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Cardiac biomarkers as indicators of right ventricular dysfunction and recovery in chronic thromboembolic pulmonary hypertension patients after balloon pulmonary angioplasty therapy – a cardiac magnetic resonance imaging cohort study

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Abstract

Background: In chronic thromboembolic pulmonary hypertension, right heart failure determines outcome. Balloon pulmonary angioplasty therapy allows right heart recovery, which can be monitored by cardiac magnetic resonance imaging. This study evaluates whether cardiac biomarkers (NT-proBNP, MR-proANP, sST2, and PAPP-A) are associated with cardiac magnetic resonance imaging findings prior to and after balloon pulmonary angioplasty therapy.

Methods: This observational cohort study enrolled 22 chronic thromboembolic pulmonary hypertension patients who underwent balloon pulmonary angioplasty therapy and completed a six-month follow-up including cardiac magnetic resonance imaging. Biomarker levels were compared with findings for right heart morphology and function derived from cardiac magnetic resonance imaging.

Results: Pulmonary hemodynamics improved after balloon pulmonary angioplasty therapy [pulmonary vascular resistance: 7.7 (6.0–9.0) vs. 4.7 (3.5–5.5) wood units, $p < 0.001$; mean pulmonary artery pressure 41 (38–47) vs. 32 (28–37) mmHg, $p < 0.001$]. Cardiac magnetic resonance imaging findings indicated right heart maladaptation at baseline and recovery after therapy [right ventricular end-diastolic volume 192 (141–229) ml vs. 143 (128–172) ml, $p = 0.002$; right ventricular end-systolic volume 131 (73–157) ml vs. 77 (61–99) ml ($p < 0.001$); right ventricular ejection fraction (RVEF) 34 (28–41) % vs. 52 (41–54) %; $p < 0.001$]. Biomarker level cut-offs [NT-proBNP 347 ng/L (area under the curve (AUC) 0.91), MR-proANP 230 pg/L (AUC 0.78), PAPP-A 14.5 mU/L (AUC 0.81), and sST2 48.0 ng/ml (AUC 0.88)] indicated a RVEF $\leq$ 35% at baseline. The dynamics of NT-proBNP ($rs = -0.79$; $p < 0.001$), MR-proANP ($rs = -0.80$; $p < 0.001$), and sST2 ($rs = -0.49$; $p = 0.02$) correlated inversely with the improvement in RVEF after therapy. A relative decrease of NT-proBNP $< 53\%$ (AUC 0.86) and MR-proANP $< 24\%$ (AUC 0.82) indicated a limited RVEF response.

Conclusions: In chronic thromboembolic pulmonary hypertension patients, cardiac magnetic resonance imaging findings illustrate right heart failure and recovery after balloon pulmonary angioplasty therapy. Cardiac biomarker levels correlate with right heart parameters at baseline and their dynamics after therapy.

Keywords

Pulmonary hypertension, balloon pulmonary angioplasty, right ventricle function and dysfunction, risk stratification and biomarkers

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Chronic thromboembolic pulmonary hypertension (CTEPH) is diagnosed in about 3% of patients who survive an acute pulmonary embolism.[1] Progressive impairment of pulmonary hemodynamics burdens the right heart and causes maladaptive morphological and functional right heart remodeling.[2] The ensuing right heart failure is the major determinant of outcome in CTEPH.[2,3]

Surgical pulmonary endarterectomy is the first-line therapy for CTEPH.[1,4] In inoperable patients, a sequence of medical therapy with riociguat and balloon pulmonary angioplasty (BPA) is the recommended therapeutic concept.[1,4] Both therapeutic approaches improve pulmonary hemodynamics and thus allow right heart recovery.[5,6] Notably, it has been suggested that changes in right heart function under specific therapy for pulmonary hypertension (PH) outperform pulmonary hemodynamics as a predictor of outcome.[7] A structured diagnostic work-up focused on the individual severity of right heart disease is therefore crucial for optimal patient management.

Cardiac magnetic resonance imaging (CMR) is the reference imaging modality for the right heart, facing particularly its complex anatomy with 3D-based measurement of dimensions and function.[8] In PH, CMR provides detailed information about the severity of morphological and functional right heart maladaptation.[9,10] However, availability, costs, and the necessity of specific expertise limit the use of CMR as a standard approach.

