Supplementary material

Table 1: Levosimendan in experimental PH and associated right heart failure (RHF).

	Model of PH	Dosing	Study design	Findings
Hansen et al. 2017[1]	Rats, PTB	3 mg/kg/day p.o.	7 weeks prevention	Improved RV function, no increase in RV myocardial oxygen consumption, improved RV myocardial external efficiency.
Hansen et al. 2016[2]	Rats, Sugen5416+ hypoxia	3 mg/kg/day p.o.	10 weeks prevention and 6 weeks reversal treatment in established RHF	Improved RV function, reduced RV afterload, and improved right ventricular-pulmonary arterial coupling. Reduced pulmonary arterial occlusive lesions, reduced BNP and ANP, increased capillary density, reduced cardiomyocyte size.
Hillgaard et al. 2016[3]	Rats, PTB	3 mg/kg/day p.o.	7 weeks prevention and 4 weeks reversal treatment in RHF	Improved RV function and contractility.
Vildbrad et al. 2014[4]	Rats, PTB and MCT	12 µg/kg for 10 min, 60 µg/kg for 10 min	Acute treatment in established RHF	Improved RV contractility and RV lusitropy in both models. Improved RV function in the MCT model but not in the PTB model. Reduced mean systemic

				blood pressure.
Wiklund et al. 2012[5]	Pigs, hypoxia	6 μg/kg for 10 min, 0.1 μg/kg for 10 min, 0.2 μg/kg for 70 min	Acute treatment in acute PH	Improved RV function. Reduced mPAP and PVR.
Reverman et al. 2011[6]	Rats, MCT	3 mg/kg/day p.o.	3 weeks reversal treatment	Reduced pulmonary vascular medial wall thickness and proliferation of pulmonary arterial smooth muscle cells. Reduced RV hypertrophy.
Schwarte et al. 2011[7]	Dogs, hypoxia	20.0 μg/kg for 15 min, 0.25 μg/kg for the remaining period	Acute treatment in acute PH	Improved RV function and contractility. Decreased systemic vascular resistance.
Chew et al. 2011[8]	Pigs, endotoxin-induced PH	0.2 μg/kg/min for 6 hours	Acute treatment in acute PH	No improvement in cardiac, renal or liver function. Increased pulmonary capillary wedge pressure. Hyperlactataemia, acidosis and increases in plasma pro-inflammatory cytokines.
Boost et al. 2008[9]	Rats, ventilator-induced lung injury	Inhalation of 240 μg, or inhalation of 24 μg, or 24 μg/kg i.v. for 10 min	Acute treatment before lung injury	Improved survival and reduced release of inflammatory mediators.
Missant et	Pigs, PA	120 μg/kg/min for 10 min,	Acute treatment in acute PH	Improved RV contractility, reduced RV afterload,

al. 2007[10]	constriction +ischemia/reperfusion	60 μg/kg/min for 45 min		and restored right ventricular arterial coupling. Increased coronary blood flow.
Kerbaul et al. 2007[11]	Piglets, repeated acute pulmonary embolisms	20 μg/kg for 10 min, 0.2 μg/kg/min for 20 min	Acute treatment in acute PH	Improved RV contractility, reduced RV afterload, and restored right ventricular arterial coupling.
Kerbaul et al. 2006[12]	Dogs, transient PA constriction	12 μg/kg for 10 min, 0.1 μg/kg/min for 20 min, 0.1 μg/kg/min for 30 min	Acute treatment in acute PH	Improved RV contractility, reduced RV afterload, and restored right ventricular arterial coupling.
Leather et al. 2003[13]	Pigs, controls	40 μg/kg/hour for 10 min, 20 μg/kg/hour for 30 min, 80 μg/kg/hour for 10 min, 40 μg/kg/hour for 30 min, 160 μg/kg/hour for 10 min, 80 μg/kg/hour for 30 min	Acute treatment in healthy pigs	Improved RV function and contractility. No change in right ventricular arterial coupling. Improved RV lusitropy. No change in right coronary artery flow and RV oxygen consumption. RV mechanical efficiency decreased at the highest dose.
De Witt et al. 2002[14]	Cats, thromboxane-induced PAH	0.3, 1, or 3 μg injection into the perfused lobar artery	Acute treatment in acute PH	Reduced pulmonary arterial perfusion pressure.

ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; MCT, monocrotaline; mPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PTB, pulmonary trunk banding; PVR, pulmonary vascular resistance; RHF, right heart failure; RV, right ventricular.

Table 2: Levosimendan in PAH

Reference	Study design	n	Population	Comparator	Dose	Follow up	Findings
Jiang et al. 2017[15]	Single arm, prospective	45	PAH patients with severe acute RHF, WHO-FC III-IV	None	0.05-0.1μg/kg/min up to 12.5 mg	7 days	WHO-FC improved by one class, improvement in Borg dyspnea scores, 6-min walk test and NT-proBNP.
Martyniuk et al. 2012[16]	Prospective, single arm	9	iPAH and severe RHF, NYHA class III and IV	None	24-hour intravenous levosimendan infusion	12 weeks	24 hour: Reduced PVR and PAP. Increased exercise tolerance. Reduced NT-proBNP. 12 weeks: Preserved improved functional status. No changes in the achieved hemodynamic parameters. No clinically relevant adverse reactions.
Cavusoglu et al. 2009[17]	Case report	2	Acutely decompensated iPAH with negative	None	12 μg/kg in 10 min, 0.1μg/kg/min for 60 min, 0.2 μg/kg/min until discontinued		Increase in PAP.

			vasoreactive response				
Kleber et al. 2009[18]	RCT	28	PH patients, NYHA class III to IV	Placebo	Visit 1: 12 μg/kg in 10 min, 0.1 μg/kg/min for 50 min, 0.2 μg/kg/min for 23 hours. Visit 2-5: 0.2 μg/kg/min for 6 hours	12 weeks	Reduced PVR and PAP. Continued efficacy with repeated dosing. No development of tolerance.

CHD, congenital heart disease; iPAH, idiopathic pulmonary arterial hypertension; LHD, left heart disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO-FC, world health organization functional class.

Table 3: Levosimendan in PH caused by left heart failure

Reference	Study design	n	Population	Inclusion criteria	Comparator	Dose	Follow-up	Findings
Mishra et al. 2016[19]	RCT	40	Patients undergoing valve replacement with PH	LVEF <50%/60% and PAH (RVSP >50 mmHg, or mPAP >40 mmHg or sPAP exceeding 50% of systemic systolic pressure).	Milrinone	10 μg/kg in 10 min, 0.1 μg/kg/min for 24 hours	24 hours	Reduced mPAP and PVR index, and improved biventricular function to the same extent as milrinone. Levosimendan resulted in a greater increase in heart rate, decrease in systemic vascular resistance, and a greater need for norepinephrine.
Alibaz-Oner et al. 2013[20]	Single arm, prospective	30	NYHA III-IV, ischaemic LHF	LVEF <40%	Baseline	0.05 μg/kg/min for 48 hours	72 hours	Improved RV systolic function indicated by TDI derived parameters. No change in RV diastolic function. Reduced sPAP and BNP. Improved NYHA class.

Sponga et al. 2012[21]	Single arm, prospective	21	Patients admitted for LVAD with RV dysfunction and RV dilatation		Baseline	0.1 to 0.2 μg/kg/min for 48 hours	72 hours	Improved CI. Decreased PAP, PCWP, and central venous pressure.
Russ et al. 2009[22]	Single arm, prospective	25	LHF following acute myocardial infarction		Baseline	12 μg/kg/min for 10 min, 0.1 μg/kg/min for 50 min, 0.05-0.2 μg/kg/min for 23 hours.	48 hours	Improved RV and LV contractility. Decreased RV afterload.
Yilmaz et al. 2009[23]	RCT	40	NYHA III-IV, acute LHF	LVEF □35%. RV dysfunction with RV fractional area change □24%.	Dobutamine	0.1 μg/kg/min for 6 hours, 0.2 μg/kg/min for 18 hours	24 hours	Improved RV function and decreased sPAP to the same extent as dobutamine. TAPSE, 24-h urine output, and creatinine improved greater in patients with levosimendan

