ (OSI) sowie die Verbesserung der „PaO_2/FiO_2-Ratio“ um ≥20% (partielle arterielle Sauerstofffraktion/ fraktionelle inspiratorische Sauerstoffkonzentration; sog. Horowtiz-Index). In 57% der Frühgeborenen wurde der primäre Endpunkt erreicht, wovon 47% als VLBW-Frühgeborene klassifiziert wurden. Die epidemiologischen Charakteristika sowie Subgruppen sind in der Table 1 der beiliegenden Originalarbeit aufgeführt (Schroeder et al., 2023c). Die Wahrscheinlichkeit für ein innerklinisches Versterben wurde für Frühgeborene ohne eine Response auf Sildenafil als dreifach erhöht kalkuliert (vergleiche hierzu die Kaplan-Meier Kurve in Fig. 1, Schroeder et al., 2023c).

Es zeigte sich in der retrospektiven Bewertung der echokardiographischen Daten eine signifikante Reduzierung der PH- und RVD-Inzidenz. Die dazugehörigen Grafiken (Fig. 4, A-C) sind der Originalarbeit zu entnehmen (Schroeder et al., 2023c). Es zeigten sich in der retrospektiven Auswertung keine Medikamenten-assoziierten Sildenafil-Nebenwirkungen wie eine schwere arterielle Hypotension.

Schlussfolgerungen: Die intravenöse Sildenafil-Therapie ist mit einer signifikanten Verbesserung des PH-Schweregrades und der RVD assoziiert und scheint bei Frühgeborenen <37 SSW sicher anwendbar zu sein. Vor allem konnte dieser Effekt auch bei VLBW-Frühgeborenen und ELGANs nachgewiesen werden.

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Intravenous sildenafil for treatment of early pulmonary hypertension in preterm infants

Lukas Schroeder[1]✉, Paulina Monno[1], Brigitte Strizek[2], Till Dresbach[1], Andreas Mueller[1] & Florian Kipfmueller[1]

Data is lacking on the effect of continuous intravenous sildenafil treatment in preterm infants with early pulmonary hypertension (PH), especially in very low birth weight (VLBW) infants. Preterm infants (< 37 weeks of gestational age) with intravenous sildenafil treatment and diagnosis of PH between 01/12 and 12/21 were retrospectively screened for analysis. The primary clinical endpoint was defined as response to sildenafil according to the improvement of the oxygenation index (OI), the saturation oxygenation pressure index (SOPI) and PaO_2/FiO_2-ratio. Early-PH was defined as diagnosis < 28 day of life (DOL). 58 infants were finally included, with 47% classified as very low birth weight (VLBW) infants. The primary endpoint was reached in 57%. The likelihood to die during in-hospital treatment was more than three times higher (72 vs 21%, p < 0.001) in infants without response to sildenafil. The echocardiographic severity of PH and right-ventricular dysfunction (RVD) decreased significantly from baseline to 24 h (p = 0.045, and p = 0.008, respectively). Sildenafil treatment leads to significant improvement of the oxygenation impairment in 57% of the preterm infants, with similar response rates in VLBW infants. Intravenous sildenafil treatment is associated with a significant decrease of the PH-severity and RVD.

Pulmonary hypertension (PH) in preterm and term newborns is a major contributor for short and long term morbidity and mortality in this cohort[1–6]. Mortality rates remain still high despite the development of new promising drugs for PH treatment over the last two decades. According to the updates and new classification system of PH on the 6th World Congress on Pulmonary Hypertension (Nice, 2018) PH in preterm and term infants is frequently related to: (1) Persistent PH of the newborn syndrome (PPHN, class I, group 1.7) and (2) PH due to lung disease; mostly in presence of bronchopulmonary dysplasia (BPD) associated PH (BPD-PH, class III)[7]. Early-PH is defined according to the occurrence in the first weeks of life (< 28 day of life-DOL). The incidence of early-PH in preterm infants was calculated with 24% in a recent Meta-analysis[8]. In contrast, in many preterm infants PH is diagnosed at later stages (diagnosis > 28 DOL) and the incidences of late-PH (including BPD-PH) are ranging between 5 and 25%[9–11].

One candidate drug for the treatment of PH in preterm and term newborns is sildenafil. Sildenafil acts via the cyclic guanosine monophosphate (cGMP) pathway and as phosphodiesterase 5 (PDE 5) inhibitor, inhibiting PDE 5, which normally breaks down cGMP in the smooth muscle cells and therefore increases cytoplasmatic cGMP levels. This leads to a calcium-efflux and induces a smooth muscle cell relaxation, leading to pulmonary vasodilation[12].

Sildenafil is available as intravenous (continuous and intermittent) and oral (sildenafil-citrate) form of administration. In recent years, several studies evaluated sildenafil as treatment for PH (BPD-PH, PPHN) in preterm and term infants in prospective trials[13–15]. The majority of the studies published to date and included in the Cochrane review of sildenafil treatment for PH (2017) were exclusively enrolling neonates with a GA > 34 weeks[16]. Despite the effort done by the studies conducted in the past, data on intravenous sildenafil treatment in preterm infants < 34 weeks and especially in VLBW infants with early PH are still lacking. Data from retrospective trials on sildenafil treatment in preterm infants are available, but predominantly focusing on oral drug administration[17,18]. More data is warranted analyzing data of intravenous sildenafil therapy in preterm infants in larger cohorts.

The aim of this study was to evaluate the data on continuous intravenous sildenafil treatment in preterm infants (< 37 weeks of GA) with diagnosis of early PH over the last decade (2012–2021), to generate more insight in the effect of intravenous sildenafil treatment for early PH.

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Material and methods

Study population. Infants treated at the NICU of the University Children´s Hospital of Bonn, Germany, during the study period 01/2012–12/2021 were retrospectively screened for study participation. Inclusion criteria: echocardiographic verification of PH, continuous intravenous sildenafil treatment, < 37 weeks of GA. Exclusion criteria were as follows: ≥ 37 weeks of GA, congenital diaphragmatic hernia (a study analyzing continuous intravenous sildenafil treatment in this subgroup was previously published[19]), oral sildenafil treatment prior to intravenous treatment or exclusive oral treatment, primary palliative care, congenital heart defect requiring surgical repair.

Ethical approval. The study was approved by the local ethics committee of the Medical Center of the University of Bonn (local running number 138/22). Informed consent was waived by decision of the ethics committee of the Medical Center of the University of Bonn due to the retrospective design of the study. The methods used for the clinical research were performed in accordance with relevant guidelines/regulation and in accordance with the Declaration of Helsinki.

Monitoring data and oxygenation scores. The following hemodynamic parameters were retrospectively recorded from the patient´s chart at baseline, 3, 6, 9, 12, 24, 48 h, and at day 7 after start of sildenafil treatment: systolic, diastolic, and mean arterial blood pressure, heart rate, pre- and postductal SpO_2, FiO_2. Arterial blood gas measurements with pH, paO2, and paCO2 were recorded when available at baseline, 3, 6, 9, 12, 24, 48 h and day 7. The (a) Oxygenation Index (OI; $\frac{FiO2\ x\ Mean\ airway\ pressure(MAP)}{paO2}$) for infants with invasive mechanical ventilation (MV), (b) the Saturation Oxygenation Pressure Index (SOPI; $\frac{CPAP\ pressure\ or\ PEEP\ x\ FiO2}{SpO2}$)[20] for infants without MV but with continuous positive airway pressure-CPAP or highflow-nasal cannula-HFNC support, and (c) PaO_2/FiO_2 (P/F)-ratio (for infants with both, MV or non-invasive support) were retrospectively calculated for the timepoints baseline, 12, 24 and 48 h to evaluate oxygenation impairment. The vasoactive-inotropic score (VIS) was calculated for the same timepoints according to the formula described elsewhere for estimation of cardiovascular drug support[21].

Diagnostic and treatment of pulmonary hypertension. PH was defined as evidence of echocardiographic signs of PH and classified as early PH when appearance was in the first 28 DOL. These definition were adopted from the definition of PH in preterm infants described elsewhere[10,11,22]. Echocardiographic PH assessment is described below in detail.

PH drug treatment was conducted by the attending physicians according to in-house standards of clinical practice for vasoactive and PH treatment. Inhaled nitric oxide (iNO) was used as primary drug therapy when PH was treated. Infants were evaluated for sildenafil therapy when echocardiographic assessment demonstrated moderate or severe PH, FiO_2 was > 0.8 despite iNO treatment, and difference in pre- and postductal SpO_2 was > 8% (in case of a patent ductus arteriosus-PDA). Sildenafil was administered routinely as continuous intravenous infusion and a dose regime of 1.6 mg/kg/day, as described previously and according to the in-house clinical standards[19,23,24]. A bolus infusion of 0.4 mg/kg over a period of 3 h was administered followed by a continuous infusion according to the decision of the attending physician. For the period of sildenafil administration all infants were treated simultaneously with iNO.

