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Prognostic value of right atrial dilation in patients with pulmonary embolism

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ABSTRACT

Aims: Right atrial (RA) dilation and stretch provide prognostic information in patients with cardiovascular diseases. We investigated the prevalence, confounding factors and prognostic relevance of RA dilation in patients with pulmonary embolism (PE).

Methods: Overall, 609 PE patients were consecutively included in a prospective single-centre registry between September 2008 and August 2017. Volumetric measurements of heart chambers were performed on routine non-electrocardiographic-gated computed tomography and plasma concentrations of mid-regional pro-atrial natriuretic peptide (MR-proANP) measured on admission. An in-hospital adverse outcome was defined as PE-related death, cardiopulmonary resuscitation, mechanical ventilation or catecholamine administration.

Results: Patients with an adverse outcome (11.2%) had larger RA volumes (median 120 (interquartile range 84–152) *versus* 102 (78–134) mL; p=0.013), RA/left atrial (LA) volume ratios (1.7 (1.2–2.4) *versus* 1.3 (1.1–1.7); p<0.001) and MR-proANP levels (282 (157–481) *versus* 129 (64–238) pmol·L^{-1}; p<0.001) compared to patients with a favourable outcome. Overall, 499 patients (81.9%) had a RA/LA volume ratio ⩾1.0 and a calculated cut-off value of 1.8 (area under the curve 0.64, 95% CI 0.56–0.71) predicted an adverse outcome, both in unselected (OR 3.1, 95% CI 1.9–5.2) and normotensive patients (OR 2.7, 95% CI 1.3–5.6). MR-proANP ⩾120 pmol·L^{-1} was identified as an independent predictor of an adverse outcome, both in unselected (OR 4.6, 95% CI 2.3–9.3) and normotensive patients (OR 5.1, 95% CI 1.5–17.6).

Conclusions: RA dilation is a frequent finding in patients with PE. However, the prognostic performance of RA dilation appears inferior compared to established risk stratification markers. MR-proANP predicted an in-hospital adverse outcome, both in unselected and normotensive PE patients, integrating different prognostic relevant information from comorbidities.

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RA dilation is a frequent finding but its prognostic performance appears inferior compared to other risk stratification markers. MR-proANP predicts an adverse outcome but elevation does not appear to be caused by RA dilation in a relevant proportion. https://bit.ly/3q55dqy

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Introduction

Pulmonary embolism (PE) is the most serious manifestation of venous thromboembolism (VTE) and is associated with relevant morbidity and mortality worldwide [1, 2]. Risk stratification is mandatory to guide decision-making on optimal management strategies [3]. Because it is broadly accepted that the extent of right ventricular (RV) dysfunction is the critical determinant of outcome in patients with acute PE, research aiming to optimise risk stratification has mainly focused on (bio-)markers indicating RV dysfunction or injury.

Considering the anatomy of the heart chambers with a thin right atrial (RA) wall and low resistance to the sudden increase of pulmonary artery pressure caused by embolisation of a thrombus to the pulmonary vasculature, dilation of the RA and increase of RA volume may be expected to occur before RV dilation can be visualised or biochemically detected [4]. Right to left atrial (RA/LA) end-systolic area ratio assessed by transthoracic echocardiography (TTE) was shown to be associated with the extent of pulmonary artery obstruction on ventilation/perfusion lung scintigraphy [5], and a RA/LA area ratio >1.0 was independently associated with a three-fold increase in long-term mortality [6]. Furthermore, the RA/LA volume ratio on computed tomography pulmonary angiography (CTPA) was significantly larger in PE patients with insufficient contrast medium filling in pulmonary veins compared to those without [7], and patients with a RA/LA volume ratio >1.2 had a higher 30-day mortality rate [8].

RA distention is not only easy to visualise by imaging modalities, it may also be detected biochemically. As a result of increased wall tension and stretch, mid-regional pro-atrial natriuretic peptide (MR-proANP) is secreted from the atria and is a useful biomarker for the diagnosis of acute and chronic heart failure [9]. Interestingly, MR-proANP was more reliable for the detection of pulmonary hypertension due to left heart disease in patients with systemic sclerosis compared to the "ventricular" N-terminal pro-B-type natriuretic peptide (NT-proBNP) [10]. While the association of NT-proBNP with the presence and extent of RV dysfunction and the prognostic value of elevated NT-proBNP levels in patients with acute PE have been consistently demonstrated [11], the prognostic value of MR-proANP and association with RA dilation in acute PE is unknown.

In the present study we aimed to investigate whether a dilated RA (defined by the RA/LA volume ratio, in order to overcome sex- and body size-related physiological differences in atrial size) on diagnostic CTPA using volumetric analyses of the cardiac chambers predicts early adverse outcomes in a large series of patients with acute PE. Further, we investigated whether plasma concentrations of MR-proANP on admission are correlated with imaging findings and provide additive prognostic information.