								compared to dobutamine.
Poelzl et al. 2008[24]	Single arm, prospective	18	Acute LHF	LVEF ≤30%, CI ≤2.5 l/min/m^2, RAP ≥10 mmHg, PCWP ≥15 mmHg	Baseline	6-12 μg/kg in 10 min, 0.075-0.2 μg/kg/min for 24 h	24 hours	Improved RV and LV contractility. No change in RV afterload. Decreased PCWP and systemic vascular resistance.
Duygu et al. 2008[25]	RCT	62	NYHA III-IV, acute LHF due to ischaemic cardiomyopathy	LVEF <40%	Dobutamine	6–12 μg/kg in 10 min, 0.1 μg/kg/min for 24 hours	24 hours	Improved RV systolic and diastolic function. Dobutamine did not improve RV function. Reduced sPAP to a greater extent than dobutamine.
Parissis et al. 2006[26]	RCT	54	NYHA III-IV, LV systolic dysfunction	LVEF <35%	Placebo	0.1-0.2 μg/kg/min for 24 h	48 hours	Improved Doppler echocardiographic markers of systolic and diastolic RV function. Decreased systolic PAP. Reduced BNP levels. Altered the balance between pro- and anti-inflammatory

								cytokines in favor of the anti-inflammatory activation.
Ukkonen et al. 2000[27]	Randomized double-blind cross-over	8	NYHA III-IV, congestive heart failure		Placebo	18 µg/kg in 10 min, 0.3 µg/kg/min		Improved LV function. Reduced coronary, pulmonary, and systemic vascular resistance. Increased mean myocardial blood flow. Neutral on biventricular oxygen consumption and LV efficiency. Improved RV mechanical efficiency.
Slawsky et al. 2000[28]	Double-blinded RCT	146	NYHA III-IV, LV systolic dysfunction	LVEF < 30% PCWP > 15 mmHg CI < 2.5 L/min/m^2	Placebo	6 µg/kg bolus initially and at hourly interval 0.1-0.4 µg/kg/min for 6 hours	6 hours	Improved LV function. Decreases PCWP, mRAP, and mPAP. Improved dyspnea and fatigue.

BNP, B-type natriuretic peptide; CI, cardiac index; LHF, left heart failure; LV, left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RCT, randomized clinical trial; RV, right ventricular; TDI, tissue doppler imaging.

Table 4: Levosimendan in PH and congenital heart disease (CHD)

Reference	Design	n	Population	Inclusion criteria	Comparator	Dose	Follow up	Findings
Rafiq et al. 2015[29]	Case study	1	End stage cardiac failure and PH due to CHD. 30 years old.		Baseline	Pulsed i.v. levosimendan; Initially 2 vials per month for 6 months, reduced to 1 vial per month for 4 months	Until death	Reduced hospital admissions, improved exercise tolerance, no longer home diuresis. Survival 1 year longer than expected.
Schwienbacher et al. 2013[30]	Case study	1	14-year-old boy with LV dysfunction and PH due to CHD, referred for heart-lung transplantation.		Baseline	0.1 μg/kg/min for 24 hours	7 weeks	Decreased pulmonary capillary wedge pressure, increased mPAP and transpulmonary pressure gradient, CI remained stable.
Ebade et al. 2013[31]	RCT	50	Children with cardiac septal defects	sPAP exceeding	Dobutamine	15 μg/kg in 10 min, 0.1–0.2 μg/kg/min for	20 hours	Both levosimendan and dobutamine reduced PAP but mPAP was lower with

			assigned for surgical correction. Mean age 17.5 months.	50% of systemic systolic pressure		24 hours		levosimendan compared with dobutamine. Both levosimendan and dobutamine improved CI but mean CI was higher with levosimendan compared with dobutamine.
Lechner et al. 2007[32]	Case report	1	Patient with TGA who underwent arterial switch operation. Postoperative LCOS and sPAP 50 mmHg, but no RV failure. Age 32 weeks.		Baseline	0.05 μg/kg/min increased to 0.1 μg/kg/min for 24 hours	24 hours	Improved LV function, reduced left atrial pressure, reduced sPAP, normalized serum lactate level, increased mixed venous saturation.
Turanlahti et al. 2004[33]	Single arm, prospecti ve, open label,	1 3	Children with CHD in the preoperative setting without LCOS. Age 3 months-7 years.		Baseline	12 μg/kg in 10 min	4 hours	Pharmacokinetic profile in children with CHD is similar to that in adults LHF. No significant changes in hemodynamics. There were no serious adverse events or unexpected adverse

	phase II							drug reactions during the study.
Luther et al. 2004[34]	Case report	1	9-months-old child with LV dysfunction and PH due to CHD.		Baseline	0.1 µg/kg/min for 24 hours	7 months	Improved LV function, increased CI, decreased pulmonary vascular resistance, and reduced the frequency and extent of the PH crises.
Braun et al. 2004[35]	Case report	1	2-month-old baby with CHD. Postoperative acute LHF, PH, and right-left-shunt.		Baseline	24 µg/kg bolus, 0.2 µg/kg/min for 48 hours	6 days	Improvement of LV function. Reduction of PVR, no right-left-shunt,