Infants with need for inotropic support were treated with dobutamine and with milrinone. Furthermore, levosimendan was administered in infants with cardiac dysfunction despite high-dose inotropic treatment. In cases of oxygenation failure unresponsive to conventional treatment, extracorporeal membrane oxygenation (ECMO) was implemented according to international guidelines and criteria[25,26].

Echocardiographic assessment. For echocardiographic measurements a Philips CX50 Compact Extreme Ultrasound system with a S12-4 sector array transducer (Philips Healthcare, Best, the Netherlands) was used. All infants with diagnosis of early or late PH were evaluated by an echocardiographic assessment daily or (when stabilized) every 48–72 h, according to the in-house standards of clinical practice. All echocardiographic data at baseline (prior to start of sildenafil administration), at 24 h, and 48 h were retrospectively screened for analysis independently by two experienced neonatal echocardiographers. Both echocardiographers have over 10 years' experience in neonatal echocardiography as senior physicians, with profound knowledge of the echocardiographic diagnosis of PH and cardiac dysfunction in preterm and term infants in a tertiary referral medical center. PH was graded as mild, moderate, or severe, using the following echocardiographic parameters: (a) flow pattern of the ductus arteriosus (DA), (b) intraventricular septum position (IVS), and (c) tricuspid valve regurgitation (TVR). Tricuspid valve regurgitation was graded as I°, II° or III°. Mild PH was diagnosed as follows: DA shunt-flow was left-to-right, IVS was flattened, and TVR was I°–II°. Moderate PH was diagnosed as follows: DA shunt-flow was alternating (left-to-right/ right-to-left), IVS was flattened, and TRV was II–III°. Severe PH was diagnosed as follows: DA shunt-flow was right-to-left, IVS was D-shaped (towards left ventricular cavity), and TRV was III°. Additionally, the end-diastolic right-ventricular to left-ventricular (RV/LV) ratio was calculated in a standard four chamber directly distal to the tricuspid and mitral annulus as a horizontal line from endocardium of the RV and LV free wall to endocardium of the interventricular septum. Presence of ventricular dysfunction was defined as (a) right-ventricular dysfunction (RVD) and (b) left-ventricular dysfunction (LVD). For the assessment of ventricular dysfunction a combined approach of quantitative and qualitative measurements was used, based on international guidelines[27,28].

Statistical analysis and outcome measures. Infants were retrospectively classified as sildenafil treatment Responder and non-Responder. A response to sildenafil treatment (primary outcome parameter) was defined as: decrease of the OI ≥ 20% (infants with MV) or the SOPI (infants without MV, but with non-invasive support) or an increase of the P/F ratio ≥ 20% (both, infants with and without MV) within the first 12–24 h after sildenafil. The following parameters were defined as secondary outcome measures: decrease of PH severity in the echocardiographic assessment during sildenafil therapy at timepoints 24 and 48 h, duration of MV, days of oxygen supplementation, oxygen supplementation at discharge, diagnosis of bronchopulmonary dysplasia (BPD) at 36 weeks of GA, survival to discharge.

For this descriptive analysis, continuous variables were described using median and interquartile range (IQR). Categorical variables were summarized as absolute number (n) and percentage. For comparison of continuous and non-normally distributed variables, a Wilcoxon-test or Mann–Whitney U test was performed to compare continuous variables between timepoints and subgroups (Responder vs non-Responder), as appropriate. For categorical variables the Pearson's Chi^2 test and Fisher's exact test was applied, as appropriate.A Kaplan–Meier plot was used to analyze the survival chance after start of sildenafil treatment. A p-value of < 0.05 was considered significant.

Results

In total, 75 infants with documented diagnosis of PH and intravenous sildenafil treatment in the electronic patient´s chart system were screened for inclusion and 58 infants were finally enrolled for the analysis. 17 infants were excluded due to the following criteria: in 6 infants the patients' charts, and documentation was incomplete, in 9 infants' sildenafil was administered oral prior to the continuous intravenous infusion, and 2 infants had a diagnosis of late-onset PH (> 28 DOL).

Epidemiological data of the cohort are displayed in Table 1. The primary endpoint (response to sildenafil therapy) was reached in 57% (n = 33), with a response rate of 54% in VLBW infants and 59% in infants with a birth weight > 1500 g. Sildenafil was administered in median at the 2 (1/3) DOL. Almost the half of the cohort (n = 26, 45%) were classified as VLBW infants and 14 (24%) was born with < 28 weeks of GA (extremely low gestational age newborns-ELGAN).

Variables	Overall cohort n = 58	Responder n = 33	Non-Responder n = 25	p-level
Gestational age, w	31.8 (28.5/34.3)	32.3 (28/34.9)	31.4 (29.2/34.1)	0.832
Female sex, n (%)	30 (51)	14 (42)	16 (64)	0.120
Birth weight, kg	1.8 (0.9/2.5)	1.8 (0.9/2.5)	1.7 (0.8/2.4)	0.423
APGAR 5 min	7 (6/8)	7.5 (6/8)	7 (5.5/8)	0.187
APGAR 10 min	8 (7/9)	8 (7/9)	8 (7/9)	0.346
CRIP-Score	11.5 (9.3/14)	11 (8.8/15.3)	13.5 (10/14)	0.585
Lowest FiO2 in the first 24 h	0.28 (0.21/0.66)	0.35 (0.21/0.75)	0.26 (0.21/0.4)	0.354
Primary diagnosis, n (%)				
(a) Twin-to-Twin-transfusion syndrome, n (%)	5 (9)	2 (6)	3 (12)	0.643
(b) Fetal hydrops, n (%)	11 (19)	6 (18)	5 (20)	0.99
(c) Fetal growth retardation, n (%)	13 (22)	7 (21)	6 (24)	0.99
(d) Lung hypoplasia	25 (43)	8 (24)	17 (68)	**0.001**
(e) Lower urinary tract obstruction (LUTO) or congenital renal disorder	9 (16)	2 (6)	7 (28)	**0.031**
(f) Genetic disorder	8 (14)	3 (9)	5 (20)	0.272
Comorbidities, n (%)				
BPD at 36 weeks of gestational age	15 (26)	12 (36)	3 (12)	**0.030**
Intraventricular hemorrhage	13 (22)	8 (24)	5 (20)	0.700
Necrotizing enterocolitis	18 (31)	10 (30)	8 (32)	0.99
Retinopathy of prematurity, grade ≥ 2	10 (17)	6 (18)	4 (16)	0.99
Sepsis	15 (26)	7 (21)	8 (32)	0.381
Mechanical ventilation, d	2.3 (0.1/22.5)	5.8 (0.7/28)	1.1 (0.1/16.5)	0.142
Oxygen supplementation, d	8 (3/36)	9 (4/52)	5 (2/23)	0.285
In-hospital mortality, n (%)	25 (43)	7 (21)	18 (72)	**< 0.001**
In-hospital mortality or BPD, n (%)	38 (66)	18 (55)	20 (80)	**0.05**
ECMO support, n (%)	4 (7)	3 (9)	1 (4)	0.627

Table 1. Demographic and treatment data. Data are demonstrated as absolute number with percentage or as median values with IQR. Infants with a decrease of ≥ 20% of the Oxygenation Index (OI), the Saturation Oxygenation Pressure Index (SOPI) or an increase ≥ 20% of the PaO2/FiO2 ratio (P/F ratio) were defined as responder to sildenafil. Parameters with a p-level < 0.05 are highlighted in bold. BPD, bronchopulmonary dysplasia at 36 weeks of gestational age; CRIP, clinical risk index for babies; ECMO, extracorporeal membrane oxygenation).

Significantly more infants in the non-Responder group suffered from a lung-hypoplasia (p = 0.001) and a lower urinary tract obstruction (LUTO) or renal congenital disorder (p = 0.031) at birth. Lung hypoplasia was defined according to the prenatal diagnosis by the obstetricians or clinical/radiological signs after birth (severe respiratory insufficiency with X-ray findings as small lung fields, diaphragmatic domes, and a bell-shaped)[29]. The rates of comorbidities after birth were equally distributed between the subgroups. The mortality rate was 43% in the overall cohort, with a significantly higher mortality rate in the non-Responder group (21 vs 72%, p < 0.001, see Kaplan–Meier-plot in Fig. 1). When looking for the combined endpoint death and/or BPD there between Responder and non-Responder infants there is still a trend to a higher rate of the combined endpoint in non-Responder infants (see Table 1, p = 0.05). Baseline characteristics in the first 24 h (APGAR 5 and 10 min, CRIP score and lowest FiO2) were similar between the subgroups.

