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Elevated systolic pulmonary artery pressure for prediction of myocardial necrosis and right ventricular dysfunction in acute pulmonary embolism*

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SOUHRN

Context: Echokardiografie je v současnosti hlavní metodou pro vyšetření dysfunkce pravé komory (right ventricular dysfunction, RVD) u akutní plicní embolie (PE). Dysfunkce pravé komory je sice spojena s nepříznivou prognózou, dosud však nebyla přijata žádná obecně uznávaná definice. Systolický tlak v plicnici (systolic pulmonary artery pressure, sPAP) většinou není součástí kritérií RVD. Cílem naší studie bylo zhodnotit možnost použití sPAP v predikci nekrózy myokardu a RVD u akutní PE.

Metody: Retrospektivně byly analyzovány údaje 182 pacientů s akutní PE. Pacienti s PE a hodnotami sPAP ≤ 30 mm Hg byli srovnáváni s pacienty s PE a hodnotami sPAP > 30 mm Hg. Vztahy mezi sPAP na jedné straně a nekrózou myokardu a RVD na straně druhé se hodnotily pomocí logistické regresní analýzy. Navíc byly vyneseny křivky ROC a vypočítány mezní hodnoty sPAP predikující nekrózu myokardu i RVD.

Výsledky: Do studie bylo zařazeno 134 pacientů (průměrného věku 67,8 ± 15,2 roku; 59,7 % žen) s akutní PE příhodou. Průměrná hodnota sPAP byla 33,96 ± 18,14 mm Hg. Pacienti s PE a s hodnotou sPAP > 30 mm Hg (59,7 %) byli významně starší (71,2 ± 13,8 roku vs. 62,7 ± 15,7 roku; $p = 0{,}000489$), častěji se jednalo o ženy (66,3 % vs. 50,0 %; $p = 0{,}0609$), byly u nich naměřeny vyšší hodnoty srdeční frekvence (98,8 ± 25,5 tepu/min vs. 87,7± 22,1 tepu/min; $p = 0{,}00266$), šokového indexu (0,76 ± 0,42 vs. 0,63 ± 0,26; $p = 0{,}00892$), srdečního troponinu I (0,15 ± 0,30 ng/ml vs. 0,14 ± 0,32 ng/ml; $p = 0{,}00670$) a RVD byla u nich diagnostikována častěji (80,0 % vs. 29,6 %; $p < 0{,}000001$).

V mnohorozměrném regresním modelu byly hodnoty sPAP spojeny s nekrózou myokardu (OR 1,021; 95% CI 0,998–1,045; $p = 0{,}0736$) a s RVD (OR 1,100; 95% CI 1,064–1,136, $p < 0{,}000001$).

Analýza ROC pro sPAP jako prediktor nekrózy myokardu nalezla hodnotu plochy pod křivkou plazmatické koncentrace (AUC) 0,628 při mezní hodnotě sPAP 41,00 mm Hg. Analýza ROC pro sPAP jako prediktor RVD prokázala hodnotu AUC 0,829 při mezní hodnotě sPAP 31,00 mm Hg.

Závěr: Hodnoty sPAP jsou spojeny s incidencí RVD i nekrózy myokardu. Systolický tlak v plicnici vysoce účinně predikoval rozvoj RVD. Hodnoty sPAP > 31 mm Hg ukazují na přítomnost RVD.

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ABSTRACT

Background: Echocardiography is currently the mainstay examination for assessment of right ventricular dysfunction (RVD) in acute pulmonary embolism (PE). RVD is associated with poorer prognosis, but there is still no generally accepted definition. Systolic pulmonary artery pressure (sPAP) is mostly not included in these RVD-criteria. We aimed to investigate sPAP for prediction of myocardial necrosis and RVD in acute PE.
Methods: Data of 182 patients with acute PE were analysed retrospectively. PE patients with sPAP ≤ 30 mmHg were compared to those with sPAP > 30 mmHg. Logistic regression models were calculated to investigate associations between sPAP and myocardial necrosis as well as RVD. Moreover ROC curves and cut-off values for sPAP predicting myocardial necrosis and RVD were computed.
Results: 134 patients (mean age 67.8 ± 15.2 years, 59.7% female) with acute PE event were included in the study. Mean sPAP value was 33.96 ± 18.14 mmHg. PE patients with sPAP > 30 mmHg (59.7%) were significantly older (71.2 ± 13.8 vs. 62.7 ± 15.7 years, $p = 0.000489$), more frequently female (66.3% vs. 50.0%, $p = 0.0609$), showed higher heart rate (98.8 ± 25.5 vs. 87.7 ± 22.1 beats/min, $p = 0.00266$), shock-index (0.76 ± 0.42 vs. 0.63 ± 0.26, $p = 0.00892$), cardiac Troponin I (0.15 ± 0.30 vs. 0.14 ± 0.32 ng/ml, $p = 0.00670$) and higher percentage of RVD (80.0% vs. 29.6%, $p < 0.000001$).
In multivariant regression model, sPAP was associated with respectively myocardial necrosis (OR 1.021, 95% CI 0.998–1.045, $p = 0.0736$) and RVD (OR 1.100, 95% CI 1.064–1.136, $p < 0.000001$).
ROC analysis for sPAP predicting myocardial necrosis revealed an AUC of 0.628 with sPAP cut-off value of 41.00 mmHg. ROC analysis for sPAP predicting RVD showed an AUC of 0.829 with sPAP cut-off value of 31.00 mmHg.
Conclusions: sPAP and respectively RVD and myocardial necrosis are both associated. sPAP is highly effective to predict RVD. sPAP values >31 mmHg indicate for RVD.