CHD, congenital heart disease; CI, cardiac index; LCOS, low cardiac output syndrome; LHF, left heart failure; LV, left ventricular; PH, pulmonary hypertension; PAP, pulmonary arterial pressure; TGA, transposition of the great arteries.

References:

1. Hansen MS, Andersen A, Tolbod L, Hansson N, Nielsen R, Vonk-Noordegraaf A, Nielsen-Kudsk, JE. Levosimendan improves cardiac function and myocardial efficiency in rats with right ventricular failure. *Pulmonary circulation*. Forthcoming 2017.

2. Hansen MS, Andersen A, Holmboe S, et al. Levosimendan prevents and reverts pressure-overload induced right ventricular failure. *European heart journal*. 2016; 37: 625.

3. Hillgaard TK, Andersen A, Andersen S, et al. Levosimendan Prevents Pressure-Overload-induced Right Ventricular Failure. *Journal of cardiovascular pharmacology*. 2016; 67: 275-82.

4. Vildbrad MD, Andersen A, Holmboe S, Ringgaard S, Nielsen JM and Nielsen-Kudsk JE. Acute effects of levosimendan in experimental models of right ventricular hypertrophy and failure. *Pulmonary circulation*. 2014; 4: 511-9.

5. Wiklund A, Kylhammar D and Radegran G. Levosimendan attenuates hypoxia-induced pulmonary hypertension in a porcine model. *Journal of cardiovascular pharmacology*. 2012; 59: 441-9.

6. Revermann M, Schloss M, Mieth A, et al. Levosimendan attenuates pulmonary vascular remodeling. *Intensive care medicine*. 2011; 37: 1368-77.

7. Schwarte LA, Schwartges I, Thomas K, Schober P and Picker O. The effects of levosimendan and glibenclamide on circulatory and metabolic variables in a canine model of acute hypoxia. *Intensive care medicine*. 2011; 37: 701-10.

8. Chew MS, Hawthorne WJ, Bendall J, et al. No beneficial effects of levosimendan in acute porcine endotoxaemia. *Acta anaesthesiologica Scandinavica*. 2011; 55: 851-61.

9. Boost KA, Hoegl S, Dolfen A, et al. Inhaled levosimendan reduces mortality and release of proinflammatory mediators in a rat model of experimental ventilator-induced lung injury. *Critical care medicine*. 2008; 36: 1873-9.

10. Missant C, Rex S, Segers P and Wouters PF. Levosimendan improves right ventriculovascular coupling in a porcine model of right ventricular dysfunction. *Critical care medicine*. 2007; 35: 707-15.

11. Kerbaul F, Gariboldi V, Giorgi R, et al. Effects of levosimendan on acute pulmonary embolism-induced right ventricular failure. *Critical care medicine*. 2007; 35: 1948-54.

12. Kerbaul F, Rondelet B, Demester JP, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Critical care medicine*. 2006; 34: 2814-9.

13. Leather HA, Ver Eycken K, Segers P, Herijgers P, Vandermeersch E and Wouters PF. Effects of levosimendan on right ventricular function and ventriculovascular coupling in open chest pigs. *Critical care medicine*. 2003; 31: 2339-43.

14. De Witt BJ, Ibrahim IN, Bayer E, et al. An analysis of responses to levosimendan in the pulmonary vascular bed of the cat. *Anesthesia and analgesia*. 2002; 94: 1427-33, table of contents.

15. Jiang R, Zhao QH, Wu WH, et al. Efficacy and safety of a calcium sensitizer, levosimendan, in patients with right heart failure due to pulmonary hypertension. *The clinical respiratory journal*. 2017.

16. Martyniuk TV, Arkhipova OA, Kobal EA, Danilov NM and Chazova IE. [Possibilities of using levosimendan in patients with idiopathic pulmonary hypertension]. *Terapevticheskii arkhiv*. 2012; 84: 83-8.