Oxygenation scores and treatment data. The course of oxygenation according to the oxygenation scores (OI, SOPI and P/F-ratio) and allocation to the Responder and non-Responder group with related statistical significances is displayed in Fig. 2A–C.

The mean VIS scores after sildenafil treatment start are illustrated in Fig. 3A. In the Responder group, the mean VIS score increased significantly from baseline to 24 h (p = 0.004), without significant changes in the non-Responder group. The mean arterial pressure (MAP, see Fig. 3B) tended to increase during the sildenafil treatment. After commencing sildenafil the median arterial lactate levels decreased significantly from baseline (2.95 mmol/l) to timepoint 48 h (2.19 mmol/l, p = 0.037). No difference was found between Responder and non-Responder.

Comparison of outcome and treatment data between subgroups are illustrated in Table 2**.** No difference was found regarding the use of concomitant drugs for PH (iNO, bosentan or levosimendan) between Responder and non-Responder.

Echocardiographic assessment. In 42 infants (71%) valid echo data were available at baseline and 24 h. Echo data at all three timepoints (+ 48 h) were available in 35 infants (59%). At baseline, 93% of the infants presented a persistent ductus arteriosus (PDA), with 33% presenting a right-to-left shunt over the PDA. At 24 h 95% of the infants presented a PDA (19% with right-to-left shunt). The course of PH, RVD and end-diastolic RV/LV-ratio is illustrated in Fig. 4A–C. In the overall cohort, the severity of PH and RVD decreased significantly from baseline to 24 h (p = 0.045, and p = 0.008, respectively). The RV/LV-ratio decreased significantly in the Responder group from baseline to 24 h (p = 0.028), without statistically significant difference in the overall cohort. Regarding the presence of LVD at baseline, 24 h and 48 h no differences were found between the Responder and non-Responder group.

Discussion

The present study summarizes a retrospective data set of 58 preterm infants with continuous intravenous sildenafil treatment and represents the biggest cohort to date of preterm infants with intravenous sildenafil treatment of early-PH. According to our results, we could demonstrate that PH severity, the incidence of RVD and the end-diastolic RV/LV ratio decreased significantly during the first 24 h during sildenafil treatment. Sildenafil

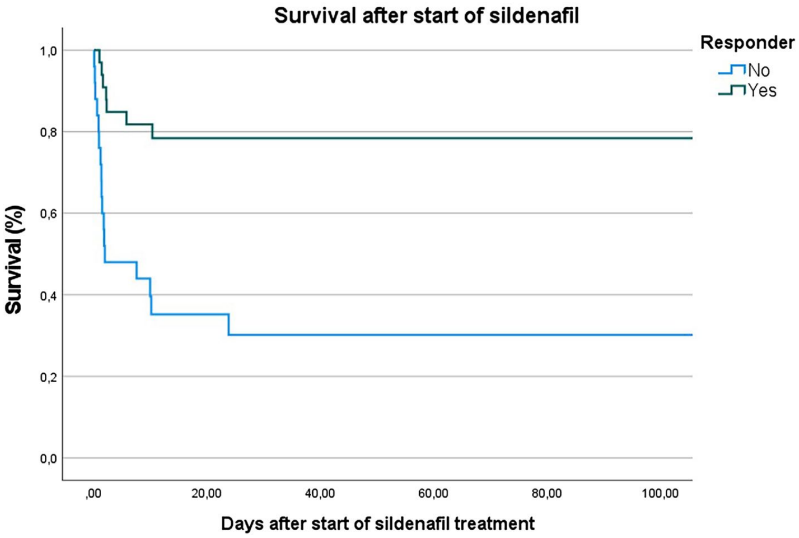

Figure 1. The Kaplan–Meier plot displays the survival rate after start of sildenafil treatment. The non-Responder infants are illustrated with the blue line, the Responder infants are illustrated with the green line.

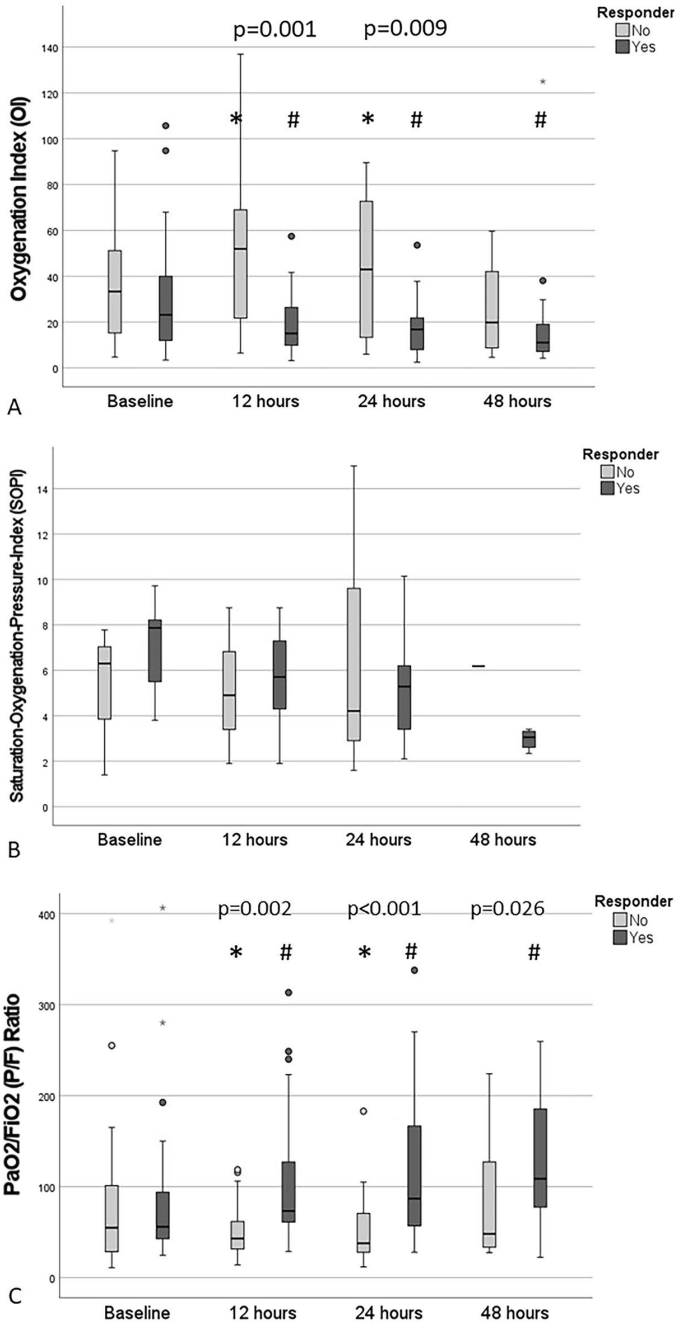

Figure 2. (**A**) The mean values for the Oxygenation Index (OI) were calculated for the subgroups (Responder vs. non-Responder). (**B**) The mean values for the Saturation Oxygenation Pressure Index (SOPI) were calculated for the subgroups (Responder vs. non-Responder). (**C**) The mean values for the PaO_2/FiO_2 (P/F) ratio were calculated for the subgroups (Responder vs. non-Responder). All values were calculated at baseline (prior to sildenafil treatment start), at 12 h, 24 h, and 48 h after sildenafil treatment start. p-values pointed out in the figures are related to significant differences between subgroups. The asterisk and the rhombus illustrate p-levels < 0.05, when comparing the value with the respective baseline value in the subgroup.