Several noninvasive biomarkers were found to be associated with different aspects of right heart maladaptation and failure. Hemodynamic right heart stress can be estimated by measurement of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) and mid-regional pro-atrial natriuretic peptide (MR-proANP).[11,12] The conversion from hemodynamic stress to cardiac tissue remodeling as a secondary maladaptive response to chronic pressure overload is more difficult to address. Biomarkers as soluble suppression of tumorigenicity 2 (sST2)[13] and pregnancy-associated plasma protein-A (PAPP-A)[14] which are expressed in response to mechanic myocardial stress but also contribute to inflammatory and fibrotic tissue remodeling pathways might be of use in this context. The current study investigates the potential of these biomarkers as indicators of right ventricular function and dimensions by using CMR as a reference method in a cohort of patients with inoperable CTEPH treated by BPA.

Methods

Study population

The present observational cohort study consecutively included 22 patients with confirmed inoperable CTEPH who were treated by BPA, completed a six-month follow-up (6-MFU) after therapy, and underwent CMR at both baseline and follow-up at the study center. The patients were deemed to be inoperable because of peripheral obstructive lesions of the pulmonary arteries. All patients were discussed in a multidisciplinary CTEPH conference to confirm the diagnosis and decide about the individual treatment. The diagnostic and therapeutic management of CTEPH patients at our center was recently published.[6,15] CMR, which is not routinely performed in all CTEPH patients, was used as supplementary imaging in these 22 patients for extended right heart assessment. The individual decision to perform a CMR was made by the multidisciplinary CTEPH conference.

Only a subset of 15 (68%) patients was treated with riociguat prior to BPA therapy, as prior to 2014 there was no approved medication for CTEPH. Meanwhile, riociguat is recommended in the guidelines.[4] Thus, we adjusted our treatment approach over time, and riociguat is administered at least for three months prior to BPA in inoperable CTEPH patients. There were no changes of medication between the baseline diagnostic assessment prior to interventional BPA therapy and the follow-up.

All patients gave written informed consent. The ethics board of our University approved the study (AZ 43/14). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Right heart catheterization

Right heart catheterization was performed routinely via the right internal jugular vein using a 6F sheath and a standard Swan-Ganz catheter. The medication was not modified prior to or during the procedure.

Balloon pulmonary angioplasty

BPA interventional therapy was performed as a standardized technique as previously published in detail.[5,15]

Cardiac magnetic resonance imaging

Imaging was performed with a 1.5-T scanner system (Avanto; Siemens Healthineers, Erlangen, Germany; gradient strength and slew rate: SQ-Engine [45 mT/m at 200 T/m/s]) using a six-element phased array cardiac coil and a dedicated CMR protocol containing axial, coronal, and sagittal thoracic survey images, steady-state-free precession sequences (SSFP), CINE in two-chamber view, three-chamber view, four-chamber view, and stacked transaxial and short-axis views from base to apex.

SSFP imaging parameters were slice thickness 8 mm; field of view: 300 × 400 mm; matrix 256 × 154; TR 59.62; and TE 1.15. The SSFP images were obtained during breath-hold, and the LV and RV systolic and diastolic volumes (absolute values) were calculated from short-axis and transaxial CINE images. Measurements were performed on end-diastolic images (first phase after the R-wave trigger) and end-systolic images (CINE with the visually smallest cavity area). Endocardial contours of the left and right ventricle were obtained by manual tracing with exclusion of papillary

muscles and trabeculae from the cavity. Ventricular volumes were estimated using the Simpson rule. The left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) was calculated as [end-diastolic volume – end-systolic volume]/end-diastolic volume. The post-processing was performed with the ARGUS software package (Siemens Syngo MMWP Version VE40A; Siemens Healthineers).

The radiologists who performed the imaging diagnostics were blinded to results from biomarker analysis.

Laboratory assessment

Venous blood samples for biomarker analysis were collected as serum samples in serum tubes (S-Monovette®, Sarstedt, Nümbrecht, Germany) at baseline prior to BPA therapy and at the 6-MFU, each at the same time as CMR and were processed for storage immediately. All serum samples were transferred to plain uncoated tubes for storage at a temperature of –80°. The median storage time was 43 (41–46) months. All measurements were carried out batch-wise on once thawed samples by experienced staff blinded to patient characteristics.

NT-proBNP levels were measured using an electrochemiluminescence immunoassay (NT-proBNP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The limit of detection (LOD) for this assay is 5 ng/L; concentrations above the measuring range are reported as >35,000 ng/L. The lowest concentration measurable with a coefficient variation (CV) of 20% is 50.0 ng/L. At the cut-off value of 150 ng/L the CV is <3%.

