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Klinke, A., Schubert, T., Müller, M. et al. (2020) Emerging therapies for right ventricular dysfunction and failure. *Cardiovascular Diagnosis and Therapy*, 10 (5). pp. 1735-1767. ISSN: 2223-3652

<https://doi.org/10.21037/cdt-20-592>

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Emerging therapies for right ventricular dysfunction and failure

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Contributions: (I) Conception and design: A Klinke, G Hansmann, V Rudolph; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Therapeutic options for right ventricular (RV) dysfunction and failure are strongly limited. Right heart failure (RHF) has been mostly addressed in the context of pulmonary arterial hypertension (PAH), where it is not possible to discern pulmonary vascular- and RV-directed effects of therapeutic approaches. In part, opposing pathomechanisms in RV and pulmonary vasculature, i.e., regarding apoptosis, angiogenesis and proliferation, complicate addressing RHF in PAH. Therapy effective for left heart failure is not applicable to RHF, e.g., inhibition of adrenoceptor signaling and of the renin-angiotensin system had no or only limited success. A number of experimental studies employing animal models for PAH or RV dysfunction or failure have identified beneficial effects of novel pharmacological agents, with most promising results obtained with modulators of metabolism and reactive oxygen species or inflammation, respectively. In addition, established PAH agents, in particular phosphodiesterase-5 inhibitors and soluble guanylate cyclase stimulators, may directly address RV integrity. Promising results are furthermore derived with microRNA (miRNA) and long non-coding RNA (lncRNA) blocking or mimetic strategies, which can target microvascular rarefaction, inflammation, metabolism or fibrotic and hypertrophic remodeling in the dysfunctional RV. Likewise, pre-clinical data demonstrate that cell-based therapies using stem or progenitor cells have beneficial effects on the RV, mainly by improving the microvascular system, however clinical success will largely depend on delivery routes. A particular option for PAH is targeted denervation of the pulmonary vasculature, given the sympathetic overdrive in PAH patients. Finally, acute and durable mechanical circulatory support are available for the right heart, which however has been tested mostly in RHF with concomitant left heart disease. Here, we aim to review current pharmacological, RNA- and cell-based therapeutic options and their potential to directly target the RV and to review available data for pulmonary artery denervation and mechanical circulatory support.

Keywords: Right ventricle; right heart failure (RHF); pulmonary arterial hypertension (PAH); remodeling; right heart failure therapy

Submitted Jun 30, 2020. Accepted for publication Aug 27, 2020.

doi: 10.21037/cdt-20-592

View this article at: <http://dx.doi.org/10.21037/cdt-20-592>

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Introduction

Right ventricular (RV) dysfunction is associated with poor clinical outcomes (1) independent of the etiology (2). Yet, specific therapies that directly target right heart dysfunction are strongly limited. RV dysfunction and failure and its pharmacological therapy have been studied predominantly in the context of pulmonary arterial hypertension (PAH) (3,4), and less commonly in left heart diseases (5). Indeed, current clinical therapies for PAH mainly pursue a reduction of pressure overload via relaxation of the pulmonary vasculature (4), although some drugs appear to have additional anti-remodeling or anti-inflammatory effects. Whether therapies specifically targeting the RV provide substantial benefit compared to existing therapies (4) is unknown. Current heart failure treatment, which has been approved for and tested in patients with left heart failure (LHF), is less effective or in some instances even ineffective or harmful in the treatment of right heart failure (RHF), given the unique geometry, mechanics, metabolism, vascularity and response to pressure overload of the RV (6-9). The scope of this article is to summarize emerging therapies of RHF. We review established vasodilatory therapies for PAH with a distinct focus on their potential or confirmed direct RV effects. We also summarize novel, innovative pharmacological, cell-based and RNA-based strategies specifically addressing the RV. Finally, we address RV-directed therapies in etiologies of RHF other than PAH, thereby creating a new focus towards the RV in

conditions dominated by failing left heart structures. RV dysfunction in the context of congenital heart disease (CHD) is covered elsewhere in this special issue (10). Moreover, the molecular mechanisms of RV dysfunction in PAH with a particular focus on the coronary vasculature, sex hormones, and glucose/lipid metabolism are reviewed elsewhere in this special issue (3).

Non-approved pharmacotherapies

Potential of approved pulmonary vasodilator therapeutics to target the RV myocardium

In patients with PAH it is difficult to discriminate between vascular and myocardial effects of any therapy—the gold standard for distinction is invasive pressure-volume loop assessment. Meta-analyses of clinical data suggest that the direct impact of established PAH medications on the myocardium is limited (11,12). In a number of trials phosphodiesterase-5 (PDE-5) inhibitors and endothelin receptor antagonists (ERAs) failed to be beneficial in patients with group 2 pulmonary hypertension (PH), in particular with heart failure with preserved ejection fraction (HFpEF) (13-16) (for main clinical study findings see *Table 1*). In contrast, PDE-5 inhibitors, stimulators of soluble guanylate cyclase (sGC) and prostacyclin analogues appear to exert advantageous effects on RV myocardium in preclinical models (for schematic overview see *Figure 1*) (34-36). The experimental model of pulmonary artery banding (PAB),

Table 1 Main findings from clinical studies using pharmacotherapeutics with an emphasis on the RV

Drug	Mechanism of action	Study design/patient cohort/reference	Benefit on (number of patients)	No benefit on (number of patients)
Using approved PAH therapeutics				
Bosentan	ETA	Multicentre, randomized, placebo-controlled pilot trial/HFpEF-PH (15)	–	Exercise capacity, hemodynamics (n=20)
Macitentan	ETA	Multicentre, placebo-controlled, randomized phase II study/PH-LV dysfunction (16)	–	Hemodynamics (n=60)
Sildenafil	PDE5-inhibitor	Multicentre, double-blind, placebo-controlled, parallel-group, randomized clinical trial/HFpEF (13)	–	Exercise capacity (n=216)
		Single-centre randomized controlled trial/HFpEF-PH (14)	–	Exercise capacity, hemodynamics (n=52)
		Retrospective non-randomized study/RHF-LVAD (17)	Hemodynamics, RV function (n=14)	–

Table 1 (continued)

Table 1 (continued)

Drug	Mechanism of action	Study design/patient cohort (reference)	Benefit on (number of patients)	No benefit on (number of patients)
Targeting adrenoceptors				
Carvedilol	β 1-RA, α 1-RA	Single-centre, double-blind, randomized, controlled trial/PAH (18)	–	Hemodynamics, RV function, exercise capacity (n=30)
		Cohort study/systemic RV (19)	Exercise capacity, RV function (n=8)	–
		Single-arm open-label pilot study/PAH (18)	RV function (n=6)	–
Bisoprolol	β 1-RA	Single-centre, randomized, placebo-controlled, crossover trial/PAH (20)	–	Exercise capacity, RV function (n=16)
		Randomized, placebo-controlled, double blind, cross-over study/PAH (21)	–	RV function (n=18)
Targeting the renin-angiotensin-aldosterone system				
Spirinolactone	Mineralo-corticoid-RA	Randomized, double-blind, placebo-controlled trial/PAH (22)	–	Exercise capacity (n=199)
Captopril	ACE inhibitor	Observational study/PH (23)	–	Hemodynamics (n=4)
		Observational study/PH (24)	–	Hemodynamics (n=7)
Targeting energy metabolism				
Dichloroacetate	PDK inhibitor	Open-label study/PAH (25)	Hemodynamics, RV function (n=16)	–
Ranolazine	Sodium current and partial FAO inhibitor	Prospective, open-label pilot study/PAH (26)	Hemodynamics, RV function, exercise capacity (n=11)	–
		Single-centre, randomized, placebo-controlled trial/PAH (27)	–	Hemodynamics, RV function (n=12)
Targeting inflammation and oxidative stress				
Tocilizumab	IL-6-RA	Open label study/PAH (28)	–	Hemodynamics (n=21)
Anakinra	IL-1-RA	Single-group, open-label phase IB/II pilot study/PAH (29)	HF symptoms (n=6)	Exercise capacity, RV function (n=6)
Selonsertib	ASK1 inhibitor	Phase II, dose-ranging, randomized, double-blind, placebo-controlled/PAH (30)	–	Hemodynamics (n=150)
rhACE2	rhACE2	Open-label pilot study/PAH (31)	Hemodynamics (n=5)	–
Targeting tyrosine kinases				
Imatinib	TKI	Randomized, double-blind, placebo-controlled pilot study/PAH (32)	Hemodynamics (n=42)	Exercise capacity, hemodynamics (mPAP) (n=42)
		Observational study (in combination with bosentan, iloprost and sildenafil)/PAH (33)	Hemodynamics, exercise capacity (n=1)	–

ACE, angiotensin converting enzyme; ASK1, apoptosis signal-regulating kinase 1; FAO, fatty acid oxidation; ETA, endothelin-1 receptor antagonist; HF, heart failure; IL, interleukin; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PDK, pyruvate dehydrogenase kinase; PH, pulmonary hypertension; RA, receptor antagonist; rh, recombinant human; RV, right ventricle; TKI, tyrosine kinase inhibitor.