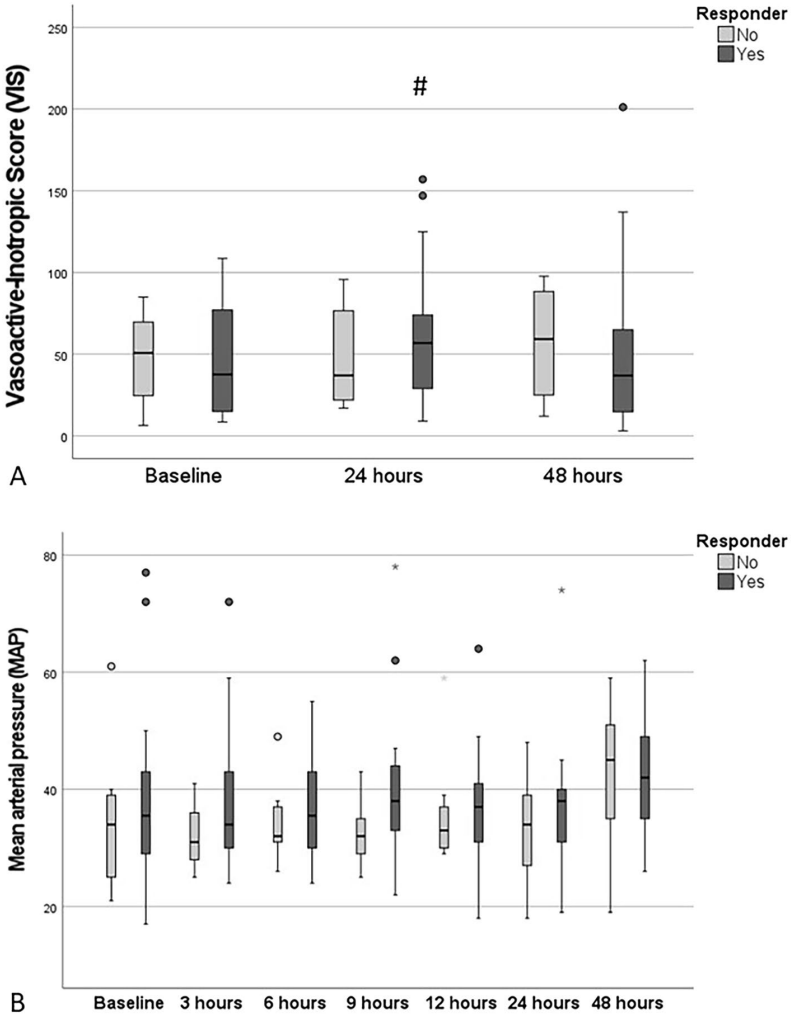

Figure 3. (**A**) The Vasoactive-Inotropic Score (VIS) was calculated for the respective subgroups (Responder vs. non-Responder) at baseline, 24 h, and 48 h. (**B**) The mean arterial pressure (MAP) was documented from the patient´s chart and electronic documentation system every 3 h ongoing from baseline to 48 h. The rhombus illustrates p-levels < 0.05, when comparing the value with the respective baseline value in the subgroup.

treatment is associated with a rapid improvement in oxygenation impairment in the mayor part of the infants, illustrated and evaluated with established oxygenation indices (OI, SOPI, and P/F ratio), both shown in VLBW and non-VLBW preterm infants. The mortality rate of infants responding to sildenafil was significantly lower compared to non-Responder. Nevertheless, about 40% of the preterm infants did not demonstrate a response to sildenafil treatment and were classified as non-Responder.

In recent prospective trials intravenous sildenafil treatment was evaluated in neonates with a gestational age > 34 weeks, but data on intravenous sildenafil in ELGAN and VLBW preterm infants < 28 GA are still lacking[13,14]. Several studies analyzed oral sildenafil treatment and only two recent studies were identified analyzing intravenous sildenafil treatment including VLBW infants with PH[15,17,30,31]. In most of these infants PH was diagnosed secondary to the timepoint of BPD diagnosis (36 weeks of GA). These studies overall report beneficial effects of sildenafil on echocardiographic grading of BPD-PH and oxygenation indices. A prospective multicenter, randomized, placebo-controlled trial on preterm infants < 29 weeks of GA at risk for PH is ongoing (SILDI-SAFE trial)[32]. Our study adds new insights on preterm and VLBW-infants with sildenafil treatment for primary early-PH in the first days of life, and with almost a third of the population classified as ELGANs and nearly half of the cohort classified as VLBW infants.

The response to sildenafil according to the improvement in oxygenation indices in our cohort was documented in 57% of the infants, without influence of GA or birth weight on the response to sildenafil. The updated

Variables	Overall cohort n = 58	Responder n = 33	Non-Responder n = 25	p-level
Sildenafil treatment data				
Start of i.v. sildenafil, DOL	2 (1/3)	2.5 (1/3)	2 (1/2.5)	0.344
Stop of i.v. sildenafil, DOL	7 (3/13)	8 (6/15)	5 (2/12.5)	0.057
Duration of i.v. sildenafil, h	120 (26/216)	141 (53/233)	41 (11/216)	0.067
Sildenafil Bolus at start of infusion (0.4 mg/kg, 3 h)	29 (50)	16 (48)	13 (52)	0.793
Dose duplication of sildenafil to 3.2 mg/kg/d after cessation of bolus infusion, n (%)	4 (8)	3 (10)	1 (5)	0.99
Oral sildenafil treatment during NICU stay, n (%)	21 (36)	16 (49)	5 (20)	**0.031**
Discharge with oral sildenafil treatment, n (%)	20 (35)	12 (36)	8 (32)	0.786
Concomitant treatment data				
iNO treatment at start of sildenafil therapy, n (%)	55 (95)	32 (97)	23 (92)	0.572
Duration of iNO treatment, h	115 (29/291)	123 (54/355)	37 (20/241)	0.083
Bosentan treatment after start of sildenafil, n (%)	8 (14)	6 (18)	2 (8)	0.445
Dobutamine dose at start of sildenafil treatment, µg/kg/min	10 (5/12)	9 (5/11)	10 (5/14)	0.456
Dobutamine dose at 24 h of sildenafil treatment, µg/kg/min	10 (6/10)	10 (5/10)	10 (8/13)	0.418
Milrinone dose at start of sildenafil treatment, µg/kg/min	0.69 (0.46/0.70)	0.7 (0.5/0.7)	0.66 (0.3/0.7)	0.360
Milrinone dose at 24 h of sildenafil treatment, µg/kg/min	0.70 (0.67/0.70)	0.7 (0.67/0.7)	0.7 (0.67/0.7)	0.928
Norepinephrine dose at start of sildenafil treatment, µg/kg/min	0.45 (0.2/0.5)	0.5 (0.18/0.5)	0.4 (0.2/0.5)	0.901
Norepinephrine dose at 24 h of sildenafil treatment, µg/kg/min	0.5 (0.25 /0.65)	0.5 (0.34/0.72)	0.5 (0.17/0.6)	0.588
Vasopressin dose at start of sildenafil treatment, mU/kg/min	0.7 (0.4/1.6)	0.6 (0.4/1.4)	0.9 (0.4/1.9)	0.489
Vasopressin dose at 24 h of sildenafil treatment, mU/kg/min	1.2 (0.6/2.3)	1.1 (0.6/2.1)	1.4 (0.6/4.0)	0.431
Levosimendan (0.2 µg/kg/min) treatment at start of sildenafil therapy, n (%)	6 (10)	3 (9)	3 (12)	0.99
Mechanical ventilation at start of sildenafil treatment, n (%)	48 (83)	26 (79)	22 (88)	0.490
Discharge with oxygen supplementation, n (%)	32 (59)	14 (45)	18 (78)	**0.024**

Table 2. Treatment data. Data are presented as median with IQR or absolute number with %. A p-value < 0.05 was considered as statistically significant and are highlighted in bold letters. d, days; CPAP, continuous positive airway pressure; DOL, day of life; h, hours; iNO, inhaled nitric oxide; i.v., intravenous; n, number; NICU, neonatal intensive care unit).

Cochrane review from 2017 on sildenafil treatment for PH in neonates highlighted, that sildenafil is effective in reducing mortality compared to placebo, with a number needed to treat of 3 patients to have a beneficial outcome[16]. Additionally, oxygenation indices improved in the first 24 h after administration of sildenafil. Nevertheless, these data are summarizing the effect of an oral sildenafil treatment. The most recent trial on intravenous continuous sildenafil was published in 2021 by Pierce et al. The study group conducted a multinational, double-blind, placebo-controlled trial, and randomized infants (> 34 weeks of GA) with PPHN or at risk for PPHN to receive either intravenous sildenafil (0.1 mg/kg bolus infusion over 30 min, followed by 0.03 mg/kg/h continuous infusion) or placebo (0.9% saline or 10% dextrose)[13]. All infants were on iNO treatment, which were the same conditions as in our study population. The authors concluded that intravenous sildenafil was not superior to placebo regarding the endpoints: treatment failure rate (need for additional drug for PPHN therapy, need for ECMO, or death prior to discharge, and time on iNO after starting sildenafil in infants without treatment failure). This phase III study raises the question, whether continuous intravenous sildenafil is effective to treat PPHN in preterm and term infants. However, the findings of the study are contrarious to other studies revealing a significant effect of intravenous sildenafil in this population[14,23]. The dose regime of sildenafil used in the phase III trial was half of the dose which was described by Steinhorn et al.[23], using a bolus infusion of 0.4 mg/kg over 3 h, followed by a maintenance dose of 1.6 mg/kg/day. The missing effect between placebo and sildenafil could potentially be biased by lower plasmatic sildenafil levels due to lower concentrations of the bolus and continuous infusion, and in total cumulative half of the dose used in the open-label, dose-escalation trial by Steinhorn et al.

