

openheart Prognostic relevance of the right ventricular myo-mechanical index (RV-MMI) in patients with precapillary pulmonary hypertension

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ABSTRACT

Objective The aim of the prospective New-RV study was to evaluate a parameter for non-invasive quantification of right ventricular (RV) dysfunction in patients with precapillary pulmonary hypertension (PH) that yields prognostic information and is applicable in daily clinical routine.

Methods Sixty-five consecutive patients with precapillary PH under guideline conform therapy (43 women, 22 men) underwent clinical assessment, serological testing, as well as a comprehensive transthoracic echocardiography including strain imaging and a detailed assessment of RV haemodynamics.

Results The mean follow-up time was 844 days. Sixteen patients died during clinical follow-up. Right ventricular myo-mechanical index (RV-MMI) was calculated by right atrial size, mean RV pressure gradient and strain imaging of the RV free wall, and was measurable in all examinations. RV-MMI was tested for its diagnostic accuracy (sensitivity of 88% and specificity of 73% for an optimal cut-off value of ≤ 0.31 mm Hg⁰; area under the curve=0.85), as well as its predictive value (HR=3.3, 95% CI 1.6 to 7.0, $p < 0.001$), and was compared in detail with established parameters. RV-MMI and N-terminal pro-brain natriuretic peptide (NTproBNP) were independent predictors of survival (HR=2.9, 95% CI 1.4 to 6.2, $p = 0.006$; and HR=2.6, 95% CI 1.5 to 4.6, $p = 0.001$, respectively).

Conclusion In a cohort of patients with precapillary PH, the RV-MMI differentiates the outcome of patients better than other available non-invasive parameters of RV function by preload and afterload adjusted quantification.

Trial registration number NCT01230294.

INTRODUCTION

Pulmonary hypertension (PH) with concomitant right ventricular (RV) dysfunction is strongly associated with increased morbidity and mortality in patients with cardiopulmonary disease. The clinical relevance of non-invasive assessment of systolic pulmonary artery pressure (sPAP) by Doppler echocardiography was questioned in the past, but current analyses in large patient populations have

Key questions

What is already known about this subject?

► Right ventricular (RV) dysfunction is a critical indicator in patients with pulmonary hypertension, but is hard to quantify.

What does this study add?

► This study presents the right ventricular myo-mechanical index (RV-MMI) as a single parameter for effective RV function, with a defined threshold and significant association with outcome.

► The RV-MMI is based on the three main determinants of RV function that are derived by established, non-invasive measurements.

How might this impact on clinical practice?

► The echocardiographic assessment is easily and efficiently applicable, which may enhance translation into clinical practice.

clarified the usefulness of this technique.^{1 2} Invasive measurement of pulmonary artery pressure (PAP) is mandatory for the diagnosis of PH and is advised for treatment decisions for patients with precapillary PH. Although standardised right heart catheterisation (RHC) delivers important haemodynamic information, the derived data do not reflect contractility or functional myocardial reserve of the RV. In this context and according to current guidelines, transthoracic echocardiography has become the first-line diagnostic approach for patients with suspected PH.^{3 4}

However, among the echocardiographic methods for RV assessment, there is no accepted reference parameter comparable with the left ventricular ejection fraction (LV-EF) as a surrogate for ventricular systolic function.^{5 6} The American Society of Echocardiography (ASE) guidelines for assessment of RV function as well as the ASE guidelines for cardiac chamber quantification weigh the opportunities and limitations of each

RV parameter in detail.^{7,8} Unfortunately, all of these measurements, including novel, technically demanding approaches like volumetry by three-dimensional echocardiography or cardiac MRI, only provide limited information on global RV function, and it is questionable if a diagnostic modality restricted to volumetry, haemodynamics or ventricular deformation alone can meet the pathophysiological aspects of RV dysfunction.^{7,9} To overcome these methodical problems, a stepwise combination of established surrogate parameters for RV function has been proposed more than 10 years ago.¹⁰ In parallel, clinical scoring systems have been introduced for patients with pulmonary arterial hypertension (PAH)^{11,12} and were combined in current guidelines for risk stratification and to trigger therapeutic decisions.³ However, a significant dependence on the examiner remains in this approach: for instance, the detection of pericardial effusion representing a well-examined indicator of adverse outcome in patients with advanced PAH can be classified as 'minimal pericardial effusion' with intermediate risk or 'pericardial effusion' with high risk for disease progress, which is hard to differentiate by echocardiographic description without standardised quantification.

Therefore, this study aimed to test quantitative measurements by up-to-date transthoracic (Doppler) echocardiography including strain imaging as well as the combination of measured values as 'right ventricular myo-mechanical index' (RV-MMI), hypothesising that this may better reflect effective RV function and may facilitate evaluation of outcome of patients with precapillary PH.