MR-proANP levels were measured by TRACE (time-resolved amplified cryptate emission) technology (BRAHMS MR-proANP KRYPTOR assay, Kryptor Compact Plus, BRAHMS GmbH, Hennigsdorf, Germany). The LOD is 2.1 pmol/L; concentrations above the measuring range are reported as >10,000 pmol/L. The intra-assay is CV ≤ 5%; inter-assay CV ≤ 6.5%.

sST2 levels were measured using an electrochemiluminescence immunoassay (Presage ST2 assay, Critical Diagnostics, San Diego, CA, USA). The LOD is 1.8 ng/ml; concentrations above the measuring range are reported as >200 ng/ml. At a concentration between 33 and 159 ng/ml, the CV ranges from 5.5 to 4.8%.

PAPP-A was measured by time-resolved amplified cryptate emission (BRAHMS PAPP-A KRYPTOR Assay, Thermo Scientific, BRAHMS GmbH, Henningsdorf, Germany). The LOD is 0.004 U/L; concentrations above the measuring range are reported as >90 U/L. The mean CV is 3.1%.

Statistical analysis

In consideration of the small study cohort, all continuous variables are expressed as median and interquartile range (IQR). Categorical variables are reported as number and percentage. Subcohorts at baseline, prior to BPA therapy, or at the follow-up were compared using the Mann-Whitney U test for all other continuous variables. The χ^2 test and Fisher-Yates test were used for categorical variables. Parameters that were obtained at baseline and at the 6-MFU were subjected to paired sample testing using the Wilcoxon signed-rank test. Correlations were analyzed using bivariate Spearman correlation (r_s).

The study assessed the diagnostic performance of non-invasive biomarkers to indicate severe right heart dysfunction at baseline and the change of right heart function after BPA therapy, using receiver operating characteristics (ROC). In the literature, inconsistent data about optimal RVEF cut-off values to predict outcome in cardiac diseases are reported[16]; however, a RVEF ≤ 35% derived from CMR was strongly associated to worse outcome in patients with pulmonary artery hypertension.[7] Accordingly, we predefined severe right heart dysfunction as a RVEF ≤ 35%, quantified by CMR.

We further defined a limited change of right heart function after therapy as a relative change of RVEF ≤ 25% compared to the baseline RVEF. Biomarkers with a correlation ($r_s \geq |0.5|$) to RVEF change after therapy were analyzed in this context.

Results are presented as area under the curve (AUC) with corresponding 95% confidence intervals (CIs). The optimal cut-off values with regard to study outcomes were calculated using Youden index quantification.

To assess the prognostic performance of optimal biomarker cut-off levels with regard to study outcomes, sensitivity, specificity, and negative (NPV) and positive (PPV) predictive values were calculated. Results are presented as odds ratios (OR) with corresponding 95% CIs.

Statistics were performed with SPSS software (IBM Corp., Armonk, NY, USA), version 21.0. A two-tailed p value <0.05 was considered to be statistically significant.

Results

Characteristics of the study cohort and treatment effects

The sociodemographic data and comorbidities of all 22 patients (12 women; median age [IQR] 70 [63–77] y) enrolled in the study are presented in Table 1. In all patients, the BPA therapy was indicated due to obstructive lesions of the pulmonary arteries, which were too peripheral for a surgical pulmonary endarterectomy. The interventional treatment included 122 BPA sessions, a median of 6 (5–7) per patient, with a median number of 10 (9–12) treated vessels. Table 1 shows the effects of therapy on physical capacity and hemodynamic findings.

Biomarker measurement and CMR findings at baseline

The detailed findings from CMR and biomarker measurements at baseline are given in Table 1. The majority (n = 19;

86%) of patients showed normal left ventricular dimensions and function at baseline. In three patients, the LVEF was mildly (n = 1) or moderately (n = 2) impaired. The levels of all four biomarkers measured, particularly the natriuretic peptides, correlated with right ventricular dimensions and RVEF at baseline (Table 2).