Methods

Study design

Patients aged ⩾18 years with objectively confirmed PE treated at the University Medical Center Göttingen, Germany, were included in an ongoing non-interventional cohort study (Pulmonary Embolism Registry of Göttingen; PERGO). The study was conducted in accordance with the amended Declaration of Helsinki, the study protocol was approved by the local independent ethics committee of the University Medical Center Göttingen, Germany, and all patients gave written informed consent for participation in the study. All decisions related to diagnostic or therapeutic management were made by the physicians caring for the patient and were not influenced by the study protocol at any time. The study protocol has been described in detail before [12].

For the present analysis, patients 1) without CTPA for diagnosis of PE, 2) with insufficient quality of CTPA (*e.g.* inaccurate detection of the cardiac chambers' boundaries by the volumetric software,

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incomplete coverage of the heart or too little contrast enhancement) and 3) who died within 2 h after hospital admission, were excluded.

The primary study outcome was an in-hospital adverse outcome (defined as at least one of the following: PE-related death, cardiopulmonary resuscitation, mechanical ventilation or catecholamine administration); the secondary study outcome was in-hospital all-cause mortality. Death was determined to be PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in the absence of an alternative diagnosis. All outcomes and causes of death were independently adjudicated by two of the authors (M.H. Lerchbaumer and K. Keller) and disagreement was resolved by a third author (M. Lankeit).

Volumetric and diameter measurements using computed tomography

All patients were examined using Siemens Healthcare multidetector computed tomography scanners (Siemens Sensation 16 (16 detector rows), Somatom Definition FLASH (128 detector rows), Somatom Definition AS+ (128 detector rows)). All CTPA scans were performed as part of clinical routine for diagnostic confirmation of PE using a non-electrocardiographic (ECG)-gated protocol. Volumetric measurements of the cardiac chambers were obtained using a fully automated algorithm (Pulmonary Arterial Analysis, Extended Brilliance Workspace, Portal Version 7, Philips Healthcare). The output consists of a reconstructed, colour-coded, three-dimensional graphic display of the heart (figure 1). RA and LA volumes were automatically calculated as the product of a single voxel volume and the sum of all voxels. RV and left ventricular (LV) diameters were measured in axial views using the largest diameter of