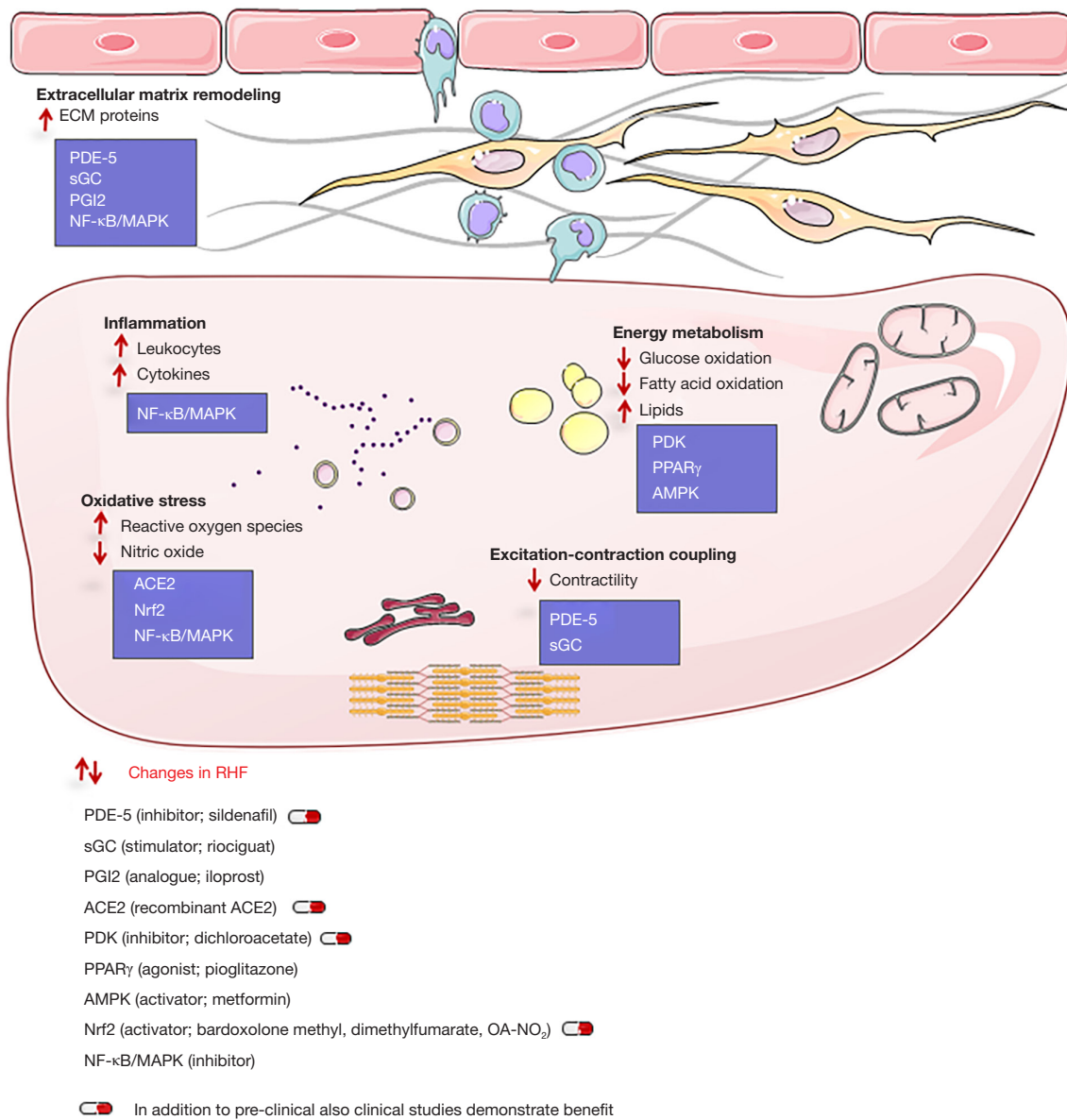


Figure 1 Scheme demonstrating main points of action of pharmacotherapeutics directly targeting RV myocardium in RHF. Key mechanisms of action and corresponding main drugs are given. ACE2, angiotensin converting enzyme 2; AMPK, 5'-adenosine monophosphate-activated protein kinase; ECM, extracellular matrix proteins; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; Nrf2, nuclear factor erythroid 2-related factor 2; PDE, phosphodiesterase; PDK, pyruvate dehydrogenase kinase; PGI2, prostacyclin; PPAR, peroxisome proliferator-activated receptor; sGC, soluble guanylate cyclase. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; <https://smart.servier.com>.

which induces RV pressure overload independently of pulmonary artery (PA) remodeling, allows for investigation of RV-directed effects (37). In PAB models PDE-5 inhibition with sildenafil prevented RV dysfunction and reversed RV fibrotic remodeling (34,36,38) (for experimental

studies see *Table 2*). sGC stimulation with riociguat improved RV systolic function and reduced RV fibrosis without affecting RV hypertrophy (RVH) in PAB-exposed mice. Likewise, the prostacyclin analogue iloprost improved RV systolic function and exercise capacity, which was

Table 2 Experimental pharmacological studies addressing RV dysfunction (indirectly, directly)

Target/mode of action	Model/species	Molecule	Main phenotypic findings	Benefit for RV contractile function	Absence of benefit for RV contractile function	Ref.
Using approved PAH therapeutics						
PDE-5, inhibition	PAB, AC-shunt, rat	Sildenafil	PAB: ↑RV systolic function, exercise capacity, RV fibrosis No effect: RVH, RV diastolic function No effect in AC-shunt	x		(38)
PDE-5, inhibition	PAB, rat	Sildenafil	↓RV fibrosis ↑RV diastolic function No effect: RV systolic function, exercise capacity		x	(34)
PDE-5, inhibition	PAB, mouse	Sildenafil	↑RV systolic function No effect: RVH, RV fibrosis	x		(36)
Prostacyclin, analogue	SuHx, PAB, rat	Iloprost	↓RV fibrosis ↑Exercise capacity (SuHx), RV systolic function (SuHx) No effect: PA remodeling, RV systolic function (PAB)	x		(35)
Soluble guanylate cyclase, activator	PAB, mouse	Riociguat	↓RV fibrosis ↑RV systolic function No effect: RVH	x		(36)
Targeting adrenoceptors						
β-adrenoceptor, blockade	MCT, rat	Arotinolol	↓RVH, RVSP			(39)
β-adrenoceptor, blockade	MCT, rat	Bisoprolol	↓RV fibrosis ↑RV systolic function	x		(40)
β-adrenoceptor, blockade	MCT, SuHx, rat	Carvedilol, metoprolol	↓RVH ↑RV systolic function, exercise capacity (SuHx), survival (MCT) No effect: RVSP, PA remodeling	x		(41)
β-adrenoceptor, blockade	MCT, rat	Nebivolol	↓PA remodeling ↑RV systolic function	x		(42)
β-adrenoceptor, enhancement of signaling	MCT, PAB, rat	Gallein	↑RV systolic function (MCT), exercise capacity (PAB)	x		(43)
α _{1A} -adrenoceptor, agonism	Bleomycin, mouse	A61603	↓RV fibrosis ↑RV systolic function No effect: PA remodeling	x		(44)

Table 2 (continued)

Table 2 (continued)

Target/mode of action	Model/species	Molecule	Main phenotypic findings	Benefit for RV contractile function	Absence of benefit for RV contractile function	Ref.
α_{1A} -adrenoceptor, agonism	PAB, mouse	A61603	↓Liver weight ↑RV systolic function, exercise capacity No effect: RVH, RV fibrosis, RV diastolic function	x		(45)
Targeting the renin-angiotensin-aldosterone system						
AT1 receptor, antagonism	MCT, rat	Losartan	↓PVR, PA remodeling ↑RV diastolic function No effect: RV contractility		x	(46)
AT1 receptor, antagonism	PAB, rabbit	Losartan	No effect: RVH, RV systolic function		x	(47)
Neprilysin, inhibition; AT1 receptor, antagonism	PAB, rat	Sacubitril/valsartan	↓RVH ↑RV systolic and diastolic function	x		(48)
ACE, inhibition	PAB, rabbit	Ramipril	No effect: RVH, RV systolic function		x	(47)
AT1 receptor + mineralocorticoid receptor, antagonism	PAB, rat	Losartan + eplerenone	No effect: RV systolic function, RV remodeling, survival		x	(49)
ACE2	PAB, mouse	ACE2	↓RVH ↑RV systolic function No effect: RV fibrosis	x		(50)
ACE2	MCT, rat	ACE2	↓RVH, PA remodeling ↑RV systolic function	x		(51)
ACE2, activation	MCT, HOX, bleomycin, rat	Diminazene aceturate	↓RVH, RV fibrosis, PA remodeling ↑RV systolic function	x		(52)
Mineralocorticoid receptor, antagonism	HOX, mouse, MCT, rat	Spironolactone	HOX: ↓RVSP, RV fibrosis, PA remodeling MCT: ↓RVSP, PA remodeling, PVR No effect: RV fibrosis, RV remodeling			(53)
Mineralocorticoid receptor, antagonism	MCT, rat	Spironolactone	↓RVSP, PA remodeling, PVR			(54)
Mineralocorticoid receptor, antagonism	SuHx, rat	Eplerenone	↓PA remodeling, PVR			(54,55)
Mineralocorticoid receptor, antagonism	SuHx, rat	Spironolactone	↓RVH, RVSP, PVR			(55)
AT1 receptor + mineralocorticoid receptor	PAB rats	Losartan + eplerenone	No effect: RV function, RV remodeling, survival		x	(49)

Table 2 (continued)

Table 2 (continued)