A total of 14 (64%) patients showed severely impaired RVEF of ≤35% at baseline. These patients were characterized by higher baseline levels of NT-proBNP [RVEF ≤ 35%: 1427 (931–3377) ng/L vs. RVEF > 35%: 214 (45–779) ng/L; p = 0.001], sST2 [RVEF ≤ 35%: 65.3 (51.7–96.8) ng/mL vs. RVEF > 35%: 42.9 (39.0–50.7) ng/mL; p = 0.003], PAPP-A [RVEF ≤ 35%: 20.6 (14.9–29.5) mU/L vs. RVEF > 35%: 13.0 (8.7–17.3) mU/L; p = 0.02], and MR-proANP [RVEF ≤ 35%: 261 (105–422) pmol/L vs. RVEF > 35%: 122 (58–149) pmol/L; p = 0.04].

An NT-proBNP level of 347 ng/L (AUC 0.91), an MR-proANP level of 230 pg/L (AUC 0.78), a PAPP-A level of 14.5 mU/L (AUC 0.81), and an sST2 level of 48.0 ng/ml (AUC 0.88) were revealed to be the optimal cut-off values for identifying patients with severely impaired RVEF (Table 3).

None of the patients (n = 4) with all biomarker levels below the listed cut-off values at baseline showed an RVEF ≤ 35% at baseline.

Changes in biomarker and CMR findings during therapy

After BPA, morphological and functional right heart parameters improved (Table 1). The absolute levels of all four biomarkers decreased after therapy (Table 1). The relative change in the RVEF correlated with the relative change in the levels of NT-proBNP (Fig. 1a), MR-proANP (Fig. 1b), and sST2 (Fig. 1c) after therapy, but not with changes in PAPP-A (Table 2). A total of 13 (59%) patients had an RVEF of ≥50% after BPA. A group of eight (36%) patients showed no significant (<25%) change of their RVEF after therapy. A relative change of the NT-proBNP level less than 53% (AUC 0.86) and a change of the MR-proANP level less than 24% (AUC 0.82) respectively was indicative for an unchanged RVEF (Table 3).

Discussion

The key findings of the current study were (I) CMR findings indicate a morphological and functional right heart impairment in CTEPH patients at baseline that improves after BPA therapy; (II) NT-proBNP, MR-proANP, sST2, and PAPP-A levels correlate with right ventricular dimensions and function at baseline; and (III) the relative change of biomarker levels, particularly NT-proBNP and MR-proANP, after therapy correlates with the relative improvement in right ventricular dimensions and function after BPA therapy.

CMR and biomarker findings at baseline

In CTEPH, impaired pulmonary hemodynamics burden the right heart, which leads to compensatory right heart remodeling and finally chronic right heart failure.[2] Considering this sequence, there is no doubt that the extent of pulmonary hemodynamic impairment is a determinant of disease severity in PH. However, the extent of maladaptive right heart remodeling as a fatal consequence can vary[9,17] and was suggested to be an even more consistent determinant of disease severity and outcome in PH than altered hemodynamics.[7]

CMR provides morphological and functional parameters of right heart maladaptation in pulmonary hypertension.[10,17–19] In comparison to reference values, gathered from CMR in healthy individuals,[20,21] the CTEPH patients in our cohort were characterized by distinct right ventricular dilatation and reduced RVEF, which is comparable to other CTEPH cohorts.[18,19,22]

Although CMR is the primary method for right heart assessment, it is unsuitable for a regular follow-up. Non-invasive biomarkers address different aspects of cardiac remodeling and might thus be a feasible tool for the assessment of structural and functional right heart impairment in PH.[11,12,23–27] Circulating levels of natriuretic peptides mirror myocardial stress due to pressure and volume overload and are established diagnostic and prognostic markers in heart failure.[28] In PH, natriuretic peptides are associated with secondary right heart failure and assessment of these biomarkers is recommended for screening, individual risk stratification, and therapy monitoring.[29] The current study found a strong correlation of NT-proBNP with right ventricular dimensions and function prior to BPA therapy, which is in line with the findings from other series.[25,30] The current guidelines on PH suggest an NT-proBNP level >300 ng/L as a cut-off to distinguish low-risk and elevated-risk patients.[29] Consistent with this, patients in our cohort with a severely impaired RVEF were identified by an NT-proBNP level ≥347 ng/L and showed a median level of 1427 ng/L at baseline, whereas patients with an RVEF > 35% had a median level of 214 ng/L. The correlation of MR-proANP levels with right heart CMR parameters was inferior to that of NT-proBNP, which might be explained by its mechanism of expression.[31] MR-proANP is produced in response to atrial stretch due to hemodynamic stress, and MR-proANP levels are related to right atrial pressure in CTEPH.[12] Considering that right atrial stress follows right ventricular deterioration in PH, right atrial failure is a strong indicator of right ventricular failure, but not vice versa.

