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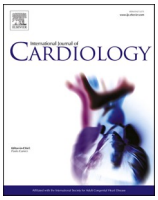

Native hepatic T1-time as a non-invasive predictor of diastolic dysfunction and a monitoring tool for disease progression and treatment response in patients with pulmonary hypertension

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ABSTRACT

Aims: Hepatic T1-time derived from cardiac magnetic resonance imaging (cMRI) reflects venous congestion and may provide a simple alternative to invasive end-diastolic elastance (Eed) for assessment of right ventricular (RV) diastolic function. We investigated the association of native hepatic T1-time with single-beat Eed and the value of hepatic T1-time for longitudinal monitoring in pulmonary hypertension (PH).

Methods and results: We retrospectively enrolled 85 patients with suspected PH (59% female; 78 with PH diagnosed; 7 with PH excluded) who underwent standard right heart catheterization and cMRI within 24 h between 2015 and 2020. Hepatic T1-time showed moderate to strong correlations (rho >0.3, $P \leq 0.002$) with pulmonary vascular resistance, native myocardial T1-time, Eed, RV size and function, brain natriuretic peptide (BNP) level, and 6-min walk distance, and a significant association with functional class (Kruskal-Wallis $P < 0.001$). Eed, myocardial T1-time, and BNP were independently linked to hepatic T1-time in multivariable regression. Hepatic T1-time > 598 ms predicted elevated Eed with 72.9% sensitivity and 82.1% specificity. Hepatic T1-time was superior to Eed in predicting clinical worsening. In 16 patients with follow-up assessments, those with decreasing hepatic T1-time (7 patients) showed significant hemodynamic improvements, whereas those with increasing hepatic T1-time (9 patients) did not. In a second retrospective cohort of 27 patients with chronic thromboembolic PH undergoing balloon pulmonary angioplasty, hepatic T1-time decreased significantly and hemodynamics improved after the procedure.

Conclusions: Hepatic T1-time predicts RV diastolic dysfunction and prognosis, and may be useful for monitoring disease progression and treatment response in PH.

1. Introduction

Pulmonary hypertension (PH) is a complex and progressive disease leading to right ventricular (RV) hypertrophy and eventually heart failure.

Right heart failure is not only characterized by forward failure, but also by “backward failure”. The latter is marked by elevated RV filling pressures due to impaired diastolic function and an ensuing increase in central venous pressure, resulting in congestion in dependent organs such as the liver [1]. Previous studies have provided evidence that increased ventricular stiffness is primarily associated with reduced right atrial function and vena cava backflow, consequently leading to venous congestion and the development of a dilated inferior vena cava [2–4]. The degree of RV diastolic stiffness is also associated with other parameters of disease severity, underscoring its pathophysiological significance [5,6]. However, the gold-standard approach for evaluating RV

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diastolic function is not established in clinical practice because it involves invasive pressure measurement and complex calculations [5–9]. Alternative approaches are therefore needed to assess diastolic dysfunction non-invasively. One such approach may be the measurement of native hepatic T1-time, a parameter derived from magnetic resonance imaging (MRI) that reflects the longitudinal relaxation times of protons in liver tissue. It can be influenced by various factors, including the presence of liver disease, inflammation, fibrosis, and changes in blood flow to the liver [10]. Since standard cardiac MRI (cMRI) scans include sections of the upper abdominal organs (especially the liver and spleen), the evaluation of hepatic T1-times would offer a simple measure of changes in the liver tissue caused by venous congestion without additional diagnostic tools. Recent studies have shown that hepatic T1-times obtained through standard cMRI scans are significantly associated with cardiac size and function and independently predict cardiovascular mortality and morbidity [11]. Additionally, increased hepatic native T1-times have been identified as poor prognostic indicators for all-cause mortality in patients with PH, and are closely linked to central venous pressure [12]. However, the link to RV diastolic function is not yet established and it remains unclear whether hepatic T1-time is reversible or responsive to improvement in RV function, or reduction in RV filling pressure, after guideline-directed medical therapy.

The aim of this study was to evaluate the association of native hepatic T1-time with the gold-standard measure of RV diastolic function (end-diastolic elastance [Eed]) and to demonstrate whether native hepatic T1-time can be utilized as a longitudinal parameter to depict hemodynamics and clinical course in patients with PH.

2. Methods

2.1. Study design and patients

We conducted a retrospective analysis involving two cohorts. The first cohort, referred to as the Giessen cohort, comprised patients with suspicion of PH who underwent right heart catheterization at the University Hospital of Giessen. These patients also underwent cMRI within 24 h of catheterization as part of the Right Heart I study (ClinicalTrials.gov Identifier: NCT03403868) between October 2015 and June 2020. Longitudinal changes in native hepatic T1-time were evaluated in a subset of these patients who underwent follow-up catheterization and cMRI.

The second cohort used to assess longitudinal changes in native hepatic T1-time comprised patients with inoperable chronic thromboembolic PH (CTEPH) who underwent balloon pulmonary angioplasty (BPA) between February 2014 and September 2017 (hereafter referred to as the BPA cohort). A part of the BPA cohort was also included in previous publications or was enrolled in ongoing studies within the Collaborative Research Center (CRC1213) [13–16]. Longitudinal changes in hepatic T1-time were evaluated in a subset of these patients who underwent pre- and post-procedural right heart catheterization and cMRI [17].

The investigation conforms with the principles outlined in the Declaration of Helsinki [18]. All participating patients gave written informed consent, and the local ethics committee (Giessen cohort: Approval No. 108/15; BPA cohort: Approval No. 43/14) approved the study.

2.2. CMRI

Imaging was performed using a 1.5 Tesla MRI scanner (Avanto, Siemens Healthineers, Erlangen, Germany) with a 6-element phased array cardiac coil and a dedicated cMRI protocol including survey images, steady-state free precession (SSFP) cine sequences aligned to 2-, 3-, and 4-chamber views, and short-axis stacks from base to apex obtained during breath hold. SSFP imaging parameters were: slice thickness, 8 mm; field of view, 300 × 400 mm; matrix, 256 × 154; temporal resolution, 59.62 ms; and echo time, 1.15 ms. Postprocessing was performed using cardiovascular imaging software version 42 (cvi42; Circle Cardiovascular Imaging). RV end-systolic volume (ESV) and end-diastolic volume (EDV; absolute and referenced values) were calculated from short-axis cine images. Right atrial area at end-systole was measured from 4-chamber views and indexed to body surface area (RAAi).