METHODS

Study design

The analysis presented here is part of the New-RV study registered at ClinicalTrials.gov (NCT01230294), with patients' written informed consent. Sixty-five consecutive patients with invasively diagnosed precapillary PH were included between 28 October 2010 and 31 July 2013. Until 30 June 2015, follow-up examinations were conducted during periodical controls at our institution with clinical assessment by WHO functional class (FC) and the 6 min walk test (6MWT), as well as serological testing including N-terminal pro-brain natriuretic peptide (NTproBNP) and cardiac troponin T (cTnT). Treatment decisions were not affected by participation in the New-RV study. Detailed echocardiographic analyses were conducted offline after completion of inclusion of patients for this study. No patient had to be excluded or was lost to follow-up.

Transthoracic echocardiography

Echocardiography examinations were performed on a commercially available ultrasound machine (Vivid E9 BT13, GE Healthcare Vingmed, Horten, Norway), using a 1.5–4.6 MHz phased array probe (M5S-D) for two-dimensional (2D) and Doppler data acquisition as described

before.² Data were transferred to a Picture Archiving and Communication System (PACS) server (EchoPAC Workstation BT13, GE Healthcare, Horten, Norway) for offline analysis by experienced examiners blinded to patients' clinical information. Geometric right heart parameters were assessed from standard 2D echocardiography: RV basal diameter (RV-end-diastolic diameter (EDD)), right atrial end-systolic area (RA-ESA), RV fractional area change (RV-FAC), tricuspid annular plane systolic excursion (TAPSE) and left ventricular eccentricity index (LV-EI), as described by the guidelines of the ASE,^{7,8} and the right ventricular automated systolic index (RV-ASI) as presented in 2012.⁵ Non-invasive haemodynamic assessment by Doppler echocardiography included estimated right atrial pressure (RAP) by diameter and collapsibility of the inferior vena cava (IVC),¹³ sPAP by adding right ventricular systolic pressure gradient (RV-sPG) to RAP,² velocity time integral (VTI) of the tricuspid regurgitation (TR), right ventricular mean pressure gradient (RV-mPG) based on the VTI of the complete TR envelope using the modified Bernoulli equation, the tricuspid annular systolic velocity (TASV), as well as the Tei-Index by tissue Doppler. Two-dimensional strain (RV-2Dstrain) of the three segments of the RV free wall was measured in an apical four-chamber view with focus on the RV by speckle tracking using the automated functional imaging tool (AFI, GE Healthcare Vingmed) as described before.⁶ LV-EF was calculated by the biplane modified Simpson's rule.

The RV-MMI was calculated dividing the absolute RV-2Dstrain value by RA-ESA indexed to the patient's body surface area (BSA), multiplied by RV-mPG and adapted for dimensions by factor 10^{-2} (figure 1).

Statistical analysis

Statistical analyses were performed using SPSS V.22. In case of normal distribution, continuous data are expressed as mean and SD, or otherwise as median with 25% and 75% percentiles. For categorical data absolute and relative frequencies are provided. Differences between survivors and non-survivors were analysed by Mann-Whitney U test, Student's t-test (unpaired, two-tailed) or χ^2 test, as appropriate. Receiver operating characteristics (ROC) with area under the curve (AUC) were calculated to assess diagnostic reliability of each parameter, and the optimal cut-off values of each parameter were defined by Youden's J Index for dichotomous analyses. Kaplan-Meier plots show the percentage of event-free survival for patient groups during a period of up to 4 years after dichotomisation. Univariate survival analyses by Cox proportional regression were conducted for each parameter, with steady inclusion of measured values, as well as dichotomised according to the ROC. Based on 65 patients in the study population and 16 events, a comprehensive multivariate analysis could not be conducted. However, dependencies of important functional cardiac parameters were tested pairwise to identify dependent predictors.