In our study, infants were treated with the dose regime provided by Steinhorn et al., but a bolus infusion was only administered in 50% of the infants, due to the decision of the attending physician. The severity of oxygenation impairment and PPHN in our cohort is comparable with the before mentioned studies, as the median OI at baseline prior to sildenafil start in our cohort was 26.2 (12.0/47.3) and both studies predominantly included infants with an OI > 15 and < 60. In 4 infants of our cohort the continuous sildenafil dose was doubled to 3.2 mg/kg/day after cessation of the bolus infusion as rescue procedure in case of severe PPHN or oxygenation failure, without difference in response to sildenafil between subgroups (see Table 2).

The preterm infants screened for this retrospective analysis were predominantly those with a delayed cardiopulmonary adaptation and impaired transition of the fetal circulation. As reported recently, preterm infants with early-PH and delayed cardiopulmonary adaptation (PH diagnosis > 48–72 h) are at risk for adverse outcome and BPD, as highlighted recently[33]. This is in line with our findings, with an overall rate of BPD of 26% in the cohort and a rate of 36% of those responding to sildenafil and surviving to discharge.

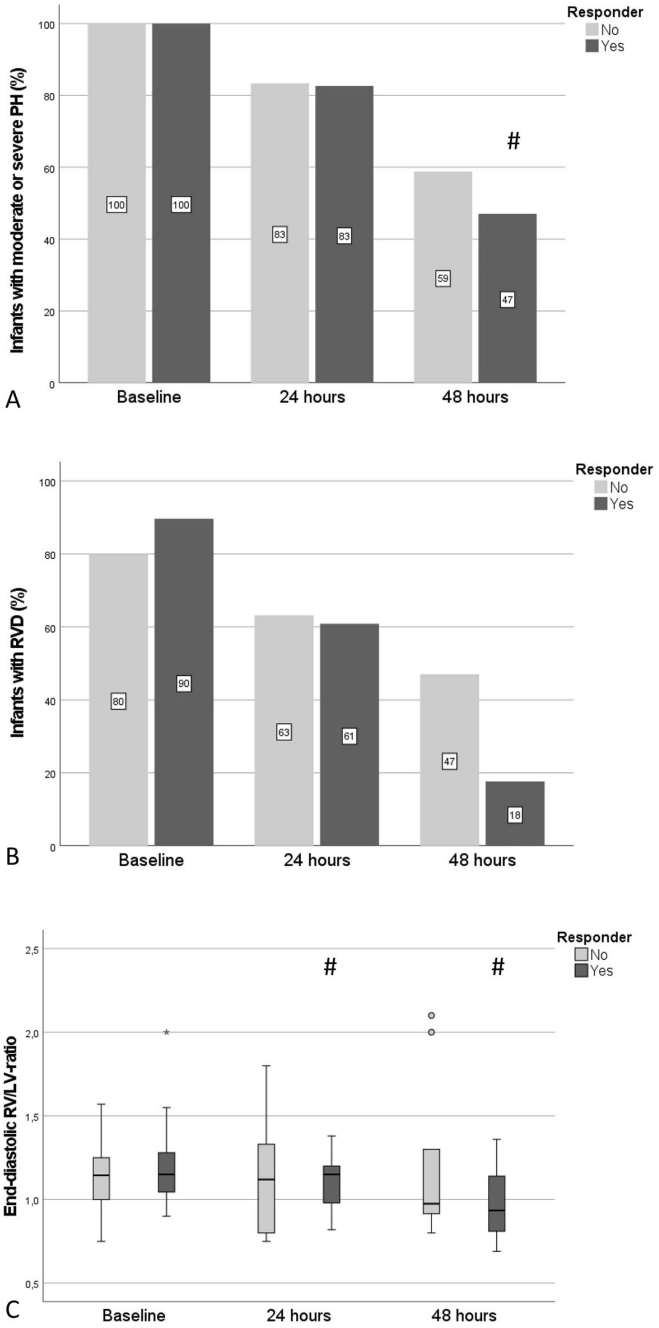

Figure 4. (**A**) The severity of PH (moderate or severe) during the sildenafil treatment was assessed according to the echocardiographic data for the timepoints baseline (prior to treatment), 24 and 48 h (after treatment start). (**B**) The incidence of the RVD (present/ not present) during the sildenafil treatment was assessed according to the echocardiographic data for the timepoints baseline (prior to treatment), 24 and 48 h (after treatment start). (**C**) The RV/LV ratio during the sildenafil treatment was calculated according to the echocardiographic data for the timepoints baseline (prior to start), 24 and 48 h (after treatment start). The rhombus illustrates p-levels < 0.05, when comparing the value with the respective baseline value in the subgroup.

Non-Responder in our cohort suffered significantly more often from lung-hypoplasia, and LUTO or congenital-renal-disorder. Infants with LUTO or congenital-renal-disorder mainly suffer from lung-hypoplasia due to oligo- or anhydramnion. Preterm infants suffering from lung-hypoplasia seem to be prone to respond less to sildenafil, which potentially can be explained by a higher degree of structural lung abnormality (vasculopathy: excessive muscularization, intima thickening, rarefaction of pulmonary arteries and vessels) and higher grade of oxygen impairment at baseline. As sildenafil is a second-line PH-therapy, the use of sildenafil in these infants needs to be evaluated carefully. The term "lung hypoplasia" is not standardized and clear definitions are missing in the current era. Therefore, this diagnosis is to a certain degree subjective.

Our results illustrate, that intravenous sildenafil treatment is associated with a significant and rapid reduction of the PH severity. This is in line with previous studies on infants with PPHN and neonates suffering from PH due to congenital lung disease or BPD-PH[15,17,19,30,31]. According to our results, the RVD improves significantly during the continuous sildenafil infusion. Several studies analyzed the relationship between sildenafil treatment and right ventricular diastolic and systolic function, as shown by magnet resonance tomography scans, in right heart catheterization and in animal models for right ventricular dysfunction[34–38]. In summary, sildenafil has afterload-reducing effects with improvement of RV unloading, leads to an improvement of diastolic RVD, improves RV myocardial remodeling due to upregulation of gene-markers for hypertrophy and inflammation, and there are conflicting results regarding the improvement of the RV systolic function. During the sildenafil treatment the RV/LV ratio decreases significantly, potentially illustrating the effect of RV unloading and higher preload of the left-ventricle in preterm infants. The incidence of LVD initially decreased from baseline to 24 h in non-Responder, followed by a significant increase from 24 to 48 h after start of sildenafil treatment in non-Responder. Sildenafil possibly can lead to a deterioration of a preexisting LV dysfunction, due to a aggravation of the LV dysfunction caused by a higher LV preload and filling pressures, which is in line with previous findings of sildenafil treatment in infants with a congenital diaphragmatic hernia[19]. On the other hand, results from adult RCT trials revealed beneficial effects of sildenafil on LV function[39].

Limitations. Our data provide important information in these patient population and we hypothesize that continuous sildenafil treatment in preterm infants with early-PH seems to be well tolerated. However, this need to be interpreted carefully, as the frequent use of concomitant vasoactive treatment could have mitigated an arterial hypotension as drug related adverse event during the sildenafil treatment. During the treatment period in 9 infants a severe arterial hypotension (5 mmHg < GA for > 60 min) was identified in the documentation system, but these episodes were not related to the sildenafil treatment, as the episodes occurred unrelated to the start of the bolus or continuous sildenafil infusion. The present study was conducted retrospectively and not designed to evaluate the safety profile of sildenafil. This needs to be considered when planning future prospective randomized-controlled trials.

A comparator cohort is missing and as mentioned before, prospective randomized trials are warranted. Therefore, it is important to get knowledge from retrospective studies as provided by our results. Furthermore, the interpretation of the echocardiographic data is at risk for bias because echocardiographic assessment is based to some extent on a qualitative grading. Finally, sildenafil treatment was started as second-line therapy in critically ill infants with a high-degree of preexisting comorbidities. This can have biased the incidence of the response rate of infants to sildenafil treatment.