Target/mode of action	Model/species	Molecule	Main phenotypic findings	Benefit for RV contractile function	Absence of benefit for RV contractile function	Ref.
Mineralocorticoid receptor, antagonism	SuHx, PAB, mouse	Eplerenone	↓RVH, RVSP, PA remodeling PAB: No effect: RVH, RV fibrosis, RV systolic function			(56)
Targeting inflammation and oxidative stress						
Nrf2, stimulation of activity and expression	HOX, SuHx, mouse	Dimethyl-fumarate	↓RVSP, RVH, PA remodeling			(57)
Nrf2, stimulation of activity and expression	HOX, mouse	Oltipraz	↓RVH, PA remodeling			(58)
SOD, SOD mimetic	MCT, rat	EUK 134	↓RV fibrosis, RVH ↑RV systolic function	x		(59)
NADPH-oxidase, decrease of expression and activity	HOX, mouse	Rosiglitazone	↓RVSP, PA remodeling			(60)
Vascular ROS release reduction; PASMCs proliferation, decrease	HOX, mouse	OA-NO ₂	↓RVSP, RVH, PA remodeling			(61)
MPO, inhibition	SuHx, rat	AZM198	↓RVSP, RVH, PA remodeling			(62)
NF-κB, inhibition	PAB, rat	E6446, Pyrrolidine dithiocarbamate	↓RV fibrosis ↑RV systolic function No effect: RVH	x		(63)
ASK1, inhibition	PAB, mouse; SuHx, MCT, rat	GS-444217	↓RV fibrosis, RVH, PA remodeling (in MCT and SuHx) ↑RV systolic function	x		(64)
p38MAPK, inhibition	PAB, HOX, mouse	PH797804	↓RV fibrosis Increased: RV systolic function	x		(65)
TNF-alpha, antagonism	MCT, rat	Etanercept	↓RVSP, PA remodeling			(66)
TNF-alpha, antagonism	Endotoxin-induced, pig	Etanercept	↓RVSP, PVR ↑RV diastolic function			(67)
IL-6, IL6R/sIL6R antagonism	MCT, SuHx, rat	ERBF	↓RVSP, RVH, PA remodeling ↑RV systolic function	x		(68)
IL-1, receptor antagonism	MCT, HOX, rat	IL-1 receptor antagonist	MCT: ↓RVH, RVSP, PA remodeling HOX: no effect			(69)
Targeting energy metabolism						
PDK, inhibition	PAB, MCT rat	Dichloroacetate	↓RVH ↑RV systolic function	x		(70)

Table 2 (continued)

Table 2 (continued)

Target/mode of action	Model/species	Molecule	Main phenotypic findings	Benefit for RV contractile function	Absence of benefit for RV contractile function	Ref.
PDK, inhibition	HOX, rat	Dichloroacetate	↓RVH, PVR, RVSP, PA constriction and remodeling ↑RV CO			(71)
PDK, inhibition	MCT, rat	Dichloroacetate	↓PA remodeling, RVH, mortality			(72)
PDK, inhibition	RV volume overload, pig	Dichloroacetate	↓RVH ↑RV contractile reserve	x		(73)
FAO, partial inhibition	PAB, rat	Trimetazidine, ranolazine	↓RVH, RV fibrosis ↑RV systolic function, exercise capacity	x		(74)
FAO, partial inhibition	MCT, HOX rat	Trimetazidine	↓RVSP, RVH, PA remodeling			(75)
RV lipid deposition, reduction	BMPR2 R899X, mouse	Metformin	↓RV lipid accumulation No effect: RV systolic and diastolic function		x	(76)
RV lipid deposition, reduction	Western diet + PAB, mouse	Metformin	↓RVSP, RVH ↑RV diastolic function		x	(77)
PPAR γ activation, reduction of RV intramyocardial lipid deposition	SuHx, rat	Pioglitazone	↓RVSP, RVEDP, RVH, RV fibrosis, PA remodeling ↑RV systolic function, RV diastolic function	x		(78)
PPAR γ , activation	ApoE-ko + HFD, mouse	Rosiglitazone	↓RVSP, RVH, PA remodeling		x	(79)
PPAR γ , activation	HOX, rat	Rosiglitazone	↓RVSP, RVH, PA remodeling			(80)
PPAR γ , activation	MCT, rat	Pioglitazone	↓RVSP, RVH, RV fibrosis, PA remodeling ↑Survival			(81)
Targeting tyrosine kinases						
Tyrosine kinase, inhibition	MCT, rat, HOX, mouse	Imatinib	↓RVH, RVSP, PA remodeling			(82)
Targeting extracellular matrix remodeling						
Galectin-3, inhibition	PAB, mouse	N-acetyllactosamine	↓RV fibrosis No effect: RV systolic function		x	(83)
Targeting HDACs						
HDAC class I, II, IV, inhibition	HOX, rat	Valproic acid, suberoylanilide	↓RVH, RVSP, PA remodeling			(84)
HDAC class I, inhibition	HOX, rat	MGCD0103	↓RVSP, PA remodeling No effect: RV systolic function		x	(85)
HDAC class I, II, inhibition	PAB, rat	Trichostatin A, valproic acid	↓RV systolic function ↑RV fibrosis			(86)

Table 2 (continued)

Table 2 (continued)

Target/mode of action	Model/species	Molecule	Main phenotypic findings	Benefit for RV contractile function	Absence of benefit for RV contractile function	Ref.
HDAC class I, inhibition	MCT, rat	Valproic acid	↓PA remodeling, RVH			(87)
HDAC class I, II, inhibition	SuHx, rat	Trichostatin A	No effect: PA remodeling, RV systolic function, RVSP, RVH		x	(88)
HDAC class VI, inhibition	SuHx, MCT, rat	Tubastatin A	↓PA remodeling, RVH, RVSP, PVR			(89)

ACE, angiotensin-converting enzyme; ApoE-ko, apolipoprotein E-knockout; AT1, angiotensin II receptor type 1; HDAC, histone deacetylase; HFD, high fat diet; HOX, hypoxia; MCT, monocrotaline; Nrf2, nuclear factor erythroid 2-related factor 2; PDE-5, phosphodiesterase-5; PA, pulmonary artery; PAB, pulmonary artery banding; PVR, pulmonary vascular resistance; RV, right ventricle; RVH, right ventricular hypertrophy; RVSP, right ventricular systolic pressure; SuHx, Sugen5416/hypoxia.

surprisingly not associated with a reduction of PA pressure and RVH in the Sugen5416/hypoxia (SuHx) rat model for PAH. Rather, it was accompanied by a marked reduction of RV fibrosis, as it was seen also in PAB-exposed rats (35). These discrepant findings underline the difficulties in translating PAH medications to treatment of RHF originating from conditions other than PAH. Recently, sildenafil administration was evaluated for prevention of acute RHF following implantation of left ventricular assist device (LVAD). LVAD implantation is an important strategy in patients with end-stage LHF, however, in 4% to 50% of cases RHF occurs early after implantation and significantly increases mortality (90). Sildenafil is frequently used off-label to treat and/or prevent RHF post LVAD implantation (91). However, a recently published analysis from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry uncovered that the incidence of RHF and the relative risk of bleeding was markedly increased with sildenafil therapy compared to controls (17). These disappointing results question the benefit of PA vasodilators for LVAD recipients (clinical trial using sildenafil: NCT03356353) (for ongoing clinical trials, see Table 3). Other clinical studies will investigate the ERA macitentan for treatment of PH following LVAD implantation (NCT02554903), and the inotropic agents levosimendan (a calcium sensitizer) (NCT03659851) or milrinone (a PDE-3 inhibitor) (NCT03217331) as pretreatment before LVAD implantation. Given that both milrinone and levosimendan have additional PA vasodilating properties, they might be particularly well suited. Levosimendan was effective to restore RV-PA coupling in

an experimental model of acute pressure overload (92) and is currently tested also in patients with HFpEF-associated PH (NCT03541603, NCT03624010).

Further preclinical studies and careful evaluation of clinical data are required to follow up on the discrepancies of experimental and clinical studies, on the promising preclinical results and to unravel potential molecular mechanisms that may directly target RV dysfunction.

Neurohormonal modulation

Beta-adrenoceptor antagonists

Use of beta-adrenoceptor antagonists (β -blocker) is an essential component of LHF therapy. In contrast, it is not clear whether β -blocker provide benefit for RHF, although at least for RHF secondary to PAH it is known that neurohormonal activation is high (93). Currently, β -blocker application is not recommended for PAH due to their negative inotropic and chronotropic effects. Clinical studies on the use of β -blockers in PAH had inconsistent results dependent on whether the β 1-selective bisoprolol (20,21), or β 1- and α 1-blockade (carvedilol) was employed. Carvedilol was safe in PAH patients and even normalized pathologically increased RV glucose uptake in PAH (18). However, whereas it improved RV function and exercise capacity in small studies with PAH or RV dysfunction of other origin than PAH (19,94), no benefit on hemodynamics or exercise capacity was observed in a larger PAH study (18) (Table 1). Small clinical trials are ongoing for PAH (NCT02507011, NCT00240656) (Table 3). In preclinical PAH models encouraging results have been

Table 3 Ongoing clinical trials

NCT number	Trial title	Drugs	Mechanism of action	Trial disease state	Main prim. endpoint	Number participants	Study type	Trial phase	Trial status	Main RV function-specific endpoints
Targeting PA vasoconstriction										
NCT03217331	CRD-102 for Right Heart Failure in Patients with Left Ventricular Assist Devices	CRD-102 (oral milrinone)	PDE3 inhibitor	RHF after assist device implant	Number of adverse events	6	N/A	1 + 2	Completed	–
NCT02554903	A Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel Group Study to Assess the Efficacy and Safety of Macitentan in Patients with Pulmonary Hypertension After Left Ventricular Assist Device Implantation	Macitentan	ETA	PH	PVR	57	Randomized	2	Completed	–
NCT03356353	Sildenafil for the Prevention of Right Heart Failure Following Continuous-Flow Left Ventricular Assist Device Implantation (The REVAD Study)	Sildenafil	PDE5 inhibitor	End stage heart failure	PVR	24	N/A	3	Recruiting	RHF
NCT03624010	Open-Label Rollover Study of Levosimendan in Patients with Pulmonary Hypertension with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)	Levosimendan	Calcium sensitizer	HFpEF, PH, RHF	Number of adverse events	36	N/A	2	Active, not recruiting	–
NCT03659851	Pretreatment with Levosimendan In Patients Undergoing Left Ventricular Assist Device Implantation	Levosimendan	Calcium sensitizer	RHF, Left Heart Failure	Laboratory parameters	50	Case-Crossover	–	Recruiting	–
NCT03541603	A Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Pulmonary Hypertension Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)	Levosimendan	Calcium sensitizer	Secondary PH (HFpEF), RHF	PCWP	36	Randomized	2	Completed	–

Table 3 (continued)

Table 3 (continued)