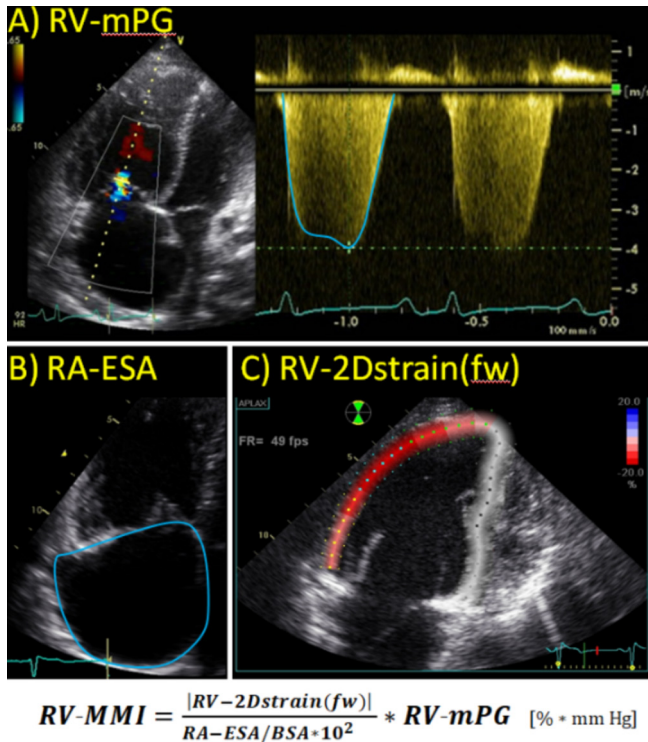


Figure 1 Right ventricular myo-mechanical index (RV-MMI), including measurements applied: RV-mPG by cw Doppler echocardiography (A), RA-ESA in the apical four-chamber view (B) and RV free wall deformation (RV-2Dstrain) (C). BSA, body surface area; cw, continuous-wave; fw, free wall; RA-ESA, right atrial end-systolic area; RV-2Dstrain, two-dimensional strain; RV-mPG, right ventricular mean pressure gradient.

RESULTS

Study population

The study population consisted of 65 patients with precapillary PH. The majority of patients were female (n=44, 64%), and the mean age was 63 (± 15) years. Thirty-one patients with PAH (PH group 1), 14 patients with idiopathic lung disease (ILD), exogenous allergic alveolitis (EAA) or chronic obstructive lung disease (COLD, PH group 3), 19 with chronic thromboembolic pulmonary hypertension (CTEPH, PH group 4) and 1 patient with multifactorial aetiology of PH (PH group 5) were included. All patients had sinus rhythm at the time of echocardiography. According to current guidelines and PH group, treatment of patients at study inclusion consisted of vasodilatory therapy (n=42, 65%; combination therapy: n=14, 22%), amlodipine (n=2, 3%), riociguat (n=2, 3%), immunosuppressive therapy (n=10, 15%), diuretics (n=45, 69%), aldosterone antagonists (n=36, 55%), oral anticoagulation (n=39, 60%), bronchodilator therapy (n=24, 37%) and long-term oxygen therapy (n=54, 83%). In this study group, no patient received lung or combined heart-lung transplantation. Body mass index (BMI), body surface area BSA as well as the age of patients did not differ-significantly between survivors and diseased patients. Risk stratification as

advised by the ESC/ERS guidelines for patients with PAH³ classified 4 patients (6%) with low risk, 22 (60%) with intermediate risk and 39 (34%) with high risk for adverse outcomes.

Non-invasive right heart measurements

All haemodynamic parameters were measurable in the comprehensive echocardiographic examination at the time of inclusion. RV outflow tract stenosis and pulmonary valve stenosis had been excluded by the initial right heart catheter examination. Geometric parameters, TAPSE, RV-FAC and RV-2Dstrain, were obtained in all patients. The 2D image quality ranged from good¹ to suboptimal,³ with a median of 2.2, but was not a reason for exclusion in this trial. The 2D image quality allowed measurement of RV-ASI by automated endocardial border delineation in 63 of 65 patients (97%).

In the group of non-survivors, right heart dilation as defined by RV-EDD and RA-ESA_(BSA) was significantly higher; however, in regard to established parameters for RV function, only TAPSE and LV-EI differed significantly. RV-FAC, Tei-Index and TASV showed no diagnostic discrimination of the patient groups. New methods for assessment of RV function like RV-ASI and RV-2Dstrain discriminated survivors and non-survivors with high significance (tables 1 and 2, online supplementary figures B1-9).

Survival analysis

The mean follow-up time was 844 days. Sixteen patients died during the follow-up period until 30 June 2015 (seven women and nine men). Male sex, WHO functional classes III and IV, as well as 6MWT (distance<330 m) showed only a non-significant trend for adverse outcome in this patient cohort (p=0.05, p=0.086 and p=0.064, respectively). In the survival analysis for each cardiac parameter, cTnT (≥ 28 ng/L), NTproBNP (≥ 4140 pg/mL), heart rate at rest (> 80 /min) and hyperdynamic LV function (LV-EF $\geq 75\%$) were associated with increased mortality. The echocardiographic parameters RV-EDD, RA-ESA_(BSA), TAPSE, LV-EI, RV-ASI, RV-2Dstrain and RV-MMI were significantly predictive, whereas diameter and collapsibility of IVC, Doppler measurements, RV-FAC, Tei-Index and TASV showed no association with outcome (table 3). Additionally, isolated non-invasive haemodynamic measurements as well as timing of RV contraction were not predictive in the whole study population nor in the subgroup without severe TR (online supplementary tables D and E).

Right ventricular myo-mechanical index

RV-MMI was measurable in all patients, with a median of 0.32 (0.22; 0.59) mm Hg^{*}%. The distribution of RV-MMI differed significantly between surviving and diseased patients (table 2). Reproducibility of RV-MMI was good, with an intraclass correlation coefficient (ICC) of 0.97 (95% CI 0.90 to 0.99, p<0.001) for interobserver measurements.