17. Cavusoglu Y, Beyaztas A, Beyaztas S, Tek M, Birdane A and Ata Eskisehir N. Levosimendan is not effective in reducing pulmonary pressures and improving clinical symptoms in patients with acutely decompensated idiopathic pulmonary arterial hypertension. *European Journal of Heart Failure, Supplement*. 2009; 8: ii177.

18. Kleber F, Bollmann T, Borst M, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study. *Journal of clinical pharmacology* 49: 109-15 (2009).

19. Mishra A, Kumar B, Dutta V, Arya VK and Mishra AK. Comparative Effect of Levosimendan and Milrinone in Cardiac Surgery Patients With Pulmonary Hypertension and Left Ventricular Dysfunction. *Journal of cardiothoracic and vascular anesthesia*. 2016; 30: 639-46.

20. Alibaz-Oner F, Gurbuz O, Oner E, Yurdakul S and Erguney M. Impact of levosimendan on right ventricular functions by using novel tissue Doppler derived indices in patients with ischaemic left ventricular failure. *Kardiologia polska* 71: 1036-41 (2013).

21. Sponga S, Ivanitskaia E, Potapov E, Krabatsch T, Hetzer R and Lehmkuhl H. Preoperative treatment with levosimendan in candidates for mechanical circulatory support. *ASAIO journal (American Society for Artificial Internal Organs : 1992)*. 2012; 58: 6-11.

22. Russ MA, Prondzinsky R, Carter JM, et al. Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. *Critical care medicine*. 2009; 37: 3017-23.

23. Yilmaz M, Yontar C, Erdem A, et al. Comparative effects of levosimendan and dobutamine on right ventricular function in patients with biventricular heart failure. *Heart and vessels* 24: 16-21 (2009).

24. Poelzl G, Zwick RH, Grander W, et al. Safety and effectiveness of levosimendan in patients with predominant right heart failure. *Herz*. 2008; 33: 368-73.

25. Duygu H, Ozerkan F, Zoghi M, et al. Effect of levosimendan on right ventricular systolic and diastolic functions in patients with ischaemic heart failure. *International Journal of Clinical Practice*. 2008; 62: 228-33.

26. Parissis J, Paraskevaidis I, Bistola V, et al. Effects of levosimendan on right ventricular function in patients with advanced heart failure. *The American journal of cardiology* 98: 1489-92 (2006).

27. Ukkonen H, Saraste M, Akkila J, et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clinical pharmacology and therapeutics* 68: 522-31 (2000).

28. Slawsky M, Colucci W, Gottlieb S, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. *Circulation* 102: 2222-7 (2000).

29. Rafiq I and Freeman LJ. Pulsed levosimendan therapy in the management of chronic end stage cardiac failure in 'adult congenital heart disease'. *International journal of cardiology*. 2015; 195: 283-4.

30. Schwienbacher M, Schweigmann U, Neu N, et al. Heart Transplantation in a 14-Year-Old Boy in the Presence of Severe Out-of-Proportion Pulmonary Hypertension due to Restrictive Left Heart Disease: A Case Report. *Case reports in cardiology*. 2013; 2013: 418565.

31. Ebade A, Khalil M and Mohamed A. Levosimendan is superior to dobutamine as an inodilator in the treatment of pulmonary hypertension for children undergoing cardiac surgery. *Journal of anesthesia* 27: 334-9 (2013).

32. Lechner E, Moosbauer W, Pinter M, Mair R and Tulzer G. Use of levosimendan, a new inodilator, for postoperative myocardial stunning in a premature neonate. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2007; 8: 61-3.

33. Turanlahti M, Boldt T, Palkama T, Antila S, Lehtonen L and Pesonen E. Pharmacokinetics of levosimendan in pediatric patients evaluated for cardiac surgery. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2004; 5: 457-62.

34. Luther YC, Schulze-Neick I, Stiller B, et al. Levosimendan - Long-term inodilation in an infant with myocardial infarction. *Zeitschrift fur Kardiologie*. 2004; 93: 234-9.

35. Braun JP, Schneider M, Kastrup M and Liu J. Treatment of acute heart failure in an infant after cardiac surgery using levosimendan. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2004; 26: 228-30.