NCT number	Trial title	Drugs	Mechanism of action	Trial disease state	Main prim. endpoint	Number participants	Study type	Trial phase	Trial status	Main RV function-specific endpoints
Targeting adrenoceptors										
NCT00240656	Spirolactone Combined with Captopril and Carvedilol for the Treatment of Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease—Focus on Pulmonary Artery Remodeling	Spirolactone, captopril, carvedilol	Aldosterone antagonist, ACE antagonist, β -blocker	PH (congenital heart disease)	Dyspnoea score, Exercise capacity, PAP	–	Non-randomized	1	Completed	RVAT, RVET, RVET/RVAT
Targeting the renin-angiotensin-aldosterone system										
NCT01712620	A Pilot Study of the Effect of Spirolactone Therapy on Exercise Capacity and Endothelial Dysfunction in Pulmonary Arterial Hypertension	Spirolactone	Aldosterone antagonist	PAH	Walk distance	70	Randomized	2	Recruiting	RV function
NCT03344159	Spirolactone Therapy in Chronic Stable Right HF Trial (STAR-HF)	Spirolactone	Aldosterone antagonist	PAH, PH, RV cardiomyopathy	NT-proBNP	40	Randomized	4	Suspended (COVID-19)	RV EF
NCT03177603	An Open-label, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of GSK2586881 in Participants with Pulmonary Arterial Hypertension	GSK2586881 (rhACE2)	rhACE2	PH	PVR, CO, mPAP	23	Non-randomized	2	Completed	–
NCT03177603	A Dose-escalation Study in Subjects with Pulmonary Arterial Hypertension (PAH)	GSK2586881 (rhACE2)	rhACE2	PAH	PVR, CO, mPAP	23	Open label	2	Completed	–
Targeting energy metabolism										
NCT03629340	Phase II Trial of Metformin for Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction	Metformin	Metabolic modulator	PH (HFpEF)	mPAP	32	Randomized	2	Active, not recruiting	–

Table 3 (continued)

Table 3 (continued)

NCT number	Trial title	Drugs	Mechanism of action	Trial disease state	Main prim. endpoint	Number participants	Study type	Trial phase	Trial status	Main RV function-specific endpoints
NCT03617458	Interventions Against Insulin Resistance in Pulmonary Arterial Hypertension	Metformin	Metabolic modulator	PAH	Walk distance, change in WHO functional class	39	Randomized	2	Recruiting	TAPSE, RVEF, RVFA, RV longitudinal strain
NCT01083524	A Phase I, Open-Label, Two Centre Study to Evaluate Dichloroacetate (DCA) in Advanced Pulmonary Arterial Hypertension.	DCA	Metabolic modulator + PDK inhibitor	PAH	Safety and tolerability of DCA	30	Non-randomized	1	Completed	RV size/function
Targeting inflammation and oxidative stress										
NCT02036970	A Dose-Ranging Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension	Bardoxolone methyl	Nrf2 inducer + NF-κB inhibitor	PAH, PH	Walk distance	166	Randomized	2	Completed	–
NCT02657356	A Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Connective Tissue Disease-associated Pulmonary Arterial Hypertension	Bardoxolone methyl	Nrf2 inducer + NF-κB inhibitor	Connective tissue disease-associated PAH	Walk distance	202	Randomized	3	Terminated (COVID-19)	–
NCT03068130	An Extended Access Program to Assess Long-term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension	Bardoxolone methyl	Nrf2 inducer + NF-κB inhibitor	PH	Long-term safety	414	N/A	3	Recruiting	–
NCT03449524	Phase 2 Multicenter, Double-Blind, Placebo Controlled, Efficacy, Safety, and Pharmacokinetic Study of 2 Doses of CXA-10 on Stable Background Therapy in Subjects with Pulmonary Arterial Hypertension	CXA-10	Nitrated fatty acid compound	PAH	RVEF, PVR	96	Randomized	2	Recruiting	–

Table 3 (continued)

Table 3 (continued)

NCT number	Trial title	Drugs	Mechanism of action	Trial disease state	Main prim. endpoint	Number participants	Study type	Trial phase	Trial status	Main RV function-specific endpoints
NCT03738150	A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept (ACE-011) for the Treatment of Pulmonary Arterial Hypertension	Sotatercept	TGF- β ligand trap (soluble activin receptor type 2A IgG-Fc fusion protein)	PAH	Peak oxygen uptake	25	N/A	2	Recruiting	–
Targeting miRNA										
NCT04045405	Phase I, Randomized, Double-blind, Placebo-controlled Study to Assess Safety, PK and PD Parameters of CDR132L in Patients with Stable Heart Failure of Ischemic Origin (NYHA 1-3)	CDR132L	miRNA-132 inhibitor	Heart failure	Incidence and severity of adverse events	28	Randomized	1	Completed	–
NCT03603431	A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose-escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of MRG-110 Following Local Intradermal Injection After Skin Excisional Wound Creation in Normal Healthy Volunteers	MRG-110	miRNA-92a inhibitor	Healthy volunteer	Number of adverse events	42	Randomized	1	Completed	–

ACE, angiotensin converting enzyme; ASK1, apoptosis signal-regulating kinase 1; DCA, dichloroacetate; ETA, endothelin receptor antagonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; mPAP, mean pulmonary arterial pressure; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B-cells; Nrf2, nuclear factor erythroid 2-related factor 2; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PDK, pyruvate dehydrogenase kinase; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHF, right heart failure; RV, right ventricle; RVEF, right ventricular ejection fraction; RVAT, right ventricular acceleration time, RVET, right ventricular ejection time.

obtained: β -blockade applied in monocrotaline (MCT) and SuHx rat models was associated with reduction of RV dysfunction, RV fibrosis and RV inflammation (39-42) (*Table 1*). However, contrasting data suggest that reinforcement of β -adrenoceptor signaling improved RV function in the MCT rat model (43). Interestingly, agonism on the α 1A-adrenoceptor prevented and reversed RHF in experimental mouse models of bleomycin- and PAB-induced RV failure (44,45,95) (*Table 2*). Here, improved RV function was linked to increased myofilament force development and associated with markedly diminished levels of reactive oxygen species (ROS) in the RV.

Modulation of the renin-angiotensin-aldosterone system (RAAS)

As it is the case for adrenoceptor blockade, modulation of the RAAS is essential in LHF therapy, but its benefit for RHF remains elusive. The vasoconstrictive, pro-fibrotic and pro-inflammatory properties of angiotensin II (AngII) render this pathway attractive also for RHF therapy, and in PAH RAAS is clearly activated (46). Nevertheless, in experimental studies the AngII type 1 (AT1)-receptor blocker losartan had no beneficial effect on the RV (47,49) (*Table 2*). Interestingly, a recent study suggested that the combination of AT1-receptor blockade with neprilysin inhibition (sacubitril/valsartan), which is successful in LHF therapy, improved RV function by attenuating adverse myocardial remodeling in PAB-exposed rats (48). Inhibition of the angiotensin-converting enzyme (ACE) was rather disappointing in small PAH patient cohorts (23,24) (*Table 1*).

More promising findings suggest to target ACE2, which converts AngI and AngII to Ang 1-7, Ang 1-9 and Ang 1-5, exerting vasodilating and anti-inflammatory effects via the Mas receptor (96,97). Application of recombinant ACE2 protein or activation of ACE2 in PAH models reduced PA and RV remodeling and improved RV function (51,52). Of note, improved RV function was also observed in the PAB model, suggesting a direct protective effect on RV myocardium (50). The current findings point towards the fact that the mechanism of action is rather related to anti-inflammatory and anti-oxidative actions than directly reducing AngII-dependent effects (98) (*Figure 1*). However, a single intravenous dose of ACE2 in PAH patients reduced pulmonary vascular resistance (PVR) and increased cardiac output (CO) (31). A phase 2 clinical trial proved good tolerability of recombinant ACE2 in patients with acute respiratory distress syndrome (99), and another phase 2 trial with PAH patients was completed

recently (NCT03177603). It needs to be considered that ACE2 serves as a receptor for coronavirus SARS-CoV2 and facilitates cell entry potentially not only to alveolar cells, but also to cardiomyocytes (100). ACE2 expression is augmented on cardiomyocytes in patients with cardiac disease, which might increase risk for cardiac complications associated with Coronavirus Disease 2019 (COVID-19) (100).

Most consistent results are derived from studies on mineralocorticoid-receptor blockade, which indicate that blocking the aldosterone receptor exerts potent effects on PA remodeling. Those are related to a decrease of PA fibrosis, increase of nitric oxide (NO) bioavailability and inhibition of proliferation of pulmonary artery smooth muscle cells (PASMCs), but the RV is not directly affected. Thus, PA remodeling and PVR and in some studies also RVH were diminished by spironolactone or eplerenone in PAH models (53-56). In contrast, no effects on RV remodeling or function were observed in PAB models (49,56) (*Table 2*). In a retrospective analysis spironolactone improved exercise capacity, brain natriuretic peptide (BNP) levels and New York Heart Association (NYHA) class in PAH patients (22). Ongoing clinical trials will further investigate the therapeutic potential of spironolactone and its modulation of vascular dysfunction for PAH patients (NCT01712620, NCT03344159) (*Table 3*).

Metabolic regulators

Metabolic remodeling is an important component of heart failure pathogenesis. As described in more detail by Agrawal and colleagues (3), due to reduced oxygen availability but also triggered by processes like inflammation and increased oxidative stress, substrate flexibility of cardiomyocytes is impaired. The mechanisms of metabolic dysregulation are not yet fully understood. In healthy myocardium, fatty acid oxidation (FAO) serves to about 70% for energy generation, and energy yield per molecule is higher than from glucose oxidation (GO), but on the other hand oxygen consumption is higher per molecule substrate. In dysfunctional cardiomyocytes, complete oxidative phosphorylation (OXPHOS) all the way through the citrate cycle (Krebs cycle) and electron transport chain (ETC, for efficient ATP production) is decreased and glycolysis is enhanced, resulting in reduced ATP generation (101). Pressure-overloaded hearts with pathological hypertrophy (RVH or LVH) revert to a fetal transcriptional and metabolic program, with increased utilization of glucose and reduced oxidative capacity (102). An important driver

of the so-called Warburg effect, i.e., predominant glycolysis despite the presence of oxygen to generate ATP, is increased activity and expression of pyruvate dehydrogenase kinase (PDK), which inhibits pyruvate dehydrogenase (PDH). The Warburg effect does not only occur in the dysfunctional or failing RV (103) but also in the pulmonary vasculature (104), with the consequence of increased proliferation of PSMCs and fibroblasts.