Table 1 Clinical characteristics of the study population

Parameters	All n=65	Survivors n=49	Non-survivors n=16	P values
Age, years	63.5±14.8	63.2±15.3	64.4±13.3	0.601
Male, n (%)	22 (34)	12 (24)	9 (56)	0.030
Height, cm	168±9	167±8	170±11	0.367
Weight, kg	73.0 (63.5; 88.0)	70 (63.5; 87.5)	81.5 (61.8; 88.8)	0.508
BMI, kg/m ²	26.0 (22.9; 29.5)	26.0 (22.9; 29.5)	26.4 (22.3; 30.7)	0.897
BSA, m ²	1.82 (1.67; 1.99)	1.80 (1.66; 1.98)	1.93 (1.67; 2.00)	0.337
Heart rate, 1/min	72 (65; 84)	71 (65; 84)	82 (74; 88)	0.017
Serological measurements				
Haemoglobin, g/dL	13.7 (11.7; 15.2)	13.0 (11.7; 15.0)	14.4 (11.5; 15.6)	0.442
NTproBNP, pg/mL	668 (182; 3500)	457 (150; 1572)	4755 (520; 7541)	0.004
cTnT, ng/L	12 (5; 27)	10 (5; 23)	26 (9; 63)	0.031
Clinical classification, n (%)				
WHO FC I	3 (5)	33 (6)	0 (0)	–
WHO FC II	21 (32)	18 (37)	3 (19)	–
WHO FC III	32 (49)	21 (43)	11 (69)	–
WHO FC IV	9 (14)	7 (14)	2 (12)	–
WHO FC>II	41 (63)	28 (57)	13 (81)	0.085
6MWT, m	348 (264; 490)	379 (278; 527)	304 (209; 444)	0.102
PH group				
1—PAH	31 (48)	24 (49)	7 (44)	–
3—ILD, EAA, COPD	14 (22)	9 (18)	5 (31)	–
4—CTEPH	19 (29)	15 (31)	4 (25)	–
5—multifactorial aetiology	1 (1)	1 (2)	0 (0)	–

Total number of patients of a category is complemented by the percentage of the according group, n (%). Variability of values is given as mean with (±SD) for parameters with normal distribution, or otherwise as median with percentiles (25%; 75%).

6MWT, 6 min walk test; BMI, body mass index; BSA body surface area; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; cTnT, cardiac troponin T; EAA, exogenous allergic alveolitis; FC, functional class; ILD, idiopathic lung disease; NTproBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

RV-MMI discriminated patient survival with the highest significance according to ROC analysis (AUC=0.85, $p<0.001$, sensitivity=88%, specificity=73% for a cut-off value of ≤ 0.31 mm Hg*%; [figure 2](#)). Poor outcome was predictable with an HR of 3.3 (95% CI 1.6 to 7.0, $\chi^2=16.4$, $p<0.001$; [figure 3](#)). The incremental predictive value of RV-MMI is visualised in [figure 4](#). Additionally, RV-MMI was independently predictive to NTproBNP measurements ([table 4](#)).

DISCUSSION

In this study population, the RV-MMI showed superior predictive power in comparison with other echocardiographic surrogate parameters of RV function, clinical classification and serological parameters in 65 patients with precapillary PH under guideline conform therapy. As novel index for effective RV performance, the RV-MMI combines the echocardiographic measurements for RV contractility, preload and afterload, that have been evaluated most precisely in the preanalyses with focus

on haemodynamic assessment. In detail, the RV-MMI consists of measurement of deformation of the RV free wall (RV-2Dstrain), adjusted by preload (RA-ESA_{BSA}) and afterload (RV-mPG), as shown in [figure 1](#).

Concept of RV-MMI

Effective RV performance depends on the interaction among intrinsic myocardial power, including contractile reserve, and the following extrinsic factors: pulmonary artery resistance (afterload) and RV filling (preload) (online supplementary figure A). LV dysfunction and ventricular interdependence, shunts or valvular flow dynamics (eg, regurgitation of the pulmonary and tricuspid valves), as well as rhythm disorders (excessive tachycardia or dyssynchrony), may contribute to altered afterload, preload or RV contractility. In contrast to the left ventricle, the RV has a conduit and reservoir function under physiological conditions and lacks adaptive capacity to short-term pressure augmentation.¹⁴ In chronic cardiopulmonary disease, RV hypertrophy is a transient compensatory mechanism to