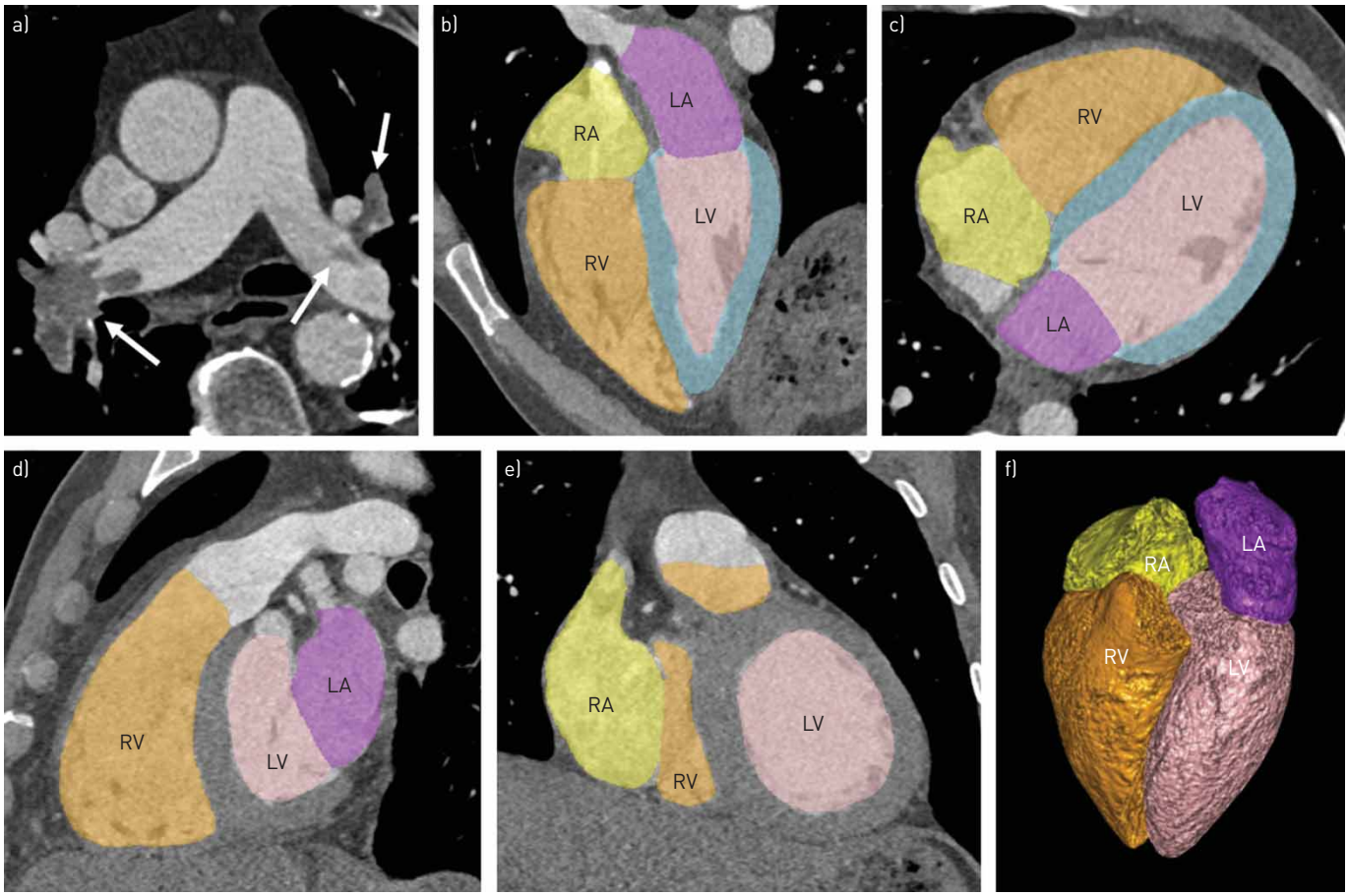

FIGURE 1 Representative case of volumetric analysis using computed tomography pulmonary angiography. A 35-year-old male patient without relevant comorbidities presenting with dyspnoea, haemoptysis and chest pain (heart rate 92 beats·min^{-1}, blood pressure 155/70 mmHg, respiratory rate 12 breaths·min^{-1}, oxygen saturation 99%) and normal biomarker plasma concentrations (mid-regional pro-atrial natriuretic peptide 84 pmol·L^{-1}, N-terminal pro-B-type natriuretic peptide 35 pg·mL^{-1} and high-sensitivity troponin T <5 pg·mL^{-1}). The patient was treated with low molecular weight heparin followed by rivaroxaban and discharged after 4 days without suffering any relevant complications. a) Central thrombus in the right (and left) pulmonary artery and thrombus in left segmental pulmonary artery (marked with arrows). b, c) Automated reconstructed b) four-chamber and c) axial view with coloured overlay: right atrium (RA) 92 mL (yellow), left atrium (LA) 75 mL (purple), RA/LA volume ratio 1.23, right ventricle (RV) 233 mL (orange), left ventricle (LV) 203 mL (pink), myocardium (light blue). d, e) Automated d) sagittal and e) coronal multiplanar reconstruction. f) 3D volumetric model of the four cardiac chambers.

each ventricle and RV/LV diameter ratios calculated. All measurements were performed by a radiologist (M.H. Lerchbaumer) in consensus with an expert radiologist (G. Aviram) unaware of the patients' characteristics and outcome. A RA/LA volume ratio cut-off value of 1.2 was defined to predict in-hospital mortality [8].

Biomarker measurement

Venous plasma samples were collected on admission, processed using standard operating procedures and immediately stored at −80°C. Plasma concentrations of MR-proANP, NT-proBNP and high-sensitivity troponin T (hsTnT) were measured in batches after a single thaw by the Institute of Clinical Chemistry of the University Medical Center Göttingen, Germany, and Amedes MVZ Wagnerstibbe, Göttingen, Germany, using commercially available assays (MR-proANP: BRAHMS GmbH, Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany; NT-proBNP and hsTnT: Roche Diagnostics, Mannheim, Germany). Elevated biomarker levels were defined *ad hoc* as NT-proBNP $\geqslant$600 pg·mL^{-1} [11] and hsTnT $\geqslant$14 pg·mL^{-1} [13] (prognostic relevant cut-off values reported for patients with PE). Given the lack of a previous investigation of MR-proANP in patients with PE, a threshold of $\geqslant$120 pmol·L^{-1} was selected based on the Biomarkers in Acute Heart Failure (BACH) study [14].

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test; variables not following a normal distribution are presented as median and interquartile range (IQR) and were compared using the Mann–Whitney U-test. Categorical variables are presented as numbers and percentages and were compared using Fisher's exact test or chi-squared test, as appropriate. RA and LA volume and RA/LA volume ratio were correlated to continuous echocardiographic, laboratory and clinical parameters. Correlation coefficients were assessed by Spearman's rank correlation test. Correlation with $r<-0.4$ or >0.4 were considered clinically relevant. Receiver operating characteristic (ROC) analyses were used to investigate the prognostic performance of continuous measures (radiological, echocardiographic and laboratory parameters) and to determine patient-cohort optimal cut-off values by using Youden index quantification; results are reported as area under the curve (AUC) with corresponding 95% confidence interval. The prognostic value of categorical parameters with regard to the primary and secondary study outcomes were investigated using univariate logistic regression analyses and results reported as odds ratios with corresponding 95% confidence interval. To identify parameters associated with MR-proANP above the median concentrations of 142 pmol·L^{-1}, univariate and multivariate (including all univariate predictors using stepwise forward selection) logistic regression analyses were performed. Subsequently, the independence of MR-proANP $\geqslant$120 pmol·L^{-1} to predict an in-hospital adverse outcome was tested using a multivariate logistic regression model simultaneously including parameters (age $\geqslant$75 years, female sex, chronic heart failure, atrial fibrillation, coronary artery disease, arterial hypertension, renal insufficiency) shown to independently predict MR-proANP elevation.