PDK inhibition

The PDK inhibitor dichloroacetate (DCA) has successfully been employed in preclinical models and patients. Improvement of RV function in line with increase in GO was shown in PAB and MCT rat models (70) and in a large animal model of RV volume overload (73) (*Table 2*). Importantly, the advantageous effects of DCA are not only related to improved substrate utilization. It also restores the expression of voltage-gated potassium channels Kv1.2, Kv1.5, Kv2.1 and Kv4.2 in PSMCs and in RV cardiomyocytes. In PSMCs this leads to preserved membrane potential and diminished vasoconstriction in hypoxia (HOX) (71) and MCT rat models (72). Restoration of potassium channel expression also affects RV cardiomyocyte repolarization (70). However, it is important to note that genetic polymorphisms can influence DCA efficacy. This was demonstrated by a recent 4-month open-label trial with 20 PAH patients. Here, DCA reduced PVR and increased exercise capacity, and this effect was more pronounced in individuals with absent or low polymorphism scores for the proteins sirtuin 3 and uncoupling protein 2, which regulate mitochondrial function in a PDK-dependent manner (25).

Partial FAO inhibition

FAO is in reciprocal relationship with GO, thus, partial inhibition of FAO is an oxygen-sparing mechanism, which renders the partial FAO inhibitors ranolazine and trimetazidine useful as anti-anginal drugs. Both have successfully been used to treat LHF (105-108), whereas the effects of ranolazine are also related to inhibition of late sodium current, thereby preventing sodium-dependent calcium overload (107). However, preclinical effects of trimetazidine and ranolazine in animal models of PAH/RV dysfunction have been small (74,75,109) (*Table 2*) and the results of the first clinical studies with trimetazidine have not been published or were negative (110,111). In patients with PAH, ranolazine had no effects in a small study (27), but significantly improved exercise capacity and

RV function in another small PAH study (26) (*Table 1*). It remains elusive whether these effects were attributed to metabolic modulation or sodium channel inhibition. Several clinical trials for ranolazine in PH particularly focusing on RV function are ongoing (NCT02829034, NCT01839110, NCT03273387) (*Table 3*). Importantly, FAO is naturally downregulated in dysfunctional myocardium, which amongst others leads to lipid accumulation in cardiomyocytes with enhanced generation of toxic lipid metabolites and reduced ATP yield [for detailed review see (101)]. Furthermore, mitochondrial fragmentation occurs in response to cellular stress in PAH/RV pressure overload and induces a metabolic switch from FAO to GO in the heart. Reversing this “FAO-to-GO switch” and restoring normal cardiac metabolism are sufficient to preserve LV function despite mitochondrial fragmentation (112). The latter finding indicates that the switch in energy generation in the failing adult ventricle may be maladaptive and likely contributes to pathogenesis of heart failure. Thus, we doubt that the concept of blocking FAO in RV or LV failure with pressure overload improves systolic performance, but may even have detrimental effects (102).

Master regulators of glucose and lipid metabolism

A current approach to address metabolic homeostasis in the heart and the pulmonary vasculature is to target the peroxisome proliferator-activated receptor gamma (PPAR γ), which is a key modulator of glucose and lipid metabolism, including mitochondrial FAO, as recently reviewed (3,113). PPAR γ is a transcription factor of the nuclear receptor superfamily and is activated by thiazolidinediones (TZDs) or endogenous ligands at specific binding sites. Pioglitazone, which is approved for therapy of diabetes mellitus type 2, was demonstrated to have a better safety profile than rosiglitazone (114,115). Interestingly, current established PAH medications, treprostinil and sildenafil exert their anti-proliferative effects via PPAR γ activation (113). In heart failure and PAH, the actions of TZDs can be attributed to a variety of mechanisms, however normalization of cardiac energy metabolism may be an important element. Intriguingly, cardiomyocyte-specific deletion of PPAR γ in mice provoked LV and RV systolic dysfunction, which was accompanied by decreased mRNA expression of genes encoding for important mediators of FAO (78). Pioglitazone inhibited exaggerated RV glucose uptake in SuHx-treated rats and reduced RV intramyocardial lipid accumulation as a possible culprit for lipotoxicity and RV failure. Pioglitazone further prevented RV fibrosis and normalized RV

cardiomyocyte mitochondrial structure and organization. This, together with attenuated PA remodeling accounted for marked reduction of RVH and normalization of RV function (Table 2, Figure 1). Interestingly, transcription of important FAO-regulating genes, including PPAR γ itself, proved to be downregulated in RV cardiomyocytes of PAH patients and were upregulated by pioglitazone in isolated neonatal cardiomyocytes (78). Besides this robust signal for the therapeutic action of TZDs via a direct effect on myocardial energy metabolism, a variety of other studies identified beneficial effects in preclinical PAH models linked to anti-inflammatory, anti-proliferative, pro-apoptotic and vasodilatory effects. Deletion of PPAR γ in SMCs led to the development of PAH in mice. It was unraveled that PPAR γ is a downstream target of bone morphogenetic protein (BMP) receptor type-2 (BMPR2), which mediates inhibition of SMC proliferation (116). Several further studies demonstrated TZD-dependent benefits in experimental PAH due to attenuation of PA vasoconstriction and remodeling (79-81,117). Importantly, since FAO also increases oxygen consumption while producing more ATP, therapeutic PPAR γ activation may require sufficient oxygen supply to the myocardium. Thus, PPAR γ activating agents may not be started in end-stage PAH with low CO and high end-diastolic ventricular filling pressures. In these situations, the failing RV may incrementally benefit from oxygen sparing therapeutic approaches at the expense of less efficient ATP production. Despite the robust evidence provided by preclinical studies, there are no ongoing clinical trials to investigate TZDs for RHF or PAH.

Metformin

Enhanced lipid accumulation has been detected in human RV tissue of patients (postmortem) and in mice with heritable PAH (76). In this study, lipid accumulation in the BMPR2 R899X transgenic mouse model of PAH could be diminished by application of the biguanide metformin, however RV function was not improved. Metformin impacts on energy metabolism via activation of 5'-adenosine monophosphate-activated protein kinase (AMPK). RV lipid accumulation was also reduced by metformin in a model of metabolic syndrome induced by Western diet, in which RV dysfunction was further exaggerated by PAB (77). Metformin reduced RVH and improved RV diastolic function. Other experimental studies related positive effects of metformin on the RV to alternative mechanisms. In HOX and MCT rat models, metformin reduced PA remodeling, which was due to stimulating endothelial NO

synthase activity and inhibiting mitogen-activated protein kinases (MAPK) (118). Moreover, in the SuHx rat model attenuated PA remodeling was linked to an inhibition of aromatase transcription, resulting in decreased estrogen levels (119). A phase 2 clinical trial investigates the effect of metformin in PAH (NCT03617458) and HFpEF-associated PH (NCT03629340).

Taken together, metabolic dysregulation in right heart dysfunction and failure is a promising therapeutic target. Further studies to understand its significance for PAH and RHF, to unravel in particular the role of FAO in RV failure, and to find appropriate, safe and efficient drugs are indispensable.

Inhibition of inflammation and oxidative stress

Inflammation has been suggested as a mediator and potential therapeutic target in cardiovascular disease (CVD), however no anti-inflammatory therapy has been approved yet. The mostly low-grade and sterile inflammatory processes in CVD comprise activation of leukocytes and fibroblasts with release of cytokines and ROS. Recent results from the CANTOS trial have shown that anti-inflammatory treatment using a neutralizing antibody to interleukin (IL)-1 β reduced hospitalization for LHF (120). In patients with PAH, levels of circulating inflammatory markers correlate with disease severity, symptom burden and survival (121-125). The majority of studies investigating the role of inflammation in PAH links it to adverse pulmonary vascular remodeling (62,125,126). In contrast, the effects of inflammation and anti-inflammatory therapy on RV remodeling and function are less clear. It is known that modulated apoptosis, increased reactive fibrosis, disturbed metabolism with mitochondrial dysfunction, altered Ca²⁺ handling and dysintegrity of sarcomere proteins are sensitive to inflammation and ROS (126-128). A number of experimental studies investigating RV remodeling and dysfunction following PAB have described increased RV cytokine levels and/or leukocyte infiltration (125). Thus, anti-inflammatory and anti-oxidative therapy is a promising tool to target PA and RV remodeling (129).

Blockade of cytokines and leukocyte enzymes

One potential strategy is blocking certain cytokines or their receptors. Cytokines like IL-1 β , IL-6 and tumor necrosis factor- α (TNF- α) are not only released in models of and patients with PAH, but their tissue levels also increased in RV myocardium following PAB in mice (130). IL-1 β is a

central mediator of the inflammasome, however antagonism of the IL-1 receptor by anakinra yielded inconsistent results in preclinical and clinical studies. Its administration to MCT-treated rats reduced PA remodeling, however it failed to exert any effects in the HOX model of PAH as tested in the same study (69) (Table 2). It has to be considered that IL-1 β regulates transdifferentiation of fibroblasts to activated myofibroblasts and may attenuate fibrotic remodeling (131-133). In a recent small single-arm open label PAH study, 14 days treatment with anakinra reduced C-reactive protein levels and symptom burden, but RV function was not significantly changed (29) (Table 1).

TNF- α inhibition appears to exert effects on PA remodeling. The specific antagonist etanercept modified PA remodeling and reduced PA pressure in experimental PAH models (66,67).