T1 mapping was performed using an optimized modified Look–Locker inversion–recovery (MOLLI; “3–3-5”) sequence. After inline motion correction, three T1 maps were acquired (basal, midventricular, and apical short-axis). Imaging parameters were: slice thickness, 8 mm; spatial resolution, 2.2 × 1.8 × 8 mm; 6/8 partial Fourier acquisition; field of view, 240 × 340 mm^2; matrix, 192 × 124; flip angle, 35°; repetition time, 740 ms; echo time, 1.06 ms; minimum time after inversion (TI), 100 ms; TI increment, 80 ms; trigger delay, 300 ms; inversions, 3; and acquisition heartbeats, 3,3,5—11 images were acquired during 17 heartbeats. To assess the native hepatic T1-times, regions of interest (ROI) of ≥2.5 cm^2 were meticulously delineated in the liver parenchyma excluding fat, focal lesions and blood vessels (Fig. 1). Myocardial native T1-times were measured at basal and midventricular short-axis sections for the septum, the upper and lower RV insertion points and RV lateral wall. A global myocardial T1-time was defined as the arithmetic mean of all individual T1-times.

2.3. Right heart catheterization

Right heart catheterization was performed in accordance with current recommendations using a Swan-Ganz catheter. Invasive variables including RV pressure, mean pulmonary arterial pressure (mPAP), and pulmonary arterial wedge pressure (PAWP) were determined. Cardiac output (CO) was calculated using the thermodilution method, and pulmonary vascular resistance (PVR) was calculated as (mPAP−PCWP)/CO. Diastolic filling pressures were measured at two specific points: the begin-diastolic pressure (BDP), which was recorded at the minimum pressure point after tricuspid valve opening (lowest point in the RV pressure curve), and the end-diastolic pressure (EDP), which was recorded at the maximal diastolic filling pressure point before the onset of isovolumic contraction, corresponding to the onset of the R-wave on the electrocardiogram.

2.4. Assessment of RV Eed

To determine the end-diastolic pressure-volume relationship, we employed a single-beat technique that involved adapting the function $P = \alpha(eV \cdot \beta - 1)$ to the diastolic part of the pressure-volume loop, where P represents pressure, V represents volume, α is a curve-fitting constant, and β is a diastolic stiffness constant. We determined the values of α and β by exponentially adjusting the function to three pressure and volume points: 1) the origin ($P = 0$, $V = 0$); 2) BDP and ESV; and 3) EDP and EDV. To minimize measurement error, we normalized BDP at 1 mmHg, and calculated EDP using the formula $EDPnormalized = 1 + EDPinitial - BDPinitial$ [5]. We then calculated Eed using the equation $Eed = \alpha \cdot \beta \cdot e^{(\beta \cdot EDV)}$. We performed these calculations using a custom Octave code (GNU Octave, version 7.3.0, https://www.octave.org).

2.5. Follow-up

Clinical worsening events from the time of right heart catheterization until December 2022 were assessed in all patients in the Giessen cohort. Seven patients were lost to follow-up. Clinical worsening was defined as any of the following: reduction in exercise capacity (−15% compared with the baseline 6-min walk test); worsening in World Health Organization (WHO) functional class; clinical deterioration requiring hospital admission; need for new pulmonary arterial hypertension therapies; lung transplantation; or death.

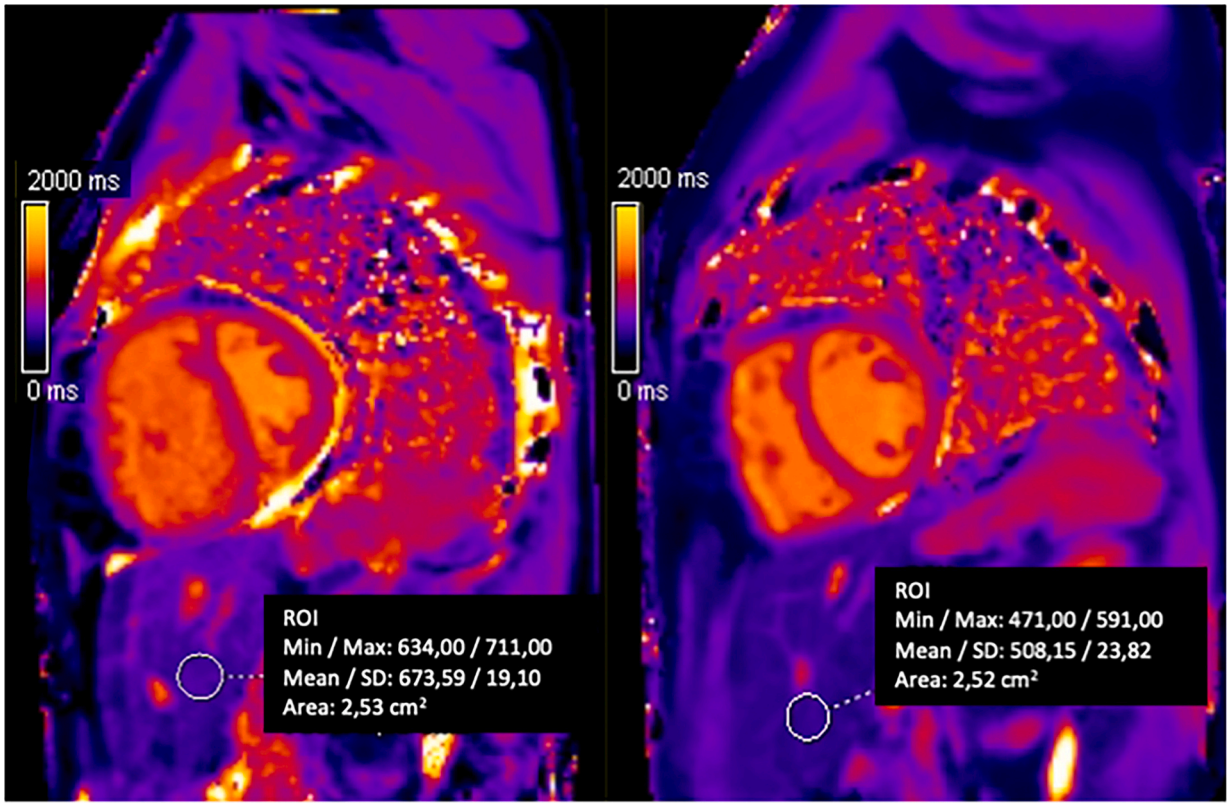


Fig. 1. Hepatic native T1-time measured by cMRI before and after BPA in a patient with CTEPH. The figure displays the color-coded native T1 maps of a patient with CTEPH before (left) and 6 months after BPA (right). Along with a hemodynamic improvement (mPAP decreased from 43 mmHg to 28 mmHg, PVR decreased from 886 dyn·s/cm^5 to 309 dyn·s/cm^5, and RV EF increased from 30% to 51%), the mean native hepatic T1-time decreased from 673.6 ms to 508.2 ms.

2.6. Statistical analyses

Data were checked for normal distribution using the Shapiro-Wilk test; a test statistic with $P > 0.05$ was considered normally distributed. Normally distributed dependent and independent samples were analyzed with paired and unpaired *t*-tests, respectively. Non-normally distributed dependent and independent samples were examined using the Wilcoxon test and Mann-Whitney *U* test, respectively. Association of WHO functional class with hepatic T1-time was assessed with the Kruskal-Wallis test and subsequent post hoc tests (Conover).