In its role as a receptor for interleukin (IL)-33, ST2 regulates the tissue-protective effects of this cytokine and exists in both transmembrane (promoting) and soluble (opposing) isoforms.[13] An upregulation of the IL-33-(s)ST2 pathway was detected in relation to inflammation, tissue injury, and remodeling[32,33] and in the context of cardiac stress

Table 1. Patient characteristics and diagnostic findings (N = 22).

Sociodemographic characteristics and comorbidities			
Age, years, median (IQR)	70 (63–77)		
Female sex, n (%)	12 (55)		
Body mass index, kg/m^2, median (IQR)	24.3 (22.4–27.0)		
Diabetes mellitus, n (%)	None		
Arterial hypertension, n (%)	13 (59)		
Smoking, n (%)	8 (36)		
Coronary artery disease, n (%)	4 (18)		
Atrial fibrillation, n (%)	2 (9)		
Glomerular filtration rate, mL/min, median (IQR)	81 (68–93)		
Creatinine, μmol/L, median (IQR)	0.92 (0.75–0.99)		
History of cancer, n (%)	5 (23)		
Chronic obstructive pulmonary disease, n (%)	1 (5)		
History acute pulmonary embolism, n (%)	18 (82)		
History of splenectomy, n (%)	1 (5)		
History of chronic inflammatory disease, n (%)	none		
	Baseline	Follow-up	
Medication			
Novel oral anticoagulants (%)	16 (73)	21 (95)	
Vitamin K antagonist (%)	6 (27)	1 (5)	
Guanylate cyclase stimulator (%); Riociguat 1–7.5 mg/d	14 (64)	15 (68)	
Endothelin receptor antagonist; Bosentan 250 mg, Macitentan 10 mg	3 (14)	3 (14)	
Inhibitor of Phosphodiesterase 5; Tadalafil 40 mg	1 (5)	1 (5)	
	Baseline	Follow-up	p-value
Clinical status			
WHO FC I/II/III/IV	0/0/13/9	14/6/2/0	<0.001
6-MWD, m (IQR)	387 (333–472)	427 (357–451)	0.03
Echocardiography			
LVEF, % (IQR)	55 (55–58)	55 (55–58)	1.0
TAPSE, mm (IQR)	20 (17–22)	24 (22–26)	0.03
Right heart catheterization			
meanPAP, mmHg (IQR)	41 (38–47)	32 (28–37)	<0.001
Relative change in meanPAP, %	Decrease of 22 (12–29)		
PVR, wood units (IQR)	7.7 (6.0–9.0)	4.7 (3.5–5.5)	<0.001
Relative change in PVR, %	Decrease of 34 (21–49)		
Cardiac index, L/min/m^2 (IQR)	2.4 (2.1–2.8)	2.7 (2.4–3.1)	0.06
RAP, mmHg (IQR)	6 (5–9)	5 (4–8)	0.05
PCWP, mmHg (IQR)	9 (8–11)	9 (8–11)	0.85
Cardiac magnetic resonance imaging			
LVEDV, ml (IQR)	87 (81–99)	108 (95–130)	0.001
LVESV, ml (IQR)	33 (22–45)	37 (26–54)	0.08
LVEF, % (IQR)	65 (56–72)	65 (62–70)	0.12
RVEDV, ml (IQR)	192 (141–229)	143 (128–172)	0.002
RVEDV index, ml/m^2 (IQR)	100 (74–129)	84 (71–97)	0.001
RVESV, ml (IQR)	131 (73–157)	77 (61–99)	0.001
RVESV index, ml/m^2 (IQR)	76 (44–87)	46 (34–52)	<0.001
RVSV, ml (IQR)	66 (51–74)	73 (67–86)	0.003
RVSV index, ml/m^2 (IQR)	37 (28–43)	39 (35–51)	0.003
RVEF, % (IQR)	34 (28–41)	52 (41–54)	<0.001
Biomarkers			
NT-proBNP, ng/L	1122 (295–2365)	149 (71–341)	<0.001
sST2, ng/mL	52.6 (43.7–76.1)	44.7 (37.6–58.4)	0.002
PAPP-A, mU/L	17.2 (13.1–28.6)	11.7 (10.3– 13.5)	0.006
MR-proANP, pmol/L	145 (102–285)	125 (58–155)	0.002

Values are presented as n (%) or median (IQR). Abbreviations: LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; meanPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; RVESV: right ventricular end-systolic volume; TAPSE: tricuspid annular plane systolic excursion; WHO FC =World Health Organization functional class; 6-MWD: 6-minute walk test distance; 6-MFU: 6-month follow-up.