The IL-6 receptor (IL-6R) is another potential therapeutic target in PAH. IL-6R on the surface of PASMC serves as a survival factor, and IL-6R antagonism not only reduced PA remodeling but improved RV function in MCT and SuHx rat models (68). However, the monoclonal antibody tocilizumab failed to achieve a change in PVR in a phase 2 open-label proof-of-concept study with PAH patients (28).

An important source of ROS is the leukocyte enzyme myeloperoxidase (MPO), that has been linked to a variety of cardiovascular conditions (134). MPO levels were increased in lungs of PAH patients. Knockout or inhibition of MPO reduced RVH, PA pressure and remodeling in the MCT rat and HOX mouse PAH models (62).

Targeting signaling mediators

A promising concept is to target central intracellular signaling cascades. The transcription factor nuclear factor E2-related factor 2 (Nrf2) induces anti-oxidative effects like increased expression of heme-oxygenase-1 (HO-1). HO-1- as well as Nrf2-deficient mice develop RV dilation and infarction or PA remodeling and RVH, respectively, under hypoxic conditions (58,135). Stimulation of Nrf2 and HO-1 expression with Protandim in the SuHx rat model of PAH attenuated RV fibrosis and capillary rarefaction and improved RV function, without changes in PA pressure or remodeling (136). Nrf2 stimulation with oltipraz showed protective effects on PA remodeling in the HOX mouse model (58). Nitro-fatty acids (NO₂-FA), a group of molecules with anti-inflammatory and anti-oxidative properties, in part via induction of HO-1 expression (137), attenuated PA remodeling, RVH and fibrosis in the HOX

mouse model (61). A current phase 2 multicenter clinical study explores NO₂-FA in patients with PAH (NCT03449524). Other Nrf2-stimulating agents (dimethyl fumarate), a superoxide dismutase (SOD) mimetic, and the PPAR γ receptor stimulator rosiglitazone all exert anti-oxidative effects and achieved benefit in preclinical PAH models (57,59,60) (Table 2). The Nrf2 and HO-1 axis is thus a promising target to reinforce anti-inflammatory and anti-oxidative processes (Figure 1). The Nrf2 activator bardoxolone methyl significantly improved exercise capacity in PAH patients in a phase 2 trial (138) (NCT02036970), although it was associated with adverse cardiovascular events in patients with end stage chronic kidney disease. Two more clinical trials are ongoing (NCT03068130; NCT02657356) (Table 3).

Furthermore, studies demonstrating inhibition of toll-like receptor 9/nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B) signaling (63) and inhibition of apoptosis signal-regulating kinase (ASK)1 and p38 MAPK activity in PAB models (64,65) are in favor of blocking inflammatory pathways. However, a clinical study on ASK1 inhibition in PAH including 150 patients failed to reach its primary endpoint (NCT02234141) (30).

Overall, modulation of inflammation and oxidative stress is a promising strategy to target maladaptive RV remodeling as well as PA constriction and remodeling in PAH at the same time. Given that a certain level of ROS is required for adaptive cell signaling and homeostasis, and that inflammatory cascades are indispensable for intact immune defense, induction of anti-oxidative and anti-inflammatory cascades may be the most prospective and feasible concept.

Modulation of extracellular matrix (ECM) remodeling

Fibrotic remodeling with enhanced deposition of interstitial and perivascular collagen and transdifferentiation of fibroblasts to myofibroblasts is a hallmark of the pressure overloaded and dysfunctional RV. Fibrosis also occurs during adaptive remodeling, but is suggested to become maladaptive when the stressor like increased afterload persists. It leads to increased ventricular stiffness and susceptibility to arrhythmias. It is widely accepted that maladaptive fibrosis of the LV contributes to impaired systolic and diastolic function and is associated with increased morbidity and mortality (139). This is, however, less clear for the RV. Preclinical studies suggest that effective therapeutic approaches to alleviate PAH or RV dysfunction upon PAB most commonly go along with a reduction of RV fibrosis (140). In the PAB model this

was the case with a p38MAPK inhibitor (65), a 5-HT₂ receptor antagonist (141), the prostacyclin analogue iloprost (35), the antioxidant protandim (136) and an ASK1 inhibitor (64). p38MAPK and ASK1 inhibition attenuated cardiac fibroblast activation and improved RV systolic function. However, recent research has challenged the concept of a causal relationship between fibrosis and RV function. A recent study by Boehm and colleagues showed that in a reversible PAB mouse model RV fibrosis slowly reversed at a time point when RV function and hypertrophy were already fully normalized (142). A promising biomarker and therapeutic target for cardiac fibrosis is galectin-3, which was linked to the development of LHF and also mortality and RV dysfunction in patients with PAH (83). In the murine PAB model, galectin-3 knockout or inhibition and also the anti-fibrotic agent pirfenidone attenuated RV fibrosis, but did not significantly affect RV function (83).

HDAC inhibitors

There is growing interest in epigenetic mechanisms in CVD. An important element of epigenetic regulation is histone acetylation, controlled by histone acetyltransferases and histone deacetylases (HDACs), which influences cell proliferation and survival. Pan-HDAC and selective HDAC inhibitors have been employed in PAH and RV pressure overload models, yet with inconsistent results. Several studies have observed reduced PA remodeling, and with this reduced PA pressure, PVR and RVH in different PAH models (84,85,87,89) (Table 2). One study could not detect any improvement of PA or RV remodeling in the SuHx rat model (88). In PAB-exposed rats, HDAC inhibition even had detrimental effects on RV function (86). These discrepancies might be related to the fact that HDAC activation is substantially different in the pulmonary circulation in different PAH models, and is further different between lung and RV (88). The potential anti-angiogenic and pro-apoptotic effects of HDAC inhibition, which may be beneficial in PA remodeling in PAH, could exert detrimental effects on the RV myocardium (88).

Approaches specifically addressing PA remodeling in PAH

A number of therapeutic approaches that clearly target PAH-specific mechanisms of PA remodeling are under investigation, and have been extensively reviewed elsewhere (110,113,143-146).

The pulmonary vasculature in PAH presents with a

distinct phenotype of hyperproliferation, resistance to apoptosis and activation of specific signaling pathways (146). Current research focuses on a variety of molecules, with ambiguous results regarding the RV. For example, oncologic drugs have been evaluated for PAH therapy. Imatinib is a tyrosine kinase inhibitor that targets, amongst others, platelet-derived growth factor receptor (PDGFR) signaling, which importantly contributes to maladaptive PA remodeling in PAH. Imatinib impressively reversed pathological remodeling in experimental PAH (82). However, given that PDGF exerts positive effects on the myocardial level, e.g., mediates adaptive remodeling upon pressure overload (147,148), the net benefit of imatinib on RHF in PAH remains elusive. Moreover, serious adverse events were observed in clinical studies, which resulted in termination of a recent trial (NCT01117987). Still, given promising results from investigations of PAH patients (32,33), tyrosine kinase inhibition is under new clinical investigation in the UK ("Positioning Imatinib for Pulmonary Arterial Hypertension"; NIHR128465).

Modulation of the bone morphogenetic signaling in the pulmonary vasculature, and possibly also in the RV, is currently a "hot topic" in the field of PH (116,149): Calvier *et al.* identified PPAR γ as the missing link that regulates the complex balance between mitogenic, glucose metabolism-promoting transforming growth factor (TGF)- β 1 signals and vasoprotective BMP2/BMP2 in vascular SMC (150). Several comprehensive studies aimed at either restoring BMP2 expression and function using FK506 (151,152), or rebalancing TGF- β /BMP signaling using the PPAR γ agonist pioglitazone (78,150,153) or ACTRIIA-Fc (sotatercept) which had therapeutic effects both at the preclinical (154) and clinical levels (NCT03738150). In addition, SMAD-specific E3 ubiquitin protein ligase 1 (SMURF1) has been identified as a critical regulator of BMP signaling, given that SMURF1 blood levels were increased in PAH patients and SMURF1-deficient mice were protected from PAH in the SuHx model (155). Early clinical studies of BMP-modulating therapies in patients with PAH provide positive proof of concept and the development of novel therapies in the area offers the promise of future patient benefit (sotatercept PULSAR phase 2 late breaking clinical study, American Thoracic Society 2020).

Non-approved cell-based therapies

Several key structural and molecular differences have

been identified in both preclinical and clinical studies that distinguish between adaptive and maladaptive pathways for RV remodeling. Although the mechanisms underlying the shift from an adaptive to maladaptive phenotype are only beginning to be understood, it is clear that metabolic and neurohormonal dysfunction, capillary rarefaction, and profibrotic pathways are emerging as important elements (3). In particular, reduced microvascular density is thought to be a harbinger of maladaptive remodeling, and a leading cause of RHF in PAH patients (143,156). RV biopsies from PAH patients with RHF show reduced microvascular density, as well as downregulation of angiogenic genes such as, VEGF and Ang-1 (157,158). This suggests that the intrinsic link between microvascular rarefaction and pathological RV remodelling may drive the progression of RV failure in some patients that could be treated with angiogenic cell therapies. Indeed, stem cell therapies with pro-angiogenic properties targeted towards the RV may represent a novel therapeutic avenue to improve its function.

The RV may represent an excellent target for cell-based therapies given its tremendous plasticity and capacity to reverse remodeling when the afterload is removed. However, to date, most cell therapy studies have targeted the pulmonary circulation, though some of the benefits may be attributable to effects of the therapy on the RV. Mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and cardiac progenitor cells (CPCs) have all demonstrated efficacy in reducing RV systolic pressure (RVSP) and RV remodeling in animal models of PAH (159). Many of these studies also noted ancillary beneficial effects on RV function; however, it is not possible to discern whether cell therapy had a direct benefit on the RV or whether any improvements occurred merely as a result of afterload reduction. For this reason, a model system that is not affected by confounding influences from effects on the pulmonary vasculature, such as the PAB model, is needed in order to provide convincing evidence for a direct effect of cell therapy on the RV.