The Spearman rank test was employed to evaluate the correlation between hepatic T1-time and various parameters. To perform the correlation analysis, all available data points were utilized, including duplicates resulting from the 16 patients who underwent follow-up catheterization. However, duplicates were excluded from the survival analysis.

For all tests, $P \leq 0.05$ was considered significant. Normally distributed parameters are reported as mean ± standard deviation and non-normally distributed parameters as median and interquartile range. Missing data were not imputed.

We used multivariable linear regression analysis to determine the association of hepatic T1-time (as the dependent variable) with other parameters. Based on clinical relevance, brain natriuretic peptide (BNP) level, RV ejection fraction (EF), Eed, myocardial T1-time, CO, mPAP, and PVR were added to the multivariate model, to avoid overfitting. Multicollinearity was assessed using the variance inflation factor. We found multicollinearity between mPAP and PVR. Therefore, PVR was removed from the model.

Receiver operating characteristic analysis was used to identify the parameter with the highest sensitivity and specificity for detection of elevated RV diastolic stiffness defined as Eed above the median.

Univariate and multivariate Cox proportional-hazards regression models and Kaplan-Meier analyses with log-rank tests were used to assess clinical worsening. Reference values for the hepatic T1-time are not yet available; therefore, we used the median hepatic T1-time for Kaplan-Meier analyses. Based on clinical relevance, RV EF, PVR, and age were entered in the multivariate Cox regression model.

To assess the inter-observer reliability of the hepatic T1-time measurements, we used the intraclass correlation coefficient.

For all analyses, MedCalc® Statistical Software version 20.211 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2023) was used.

3. Results

3.1. Patients

85 patients were enrolled in the Giessen cohort and 27 in the BPA cohort. The demographic data of the BPA cohort have already been published [17]. However, we had to exclude 3 patients from the original 30-patient cohort because of insufficient image data. In the Giessen cohort, the mean age was 56.9 ± 14.0 years and 59% of the patients were female. PH was classified as Group 1 in 64 patients, Group 2 in one patient, Group 3 in four patients, Group 4 (CTEPH) in eight patients, and Group 5 in one patient; in seven patients, PH was excluded. A total of 68 patients received targeted therapies (specific monotherapy [$n = 27$], dual combination therapy [$n = 23$], triple combination therapy [$n = 18$]).

3.2. Inter-observer reliability of hepatic T1-time

Two observers measured hepatic T1-time independently in a subset of 60 patients. The intraclass correlation coefficient was 0.9768 (95% confidence interval [CI]: 0.9578–0.9868), indicating excellent

agreement and high reliability among the two observers.

3.3. Association between hepatic T1-time and RV diastolic dysfunction

The median hepatic T1-time across the entire cohort (duplicates caused by follow-up included) was 595.85 ms, aligning with previously published data [11,12]. Of significance, no correlation was found between hepatic T1-time and age or body mass index. We identified moderate to strong correlations between hepatic T1-time and RV afterload represented by PVR (Fig. 2A), RV myocardial stiffness represented by myocardial T1-time (Fig. 2B) and stiffness coefficient β (rho = 0.452, $P < 0.001$; Fig. S1 in data supplement), RV diastolic impairment represented by Eed (Fig. 2C), RV EDP (Fig. 2D), RV ESV (Fig. 2E), BNP level (Fig. 2F) and RAAi (rho = 0.383, $P < 0.001$; Fig. S1 in data supplement). Hepatic T1-time was also associated with RV function, measurable as a moderate inverse correlation with RV EF (rho = −0.375, $P < 0.001$; Fig. S1 in data supplement). In addition, hepatic T1-time showed low correlations with mPAP (rho = 0.288, $P = 0.007$), CO (rho = −0.260, $P = 0.014$), and heart rate (rho = 0.251, $P = 0.019$) (Fig. S1 in data supplement). We also found a moderate correlation of hepatic T1-time with functional capacity represented by the 6-min walk distance (Fig. 2G) and a significant increase in hepatic T1-time with