A two-sided significance level of $\alpha<0.05$ was defined appropriate to indicate statistical significance. All statistical analyses were performed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Overall, 718 PE patients were included in PERGO over a 9-year period (September 2008 to September 2017). Of these, 114 patients (15.9%) were excluded for the following reasons: 47 patients (6.5%) because of missing CTPA scans and 62 (8.6%) because of insufficient quality of CTPA scans. Thus, the present study cohort consists of 609 patients (median age 69, IQR 56–77 years; 47.0% male). Baseline characteristics, comorbidities and clinical findings of the study patients are shown in table 1, left column. Of note, 53 patients (8.7%) were classified as high risk using the algorithm suggested by the 2019 European Society of Cardiology (ESC) guideline [3].

Representative images of volumetric analysis using CTPA are shown in figure 1. In the overall cohort, the median RA and LA volume was 102 (IQR 78–134) and 71 (IQR 57–93) mL, respectively, and the median RA/LA volume ratio was 1.37 (IQR 1.05–1.80). As shown in supplementary table S1, patients with cardiovascular comorbidities, and male and elderly ($\geqslant$75 years) patients, had larger RA and LA volumes, respectively; cancer patients had a smaller RA and LA volume. While patients with cardiovascular comorbidities and cancer had a smaller RA/LA volume ratio, patients with more severe PE (*e.g.* indicated by tachycardia, syncope, elevation of laboratory biomarkers or higher ESC risk class) had a larger RA/LA volume ratio (table S1). Similarly, as shown in table S2, patients with a RA/LA volume ratio <1.4 more frequently had cardiovascular comorbidities and cancer while patients with a RA/LA volume ratio $\geqslant$1.4 more frequently had more severe PE. The median RV/LV diameter ratio was 1.17 (IQR 0.98–1.51) and as many as 445 patients (73.1%) had a RV/LV diameter ratio $\geqslant$1.0.

TABLE 1 Baseline characteristics, comorbidities and clinical findings in pulmonary embolism patients, stratified according to the median MR-proANP concentration, and odds ratios for predicting MR-proANP ⩾142 pmol·L^{-1}

	All study patients	MR-proANP <142 pmol·L^{-1}	MR-proANP ⩾142 pmol·L^{-1}	p-value	OR (95% CI)	p-value
Patients n	609	261	261			
Age years	69 (56–77)	57 (43–70)	76 (69–82)	**<0.001**	age ⩾75 years: 8.86 (5.75–13.66)	**<0.001**
Female sex	323 (53.0)	118/261 (45.2)	155/261 (59.4)	**0.001**	1.96 (1.32–2.91)	**0.001**
Comorbidities						
Active cancer	107/608 (17.6)	45/261 (17.2)	46/260 (17.7)	0.892	1.07 (0.64–1.78)	0.810
Chronic pulmonary disease	88/608 (14.4)	32/261 (12.3)	43/260 (16.5)	0.165	1.32 (0.76–2.30)	0.325
Chronic heart failure	88 (14.4)	14/261 (5.4)	57/261 (21.8)	**<0.001**	5.09 (2.56–10.15)	**<0.001**
Atrial fibrillation	64/603 (10.6)	9/258 (3.5)	45/260 (17.3)	**<0.001**	7.89 (3.02–20.62)	**<0.001**
Coronary artery disease	105 (17.2)	22/261 (8.4)	64/261 (24.5)	**<0.001**	3.23 (1.83–5.71)	**<0.001**
Arterial hypertension	370/609 (60.8)	121/261 (46.4)	196/2261 (75.1)	**<0.001**	3.54 (2.32–5.41)	**<0.001**
Renal insufficiency	187/601 (31.1)	30/260 (11.5)	128/261 (49.0)	**<0.001**	7.02 (4.16–11.82)	**<0.001**
Symptoms on admission						
Dyspnoea	477/605 (78.8)	199/261 (76.2)	204/257 (79.4)	0.392	1.10 (0.66–1.86)	0.708
Chest pain	279/603 (46.3)	139/261 (53.3)	100/256 (39.1)	**0.001**	0.58 (0.39–0.86)	**0.006**
Syncope	96/607 (15.8)	24/261 (9.2)	56/259 (21.6)	**<0.001**	2.89 (1.53–5.44)	**0.001**
Tachycardia[#]	214/589 (36.3)	79/257 (30.7)	107/247 (43.3)	**0.003**	1.83 (1.21–2.78)	**0.004**
Hypoxia	162/523 (31.0)	45/220 (20.5)	95/230 (41.3)	**<0.001**	2.54 (1.59–4.15)	**<0.001**
Cardiogenic shock	51/608 (8.4)	12/261 (4.6)	32/260 (12.3)	**0.002**	5.71 (1.64–19.90)	**0.006**
Laboratory biomarkers						
hsTnT ⩾14 pg·mL^{-1}	367/568 (64.6)	101/257 (39.3)	227/257 (88.3)	**<0.001**	9.33 (5.60–15.55)	**<0.001**
NT-proBNP ⩾600 pg·mL^{-1}	286/554 (51.6)	72/257 (28.0)	197/260 (75.8)	**<0.001**	8.21 (5.23–12.89)	**<0.001**
ESC 2019 algorithm						
High risk	53/608 (8.7)	12/261 (4.6)	34/260 (13.1)	**0.001**	3.12 (1.58–6.18)	**0.001**
Intermediate–high risk	160/608 (26.3)	40/261 (15.3)	101/260 (38.8)	**<0.001**	3.51 (2.31–5.34)	**<0.001**
Intermediate–low risk	295/608 (48.4)	129/261 (49.4)	118/260 (45.4)	0.356	0.85 (0.60–1.20)	0.356
Low risk	100/608 (16.4)	80/261 (30.7)	7/260 (2.7)	**<0.001**	0.06 (0.03–0.14)	**<0.001**