Table 2. Bivariate Spearman correlation of biomarker levels and right heart parameters derived from CMR findings and other diagnostic findings.

Parameter	NT-proBNP (ng/L)	MR-proANP (pmol/L)	sST2 (ng/ml)	PAPP-A (mU/L)
Baseline				
RVEDV, ml	$r_s = 0.68$; $p = 0.001$	$r_s = 0.34$; $p = 0.12$	$r_s = 0.36$; $p = 0.11$	$r_s = 0.46$; $p = 0.03$
RVEDV index, ml/m^2	$r_s = 0.73$; $p < 0.001$	$r_s = 0.49$; $p = 0.02$	$r_s = 0.45$; $p = 0.04$	$r_s = 0.47$; $p = 0.03$
RVESV, ml	$r_s = 0.80$; $p < 0.001$	$r_s = 0.46$; $p = 0.03$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.48$; $p = 0.02$
RVESV index, ml/m^2	$r_s = 0.81$; $p < 0.001$	$r_s = 0.56$; $p = 0.007$	$r_s = 0.58$; $p = 0.004$	$r_s = 0.42$; $p = 0.05$
RVEF, %	$r_s = -0.80$; $p < 0.001$	$r_s = -0.59$; $p = 0.004$	$r_s = -0.63$; $p = 0.002$	$r_s = -0.48$; $p = 0.02$
meanPAP, mmHg	$r_s = 0.27$; $p = 0.24$	$r_s = -0.01$; $p = 0.98$	$r_s = 0.19$; $p = 0.39$	$r_s = 0.22$; $p = 0.34$
PVR, wood units	$r_s = 0.61$; $p = 0.004$	$r_s = 0.50$; $p = 0.02$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.18$; $p = 0.44$
Cardiac index, L/min/m^2	$r_s = -0.73$; $p < 0.001$	$r_s = -0.67$; $p = 0.001$	$r_s = -0.61$; $p = 0.003$	$r_s = -0.13$; $p = 0.57$
RAP, mmHg	$r_s = 0.57$; $p = 0.03$	$r_s = 0.44$; $p = 0.04$	$r_s = 0.48$; $p = 0.03$	$r_s = 0.1$; $p = 0.66$
Relative change from baseline to 6-month follow-up				
RVEDV, %	$r_s = 0.56$; $p = 0.01$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.09$; $p = 0.68$	$r_s = 0.30$; $p = 0.17$
RVEDV index, %	$r_s = 0.56$; $p = 0.01$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.09$; $p = 0.68$	$r_s = 0.30$; $p = 0.17$
RVESV, %	$r_s = 0.83$; $p < 0.001$	$r_s = 0.89$; $p < 0.001$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.42$; $p = 0.05$
RVESV index, %	$r_s = 0.83$; $p < 0.001$	$r_s = 0.89$; $p < 0.001$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.42$; $p = 0.05$
RVEF, %	$r_s = -0.79$; $p < 0.001$	$r_s = -0.80$; $p < 0.001$	$r_s = -0.49$; $p = 0.02$	$r_s = -0.28$; $p=0.21$
meanPAP, %	$r_s = 0.13$; $p = 0.57$	$r_s = 0.02$; $p = 0.92$	$r_s = 0.08$; $p = 0.70$	$r_s = 0.005$; $p = 0.98$
PVR, %	$r_s = 0.34$; $p = 0.15$	$r_s = 0.27$; $p = 0.25$	$r_s = 0.57$; $p = 0.007$	$r_s = 0.006$; $p = 0.98$
Cardiac index, %	$r_s = 0.61$; $p = 0.003$	$r_s = 0.58$; $p = 0.005$	$r_s = 0.61$; $p = 0.003$	$r_s = 0.25$; $p = 0.27$
RAP, %	$r_s = 0.44$; $p = 0.05$	$r_s = 0.49$; $p = 0.02$	$r_s = 0.23$; $p = 0.3$	$r_s = 0.25$; $p = 0.27$

Abbreviations: LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; meanPAP: mean pulmonary artery pressure; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAPP-A: pregnancy-associated plasma protein-A; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; RVESV: right ventricular end-systolic volume; sST2: soluble suppression of tumorigenicity 2.