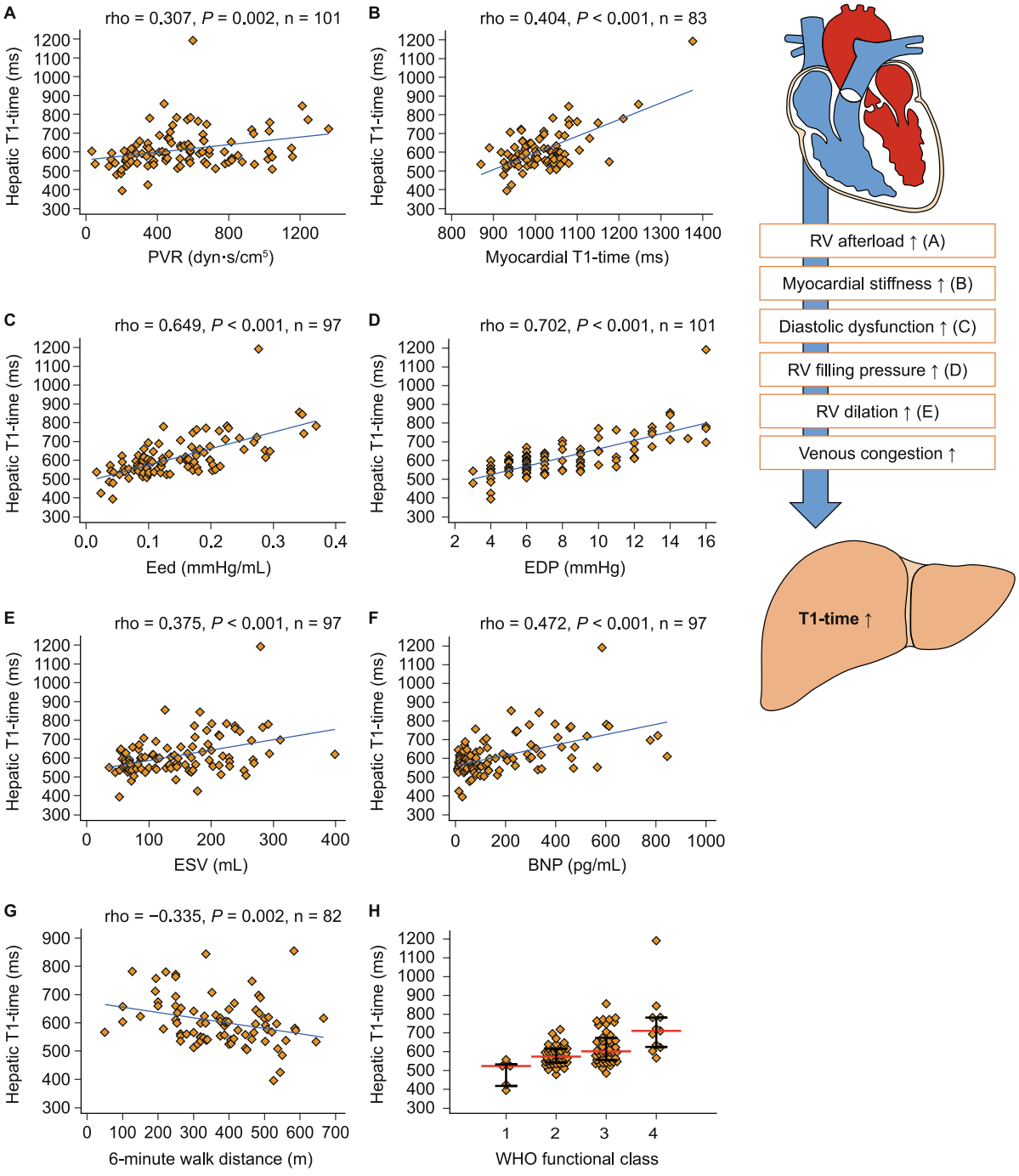


Fig. 2. Association between hepatic T1-time and RV diastolic dysfunction. The illustration shows the pathophysiological cascade originating from the right ventricle, resulting in an elevated T1-time in the liver. Spearman's rho was used to determine the association of hepatic T1-time (as the dependent variable) with the following key clinical parameters in the Giessen cohort: (**A**) PVR; (**B**) myocardial T1-time; (**C**) Eed; (**D**) EDP; (**E**) ESV; (**F**) BNP; and (**G**) 6-min walk distance. (**H**) The association of hepatic T1-time with WHO functional class was assessed using the Kruskal-Wallis test ($P < 0.001$, Kruskal-Wallis test statistic [H] 25.72).

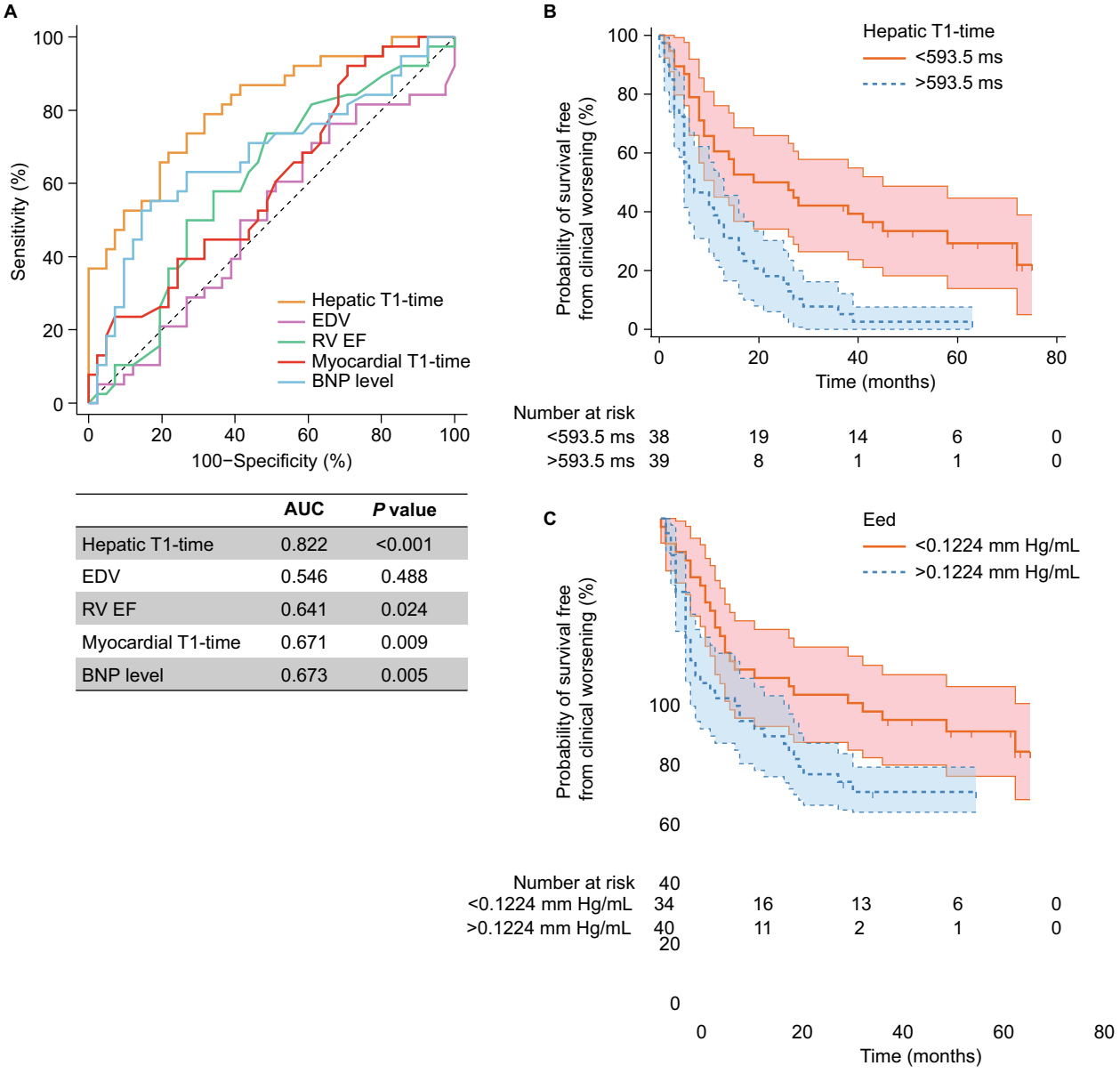
increasing WHO functional class (Fig. 2H). Post hoc tests (Conover) confirmed that all WHO classes had significantly different hepatic T1-times. Regarding hepatic laboratory parameters, only a moderate, interestingly inverse relationship was observed between hepatic T1-time and the transaminases aspartate aminotransferase (AST; rho = −0.351, $P < 0.001$) and alanine aminotransferase (ALT; rho = −0.376, $P < 0.001$) (scatter plots not shown).

3.4. Hepatic T1-time as a predictor of RV diastolic dysfunction

To determine the parameter with the strongest impact on hepatic T1-time, we conducted a multivariable regression analysis, including RV EF, BNP level, Eed, myocardial T1-time, mPAP, and CO. The results showed that only Eed ($P < 0.001$), myocardial T1-time ($P < 0.001$), and BNP level ($P = 0.0351$) were independently linked to hepatic T1-time and were significant within the model. The overall model had an R^2 of 0.6591, indicating a high level of fit. Given the strong correlation between Eed and hepatic T1-time, we assessed the ability of hepatic T1-time and other non-invasive parameters to predict diastolic dysfunction defined as Eed above the median. Using receiver operating characteristic analysis, we found that elevated Eed can be identified with a specificity of 82.1% by hepatic T1-times >598 ms (area under the curve [AUC] = 0.822, $P < 0.001$, sensitivity 72.9%, Youden index 0.55). Among non-invasive parameters (including EDV, RV EF, myocardial T1-time, and BNP level), hepatic T1-time had the highest AUC for the prediction of elevated Eed (Fig. 3A).