Continuous variables are presented as median (interquartile range), categorical variables are presented as absolute/total numbers (%). MR-proANP: mid-regional pro-atrial natriuretic peptide; hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ESC: European Society of Cardiology. [#]: heart rate ⩾100 beats·min^{-1}. Bold indicates p<0.05.

Plasma concentrations of MR-proANP were measured in 522 patients (85.7%; median 142, IQR 68–266, range 14–989 pmol·L^{-1}), of NT-proBNP in 554 patients (91.0%; median 674, IQR 124–2620, range 8–35 645 pg·mL^{-1}) and of hsTnT in 568 patients (93.3%; median 27, IQR 10–65, range 3–3094 pg·mL^{-1}). The baseline characteristics, comorbidities and clinical findings in study patients stratified according to the median MR-proANP concentration are shown in table 1, middle columns. Older age and female sex, cardiovascular comorbidities, as well as symptoms and laboratory biomarkers indicating more severe PE, were associated with MR-proANP levels ⩾142 pmol·L^{-1}. The highest odds ratios for MR-proANP ⩾142 pmol·L^{-1} were observed for age ⩾75 years, atrial fibrillation and renal insufficiency (table 1, right columns); RA dilation assessed by CTPA or TTE was not associated with MR-proANP ⩾142 pmol·L^{-1}.

As shown in table S3, MR-proANP correlated with hsTnT (r=0.561), NT-proBNP (r=0.637) but also with age (r=0.623) and glomerular filtration rate (GFR; r=−0.495).

Prognostic performance of radiological, laboratory and clinical parameters

During the in-hospital stay, 68 patients (11.2%) had an adverse outcome (25 (37.3%) required cardiopulmonary resuscitation, 47 (70.1%) mechanical ventilation and 54 (79.4%) catecholamine administration) and 36 patients (5.9%) died; of those 26 (72.2%) due to PE. As expected, the highest rate of an adverse outcome was observed for patients classified as high risk (69.8%) followed by patients classified as intermediate–high (10.6%) and intermediate–low (4.8%) risk based on the algorithm suggested by the 2019 ESC guideline [3]; none of the patients classified as low risk had an unfavourable clinical in-hospital course.

Patients with an in-hospital adverse outcome had larger RA volumes on CTPA (120, IQR 84–152 *versus* 102, IQR 78–134 mL; p=0.013) and higher RA/LA volume ratios (1.66, IQR 1.19–2.35 *versus* 1.33, IQR 1.05–1.74, p<0.001) compared to patients with a favourable clinical course. However, RA volume was only weakly associated with an in-hospital adverse outcome (AUC 0.59, 95% CI 0.52–0.67) while LA volume was not of prognostic value (AUC 0.44, 95% CI 0.36–0.53). Results remained unchanged if RA and LA volumes were corrected for body surface area (shown in the supplementary material). The AUC of the RA/LA volume ratio with regard to an adverse outcome was 0.64 (95% CI 0.56–0.71; figure 2a). As shown in table 2, increasing RA/LA volume ratios were associated with increasing specificity with regard to the prediction of an adverse outcome. While the predefined RA/LA volume ratio cut-off value of 1.2 was not associated with an increased risk, a calculated patient-cohort optimised cut-off value of 1.8 was associated with a 3.1-fold increased risk (95% CI 1.9–5.2) for an in-hospital adverse outcome. A RV/LV diameter ratio above the established cut-off value of 1.0 failed to predict an in-hospital adverse outcome.