Conclusion

Continuous intravenous sildenafil treatment is associated with a significant improvement of the oxygenation impairment in preterm infants, including ELGAN and VLBW infants. Additionally, continuous intravenous sildenafil treatment is associated with an improvement of PH, RVD and RV/LV ratio in the echocardiographic assessment in this population. Nevertheless, a substantial proportion (43%) of preterm infants do not respond to sildenafil, especially infants with prenatal diagnosed lung-hypoplasia. These infants are at high risk for in-hospital mortality.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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4. Diskussion

Die CD und PH bei kritisch kranken Früh- und Neugeborenen verschlechtern das Outcome in diesen Patientengruppen und prädisponieren für weitere Komplikationen und Organstörungen, welche neben der primären kardio-pulmonalen Funktionseinschränkung auftreten. Bekannte Komplikationen, welche mit der CD und der PH in Zusammenhang gebracht werden, sind ein akutes Nierenversagen, ein respiratorisches Versagen mit Notwendigkeit der maschinellen Beatmung, eine BPD, ein verlängerter Intensivaufenthalt und letztlich auch eine deutlich erhöhte Mortalität (Rossano et al., 2012; Lasa et al., 2020; Varghese et al., 2021). Das Auftreten einer frühen PH (<28 Lebenstag) bei Frühgeborenen ist eindeutig mit einer signifikant erhöhten innerklinischen Mortalität und dem Auftreten einer BPD assoziiert (Berenz et al., 2017). Bei Frühgeborenen erhöht sich zudem das Risiko für eine nekrotisierende Enterokolitis, eine Retinopathie (Rethinopathia praematurorum, ROP), und auch für einen zerebralen Perfusionsschaden mit nachfolgender neurologischer Einschränkung. Diese Assoziation wurde vor allem für Neugeborene mit einem angeborenen Herzfehler und einer CD beschrieben (Norman et al., 2020). In der prospektiven Multicenter-Studie von Lasa et al. wird das Auftreten der CD bzw. akuten Herzinsuffizienz im neonatalen Alter als unabhängiger Risikofaktor für eine erhöhte Mortalität auf der Intensivstation beschrieben. Zudem wird eine parallel bestehende PH als zusätzlicher Risikofaktor für eine erhöhte Mortalität definiert (Lasa et al., 2020). Ein weiterer Punkt, welchen man in der Diskussion der oben genannten Ergebnisse nicht außer Acht lassen kann, ist, dass allein die Frühgeburtlichkeit schon für kardiovaskuläre Probleme im adulten Alter wie eine arterielle Hypertension und eine Herzinsuffizienz prädisponiert (Bassareo et al., 2017). Daher ist es umso wichtiger den Fokus auf eine rationale und innovative Diagnostik sowie Therapie der frühen neonatalen CD und PH zu legen, da sowohl schwere Kurzzeit- als auch Langzeit-Schädigungen für diese Patienten drohen. Daher kommt dem Assessment der CD und PH durch die neonatale Echokardiographie sowie durch Blut-Plasma Biomarker und der Pharmakotherapie eine sehr wichtige Rolle zu. Dieser Rolle widmeten sich die hier vorliegenden Studien. Der neonatalen Echokardiographie und der echokardiographischen Diagnostik der CD sowie PH haben sich zwei Übersichtsartikel von führenden Experten gewidmet (Boode et al., 2018; Levy et al., 2018).

Eine mögliche weitere der oben aufgezählten Komplikationen einer neonatalen CD oder PH ist die fehlende Adaptation auf hämodynamische Umstellungen, welche zum Beispiel unter dem Wechsel von der maschinellen Beatmung auf die Spontanatmung im Rahmen der Extubation induziert werden (Zapata et al., 2011). Um diese vulnerable Phase bei Neugeborenen mit einer CD und PH besser identifizieren zu können, widmeten wir uns der Diagnostik des Biomarker NT-proBNP, bestimmt vor und nach der Extubation der Neugeborenen (Schroeder et al., 2023b). Bereits in der Studie von Zhang et al. an 88 Frühgeborenen mit einem Atemnotsyndrom (ANS) wurde NT-proBNP als Biomarker für ein „Weaning"-Versagen vor der geplanten Extubation identifiziert (Zhang et al., 2014). In dieser Arbeit wurde ein „cut-off" Wert des NT-proBNP von >18.500 pg/ml als hoch prädiktiv für ein Extubations-Versagen für dieses Kollektiv kalkuliert. In der beschriebenen Arbeit wurden Früh- und Neugeborene mit einer CD und PH nicht evaluiert und somit lieferte unsere Arbeit wertvolle Informationen zu diesem vulnerablen Kollektiv. Aus einer Metaanalyse von Deschamps et al. wurden BNP und NT-proBNP als Biomarker evaluiert für die Prädiktion eines Extubations-Versagens (Deschamps et al., 2020). Die Autoren schlussfolgerten, dass zu pädiatrischen Patienten keine Aussagen getroffen werden könnten, auf Grund der unzureichenden Datenlage. Daher sind Studien gerade aus dem neonatalen und pädiatrischen Bereich notwendig, um diese Wissenslücke zu minimieren. Ein Problem in der Interpretation der NT-proBNP Werte ist die Abhängigkeit der Werte vom Alter der Patienten und dies wird daher in pädiatrischen Populationen kritisch diskutiert (Cantinotti et al., 2015). Um dieses Problem zu umgehen, wurde von Palm et al. die Z_{log}-Transformation für NT-proBNP beschrieben, damit die Werte alters-unabhängig interpretiert werden können (Palm et al., 2020). Die Z_{log}-Transformation für NT-proBNP als Biomarker führt aus unserer Sicht zu einer besseren Interpretation der Ergebnisse und wurde für Neugeborene mit einer CD und/ oder PH das erste Mal beschrieben (Schroeder et al., 2023b). Neben dem Biomarker NT-proBNP wurden bereits weitere Biomarker für die Diagnostik einer kardialen Belastung und PH validiert. Der Tumormarker CA125 (Carbohydrat Antigen 125) wurde in einer Arbeit unserer Arbeitsgruppe als valider und neuer Biomarker für Neugeborene mit einer CDH beschrieben und korrelierte signifikant mit der CD und dem PH-Schweregrad (Schroeder et al., 2023e). Weitere neue validierte Biomarker für die CD in pädiatrischen Populationen sind das MR („Midregional") pro-atriales natriuretisches Peptid (MR-proANP) oder die lösliche Form des Interleukin-1 Rezeptor

(s-ST2) (Hauser et al., 2016). Für die Diagnostik bei Frühgeborenen mit einer PH und der Vorhersage für eine BPD eignet sich der Parameter Cyfra 21-1 (lösliches Fragment des Cytokeratins 19) als neuer Biomarker (Panahabadi et al., 2021). Der Biomarker sRAGE („soluble receptor for advanced glycation end products“) zeigte sich signifikant mit dem PH-Schweregrad bei Neugeborenen mit einer CDH assoziiert (Kipfmueller et al., 2019).

Neben den innovativen Diagnose-Tools wie der neonatalen Echokardiographie und Plasma-Biomarkern ist die Pharmakotherapie ein essenzieller Baustein der intensivmedizinischen Therapie. Der Calciumsensitizer Levosimendan wurde in großen prospektiven Multicenter-Studien bei erwachsenen Patienten seit den 2000er Jahren analysiert und sowohl positiv als auch kritisch diskutiert (Follath et al., 2002; Landoni et al., 2017; Cholley et al., 2019). Ebenso zeigt sich eine umfangreiche Datenlage zu pädiatrischen Populationen, vor allem mit Studien zu Neugeborenen und Kindern mit angeborenen Herzfehlern vor und nach einem herzchirurgischen Eingriffen (Lechner et al., 2012; Hummel et al., 2017; Silvetti et al., 2022). Die pharmakologischen Effekte, welche Levosimendan zu einer vielversprechenden Therapie-Option bei CD und auch PH machen, basieren auf folgenden Mechanismen: Levosimendan bindet an den Calcium-gesättigten N-Terminus des myokardialen Troponins C und erhöht somit die kardiale Kontraktilität durch eine erhöhte Sensitivität von Calcium mit dem Troponin-Komplex. Die intrazelluläre Calcium-Konzentration bleibt dabei unverändert. Der lusitrope Effekt von Levosimendan wird durch das Öffnen von ATP-sensitiven Kaliumkanälen vermittelt, wodurch es zu einer Vasodilatation kommt. Levosimendan beeinflusst wahrscheinlich über diesen Mechanismus auch positiv die periphere Mikrozirkulation. Ein möglicher kardio-protektiver Effekt wird durch das Öffnen von mitochondrialen ATP-sensitiven Kaliumkanälen erreicht, was zu einer Kardioprotektion führt durch eine mögliche Reduktion von Komplikationen wie oxidativem Stress, Apoptose der Zellen oder Re-Perfusionsschäden (Hansen et al., 2018). Levosimendan scheint den Sauerstoffverbrauch der Myokardiozyten nicht zu erhöhen, scheint weniger Arrhythmien auszulösen gegenüber anderen Vasoaktiva und scheint zudem positiv inotrop über eine partielle PDE-III Hemmung zu wirken (Ukkonen et al., 2000; Ørstavik et al., 2015). Über den Metaboliten OR-1896 entfaltet Levosimendan eine Langzeitwirkung, mit einer Halbwertszeit von 70-80 Stunden. Diese Mechanismen führen in Zusammenschau zu dem inotropen, lusitropen und dem vasodilatatorischen Effekt von Levosimendan. Laut Studienlage hat Levosimendan