3.5. Prognostic relevance of hepatic T1-time

During a median follow-up time of 11 [5–29] months, 65 clinical worsening events were observed. The most frequent adverse event was PH therapy escalation ($n = 23$), followed by PH-related hospitalization ($n = 16$), functional deterioration or worsening 6-min walk test ($n = 13$). Eleven deaths occurred during follow-up and two patients underwent



	AUC	*P* value
Hepatic T1-time	0.822	<0.001
EDV	0.546	0.488
RV EF	0.641	0.024
Myocardial T1-time	0.671	0.009
BNP level	0.673	0.005

Fig. 3. Prediction of diastolic stiffness and prognosis. (**A**) Receiver operating characteristic analysis of the non-invasive parameters hepatic T1-time, EDV, RV EF, myocardial T1-time, and BNP for discriminating diastolic stiffness (defined as Eed above the median) in the Giessen cohort. Diagonal segments are produced by ties. (**B, C**) Kaplan-Meier analyses of time to clinical worsening in the Giessen cohort dichotomized at (**B**) the median hepatic T1-time (log-rank $P < 0.001$) and (**C**) the median Eed (log-rank $P = 0.004$). The shaded areas represent the 95% CI.

lung transplantation. In univariate Cox regression analysis, hepatic T1-time emerged as a significant predictor of clinical worsening with a hazard ratio of 1.697 per 100 ms increase (95% CI: 1.284–2.218; $P < 0.001$]. Kaplan-Meier analysis (Fig. 3B) revealed that patients with hepatic T1-times below the median had a better significantly better prognosis than those with hepatic T1-times above the median (log-rank $P < 0.001$). The hazard ratio for clinical worsening was 2.894 (95% CI: 1.695–4.938) in the group with hepatic T1-times above the median. Data of both groups are displayed in Table 1.

We also aimed to compare the prognostic value of hepatic T1-time with that of the gold-standard measure of diastolic stiffness, Eed. Kaplan-Meier analysis (Fig. 3C) showed that patients with Eed values below the median had a significantly better prognosis than those with Eed values above the median (log-rank $P = 0.004$. The hazard ratio was 2.171 (95% CI: 1.274–3.700), which is slightly lower than the hazard ratio calculated for hepatic T1-time. We performed a stepwise Cox regression analysis to determine how hepatic T1-time and Eed affected the time to clinical worsening, with age and sex included in the model as covariates. Our results showed that only hepatic T1-time remained a significant predictor of time to clinical worsening (hazard ratio per 100 ms increase: 1.714 [95% CI: 1.296–2.263]; $P < 0.001$).

Table 1
baseline demographic and clinical data in the Giessen cohort stratified by the median hepatic T1-time.

	Hepatic T1-time < 593.5 ms $n = 43$	Hepatic T1-time > 593.5 ms $n = 42$	*P* value
Age, years	57.3 ± 12.8	56.5 ± 15.3	0.775
Male/female gender, n/n	23/20	12/30	0.020
Body mass index, kg/m^2	27.0 ± 6.0	27.3 ± 5.4	0.814
WHO functional class I/II/III/IV, n/n/n/n	4/23/15/1	0/15/19/8	0.011
BNP, pg/mL	64 (27–121)	236 (70–417)	<0.001
6-min walk distance, m	414 ± 124*	330 ± 138*	0.010
Right heart catheterization			
sPAP, mmHg	64.9 ± 26.0	71.6 ± 19.2	0.144
mPAP, mmHg	35.0 (24.5–49.5)	44.0 (35.0–48.0)	0.144
PAWP, mmHg	9.0 (6.3–11.0)	9.0 (7.0–11.0)	0.753
CO, L/min	4.77 (3.92–5.67)	4.42 (3.70–5.47)	0.129
PVR, dyn·s/cm^5	379 (225–684)	542 (372–776)	0.027
EDP, mmHg	6 (4–7)	10 (7–13)	<0.001
Heart rate, beats/min	69.3 ± 11.0	74.3 ± 10.7	0.039
CMRI			
EDV, mL	186.8 (145.8–257.6)*	235.0 (180.2–298.8)*	0.022
ESV, mL	94.4 (66.2–165.8)*	171.7 (93.0–221.9)*	0.006
EF, %	48.0 (35.0–53.0)*	36.0 (24.2–47.0)*	0.003
Myocardial T1-time, ms	980 (944–1036)†	1020 (970–1065)†	0.003
Hepatic T1-time, ms	547 (528–567)	646 (615–722)	<0.001
Diastolic stiffness			
Eed, mmHg/mL	0.092 (0.060–0.130)*	0.183 (0.123–0.249)*	<0.001
β-coefficient	0.017 ± 0.001*	0.022 ± 0.005*	<0.001
Liver function tests			
GGT, U/L	34.0 (19.3–60.8)	36.5 (24.0–71.5)	0.430
AST, U/L	27.0 (18.3–36.0)	20.0 (16.0–23.0)	0.002
ALT, U/L	20.0 (16.0–31.0)	15.5 (11.0–19.5)	<0.001
Alkaline phosphatase, U/L	70.0 (56.0–86.0)	70.5 (62.0–97.0)	0.484
Bilirubin, mg/dL	0.60 (0.50–1.0)	0.70 (0.50–1.35)	0.572
Albumin, g/L	43.1 (39.2–44.6)	41.4 (38.9–43.7)	0.412

Values represent mean ± standard deviation or median (interquartile range) unless otherwise specified. GGT, gamma-glutamyl transferase; sPAP, systolic pulmonary arterial pressure.
* Missing data, $n = 2$.
† Missing data, $n = 7$.

3.6. Hepatic T1-time as a longitudinal parameter

Sixteen patients in the Giessen cohort underwent follow-up assessments with both right heart catheterization and cMRI, with a median time interval of 202 days (108–314.5 days) between baseline and follow-up evaluations. Of these patients, nine showed an increase in hepatic T1-time from baseline, whereas seven exhibited a decrease. The baseline data of these two subgroups are displayed in Table 2. Notably, the decrease in hepatic T1-time was significantly associated with hemodynamic improvements, including reductions from baseline in Eed, EDP, BNP level, and PVR, as well as increases in cardiac index and 6-min walk distance (Fig. 4A–F). Conversely, no significant changes were observed in the group with an increase in hepatic T1-time (not shown). Moreover, the longitudinal changes of hepatic T1 time exhibited a strong positive and highly significant correlation with the changes in Eed (rho = 0.635, $P = 0.015$), RAAi (rho = 0.679, $P = 0.004$), EDP (rho = 0.504, $P = 0.046$), PVR (rho = 0.547, $P = 0.028$), PAWP (rho = 0.650, $P = 0.006$), and BNP (rho = 0.644, $P = 0.013$). Conversely, a significant negative association was observed between the alteration of hepatic T1 time and changes in CI (rho = −0.582, $P = 0.018$) and 6-min walk test distance (rho = 0.745, $P < 0.001$). Respective scatterplots are shown in the data supplement (Fig. S2).