Table 2 Echocardiographic assessment

Parameters	All n=65	Survivors n=49	Non-survivors n=16	P values
LV-EF, %	68 (65; 73)	67 (65; 72)	72 (68;77)	0.018
Right heart geometric parameters				
RV-EDD, cm	41 (36; 49)	40 (35; 47)	48 (40; 55)	0.033
RA-ESA, cm ²	21 (15; 29)	19 (14; 27)	30 (16; 36)	0.023
RA-ESA _(BSA) , cm ² /m ²	11 (8; 16)	11 (8; 14)	16 (10; 18)	0.035
IVC diameter, mm	20 (17; 23)	19 (16; 23)	21 (18; 24)	0.432
Right heart haemodynamic assessment				
Impaired IVC collapsibility, n (%)	42 (64)	33 (67)	9 (56)	0.998
Estimated RAP, mm Hg	10 (5; 15)	10 (5; 15)	12.5 (5; 20)	0.171
RV-sPG, mm Hg	54 (38; 80)	57 (38; 81)	50 (38; 76)	0.563
RV-mPG, mm Hg	35 (25; 49)	35 (25; 51)	29 (24; 44)	0.433
VTI, cm	127 (107; 165)	129 (110; 167)	125 (86; 154)	0.226
Estimated sPAP, mm Hg	65 (45; 91)	66 (46; 91)	65 (43; 91)	0.648
TR flow time, ms	461 (431; 498)	466 (444; 498)	437 (374; 498)	0.212
TR time-to-peak-flow, ms	247 (205; 277)	251 (214; 282)	222 (193; 257)	0.077
dp/dt 1–2, mm Hg/ms	800 (511; 1145)	857 (522; 1145)	709 (500; 1150)	0.441
dp/dt 0.5–2, mm Hg/ms	625 (429; 789)	625 (441; 811)	476 (278; 787)	0.647
dp/dt 1–3, mm Hg/ms	438 (226; 771)	438 (204; 771)	536 (379; 762)	0.726
TR mean acceleration, cm/s ²	15.5 (13.2; 18.3)	15.3 (13.0; 17.9)	16.3 (15.0; 19.5)	0.091
Surrogate parameters of RV function				
RV-FAC, %	28 (22; 38)	29 (23; 38)	24 (16; 34)	0.209
TAPSE, cm	1.7 (1.4; 1.9)	1.7 (1.5; 2.0)	1.4 (1.1; 1.7)	0.010
LV-EI	1.3 (1.1; 1.7)	1.3 (1.1; 1.5)	1.7 (1.4; 2.2)	0.009
Tei-Index	0.68 (0.52; 0.99)	0.66 (0.51; 0.97)	0.74 (0.52; 1.11)	0.946
TASV, cm/s	10 (8; 12)	10 (8; 12)	10 (8; 12)	0.481
RV-ASI, %	41 (35; 47)	41 (36; 48)	36 (29; 41)	0.028
RV-2Dstrain, –%	16 (10; 20)	17 (11; 21)	10 (8; 16)	0.002
RV-MMI, mm Hg*%	0.38 (0.22; 0.59)	0.49 (0.31; 0.62)	0.19 (0.16; 0.29)	0.001

Variability of values with non-parametric distribution is presented as median with 25% and 75% percentiles.

ASI, automated systolic index; BSA, body surface area; dp/dt, physical formula in SI, representing pressure augmentation per time; EDD, end-diastolic diameter; FAC, fractional area change; IVC, vena cava inferior; LV-EF, left ventricular ejection fraction; LV-EI, left ventricular eccentricity index; mPG, mean pressure gradient; RA-ESA, right atrial end-systolic area; RAP, right atrial pressure; RV, right ventricular; RV-2Dstrain, two-dimensional strain; RV-MMI, right ventricular myo-mechanical index; sPAP, systolic pulmonary artery pressure; sPG, systolic pressure gradient; TAPSE, tricuspid annular plane systolic excursion; TASV, tricuspid annular systolic velocity; TR, tricuspid regurgitation; VTI, velocity time integral.

increased afterload, but can promptly reach a critical point resulting in severe RV dysfunction and failure.¹⁵ According to these preconditions, invasively or non-invasively measured PAP as a marker for PH progress is inadequate, as the pressure generated depends on RV function. For example, an increasing pulmonary vascular resistance (PVR) may result rapidly in a drop of PAP instead of an increase, due to failing RV contractility and consecutive low cardiac output. Consistently, the non-survivors in this study showed a non-significant trend to decreased RV-sPG and RV-mPG (table 2). On the other hand, an increase of RV pressure gradients may indicate a recovering RV myocardium under treatment. Therefore, isolated haemodynamic assessment

at rest may not be useful in regard to treatment decisions. Non-invasive haemodynamic measurements in this study were not associated with outcome in patients with precapillary PH, contradicting a former study in regard to non-invasive dp/dt (RV) measurement.¹⁶ In contrast, non-invasive measurement of sPAP augmentation during symptom-limited exercise echocardiography may deliver information about RV contractile reserve and on survival.¹⁷ However, this examination is used only by few expert centres in these critically ill patients. In this scenario, RV-MMI combines important aspects of right heart failure and can be obtained non-invasively bedside.