Moreover, these studies used intravenous, intrajugular, or intratracheal routes of administration that favours targeting of cells to the lung vasculature, and it is not known to what extent (if any) cells would be delivered to the RV. Indeed, studies of cell therapies targeted to the LV have revealed poor cell engraftment after intravenous delivery (160). However, this does not exclude the possibility of an indirect paracrine effect following the delivery of stem/progenitor cells or cell-derived extracellular components [e.g., extracellular vesicles (EVs), miRNA]; for example,

a reduction in inflammatory mediators, which could beneficially effect RV remodeling. Nonetheless, for a cell-based therapy to have maximal impact on RV function, local delivery of stem cells either by intramyocardial or intracoronary injection, would likely be preferable. *Table 4* summarizes preclinical studies that have used models with a relatively fixed RV afterload (i.e., PAB or chronic thromboembolic models) to assess the effects of targeted RV delivery of CPCs, EPCs, mononuclear cells (MNCs), or MSCs on RV structure and function. It is encouraging that all these studies demonstrated improved RV function associated in many cases with increased RV capillary density, decreased RV fibrosis and RVH, as summarized in this table.

Although clinical trials targeting the LV have demonstrated that stem cell delivery via transcatheter, transatrial, intramyocardial and intravenous delivery is safe and feasible, they have produced mixed results regarding efficacy. There is more limited literature of targeted RV clinical cell therapy trials, and much of the available human evidence for RV targeted therapy comes from pediatric patients with CHD (10). The TICAP (Transcatheter Infusion of Cardiac Progenitor cells) phase 1 trial evaluated the safety of autologous cardiosphere-derived cells (CDC) in children with hypoplastic left heart syndrome (systemic RV) (165). In these patients, intracoronary CDC administration was safe and improved RVEF and clinical status as compared to patients that received standard therapy. The efficacy of CDC therapy for this patient population was recently confirmed in the phase 2 PERSEUS trial (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) (166). Results demonstrate that CDCs markedly improve RV function (RVEF, 3 months \uparrow 6.4%, 12 months \uparrow 7.4%) and heart failure status and mitigate cardiac fibrosis. Moreover, in a preclinical PAB model, intramyocardial administration of CPCs improved RV contractile function, increased RV microvascular density, and reduced RVH and fibrosis (161). The study further demonstrated that the proangiogenic and antifibrotic actions of CPCs were mediated by exosomes (CD9⁺, 96.1 \pm 6.1 nm). A phase 1 study (ALPHA trial: NCT03145298) is currently evaluating the safety and feasibility of intravenous delivery of allogeneic human CDC in patients with PAH. In this trial, an exploratory endpoint is evaluating the effect of cell therapy on RV function and pulmonary hemodynamics. Two other trials are currently ongoing assessing the safety and efficacy of adipose-derived MSC (NCT04055415), and eNOS-enhanced

Table 4 Preclinical studies evaluating the efficacy of RV targeted cell therapy

Studies	Model	Cell type	Delivery	RV benefit
Trac <i>et al.</i> , 2019 (161)	Rat PAB	CPC	RV intramyocardial	↑RV systolic function ↑RV capillary density ↓RV fibrosis
Wehman <i>et al.</i> , 2017 (162)	Swine PAB	CPC	RV intramyocardial	↑RV systolic function ↓RV dilation ↑RV capillary density ↓RV fibrosis
Loisel <i>et al.</i> , 2019	Swine CTEPH Model	EPC	RCA infusion	↑RV Systolic function ↓RVH ↑RV capillary density
Oommen <i>et al.</i> , 2015	Mice PAB	UCB-MNCs	RV intramyocardial	↑RV systolic function ↑RV capillary density ↓RV fibrosis
Chery <i>et al.</i> , 2019 (163)	Rat PAB	Nt-MSCs	Sheet scaffold application to the free wall of the RV	↑survival ↑RV systolic function ↑RV capillary density ↓RV fibrosis
Liufu <i>et al.</i> , 2020 (164)	Mice PAB	BMSCs	RV intramyocardial	↓RVH ↑RV capillary density ↓RV fibrosis
Davies <i>et al.</i> , 2010	Sheep PAB	CBSC	Epicardial injection	↑RV systolic and diastolic function

CBSC, cord blood stem cell; PAB, pulmonary artery banding; CTEPH, chronic thromboembolic pulmonary hypertension; BMSCs, bone marrow derived MSC; UCB, umbilical cord blood; Nt-MSCs, neonatal thymus MSC.

EPCs (SAPPHIRE, NCT03001414) in patients with PAH. While these studies are targeting the lung vasculature by delivering cells intravenously, RV structure and function will be assessed as a secondary endpoint.

Several recent studies have explored the intravenous effect of MSC-derived EVs, on PA remodeling, RVH and pressure, in rodent models of PAH, such as SuHx rat (167,168) and MCT rat (169). Others have investigated the effect of intravenous delivery of EVs for treatment of PH associated with bronchopulmonary dysplasia (170), and a clinical trial is underway (NCT03857841). However, as mentioned above no direct effect on the hypertensive RV can be demonstrated in these studies due to the animal models used.

To our knowledge, no human trial is currently

assessing the impact of intramyocardial or intracoronary administration of stem cells or stem-cell derived components (e.g., EVs) in patients with PAH and RV failure. This relatively unexplored therapeutic avenue may have tremendous potential as RV function is a critical determinant of prognosis, with RV failure representing the leading cause of death in these patients (1). The accumulating preclinical evidence seems to suggest a direct and robust RV benefit, providing a strong rationale for future translation to human trials.

Non-approved RNA-based therapies

Noncoding RNAs, including microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), and

Y RNAs in CVD have been comprehensively reviewed elsewhere (171-173). Although non-coding RNA-based therapy in LHF has received significant attention in both preclinical models and, to a lesser degree, in clinical trials (NCT04045405; NCT03603431) (173), its therapeutic potential in RV failure remains largely unexplored.

At the molecular level RV remodeling is characterized by a return to a fetal-like pattern of energy substrate metabolism, enhanced inflammation and ischemia due to capillary rarefaction (174) promoting the loss of cardiomyocytes and the appearance of pronounced interstitial and perivascular collagen deposition (fibrosis) (175). With the technological advances of “omics”, numerous studies have linked these changes to the altered expression of many non-coding RNAs including lncRNAs, miRNAs and circRNAs (176-178), but so far only few miRNAs have been therapeutically investigated directly in the RV.

miRNA-based therapies for PAH-associated RV dysfunction

Although *in vivo* modulation of miRNA expression levels is challenging (179), the development of synthetic small duplex RNA designed to specifically inhibit (AntimiR) or supplement (mimics) endogenous miRNAs now represents a promising approach to treat various disorders. This approach has been extensively explored in animal models of PH to prevent or reverse pulmonary vascular remodeling (180-183), and most of the studies showed improvement in PH and in RV function. However, to the best of our knowledge, only the role of miR-126 (158), miR-208 (184), and miR-223 (185) have been investigated in RV failure independently of the effects on the lungs. miR-126 is known as an angiogenesis-regulating miRNA. It is one of the few EC-specific miRNAs, and regulates vascular integrity and developmental angiogenesis. miR-126 was downregulated in both the failing human and rat RV and negatively correlated with disease severity. Its enforced expression *in vivo* using mimics improved RV function by increasing vascular density and reducing fibrosis (158). Along with miR-126, the muscle-specific miRNA miR-208a was also decreased during RV decompensation. Its diminution associated with the rise in TNF-mediated inflammatory response was suggested to indirectly repress the transcription factor MEF-2, thus promoting entrance into a decompensated phase (184). Finally, miR-223 is known to be downregulated in many hyperproliferative diseases like cancer and PH, but has also profound effects on RV function independent of

its function in the lung. miR-223 overexpression targeting cardiomyocytes improved CO in animals exposed to HOX, whereas its downregulation in rats subjected to PAB elicited opposite effects (185). Despite the fact that RV-based research remains the Cinderella area of most PH research, several new treatments exhibiting important RV improvement in PH models have been preclinically identified and are now under clinical investigation (144). Although for most of the new (experimental and approved) therapies effects on non-coding RNA signaling remains unknown, some of these treatments have clearly shown their ability to regulate non-coding RNA expression. For example, PPAR γ activation by pioglitazone fully reversed PH and prevented RV failure, as mentioned above. The restoration of disturbed lipid metabolism and mitochondrial morphology/function led to normalization of the expression of several miRNAs (78). Consistently, pre-miRs-197 and -146b greatly repressed genes that drive FAO (Cpt1b, Fabp4) in cultured primary cardiomyocytes. Importantly, these major pathogenic findings in SuHx rats were recapitulated in human end-stage PAH, i.e., miR-197 and miR-146b were upregulated in the pressure-overloaded failing RV (78). A clinical trial was launched on the use for pioglitazone in PAH (NCT00825266) but was terminated due to difficulties in recruitment, probably because of insulin resistance being a mandatory inclusion criterion.

In human PSMC, the BMP2/BMP2-PPAR γ axis upregulated miR-148a and miR-331-5p, thereby inhibiting SMC proliferation and glucose metabolism (150,153). miR-331-5p downregulated the platelet isoform of phosphofructokinase (PFKP) messenger RNA (150), a rate limiting enzyme of glycolysis and, as such, a pro-proliferative factor that is overexpressed *in situ* in the pulmonary arteries of patients with idiopathic PAH. However, neither the aforementioned axis nor downstream miRNA have been studied systematically in the hypertensive RV or cultured cardiomyocytes.

LncRNA-based therapies for RHF

It has been demonstrated recently, that the lncRNA H19 is causally involved in pathological RV remodeling and has a predictive value (186). Silencing H19 reduced RV remodeling and improved RV function in MCT and PAB rat models. In PAH patients it was upregulated particularly in decompensated RV, and circulating H19 levels predicted survival in PAH patients (186). Whereas these findings identify H19 as a promising therapeutic target, they at

the same time underscore the fundamental differences between the LV and RV, given that H19 has been shown to be downregulated in failing LV and that gene therapy augmenting cardiac H19 levels reversed pressure-induced LHF (187).