To further investigate the suitability of hepatic T1-time as a longitudinal parameter, we analyzed cMRI data taken before and after BPA in a cohort of 27 patients with CTEPH. The global and pulmonary hemodynamics of these patients have already been published [17] and significantly and substantially improved after BPA as measurable by marked reductions in mPAP (from 42 ± 8 mmHg to 33 ± 8 mmHg; $P <$

Table 2
Baseline data in the longitudinal analysis subset of the Giessen cohort stratified by change in hepatic T1-time during follow-up.

	Increasing hepatic T1-time n = 7	Decreasing hepatic T1-time $n = 9$	*P* value
Age, years	54.6 ± 10.7	50.0 ± 15.2	0.511
Male/female gender, n/n	3/4	5/4	0.625
Body mass index, kg/m^2	26.1 ± 2.7	26.3 ± 5.7	0.926
WHO functional class II/III/IV, n/n/n	2/4/1	4/4/1	0.810
BNP, pg/mL	91 (62–356)	224 (115–398)*	0.397
6-min walk distance, m	470 (306–505)	317 (259–361)*	0.213
Right heart catheterization			
sPAP, mmHg	73.3 ± 14.7	85.4 ± 19.6	0.194
mPAP, mmHg	42.3 ± 4.7	51.1 ± 12.6	0.102
PAWP, mmHg	7.6 ± 4.5	8.7 ± 3.2	0.579
CO, L/min	4.17 (3.69–5.20)	3.80 (2.89–4.21)	0.125
PVR, dyn·s/cm^5	509 (450–633)	944 (568–1221)	0.050
EDP, mmHg	6.0 (5.3–10.5)	7.0 (6.0–11.0)	0.354
Heart rate, beats/min	64.6 ± 8.7	74.2 ± 10.3	0.067
CMRI			
EDV, mL	225.8 ± 49.4	263.7 ± 36.7*	0.124
ESV, mL	141.7 ± 51.5	200.9 ± 42.9*	0.037
EF, %	38.5 ± 10.5	23.9 ± 11.0*	0.027
Myocardial T1-time, ms	1023 ± 20*	1032 ± 64*	0.779
Hepatic T1-time, ms	567 (556–611)	635 (580–734)	0.351
Diastolic stiffness			
Eed, mmHg/mL	0.102 (0.077–0.226)	0.155 (0.112–0.233)*	0.345
β-coefficient	0.0197 ± 0.003	0.0236 ± 0.004*	0.087

Values represent mean ± standard deviation or median (interquartile range) unless otherwise specified.
* Missing data, $n = 1$.

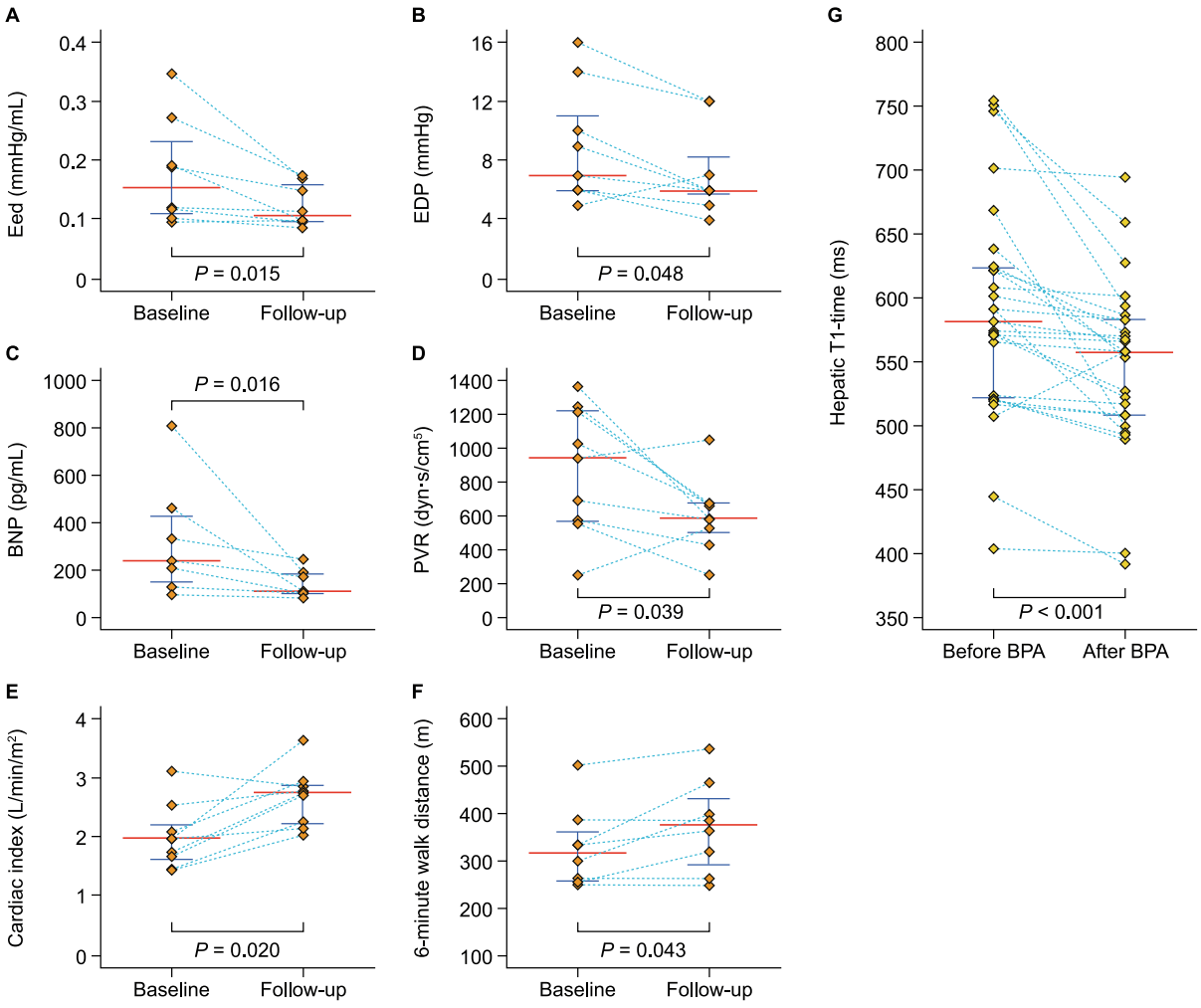


Fig. 4. Hepatic T1-time as a longitudinal parameter. In patients with PH who had follow-up data and a decreasing hepatic T1-time from baseline to follow-up (subset of the Giessen cohort; n = 9), changes in the following clinical parameters were assessed: (**A**) Eed; (**B**) EDP; (**C**) BNP; (**D**) PVR; (**E**) cardiac index; and (**F**) 6-min walk distance. (**G**) In a cohort of 27 patients with CTEPH who underwent BPA, we measured hepatic T1-time before and after the procedure. Significance was assessed using the paired-samples Wilcoxon test.