Table 3 Diagnostic accuracy by ROC and univariate, unadjusted survival analysis by Cox proportional regression

Parameters	AUC by ROC (95% CI)	Optimal cut-off	HR	95% CI	χ^2
Age, years	0.51† (0.35 to 0.67)	>72	1.3†	0.79 to 2.1	–
Sex	0.65† (0.49 to 0.81)	Male	2.7† ^(0.05)	1.0 to 7.2	4.2† ^(0.054)
Heart rate, /min	0.70* (0.56 to 0.84)	>80	1.8*	1.0 to 7.2	5.7*
Haemoglobin, g/dL	0.56† (0.39 to 0.74)	≥14.4	1.4†	0.9 to 2.3	–
WHO FC	0.60† (0.46 to 0.75)	>II	1.7† ^(0.086)	0.9 to 3.3	3.6† ^(0.071)
6MWT, m	0.66† (0.51 to 0.80)	<330	1.8† ^(0.081)	0.9 to 3.6	3.4† ^(0.064)
NTproBNP, pg/mL	0.67* (0.59 to 0.91)	≥4140	2.8***	1.6 to 4.8	18.2***
cTnT, ng/L	0.63† (0.51 to 0.87)	≥28	2.1**	1.2 to 3.7	8.6**
LV-EF, %	0.70* (0.54 to 0.86)	>75	2.1**	1.2 to 3.5	9.2**
RA-ESA _{BSA} , cm ² /m ²	0.68* (0.50 to 0.85)	≥15	1.7*	1.0 to 2.9	4.7*
RV-EDD, mm	0.68* (0.51 to 0.85)	>48	2.1**	1.3 to 3.4	7.8**
TAPSE, mm	0.71* (0.55 to 0.88)	<16	2.3**	1.3 to 3.9	10.2**
RV-FAC, %	0.61† (0.43 to 0.78)	<22	1.7†	0.8 to 11.4	–
RV-ASI, %	0.69* (0.52 to 0.87)	<37	1.7*	1.5 to 2.8	4.4*
LV-EI	0.68** (0.51 to 0.86)	≥1.7	2.5**	1.5 to 4.2	11.9***
TASV, cm/s	0.51† (0.33 to 0.68)	<10	1.2†	0.7 to 2.0	–
Tei-Index	0.56† (0.39 to 0.73)	≥0.72	1.1†	0.6 to 1.7	–
RV-2Dstrain, –%	0.78** (0.62 to 0.90)	≤ 12	2.3**	1.4 to 3.9	10.5***
RV-MMI, mm Hg ⁺ %	0.85*** (0.76 to 0.95)	≤0.31	3.3**	1.6 to 7.0	16.0***
ESC/ERS PAH risk score	0.64† (0.49 to 0.79)	>10%	1.9*	1.0 to 3.5	4.4*

*P<0.05, **P<0.01, ***P<0.001.

†Not significant.

6MWT, 6 min walk test; ASI, automated systolic index; AUC, area under the curve; BSA, body surface area; cTnT cardiac troponin T; EDD, end-diastolic diameter; ERS, European Respiratory Society; ESC, European Society of Cardiology; FAC, fractional area change; FC, functional class; LV-EF, left ventricular ejection fraction; LV-EI, left ventricular eccentricity index; NTproBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RA-ESA, right atrial end-systolic area; ROC, receiver operating characteristics; RV, right ventricular; RV-2Dstrain, two-dimensional strain; RV-MMI, right ventricular myo-mechanical index; TAPSE, tricuspid annular plane systolic excursion; TASV, tricuspid annular systolic velocity.

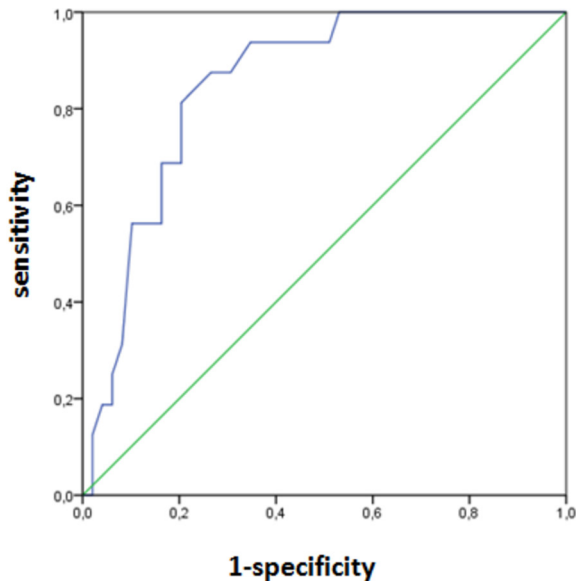
Reliability of RV-MMI

Although the calculation of RV-MMI is based on three separate echocardiographic measurements, a good reproducibility of RV-MMI with an ICC of 0.97 (0.90 to 0.99) was present for interobserver measurements, which could be based on a compensation effect: for example, Doppler measurements can be conducted reliably, although 2D image quality is reduced for speckle tracking and RA size assessment. Vice versa, good image quality including semiautomatic assessment of RV-2Dstrain may balance variations in Doppler measurements and the resulting spectral curves, for example, in patients with arrhythmia or severe TR. Of course, a complete spectral curve of the TR had to be recorded and traced thoroughly in all patients for reliable assessment of RV-mPG.²