Table 3. Prognostic performance of biomarkers.

Biomarker level at baseline for the identification of patients (N = 14/22) with severely impaired right ventricular ejection fraction

	Cut-off value	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
NT-proBNP, ng/L	347	0.91 (0.79–1)	92 (64–100)	75 (35–97)	85 (44–97)	87 (66–96)	36 (2.7–481)
sST2, ng/mL	48.0	0.88 (0.72–1)	93 (66–100)	75 (35–97)	86 (46–98)	87 (66–96)	39 (2.9–519)
PAPP-A, mU/L	14.5	0.81 (0.60–1)	86 (57–98)	75 (35–97)	75 (44–92)	86 (64–95)	18 (2–161)
MR-proANP, pmol/L	230	0.78 (0.58–0.99)	57 (29–82)	100 (63–100)	57 (42–71)	100 (100)	not calculated[a]

Relative change of biomarker level after therapy for the identification of patients (N = 8/22) without a change of right ventricular ejection fraction

	Cut-off value (%)	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
NT-proBNP change, %	<53	0.86 (0.66–1)	88 (47–100)	92 (66–100)	93 (68–99)	87 (51–98)	91 (4.9–1687)
MR-proANP change, %	<24	0.82 (0.63–1)	88 (47–100)	79 (49–95)	92 (64–99)	07 (45–87)	26 (2.3–298)

Abbreviations: AUC: area under the curve; CI: confidence interval; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OR: odds ratio; PAPP-A: pregnancy-associated plasma protein-A; sST2: soluble suppression of tumorigenicity 2; NPV: negative predictive value; PPV: positive predictive value.

[a]No patient with a severely impaired RVEF showed a MR-proANP level below the cut-off.

and remodeling.[13,34–36] Moreover, there is evidence for an association of elevated sST2 levels with right ventricular dilatation and dysfunction[26,37] and increased mortality in PH.[33] Recent studies reported elevated sST2 levels in PH and CTEPH patients compared with healthy controls.[23,38] Thus, serum levels >65 ng/ml were associated with severe hemodynamic impairment and mortality.[23,39] Consistent with these finding, sST2 levels correlated with right heart parameters from CMR: they were significantly elevated in patients with an RVEF < 35%, and a level >48.0 ng/ml was associated with a severe impairment of RVEF in our study.

Pregnancy-associated plasma protein-A (PAPP-A) is a regulator of insulin-like growth factor (IGF)/IGF-binding protein pathways,[40] which promote inflammation,

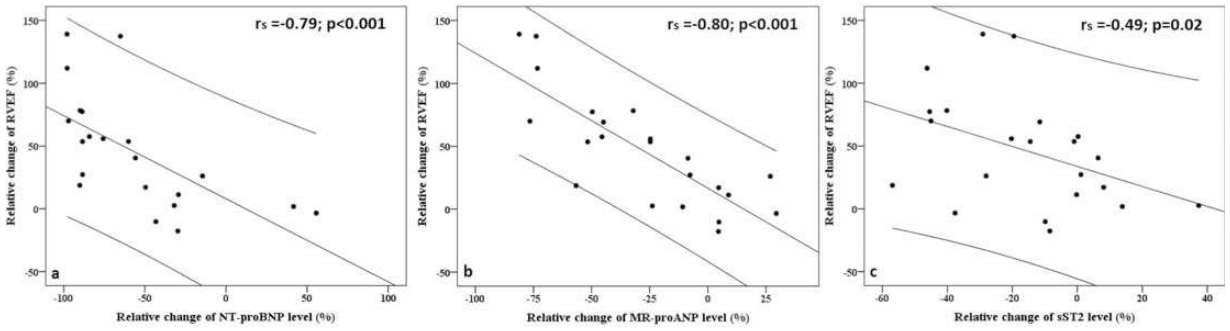

Fig. 1. Correlation between the relative change in biomarker levels and right ventricular ejection fraction (RVEF). NT-proBNP: N-terminal pro-B-type natriuretic peptide; MR-proANP: mid-regional pro-atrial natriuretic peptide; RVEF: right ventricular ejection fraction; sST2: soluble suppression of tumorigenicity 2.

anti-apoptosis, and proliferation in various cell types such as endothelial and smooth muscle cells.[41,42] There is some evidence for an involvement of PAPP-A and IGF-I/IGF-receptor signaling in PH.[24,43,44] Recently, our group found elevated PAPP-A levels in patients with CTEPH and non-CTEPH PH compared with healthy controls that were not associated with pulmonary hemodynamics.[24] In the present study, PAPP-A levels moderately correlated with right heart parameters from CMR: patients with an RVEF $< 35\%$ had elevated PAPP-A levels, and a level >14.5 mU/L was associated with an RVEF $\leq 35\%$.