positive Effekte auf die rechts- und linksventrikuläre Funktion, und ist signifikant mit der Reduzierung der PH assoziiert (Kleber et al., 2009; Levin et al., 2012; Ebade et al., 2013; Hansen et al., 2018). Durch die vielversprechenden Daten und neuen Therapieeffekte wurde Levosimendan seit 2018 bei Neugeborenen mit schwerer CD und PH in unserer Klinik für Neonatologie und Pädiatrische Intensivmedizin am UKB eingesetzt. Somit bot sich die Möglichkeit auf retrospektive Daten zurückzugreifen, um die Levosimendan-Therapie in dieser noch unbeschriebenen Kohorte von Früh- und Neugeborenen ohne angeborene Herzfehler zu evaluieren. Unsere Ergebnisse decken sich mit der aktuellen Datenlage und wir konnten ebenso in den beiden durchgeführten Studien eine signifikante Verbesserung der CD und des PH-Schweregrades unter der Levosimendan-Therapie beobachten (siehe obige Originalpublikationen). In der zweiten Studie wurde die Levosimendan-Therapie bei Neugeborenen mit einer CDH zum ersten Mal evaluiert. Andere Studien oder Studienprotokolle zu Neugeborenen mit einer CDH beschäftigten sich mit der Evaluation von neueren vasoaktiven Medikamenten wie dem Inodilator Milrinon, welchem ähnliche Effekte wie Levosimendan zugesprochen werden (Patel, 2012; Lakshminrusimha et al., 2017; Mears et al., 2020). Da die CD und PH zwei der Haupt-Risikofaktoren für die Morbidität und Mortalität bei Neugeborenen mit einer CDH sind, muss das Augenmerk auf der Evaluation von neuen Behandlungs-Optionen liegen (Patel et al., 2019; Gupta and Harting, 2020a). Der Therapie-Effekt von Levosimendan in Frühgeborenen mit einer CD und PH wurde in einer weiteren Studie durch unsere Arbeitsgruppe analysiert (siehe obige Originalpublikation). Ähnlich zu dem Kollektiv der Neugeborenen mit einer CDH zeigten sich gleichsinnige Therapie-Effekte und eine signifikante Verbesserung der CD und PH. Lechner et al. beschrieben bereits im Jahr 2007 die erfolgreiche Verwendung des damals noch neuen Wirkstoffes bei einem Frühgeborenen mit einem angeborenen Herzfehler und Notwendigkeit einer herzchirurgischen Operation (Lechner et al., 2007). Viele pädiatrische Studien berichten ein sicheres Nebenwirkungs- und Risikoprofil von Levosimendan und auch in unserer retrospektiven Evaluation zeigten sich keine relevanten Levosimendan-assoziierten Nebenwirkungen. Somit scheint Levosimendan eine Therapie-Alternative gerade auch für Frühgeborene zu sein. Risiko Frühgeborene wie Zwillinge mit einem FFTS oder mit einem schweren IUGR und einer CD und/ oder PH könnten von einer Levosimendan-Therapie profitieren und Levosimendan sollte als Therapie-Alternative zu klassischen Medikamenten wie Dobutamin oder Dopamin diskutiert werden. Trotz

der vielversprechenden Ergebnisse müssen die Limitationen der beiden Studien diskutiert werden. Die Ergebnisse basieren auf retrospektiven Datenerhebungen und somit besteht ein Risiko für eine mögliche Datenverzerrung (Bias) durch Störfaktoren, welche retrospektiv nicht vollständig eliminiert werden können.

Ein anderer Therapieansatz, welcher mittels kardialer Stimulantien wie vasoaktiven Substanzen erreicht wird, ist die Herzfrequenzkontrolle zur Senkung einer überschießenden Sinustachykardie oder Tachyarrhythmie. Es ist bekannt, dass eine Sinustachykardie eine diastolische und systolische ventrikuläre Funktionsstörung noch verschlechtern kann und die ventrikuläre Interaktion zwischen RV und LV stört (Custodis et al., 2013; Reil et al., 2013; Shen et al., 2019; Hohneck et al., 2021). Landiololhydrochlorid ist ein ultra-schnell wirkender und hoch-selektiver ß1-Rezeptor Blocker (Ratio ß1/ß2: 255) mit einem selektiven negativ chronotropen Effekt und kaum negativ inotroper Wirkung. Landiolol entfaltet sein Wirkmaximum nach ca. 5 Minuten und besitzt eine Halbwertszeit von ca. 4 Minuten (Murakami et al., 2005). Somit können Therapieeffekte schnell erreicht werden. Eine Alternative zu ß1-Blockern sind die sogenannten I_f-Kanal Blocker wie der Wirkstoff Ivabradin, welcher in pädiatrischen Studien evaluiert wurde (Selby et al., 2011). Bezüglich der Landiolol-Therapie stellt unsere Studie die erste Evaluation im neonatalen Bereich bei Patienten mit einer CD und PH dar, da bis dato nur Studien zu pädiatrischen Patienten mit Tachyarrhythmien nach herzchirurgischen Eingriffen durchgeführt wurden (Tokunaga et al., 2013; Yoneyama et al., 2018b). In unserer Studie konnten wir zeigen, dass mittels Landiolol eine rasche Herzfrequenzkontrolle innerhalb von 2 Stunden erreicht werden konnte und die Therapie bei Früh- und Neugeborenen sicher anzuwenden ist. Die Herzfrequenzkontrolle ist signifikant mit einer Verbesserung der CD und PH assoziiert. Bei einer schweren und langanhaltenden CD sowie PH sollte daher über eine Herzfrequenzkontrolle frühzeitig nachgedacht werden. Durch eine Verlangsamung der Herzfrequenz kann die diastolische Füllung des Ventrikels verbessert werden, der myokardiale Sauerstoffverbrauch wird reduziert und die ventrikuläre Interaktion wird verbessert. Es ist Gegenstand einer fachlichen Diskussion, ob die gleichzeitige Verwendung von vasoaktiven Substanzen und ß-Blockern sinnvoll ist, durch eine ß-Rezeptor Blockade auf der einen Seite und eine ß-Rezeptor Stimulation durch Wirkstoffe wie Dobutamin auf der anderen Seite. Daher scheint die parallele Verwendung von vasoaktiven Wirkstoffen mit einem alternativen Wirkmechanismus (z.B. Milrinon als PDE-III Hemmer und Levosimendan als Calciumsensitizer)

außerhalb der ß-Rezeptor Stimulation sinnvoll zu sein. Jedoch wurde von Sakai et al. auch die erfolgreiche Verwendung von Vasoaktiva wie Dobutamin gleichzeitig zu einer ß-Blockade mit Landiolol beschrieben (Sakai et al., 2019). Wir konnten den gleichen Effekt in unserer neonatalen Kohorte beobachten und halten eine parallele Therapie für sinnvoll, auch wenn über eine bevorzugte Verwendung von Kombinationen wie Levosimendan + Landiolol oder Milrinon + Landiolol nachgedacht werden sollte (Kobayashi et al., 2019; Dabrowski et al., 2020).

Das medikamentöse Behandlungskonzept der neonatalen PH basiert auf verschiedenen Wirkstoffklassen. Als „first-line“ Therapie gilt die Therapie mit O_2 und iNO, welches in vielen Studien im pädiatrischen Bereich evaluiert wurde. Die O_2-Therapie führt zu einer Vasodilatation im pulmonalen Gefäßbett durch eine direkte Aktivierung von Calcium-abhängigen Kalium-Kanälen und eine dadurch erhöhte NO-Produktion (Cornfield et al., 1996). Jedoch führt anderseits eine Hyperoxie mit einem supratherapeutischen paO_2 durch eine Bildung von freien Sauerstoffradikalen zu einer pulmonalen Vasokonstriktion und triggert so eine PH (Rawat et al., 2022). Inhalatives NO ist das einzige von der nordamerikanischen Arzneimittelbehörde FDA („Food and Drug Administration“) sowie der europäischen Arzneimittelbehörde EMA („European Medicine Agency“) zugelassene Medikament für die Behandlung der PH ab einem Gestationsalter von ≥34 SSW. Die weiteren PH-Medikamente können anhand ihres Wirkmechanismus eingeteilt werden in a) Wirkstoffe, welche ihre Wirkung cGMP-vermittelt entfalten, b) Wirkstoffe, welche den cAMP-Stoffwechselweg nutzen und c) Wirkstoffe, welche eine Endothelin-Blockade auslösen (Lakshminrusimha et al., 2016). Zu ersterer Gruppe zählen der Wirkstoff Sildenafil und auch iNO. Zur zweiten Gruppe zählen unter anderem die Prostaglandin-Wirkstoffe, wie das klassische Prostazyklin I_2 (PGI_2), die Prostaglandin-Analoga (Epoprostenol, Treprostinil, Iloprost oder Beraprost) und Prostglandin E_2 (PGE2) (Lakshminrusimha et al., 2016). Zu den Endothelin-Rezeptor-Antagonisten zählen Wirkstoffe wie Bosentan, Macitentan oder Ambrisentan. Der Wirkstoff Sildenafil ist von der EMA ab dem Alter von 1 Jahr zugelassen und die Anwendung bei Früh- und Neugeborenen findet als „off-label“ Verwendung statt außerhalb der regulären Anwendung. Jedoch wird in der Stellungnahme der Deutschen Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler (DGPK) auf die Notwendigkeit des off-label Einsatzes von PH-Medikamenten bei pädiatrischen Patienten hingewiesen (Hansmann et al., 2020). Die erfolgreiche Wirkung von Sildenafil wurde sowohl im Tiermodel als auch bei