PA denervation

Patients with PAH show signs of sympathetic overdrive (188) that is associated with adverse clinical outcomes (189). Lungs and pulmonary vasculature contribute to circulating catecholamine levels (190) and are one of the major sites of ACE expression and AngII production. Modulation of the sympathetic and renin-angiotensin-aldosterone systems is an established treatment for heart failure. Both β -blockers and ACE inhibitors have been shown to attenuate disease in experimental models (40,42,191), however, there is no evidence of benefit in patients with PAH (20,192,193). Targeted, catheter-based, renal denervation reduces blood pressure in patients with systemic hypertension both on or off anti-hypertensive therapy (194-196). The development of such technologies offers the opportunity to modulate sympathetic activity through targeted denervation of the pulmonary vasculature, potentially avoiding the adverse effects of systemically active therapies.

Sympathetic and parasympathetic nerves derived from the spinal ganglions (sympathetic) and vagus nerve (parasympathetic) merge to form the pulmonary plexus, which was larger around the main PA (197). Running with the pulmonary vasculature, nerves branch, reducing in size after the bifurcation of the main PA forming a circumferential network around the vessels before the hilum of the lungs. Preclinical studies have demonstrated that pulmonary artery denervation (PDN) improves pulmonary haemodynamics in acute (198,199) and chronic models of PH (200). The application of radiofrequency energy, which induces long-term alterations in nerve conduction, to a specific location at the bifurcation is reported to provide an acute improvement in hemodynamic status that persists to 3 months despite the withdrawal of disease-specific therapy in patients with PAH (201). Early indicators of efficacy have also been reported in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and left heart disease associated PH (202,203).

Current European guidelines indicate that patients with PAH and high-risk features should be treated with two disease-specific therapies (204). Using an alternative

catheter-based ultrasound denervation procedure (197) the recent TROPHY study enrolled 23 patients with PAH established on a minimum of dual oral therapy (205). Four to 6 months following ultrasound PDN, PVR was reduced by $94 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ and 6-minute walking distance (6MWD) increased by 42 m, a result that is congruent with a minimally important clinical difference of 33 m (206). The observed increase in daily activity and improved clinical risk score further indicate a potential benefit of this novel therapy, on a background of guideline-directed medical therapy.

Further studies are required to evaluate efficacy, safety, and clinical impact of PDN in patients with PAH and other forms of pulmonary hypertension.

Mechanical circulatory support (MCS)

In contrast to MCS for LHF, MCS for RHF is still in its early stages and experience is, with a few exceptions, limited to case reports and series. Indications comprise acute myocardial infarction, pulmonary embolism, post-cardiac surgery, post heart transplantation, myocarditis as well as decompensated chronic heart failure and thus mostly involve concomitant left ventricular disease. A special indication is RHF after LVAD implantation. It is important to differentiate between acute MCS and efforts to achieve durable results. In general, RHF may be bridged by bypassing the RV [right atrium (RA) to PA] or the RV and LV [RA to aorta (AO)], and there is considerable debate which approach should be used in different conditions. Most centers prefer a bypass of both ventricles in conditions where pulmonary resistance is elevated by the condition, such as pulmonary hypertension or pulmonary embolism. In contrast, a pure RV bypass is usually employed when RV failure results from a cardiac cause, such as RV myocardial infarction.

Acute MCS

The percutaneous Impella RP microaxial pump is introduced via the femoral vein and transports blood from the RA to the PA via an impeller. It has no option to oxygenate blood. The Tandem Heart right ventricular assist device (RVAD) requires two femoral vein cannulations, one for the draining cannula placed in the RA and one for the outflow cannula placed in the PA. Cannulation of right jugular vein is used in some cases. Additional oxygenation and carbon dioxide removal is possible with

Table 5 Overview of mechanical circulatory support

Device	Draining	Outflow	Approved time of use	Studies
Acute MCS				
Impella RP	RA	PA	14 d	n=30 (18 LVAD, 12 post-cardiac surgery), 30 d survival 73% (recover right) (208)
Tandem Heart	RA	PA	4 d	n=46 (18 post-cardiac surgery, 12 myocardial infarction, 5 LVAD, 5 post HTX), in-hospital mortality 57% (209)
V-Pa ECMO	RA	PA	30 d	Restricted to case series
V-A ECMO	RA	FA	30 d	n=179 (70 post-cardiac surgery, 46 myocardial infarction), in-hospital mortality 39% (210)
CentriMag	RA	PA	30 d	n=38 (14 myocardial infarction, 12 LVAD, 12 post-cardiac surgery), mean duration of support 13 d (1–60 d), in-hospital mortality 58%, 30 d (211)
Durable MCS				
Berlin Heart	RA	PA	–	Mostly children, restricted to case series
Heart Ware/ Heart Mate 3	RV	PA	–	Heart Ware (meta-analysis): n=56 (85% non-ischemic cardiomyopathy), 30-day mortality 9%, time on device 156 (IQR, 66–351), heart transplantation 46% (212) Heart Mate 3: n=14 (50% DCM; 28% ICM), 9 patients died within 6 months, 1 successful heart transplantation, 8 patients continuing support for 266 (95–636 days) (213)
Total artificial heart*	RA	PA (requires RV explantation)	–	n=450 (50% DCM, 20% ICM), 266 underwent heart transplantation, 12-month survival 53% (214)
BiVACOR*	Requires native cardiectomy		–	Pre-clinical
RealHeart*	Requires native cardiectomy		–	Pre-clinical
Carmat*	Requires native cardiectomy		–	Early feasibility trial approved

*, biventricular support devices. DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; FA, femoral artery; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; PA, pulmonary artery; RA, right atrium; RV, right ventricle; V-A, veno-arterial; V-Pa, veno-pulmonary arterial.

this system. The same configuration can be built with standard extracorporeal membrane oxygenation (ECMO) machines, using a femoral venous draining cannula and a flexible supply cannula, which is inserted through the jugular vein and the RV to the PA (207). The Protek Duo dual-lumen cannula, which is also commonly inserted via the jugular vein, combines right artery draining and PA outflow in one cannula. Veno-arterial ECMO (V-A ECMO) differs from the previous systems in that it delivers blood from the RA via an oxygenator to the arterial circulation. As a consequence, these systems increase left ventricular afterload, thereby promoting pulmonary edema particularly in the presence of left ventricular dysfunction. The most important characteristics of the described systems are summarized in *Table 5*.

Durable MCS

Durable MCS devices were formerly implanted as bridge-to-transplantation. Recently, durable MCS is more frequently employed as destination therapy, given the shortage of donor hearts. In addition, it is used as bridge-to-decision, i.e., in instances where support is required for prolonged time intervals. All systems require surgical implantation and can be divided into those employing extracorporeal pumps (Berlin Heart Excor, Total artificial heart) and fully implantable systems. For the former, in-hospital treatment is mandatory because of their set-up and the intense supervision required. The latter mostly comprise LVAD connected to the RA (draining) and PA (outflow), with implantation techniques increasingly being

adapted and smaller systems emerging which might be better suitable for RV support. Evidence for all of these systems is restricted to case examples.

Conclusion and perspective

Despite remarkable advancements in PAH therapy during the last decade, PAH-related mortality, especially from RV failure, remains high. It is a matter of debate whether PAH patients will substantially benefit from therapies directly targeting the RV myocardium. Particularly promising, novel therapeutic targets in RHF include RV metabolic imbalance, inflammation and oxidative stress.

Besides pharmacological therapies (be it “repurposed” or newly developed), cell and RNA-based therapies have generated substantial recognition, due to solid preclinical and early clinical study results. Discrepant mechanistic profiles in different pre-clinical models and contrasting pathomechanisms in the pulmonary vasculature and RV myocardium in PAH complicate the development of effective therapeutics. Further experimental research and clinical studies are required to successfully advance therapeutic options for PAH and RV failure.

Acknowledgments

Funding: VR is supported by the German Research Foundation (DFG, RU1678/3-3). GH receives financial support from the DFG (HA4348/2-2 and HA4348/6-2 KFO311), the Federal Ministry of Education and Research (BMBF ViP+ program-03VP08053; BMBF 01KC2001B) and the European Pediatric Pulmonary Vascular Disease Network (www.pvdnetwork.org). AMKR is supported by a Wellcome Trust Clinical Research Career Development Fellowship (206632/Z/17/Z).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Cardiovascular Diagnosis and Therapy* for the series “Right Ventricular Dysfunction”. The article was sent for external peer review organized by the Editor-in-Chief and the editorial office.

Peer Review File: Available at <http://dx.doi.org/10.21037/cdt-20-592>

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <http://dx.doi.org/10.21037/cdt-20-592>). The series “Right Ventricular Dysfunction” was commissioned by the editorial office without any funding or sponsorship. GH served as the unpaid Guest Editor of the series. LCN reports grants and personal fees from Abiomed, grants and personal fees from Cytosorbents, personal fees from Maquet, personal fees from Orion, personal fees from Abbott, personal fees from Zoll, personal fees from Bayer, non-financial support from Edwards, all outside the submitted work. AMKR reports grants from Medical Research Council (UK) and Wellcome Trust (206632/Z/17/Z), research support from Actelion, Novartis, Medtronic, Abbott, and personal fees and research support from SoniVie and Endotronix. SB reports personal fees from Actelion, personal fees from Janssen, personal fees from Allienneaire, personal fees from morphic therapeutic, outside the submitted work. The other authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Klinke A, Schubert T, Müller M, Legchenko E, Zelt JGE, Shimauchi T, Napp LC, Rothman AMK, Bonnet S, Stewart DJ, Hansmann G, Rudolph V. Emerging therapies for right ventricular dysfunction and failure. *Cardiovasc Diagn Ther* 2020;10(5):1735-1767. doi: 10.21037/cdt-20-592