0.001), PVR (from 552 ± 203 dyn·s/cm^5 to 378 ± 147 dyn·s/cm^5; $P <$ 0.001) and right atrial pressure (RAP) (from 7.0 ± 3.3 mmHg to 5.3 ± 2.3 mmHg; $P = 0.011$) and an increase in RV EF (from 36.4 ± 10.6% to 48.0 ± 8.1%; $P < 0.001$). In accordance with the significant hemodynamic improvement, we measured a marked and significant decrease in hepatic T1-time from 582 (523–624) ms to 558 (509–584) ms in these patients (Fig. 4G). The observation that only the longitudinal alteration in RAP significantly correlated with changes in hepatic T1 time (rho = 0.504, $P = 0.007$) highlights the impact of diastolic function on the latter (Supplemental Fig. S3).

4. Discussion

This study provides the first evidence that the native hepatic T1-time, as measured from cMRI, serves as a reliable non-invasive predictor of elevated Eed (the gold-standard measure of RV diastolic dysfunction), outperforms Eed in predicting time to clinical worsening, and responds to hemodynamic improvements in patients with PH.

Our results show that hepatic T1-time mainly reflects impaired RV diastolic function. This fits very well with the concept of backward venous flow and systemic congestion mainly being caused by impaired diastolic function of the volume- and pressure-overloaded right ventricle. We have previously demonstrated that increased ventricular stiffness, as measured by Eed and EDP, is associated with a larger diameter of the vena cava and reduced right atrial function [4], and is less strongly associated with forward function measured by RV-pulmonary arterial coupling. Markus et al. showed that the venous congestion mostly occurs during atrial contraction due to impaired RV filling and increased RV stiffness [3]. Global RV T1 mapping was recently linked to diastolic stiffness and elevated RV filling pressures [9]. To the best of our knowledge, this is the first study to link elevated RV diastolic stiffness caused by high afterload with liver congestion, as measured by T1 mapping. Among non-invasive parameters, hepatic T1-time had the highest AUC for prediction of diastolic stiffness. Hepatic T1-times above 598 ms were associated with worse prognosis in our cohort, consistent with recently published data which identified 610 ms as a threshold associated with increased cardiovascular risk in a large all-comer cMRI cohort [11].

Prior research has demonstrated the clinical relevance of hepatic T1 mapping using cMRI in various cardiovascular conditions, including tetralogy of Fallot repair [19], Fontan palliation [20], idiopathic dilated cardiomyopathy [21], and PH [12]. Our findings support these previous studies, but also provide a novel comparison with Eed, the gold-standard measurement of RV diastolic function. The superiority of hepatic T1-time over Eed in predicting clinical worsening may be explained by its ability to reflect the involvement of other organs in the disease beyond the cardiovascular system. This suggests that hepatic T1-time may provide a more comprehensive assessment of disease severity than Eed

in patients with PH.

This is the first study to establish the potential of hepatic T1-time as a longitudinal parameter to monitor disease progression and treatment response in patients with PH. The decline in hepatic T1-time exhibited a notable association with hemodynamic improvements. As previously demonstrated [17], BPA leads to substantial hemodynamic improvements, making the BPA cohort an excellent proof-of-concept model to assess longitudinal changes in hepatic T1-time. Indeed, in this cohort, we observed a significant decrease in hepatic T1-time, which accompanied the hemodynamic improvement across the entire study population. These findings have important clinical implications, as they suggest that hepatic T1-time can be used as a non-invasive and effective tool for monitoring treatment response in patients with PH. Interestingly, changes in hepatic T1-time can be detected after a relatively short period of time (202 days). Such medium-term changes would not be expected in cases of manifest organ fibrosis. One possible explanation is that the hepatic T1-time represents a mixture of T1-times of the liver parenchyma, bile ducts, and blood pool [10]. In particular, the amount of blood pool could change quickly due to improved hemodynamics and reduced congestion, and could be primarily responsible for the longitudinal changes shown in this study. Furthermore, the hepatic T1-times were mostly substantially lower than the values already published for liver cirrhosis, indicating that most patients in our cohort probably did not have manifest liver cirrhosis [22].

4.1. Limitations

The study is limited by its inclusion of two different cohorts and its retrospective design, which does not allow control over the exposure or the selection of participants. In addition, further studies are needed to fully evaluate the applicability of hepatic T1-time monitoring in patients with PH who have other comorbidities (e.g. left heart disease) or who are receiving other forms of treatment.

5. Conclusion

In conclusion, this study demonstrates the potential of hepatic T1-time as a valuable non-invasive predictor of RV diastolic function, a prognostic indicator for patients with PH, and a longitudinal monitoring parameter for disease progression and treatment response. The study establishes a clear connection between the native T1-time of the liver and diastolic dysfunction, which was not previously reported in the literature, and highlights the superiority of hepatic T1-time over gold-standard Eed in predicting clinical worsening in patients with PH. The study findings have important clinical implications, suggesting that hepatic T1-time can be used as a non-invasive and reliable tool for monitoring treatment response in patients with PH.

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CRediT authorship contribution statement

Nils Kremer: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Fritz C. Roller:** Writing – review & editing, Validation, Investigation, Formal analysis. **Sarah Kremer:** Investigation, Formal analysis. **Simon Schäfer:** Investigation. **Vitalii Kryvenko:** Investigation. **Zvonimir A. Rako:** Investigation. **Bruno R. Brito da Rocha:** Investigation. **Athiththan Yogeswaran:** Investigation. **Werner Seeger:** Supervision. **Stefan Guth:** Investigation. **Christoph B. Wiedenroth:** Writing – review & editing, Investigation. **Khodr Tello:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

NK has received speaking fees from Janssen outside the submitted work. AY has received personal fees from MSD outside the submitted work. WS has received speaker/consultancy fees from Pfizer and Bayer Pharma AG. CBW has received speaker fees and/or consultant honoraria from Actelion, AOP Orphan Pharmaceuticals AG, Bayer AG, BTG, MSD, and Pfizer. KT has received speaking fees from Actelion, Janssen, and Bayer. All other authors report no relationships that could be construed as a conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132189.