Neugeborenen bereits beschrieben (Shekerdemian et al., 2002; Baquero et al., 2006; Steinhorn et al., 2009; Luong et al., 2011). Zwei randomisierte Studien widmeten sich sowohl der intravenösen als oder auch der oralen Applikation von Sildenafil bei Neugeborenen mit einer GA ≥34 SSW (Pierce et al., 2021; Chetan et al., 2022). Zudem wurde die signifikante Reduzierung der PH auch bei speziellen Krankheitsbildern wie der CDH und bei der BPD-assoziierten PH bereits beschrieben (Wardle et al., 2015; Kipfmueller et al., 2018). Sildenafil wurde in der von uns beschriebenen Studie in einer Konzentration von 1.6mg/kg/d appliziert, welche zurückzuführen ist auf die Studie von Steinhorn et al., in welcher unter dieser Dosis die besten therapeutischen Spiegel erreicht werden konnten (Steinhorn et al., 2009). Unter dieser Dosis zeigte sich in unserer retrospektiven Kohorten-Studie eine positive Response auf Sildenafil in 60% der Fälle. Die Frühgeborenen mit einer Response auf Sildenafil zeigten eine signifikant niedrigere Mortalitätsrate als Nicht-Responder auf Sildenafil. Wie bereits in multiplen Studien beschrieben, zeigten sich auch in unserer Kohorte von Frühgeborenen eine signifikante Reduktion des PH-Schweregrades und der RVD. In der Detail-Analyse des Frühgeborenen-Kollektivs konnten wir in unserer Studie zeigen, dass vor allem Frühgeborene mit einem länger zurückliegenden Blasensprung in der Fetalzeit (PPROM, „preterm premature rupture of membranes“), Frühgeborene mit einer vorbeschriebenen Nierenfunktionsstörung in der Fetalzeit wie eine LUTO („lower urinary tract obstruction“) und Frühgeborene mit einer Lungenhypoplasie signifikant seltener eine Response auf die Sildenafil-Therapie zeigten. Bei dieser Subgruppe an Frühgeborenen sollte die Sildenafil-Therapie im Einzelfall kritisch diskutiert werden. Unsere Studie fügt trotz des retrospektiven Designs wichtige Daten zur intravenösen Sildenafil-Therapie der früh auftretenden PH bei Frühgeborenen zur aktuellen Studienlage hinzu. Gerade die Daten zu ELGANs und VLBW-Frühgeborenen sind aus unserer Sicht von besonderer Wichtigkeit.

5. Zusammenfassung

Die neonatale CD und PH bei Früh- und Neugeborenen ist mit relevanten Komplikationen assoziiert, wie einem längeren Intensivaufenthalt, einer respiratorischen Insuffizienz und Notwendigkeit der maschinellen Beatmung, einem akuten Nierenversagen sowie einer erhöhten Mortalität. Daher kommt der frühzeitigen Diagnose sowie einer innovativen multimodalen Pharmakotherapie eine wichtige Rolle zu. In den letzten zwei Dekaden wurden viele Studien zu neuen kardialen Biomarkern und Studien zu neuen medikamentösen Wirkstoffen wie Inodilatoren, PDE-Hemmern und ultra-schnell wirksamen ß-Blockern zur CD- und PH-Therapie durchgeführt. Jedoch fehlten weiterhin Daten zu sehr vulnerablen Patientengruppen wie Früh- und Neugeborene. Diesem Kollektiv widmeten sich die fünf vorliegenden und zusammengefassten Originalpublikationen. Um der Identifikation von Früh- und Neugeborenen mit einer CD und PH in der Vorgeschichte und dem Risiko für ein Extubations-Versagen näher zu kommen, untersuchten wir den Biomarker NT-proBNP und das Z_{log}-transfomierte NT-proBNP in einer retrospektiven Kohorte von 43 Früh- und Neugeborenen. Wir konnten NT-proBNP und das Z_{log}-transformierte NT-proBNP als mögliche neue Biomarker für ein Extubations-Versagen bei diesen Patienten identifizieren und beide Parameter korrelierten signifikant mit der CD und dem PH-Schweregrad. Als Schlussfolgerung der Studienergebnisse sollte NT-proBNP und das Z_{log}-transformierte NT-proBNP in die klinische Routine-Diagnostik mit einfließen, um die Extubations-Bereitschaft sowie den Extubations-Erfolg vor und nach Beendigung der maschinellen Beatmung kritisch zu evaluieren.

Die weiteren vorliegenden Originalarbeiten widmeten sich der Evaluation neuerer medikamentösen Wirkstoffe zur Therapie der neonatalen CD und PH. Dem Wirkstoff Levosimendan widmeten sich zwei der vorliegenden Arbeiten. In einer Kohorten-Studie an 24 Neugeborenen mit einer CDH konnte erstmalig der erfolgreiche Einsatz von Levosimendan zur Therapie einer schweren ventrikulären Dysfunktion (RVD, LVD oder BVD) sowie einer PH beschrieben werden. Die multiplen pharmakologischen Ansatzpunkte des Wirkstoffes machen Levosimendan zu einer vielversprechenden Therapie-Alternative bei Katecholamin-refraktärer CD und persistierender hochgradiger PH. Ähnliche Ergebnisse lieferte die Kohorten-Studie, welche die Levosimendan-Wirkung in 105 Frühgeborenen retrospektiv beleuchtete. Es konnte eine signifikante Verbesserung der RVD und LVD sowie eine Verbesserung des PH-

Schweregrades unter der Therapie beobachtet werden. Die Levosimendan-Therapie scheint in VLBW-Frühgeborenen sowie Frühgeborenen mit einem Geburtsgewicht >1500g (non-VLBW) sicher anwendbar zu sein. Die selektive Herzfrequenzkontrolle mit ultra-schnell wirksamen Wirkstoffen wie Ivabradin oder Landiolol zählt zu den neuen Therapieansätzen in der Neonatologie und pädiatrischen Intensivmedizin. Studiendaten zu Früh- und Neugeborenen ohne angeborene Herzfehler waren bis dato nicht vorhanden. Somit konnte unsere Studie zum Einsatz des ultra-schnell wirksamen ß-Blocker Landiolol in einer retrospektiven Kohorte von 62 Neonaten eine wichtige Wissenslücke schließen. Der Einsatz von Landiolol führte zu einer raschen Herzfrequenzkontrolle und war mit einer signifikanten Verbesserung der CD sowie des PH-Schweregrades verbunden. Zudem scheint der Einsatz von Landiolol bei diesen Patienten sicher zu sein. Bei persistierender Sinustachykardie sollte eine selektive Herzfrequenzkontrolle aus unserer Sicht in Betracht gezogen werden. Die letzte Studie widmete sich dem PDE-V Hemmer Sildenafil und dessen Einsatz im Rahmen einer früh diagnostizierten PH (<28 Lebenstage) bei Frühgeborenen. Der Einsatz von intravenös verabreichtem Sildenafil in einer Dosis von 1.6mg/kg/d war mit einer signifikanten Reduktion des PH-Schweregrades sowie der RVD assoziiert und ca. 60% der Kohorte (n=58 Frühgeborene) zeigte eine positive Response auf die Therapie. Zwischen VBLW- und non-VLBW-Frühgeborenen zeigte sich kein Unterschied in der Response-Rate. Als wichtiges Ergebnis der Detail-Analyse der Kohorte zeigte sich, dass bestimmte pränatale Erkrankungen wie ein PPROM, eine Lungenhypoplasie sowie eine LUTO das Risiko für eine fehlende Response auf Sildenafil erhöhen. Diese Patienten scheinen nicht von der Therapie zu profitieren. Allen hier vorliegenden Studien liegt ein retrospektives Studien-Design zu Grunde und daher sollten unsere Ergebnisse in größeren prospektiven Studien-Kollektiven bestätigt werden.

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