Dynamics of CMR and biomarker findings after BPA therapy

BPA therapy improves pulmonary hemodynamics and thus allows right heart recovery with consequent positive effects on clinical symptoms and physical capacity.[1,11] Right heart reverse remodeling, manifested by a normalization of right heart dimensions and improved RVEF, was illustrated by imaging studies.[17,19,45,46] In pulmonary artery hypertension, the RVEF and the indexed right ventricular end-systolic volume (RVESVi), gathered from CMR at baseline, distinguished patients with a low, intermediate, or high risk of one-year mortality. Remarkably, the outcome of patients who moved to the low-risk RVEF or RVESVi group after specific PH therapy, documented by a follow-up CMR, was comparable to those patients with low-risk characteristics at baseline.[47]

This again confirms right heart recovery as the major therapy goal in CTEPH. In line with other series, right ventricular dimensions and RVEF improved after BPA therapy in the vast majority of patients in our study, which was documented by CMR findings.[17,19,45,46] As a consequence of right heart dilatation, interventricular septum shift, and septum dyssynchrony, concomitant left heart impairment, with a reduced left ventricular filling, is regularly observed in PH.[48] Concomitant to right heart recovery, CMR findings documented a reexpansion of the left ventricle after BPA therapy in our cohort, which might allow improved left ventricular filling.

Although an optimal assessment of right heart conditions should be a major focus of CTEPH follow-up regimes, routine assessment by CMR would not seem to be applicable due to the limitations mentioned. A few studies reported a correlation of NT-proBNP[49,50] and sST2[26] with right heart dimensions and function and their response to therapy in PH. In our cohort, there was a significant decrease in the levels of all four biomarkers measured after BPA therapy. Particularly the changes in NT-proBNP (RVESVi: $r_s = 0.83$; $p < 0.001$; RVEF: $r_s = -0.79$; $p < 0.001$) and MR-proANP (RVESVi: $r_s = 0.89$; $p < 0.001$; RVEF: $r_s = -0.80$; $p < 0.001$) strongly correlated with the dynamics of right heart dimensions and function after therapy.

A limited decrease of the baseline NT-proBNP level (<53%) or MR-proANP level (<24%) was indicative for an unchanged RVEF after therapy. Including NT-pro-BNP and MR-proANP measurement in the follow-up examinations of CTEPH patients might be an easily applied tool for noninvasive right heart "imaging."

Certain limitations of the study need to be mentioned. This study included a relatively small number of patients. Furthermore, CMR is not included in the routine diagnostic work-up of CTEPH patients. The decision to perform a CMR was made by the interdisciplinary CTEPH conference. Thus, the study consecutively included patients with a CMR, but not those CTEPH patients in between without a CMR. The results, particularly those concerning the diagnostic strength of biomarkers to predict CMR findings, should be interpreted as hypothesis-generating findings.

In conclusion, CMR findings illustrate significant right heart remodeling and failure in CTEPH patients. BPA therapy allows right heart recovery, particularly an improvement of right ventricular function. In consideration of the mentioned limitations, our study suggests that cardiac biomarkers can identify patients with a severely reduced RVEF at baseline, CMR documents changes in RV reverse remodeling, and changes in biomarker levels correlate with RV functional improvement after therapy.

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Conflict of interest

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Ethical approval

The ethics board of the Justus Liebig University of Giessen approved the study (AZ 43/14).

Guarantor

SDK and CBL.

Authors' contribution

SDK: study conception, interpretation of data, data management, first draft of the manuscript; JMV: interpretation of data, proofreading of the manuscript; CBW: treatment of patients, interpretation of data, proofreading of the manuscript; FR and MB: follow-up of patients, data management, proofreading of the manuscript; JSW: statistics, interpretation of data, proofreading of the manuscript; MH: treatment of patients, interpretation of data, proofreading of the manuscript; UFR, MW, AR, CWH, EM, SG, and TK: interpretation of data, proofreading of the manuscript; FCR: CMR diagnostics, interpretation of data, proofreading of the manuscript; CL: study conception, treatment of patients, interpretation of data, proofreading of the manuscript.

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