Patients with an in-hospital adverse outcome had higher median biomarker concentrations compared to patients with a favourable clinical course (MR-proANP: 282, IQR 157–481 *versus* 129, IQR 64–238 pmol·L^{-1}, p<0.001; NT-proBNP: 1538, IQR 440–3629 *versus* 556, IQR 114–2461 pg·mL^{-1}, p=0.001 and hsTnT: 58, IQR 27–101 *versus* 24, IQR 8–57 pg·mL^{-1}, p<0.001). The AUC of MR-proANP with

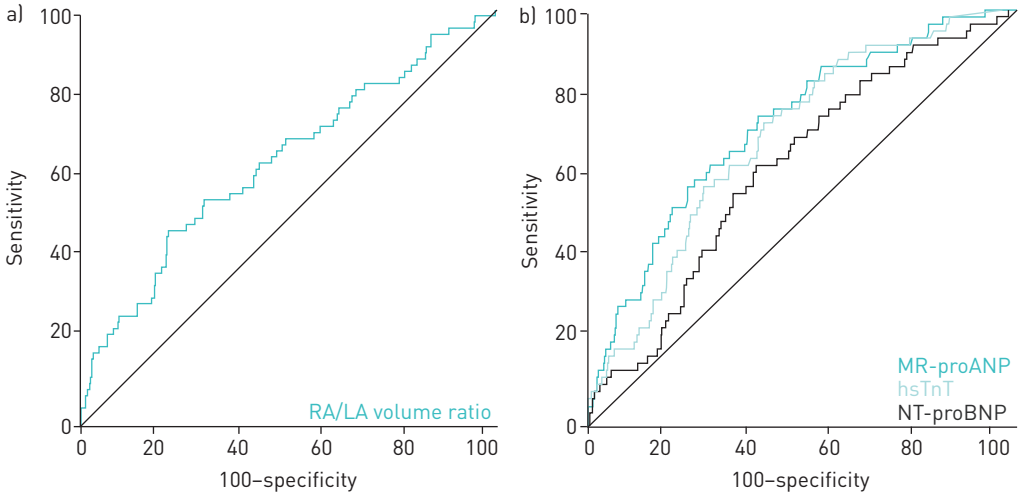

FIGURE 2 Prognostic performance of a) radiological and b) laboratory parameters, with regard to an in-hospital adverse outcome in pulmonary embolism patients. Area under the curve assessed by receiver operating characteristic analysis of a) right to left atrial (RA/LA) volume ratio on computed tomography pulmonary angiography, and b) mid-regional pro-atrial natriuretic peptide (MR-proANP), high-sensitivity troponin T (hsTNT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

TABLE 2 Prognostic performance of right to left atrial (RA/LA) volume ratio using different cut-off values, with regard to an in-hospital adverse outcome in patients with pulmonary embolism

RA/LA volume ratio	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
⩾1.0	60/499	1.71 (0.80–3.69)	0.172	88 (78–94)	19 (15–22)	12 (9–15)	93 (86–96)
⩾1.2	50/382	1.73 (1.00–3.05)	0.057	74 (62–83)	38 (34–43)	13 (10–17)	92 (88–95)
⩾1.4	43/286	2.10 (1.24–3.53)	**0.005**	63 (51–74)	55 (51–59)	15 (11–20)	92 (89–95)
⩾1.6	37/207	2.59 (1.56–4.32)	**<0.001**	54 (43–66)	68 (64–72)	18 (13–24)	92 (89–94)
⩾1.8	32/152	3.10 (1.85–5.21)	**<0.001**	47 (36–59)	78 (74–81)	21 (15–28)	92 (89–94)
⩾2.0	22/118	2.21 (1.27–3.84)	**0.005**	32 (22–44)	82 (79–85)	19 (13–27)	91 (88–93)
⩾2.2	18/91	2.30 (1.27–4.16)	**0.006**	26 (17–38)	86 (83–89)	20 (13–29)	90 (87–93)
⩾2.4	16/63	3.22 (1.71–6.08)	**<0.001**	24 (15–35)	91 (89–93)	25 (16–37)	90 (88–93)
⩾2.6	13/45	3.75 (1.86–7.56)	**<0.001**	19 (12–30)	94 (92–96)	29 (18–43)	90 (87–92)

n: patients with an in-hospital adverse outcome; N: patients with positive finding; PPV: positive predictive value; NPV: negative predictive value. Bold indicates p<0.05.

regard to an adverse outcome (0.72, 95% CI 0.65–0.79) was larger compared to that of NT-proBNP (0.62, 95% CI 0.55–0.70) and hsTnT (0.69, 95% CI 0.63–0.76; figure 2b). Established laboratory (such as NT-proBNP ⩾600 pg·mL^{-1} and hsTnT ⩾14 pg·mL^{-1}) and clinical (such as chronic heart failure, renal insufficiency, syncope or tachycardia) parameters provided valuable prognostic information with regard to an in-hospital adverse outcome (table 3). MR-proANP ⩾120 pmol·L^{-1} was associated with a 4.6-fold increased risk (95% CI 2.3–9.3) for an in-hospital adverse outcome. Of note, if corrected for age, sex and comorbidities affecting MR-proANP concentrations (as described in the Methods section), the prognostic value of MR-proANP remained independent (OR_{adj} 4.0, 95% CI 1.8–9.0).