As a relevant TR influences RV haemodynamics and measurement of pressure gradient, RV-MMI was tested in subgroups differentiated for severe TR (n=13, 20%). Importantly and in contrast to other parameters on RV function, RV-MMI remained predictive without loss of predictive power in both subgroups (online supplementary tables D and E). This may be explained considering

the definition of RV-MMI: in case of significant TR, the resulting increase of preload, as well as a potential drop of PAP due to reduced output, results in a decrease of RV-MMI. Thus, RV-MMI reflects the effective RV performance even in the case of severe TR, and a failing RV myocardium will not be masked by altered preload or afterload. Online supplementary figure C visualises the concept of RV-MMI in respect to the course of the disease in this complex situation, incorporating the possible changes of the three main factors in the RV dysfunction.

As an important point, the calculation of RV-MMI is dependent on the non-invasive assessment of PAP. Comparable with our precursor studies on PAP assessment,^{1,2} all of our 65 patients with invasively diagnosed precapillary PH presented a good traceable TR signal without selection on the acoustic window by the study design. Echocardiographic image quality was moderate to suboptimal in mean as described above. A diagnostic gap in which RV-MMI cannot be applied may be assumed in patients with 'latent' PH (invasive mean PAP of 20–24 mm Hg). However, according to current guidelines, these patients do not receive targeted therapy until definite diagnosis of



AUC RV-MMI	95%CI	p
0.85	0.76-0.95	<0.001
c/o	Sens	Spec
≤0.31 mmHg*%	88%	73%

Figure 2 Diagnostic accuracy of RV-MMI (blue line, green line with AUC=0.5 as reference). AUC, area under the curve; c/o, cut-off value; RV-MMI, right ventricular myo-mechanical index; Sens, sensitivity; Spec, specificity.

precapillary PH and RV-MMI aims for effective treatment control in patients under therapy.

Comparison with established parameters on RV function

The prospective New-RV study includes a detailed work-up of established and new echocardiographic methods (table 3, online supplementary tables C, D, please correct for: tables D and E). Various haemodynamic measurements and indices were tested comprehensively for their prognostic value, including correction for heart rate, duration of RV systole and time to systolic peak flow (data not shown). Comparable with isolated, non-invasive haemodynamic measurements, the derived haemodynamic-based indices including TASV and Tei-Index without information on preload or RV contractility showed no prognostic value in this study population (online supplementary tables C, D, please correct for: tables D and E). The best predictive information was obtained by RV-2Dstrain, NTproBNP and RV-MMI. Additionally, hyperdynamic LV function (LV-EF >75%) and elevated heart rate (>80/min) indicate poor outcome, probably due to a more acute disease progression with failing compensatory mechanisms (table 3). Elevated cTnT ≥ 28 ng/mL may be caused by hyperdynamic LV function as well as by increased RV myocardial burden.¹⁸ In contrast to cTnT, LV-EF and other parameters tested, the RV-MMI remained independently predictive to NTproBNP (table 4).

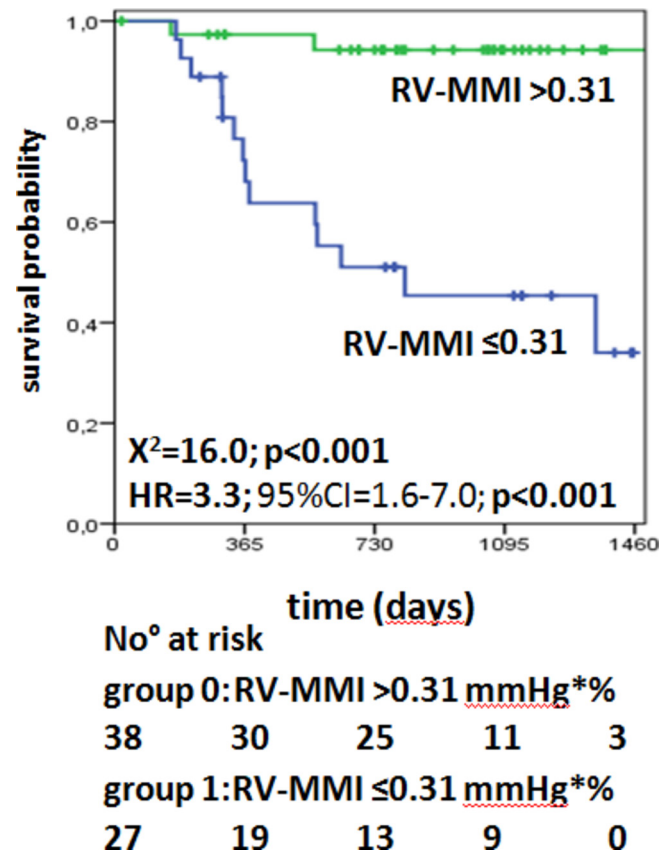


Figure 3 Prediction of survival by right ventricular myo-mechanical Index (RV-MMI). Group 0 with RV-MMI>0.31 in green, group1 with RV-MMI ≤0,31 in blue.