References

[1] S. Rosenkranz, L.S. Howard, M. Gomberg-Maitland, M.M. Hoeper, Systemic consequences of pulmonary hypertension and right-sided heart failure, Circulation 141 (2020) 678–693, https://doi.org/10.1161/CIRCULATIONAHA.116.022362.
[2] J.N. Wessels, S.A. Mouratoglou, J. Van Wezenbeek, M.L. Handoko, J.T. Marcus, L. J. Meijboom, et al., Right atrial function is associated with right venticular diastolic stiffness: RA–RV interaction in pulmonary arterial hypertension, Eur. Respir. J. 59 (2022) 2101454, https://doi.org/10.1183/13993003.01454-2021.
[3] J.T. Marcus, B.E. Westerhof, J.A. Groeneveldt, H.J. Bogaard, F.S. De Man, Noordegraaf A. Vonk, Vena cava backflow and right ventricular stiffness in pulmonary arterial hypertension, Eur. Respir. J. 54 (2019) 1900625, https://doi.org/10.1183/13993003.00625-2019.
[4] K. Tello, A. Dalmer, R. Vanderpool, H.A. Ghofrani, R. Naeije, F. Roller, et al., Right ventricular function correlates of right atrial strain in pulmonary hypertension: a combined cardiac magnetic resonance and conductance catheter study, Am. J. Physiol. Heart Circ. Physiol. 318 (2020) H156–H164, https://doi.org/10.1152/ajpheart.00485.2019.
[5] S. Rain, M.L. Handoko, P. Trip, C.T.-J. Gan, N. Westerhof, G.J. Stienen, et al., Right ventricular diastolic impairment in patients with pulmonary arterial hypertension, Circulation 128 (2013) 2016–2025, https://doi.org/10.1161/CIRCULATIONAHA.113.001873.
[6] P. Trip, S. Rain, M.L. Handoko, C. Van Der Bruggen, H.J. Bogaard, J.T. Marcus, et al., Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension, Eur. Respir. J. 45 (2015) 1603–1612, https://doi.org/10.1183/09031936.00156714.
[7] M.I. Brener, A. Masoumi, V.G. Ng, K. Tello, M.B. Bastos, W.K. Cornwell, et al., Invasive right ventricular pressure-volume analysis: basic principles, clinical applications, and practical recommendations, Circ. Heart Fail. 15 (2022) e009101, https://doi.org/10.1161/CIRCHEARTFAILURE.121.009101.
[8] K. Tello, A. Dalmer, R. Vanderpool, H.A. Ghofrani, R. Naeije, F. Roller, et al., Cardiac magnetic resonance imaging-based right ventricular strain analysis for assessment of coupling and diastolic function in pulmonary hypertension, JACC Cardiovasc. Imaging 12 (2019) 2155–2164, https://doi.org/10.1016/j.jcmg.2018.12.032.
[9] K. Tello, A. Dalmer, J. Axmann, R. Vanderpool, H.A. Ghofrani, R. Naeije, et al., Reserve of Right Ventricular-Arterial Coupling in the setting of chronic overload, Circ. Heart Fail. 12 (2019) e005512, https://doi.org/10.1161/CIRCHEARTFAILURE.118.005512.
[10] V.C. Obmann, A. Berzigotti, D. Catucci, L. Ebner, C. Gräni, J.T. Heverhagen, et al., T1 mapping of the liver and the spleen in patients with liver fibrosis—does normalization to the blood pool increase the predictive value? Eur. Radiol. 31 (2021) 4308–4318, https://doi.org/10.1007/s00330-020-07447-8.

[11] K. Mascherbauer, C. Donà, M. Koschutnik, V. Dannenberg, C. Nitsche, F. Duca, et al., Hepatic T1-time predicts cardiovascular risk in all-comers referred for cardiovascular magnetic resonance: a post-hoc analysis, Circ Cardiovascular Imaging 15 (2022), https://doi.org/10.1161/CIRCIMAGING.122.014716.
[12] J. Guo, L. Wang, J. Wang, K. Wan, C. Gong, X. Chen, et al., Prognostic value of hepatic native T1 and extracellular volume fraction in patients with pulmonary arterial hypertension, JAHA 11 (2022) e026254, https://doi.org/10.1161/JAHA.122.026254.
[13] C.B. Wiedenroth Md, A.J. Rieth Md, Md S. Kriechbaum, H.-A. Ghofrani Md, Md A. Breithecker, Md M. Haas, et al., Exercise right heart catheterization before and after balloon pulmonary angioplasty in inoperable patients with chronic thromboembolic pulmonary hypertension, Pulm Circ 10 (2020), https://doi.org/10.1177/2045894020917884, 2045894020917884.
[14] K.M. Olsson, C.B. Wiedenroth, J.-C. Kamp, A. Breithecker, J. Fuge, G.A. Krombach, et al., Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience, Eur. Respir. J. 49 (2017) 1602409, https://doi.org/10.1183/13993003.02409-2016.
[15] S.D. Kriechbaum, C.B. Wiedenroth, M.L. Hesse, R. Ajnwojner, T. Keller, J. Sebastian Wolter, et al., Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension, Scand. J. Clin. Lab. Invest. 79 (2019) 268–275, https://doi.org/10.1080/00365513.2019.1601765.
[16] F.C. Roller, S. Kriechbaum, A. Breithecker, C. Liebetrau, M. Haas, C. Schneider, et al., Correlation of native T1 mapping with right ventricular function and pulmonary haemodynamics in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty, Eur. Radiol. 29 (2019) 1565–1573, https://doi.org/10.1007/s00330-018-5702-x.
[17] F.C. Roller, A. Schüssler, A. Hasse, S. Kriechbaum, M. Richter, S. Guth, et al., Effects of BPA on right ventricular mechanical dysfunction in patients with inoperable CTEPH – a cardiac magnetic resonance study, Eur. J. Radiol. 147 (2022) 110111, https://doi.org/10.1016/j.ejrad.2021.110111.
[18] Human experimentation: code of ethics of W.M.A, BMJ 2 (1964) 177, https://doi.org/10.1136/bmj.2.5402.177.
[19] I. Kazour, S.D. Serai, S.A. Xanthakos, R.J. Fleck, Using T1 mapping in cardiovascular magnetic resonance to assess congestive hepatopathy, Abdom Radiol 43 (2018) 2679–2685, https://doi.org/10.1007/s00261-018-1528-x.
[20] P. Ramachandran, S.D. Serai, G.R. Veldtman, S.M. Lang, W. Mazur, A.T. Trout, et al., Assessment of liver T1 mapping in fontan patients and its correlation with magnetic resonance elastography-derived liver stiffness, Abdom Radiol 44 (2019) 2403–2408, https://doi.org/10.1007/s00261-019-01990-9.
[21] J. Bogaert, R. Symons, P. Rafouli-Stergiou, W. Droogné, T. Dresselaers, P.G. Masci, Assessment of right-sided heart failure in patients with dilated cardiomyopathy using magnetic resonance Relaxometry of the liver, Am. J. Cardiol. 149 (2021) 103–111, https://doi.org/10.1016/j.amjcard.2021.03.012.
[22] J.H. Yoon, J.M. Lee, M. Paek, J.K. Han, B.I. Choi, Quantitative assessment of hepatic function: modified look-locker inversion recovery (MOLLI) sequence for T1 mapping on Gd-EOB-DTPA-enhanced liver MR imaging, Eur. Radiol. 26 (2016) 1775–1782, https://doi.org/10.1007/s00330-015-3994-7.