The prognostic performance of radiological, echocardiographic, laboratory and clinical parameters with regard to in-hospital all-cause mortality is shown in table S4 and with regard to an in-hospital adverse outcome in 556 (91.3%) normotensive patients in table S5.

Discussion

The present study findings in 609 consecutive PE patients included over a 9-year period (September 2008 to September 2017) in a single centre can be summarised as follows: 1) patients with an in-hospital adverse outcome had larger RA volumes and RA/LA volume ratios on CTPA and higher MR-proANP concentrations compared to patients with a favourable clinical course; 2) a calculated patient-cohort optimised RA/LA volume ratio cut-off value of 1.8 was able to predict an in-hospital adverse outcome, both in unselected (OR

TABLE 3 Prognostic performance of radiological, laboratory and clinical parameters, with regard to an in-hospital adverse outcome in patients with pulmonary embolism

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RV/LV diameter ratio ⩾1.0 on CTPA	56/445	1.85 (0.97–3.55)	0.064	82 (72–90)	28 (25–32)	13 (10–16)	93 (88–96)
Chronic heart failure	17/87	2.23 (1.22–4.08)	**0.009**	25 (16–36)	87 (84–90)	20 (13–29)	90 (87–92)
Renal insufficiency	41/187	4.00 (2.38–6.75)	**<0.001**	60 (48–71)	27 (24–31)	10 (7–13)	84 (78–89)
Syncope	24/96	3.61 (2.07–6.31)	**<0.001**	36 (25–48)	87 (83–89)	25 (17–35)	92 (89–94)
Tachycardia[#]	29/214	1.87 (1.08–3.22)	**0.025**	50 (38–62)	65 (61–69)	14 (10–19)	92 (89–95)
hsTnT ⩾14 pg·mL^{-1}	55/365	4.92 (2.20–11.01)	**<0.001**	91 (80–97)	38 (34–42)	13 (10–17)	98 (94–99)
NT-proBNP ⩾600 pg·mL^{-1}	44/284	2.54 (1.43–4.53)	**0.001**	78 (64–88)	49 (45–54)	15 (11–20)	95 (91–97)
MR-proANP ⩾120 pmol·L^{-1}	50/289	4.63 (2.29–9.34)	**0.001**	88 (72–95)	48 (43–53)	13 (9–18)	98 (95–99)
ESC 2019 high risk[¶]	37/53	39.01 (19.58–77.73)	**<0.001**	54 (43–66)	97 (95–98)	70 (56–80)	94 (92–96)

n: patients with an in-hospital adverse outcome; N: patients with positive finding; PPV: positive predictive value; NPV: negative predictive value; RV/LV: right/left ventricle; CTPA: computed tomography pulmonary angiography; hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; MR-proANP: mid-regional pro-atrial natriuretic peptide; ESC: European Society of Cardiology. [#]: heart rate ⩾100 beats·min^{-1}; [¶]: high risk *versus* not high risk (stratified according the ESC 2019 guideline algorithm) [3]. Bold indicates p<0.05.

3.1, 95% CI 1.9–5.2) and normotensive patients (OR 2.7, 95% CI 1.3–5.6); and 3) MR-proANP $\geqslant$120 pmol·L^{-1} was identified as an independent predictor of an in-hospital adverse outcome, both in unselected (OR 4.6, 95% CI 2.3–9.3) and normotensive patients (OR 5.1, 95% CI 1.5–17.6).

Prognostic relevance of RA dilation in PE

Obstruction of the pulmonary vasculature by embolised thrombi leads to an increase of pulmonary artery pressure and pulmonary vascular resistance resulting in RV dilation and dysfunction [3, 15]. As early as 1971, McIntyre and Sasahara [16] reported that the degree of pulmonary embolic obstruction and mean pulmonary artery pressure correlate with mean RA pressure. In a more recent study, investigating 1640 consecutive patients who underwent TTE, increasing RV/RA pressure gradients were associated with an increase in RA dilation [17]. The RA/LA area ratio assessed by TTE correlated with the extent of pulmonary artery obstruction on ventilation/perfusion lung scintigraphy in 63 retrospectively studied PE patients [5] and a higher clot load in the pulmonary arteries was associated with a larger RA area and a smaller LA area on CTPA in a retrospective study of 137 PE patients [4]. In the present study, as many as 81.9% of patients had RA dilation (defined as RA/LA volume ratio $\geqslant$1.0) on CTPA. While patients with cardiovascular comorbidities and cancer had a smaller RA/LA volume ratio, patients with more severe PE (*e.g.* indicated by tachycardia, syncope, elevation of laboratory biomarkers or higher ESC risk class) had a larger RA/LA volume ratio (table S1).