The incremental predictive value by calculation of RV-MMI was tested in detail and compared with each involved parameter, as well as with the guideline conform risk stratification and a scoring algorithm that was based on the three echocardiographic parameters, defining elevated risk when at least two of the three parameters were pathological. The quantification of RV function by calculation of RV-MMI with a defined threshold delivered superior predictive power in this patient cohort, as visualised in figure 4.

Translation into clinical practice

Chronic right heart failure has been hard to trace until now.¹⁹ Furthermore, chronic maladaptations during the patient's course of disease like renal failure, recurrent infections, insufficient nutrition or loss of physical strength have to be discriminated from the underlying cardiopulmonary disease for effective treatment regularly. In contrast to the invasively derived RV stroke work index or RV preload recruitable stroke work index, the RV-MMI incorporates direct information on RV myocardial deformation and is an easily applicable, non-invasive tool for detailed assessment of RV function by transthoracic echocardiography. Its practical validation in combination with serological testing of NTproBNP in daily clinical routine seems a promising approach for patients with precapillary PH.

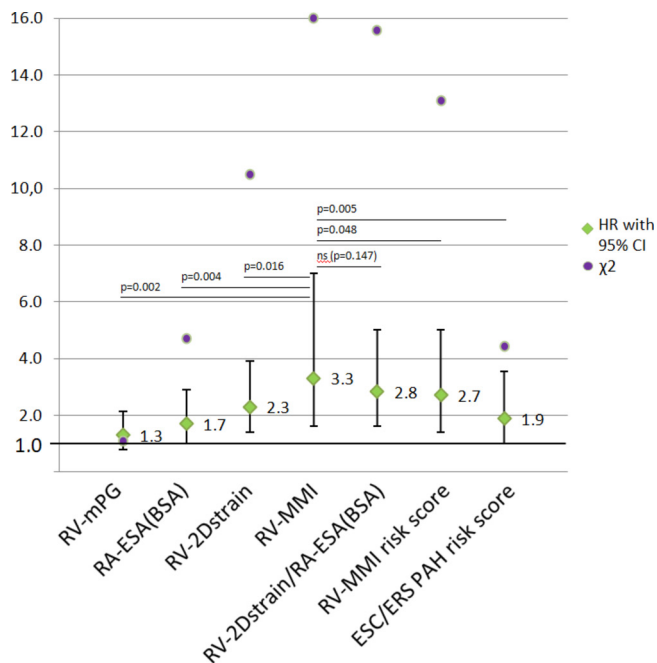


Figure 4 Visualisation of the prognostic value of RV-MMI compared with single parameters and risk stratification by scoring systems. BSA, body surface area; ERS, European Respiratory Society; ESC, European Society of Cardiology; mPG, mean pressure gradient; PAH, pulmonary arterial hypertension; RA-ESA, right atrial end-systolic area; RV, right ventricular; RV-2Dstrain, two-dimensional strain; RV-MMI, right ventricular myo-mechanical index.

Limitations

The prospective New-RV trial is a single-centre study focused on patients with precapillary PH. The study population was limited to 65 patients including 16 events. Especially for definition of valid cut-off values and multivariate analyses, RV-MMI has to be tested in larger patient collectives.

As invasive data by RHC for diagnosis of precapillary PH as well as for targeted therapy were conducted prior to inclusion in the New-RV trial for all patients, data by RHC did not match non-invasive measurements chronologically and were not analysed within the New-RV study.

Additionally, a lead time bias cannot be excluded in a study with patients under treatment and at different stages of disease. However, RV-MMI was evaluated for a clinical scenario with follow-up examinations and significantly identified the patients with high risk for adverse outcome in this study.

Table 4 Independent prediction of survival by NTproBNP and RV-MMI

Parameters	HR	95% CI	P values
NTproBNP (≥ 4140 pg/mL)	2.61	1.48 to 4.59	0.001
RV-MMI (≤ 0.31 mm Hg %)	2.90	1.37 to 6.17	0.006

NTproBNP, N-terminal pro-brain natriuretic peptide; RV-MMI, right ventricular myo-mechanical index.

CONCLUSION

In a cohort of patients with precapillary PH, the RV-MMI indicates outcome of patients better than other available, non-invasive RV parameters by preload and afterload adjusted quantification of RV function, and independent of NTproBNP measurements.

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Ethics approval The study was carried out prospectively after approval by the Ethics Committee of the University of Heidelberg, in concordance with the Declaration of Helsinki.

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