Recent studies indicate that RA dilation constitutes a prognostically relevant finding in patients with various cardiopulmonary diseases [18, 19]. For example, a RA/LA area ratio >1.0 on TTE was related to long-term all-cause mortality independently of LV ejection fraction in 289 elderly patients hospitalised for heart failure [20] and independently associated with a three-fold increased risk of long-term mortality in 193 patients with PE [6]. In a study investigating 636 PE patients, patients with a RA/LA volume ratio >1.2 on CTPA had a higher 30-day mortality rate [8]. In the present study, patients with an in-hospital adverse outcome had larger RA volumes and RA/LA volume ratios on CTPA and a calculated patient-cohort optimised RA/LA volume ratio cut-off value of 1.8 was able to predict an in-hospital adverse outcome, both in unselected (OR 3.1, 95% CI 1.9–5.2) and normotensive patients (OR 2.7, 95% CI 1.3–5.6), while the previously proposed cut-off value of 1.2 appeared too low to provide prognostic information. This difference might be attributed to differences in patient population, observation time and a larger number of patients with active cancer included in the study by Aviram *et al.* [8] (34.3%, compared to 17.6% in the present study), of whom 26.1% died during the first 30 days, contributing to 67.9% of all deaths. In comparison, in the present study, 72.2% of all deaths were due to PE. Although evidence appears to accumulate that a dilated RA may be of prognostic value in patients with acute PE, further studies are needed to investigate underlying mechanisms and to define its prognostic significance.

Prognostic relevance of MR-proANP

The major stimulus for atrial natriuretic peptide (ANP) (and thus MR-proANP) release is increased atrial wall tension [9]. A number of studies have demonstrated that MR-proANP is a useful biomarker for the diagnosis of atrial fibrillation and heart failure. For example, in the BACH study including 1641 patients, MR-proANP $\geqslant$120 pmol·L^{-1} was as useful as NT-proBNP for a diagnosis of acute heart failure in dyspnoeic patients [14]. Further, MR-proANP was identified as a predictor of long-term mortality in patients after acute myocardial infarction [21] and community patients [22]. The first study investigating ANP in patients with PE was published 30 years ago [23], followed by two small studies: Kiely *et al.* [24] reported that ANP levels were higher in 17 patients with high probability of PE on ventilation/perfusion lung scan compared to 77 patients with low/intermediate probability and 20 patients with normal scans; Gutte *et al.* [25] reported that proANP levels were higher in seven PE patients with RV dysfunction compared to 22 PE patients without RV dysfunction. In the present study, patients with an in-hospital adverse outcome had higher MR-proANP concentrations compared to patients with a favourable clinical course and MR-proANP $\geqslant$120 pmol·L^{-1} was identified as an independent predictor of an in-hospital adverse outcome, both in unselected (OR 4.6, 95% CI 2.3–9.3) and normotensive patients (OR 5.1, 95% CI 1.5–17.6). However, older age, cardiovascular comorbidities (in particular atrial fibrillation) and renal insufficiency were associated with MR-proANP elevation $\geqslant$142 pmol·L^{-1}. Despite the pathophysiological association between atrial wall distension and MR-proANP release, RA dilation assessed by CTPA or TTE was not able to predict elevated MR-proANP levels and only weak correlations for MR-proANP concentrations and RA volume on CTPA (r=0.369) were observed. In contrast, moderate correlations were found between MR-proANP concentrations and known risk factors such as age (r=0.623), GFR (r=−0.495) and NT-proBNP (r=0.637). Thus, the present study findings indicate that elevation of MR-proANP in patients with acute PE may only be explained to a small extent by the severity of the PE but rather appears to integrate different prognostic relevant information from comorbidities.

Limitations

Only 25.2% of study patients had an electronically stored TTE examination performed within 48 h after diagnosis of PE in sufficient quality for reassessment; thus, study findings related to TTE must be interpreted with caution considering the small sample size. Therefore, we opted not to perform advanced statistical analysis (such as multivariate models) or to discuss the findings in detail, which are presented in the supplementary material only.

Volume measurements of RA and LA were performed in routine CTPA scans without ECG-gated information on the cardiac cycle. Thus, volumes were not assessed during end-systole only. Further, 17.7% of all CTPA scans required manual corrections of the automated volumetric measurements; however, manual changes were minimal (<5 mL per cardiac chamber) and did not result in differences in the prognostic performance.

Conclusion

We demonstrate that RA dilation assessed by volumetric analysis of the heart chambers on routine diagnostic CTPA is a frequent and prognostic relevant finding in both unselected and normotensive patients with PE. However, the prognostic performance of RA dilation appeared inferior compared to other established risk stratification markers. Although MR-proANP elevation did not appear to be caused by RA dilation to a relevant proportion, MR-proANP $\geqslant$120 pmol·L^{-1} was identified as a predictor of an in-hospital adverse outcome, both in unselected and normotensive PE patients, integrating different prognostic relevant information from comorbidities.

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