Keywords:
Myocardial necrosis
Pulmonary embolism
Right ventricular dysfunction
Risk stratification
Systolic pulmonary artery pressure

Introduction

The current European and American guidelines for acute pulmonary embolism (PE) emphasise the central role of early risk stratification to identify PE patients with higher risk of early death who could benefit from more intensive surveillance and especially more aggressive therapy [1,2]. Rapid risk stratification in acute PE is crucial in deciding appropriate therapy management [3–5].

The mortality after an acute PE event is closely related to the initial hemodynamic status and the resulting cardiac adaptations [6–15]. It is well known, that right ventricular dysfunction (RVD) as well as myocardial necrosis, seen as elevated cardiac Troponin (cTn) levels, both appear to alter patients' prognosis significantly [2,7–12,16–28]. The systolic pulmonary artery pressure (sPAP) measured in the transthoracic echocardiography is a not well established marker in the field of risk stratification process in acute PE. Although, there are several powerful and useful parameters of RVD to predict poorer outcome and prognosis in acute PE [29], sPAP is a standard tool used in the follow up examinations to screen for development of pulmonary hypertension after acute PE [30–32]. There is a growing body of evidence that the intensity of sPAP increase during acute PE event seems to have an impact on the development of pulmonary hypertension after PE in long-term [33,34]. Therefore we decided to focus this analysis on evaluation of sPAP for the early course of in-hospital stay after acute PE.

The aim of our study was to investigate the parameter of sPAP for risk stratification and especially for prediction of myocardial necrosis and RVD in acute PE event.

Methods and patients

We conducted a retrospective analysis of patients with a confirmed diagnosis of acute PE. Included patients were treated in the Internal Medicine department between May 2006 and June 2011. PE patients were identified with a search in the hospital information system database for the diagnostic code of PE (ICD-Code: I26).

Studies in Germany involving the retrospective analysis of diagnostic standard data do not require an ethics statement.

Enrolled subjects

Patients were eligible for this study

1. if the diagnosis of acute PE was confirmed by identified filling defect in the pulmonary artery system in computed tomography pulmonary angiogram (CT) of the chest or positive venous ultrasound/phlebography of an extremity consistent with DVT in patients with typical symptoms of PE (chest pain or dyspnea) and a detected positive D-Dimer or scintigraphic ventilation-perfusion (V/Q) scan read as high probability for PE,
2. if sPAP was measured accurately in a transthoracic echocardiography examination,
3. if the PE patients were treated in the Internal Medicine department of the hospital,
4. and if the patients were at least 18 years old.

All CT and scintigraphic images were analyzed by experienced radiologists. If diagnosis of PE was not confirmed by the criteria above, the patients were not included in this study.

Definitions

Definition of cardiac injury

According to the American Heart Association (AHA) scientific statement from 2011, myocardial necrosis was defined as a cardiac Troponin I (cTnI) elevation >0.4 ng/ml [2].

D-Dimer elevation

Per definition, D-Dimer values were elevated, if they exceed 0.110 mg/l.

Definition of right ventricular dysfunction

Right ventricular dysfunction was defined according to the AHA scientific statement [2] as a quotient of right ventricular (RV) septal-lateral diameter/left ventricular (LV) septal-lateral diameter in 4-chamber view of thransthoracic echocardiography >0.9 [2]. Moreover, the RVD was defined as RV hypokinesis and tricuspid regurgitation in echocardiography [2].

High-risk PE stadium

PE patients with a systolic blood pressure value of <90 mmHg at admission were classified as high-risk PE according to the definition of the European Society of Cardiology (ESC) guidelines [1,11] and AHA scientific statement [2].

Study parameters

The retrospectively analysis of the PE patients focused on echocardiographic examination results and cardiac biomarkers (cTnI). The sPAP was measured in the 4-chamber view in transthoracic echocardiography.

Statistics

Descriptive statistics for the relevant baseline characterization of PE patients with sPAP ≤ 30 mmHg compared to PE patients with sPAP > 30 mmHg are provided with mean and standard deviation or corresponding frequency. Continuous variables, which did not follow a normal Gaussian's distribution, were compared with the help of Wilcoxon–Whitney-U--test. Normal distributed continuous variables were compared using Students' T-test, as appropriate.

Table 1 – PE patients' characteristics. PE patients were subdivided in group of PE patients with systolic pulmonary artery pressure ≤ 30 mmHg and those with systolic pulmonary artery pressure > 30 mmHg. Results were described as mean values with standard deviation or relative percentages. Groups were compared with Wilcoxon-Mann-Whitney-U-Test. Normal distributed continuous variables were compared using Student's T-test, as appropriate. *P*-values of <0.05 were considered as statistically significant.

Parameter	PE patients with sPAP ≤ 30 mmHg	PE patients with sPAP > 30 mmHg	*P*-value for difference
Number of patients	54 (40.3%)	80 (59.7%)	
Age at event (years)	62.7 ± 15.7	71.2 ± 13.8	**0.000489**
Female gender	50.0%	66.3%	0.0609
Comorbidities			
Surgery or trauma in last 3 months before PE event	22.2%	17.5%	0.499
DVT or PE in patient's history	20.4%	26.3%	0.470
DVT actually	68.5%	70.0%	0.856
Cancer disease actually or in patient's history	13.0%	18.8%	0.377
Lung infarction with pneumonia	40.7%	43.8%	0.731
In-hospital death	1.9%	1.3%	0.779
High-risk PE stadium	1.9%	5.0%	0.347
Symptoms			
Chest pain	42.6%	27.5%	0.071
Dyspnoea	75.9%	92.5%	**0.00720**
Hemoptysis	1.9%	5.0%	0.341
Syncope or collaps	9.3%	12.5%	0.561
Physical examination			
Systolic blood pressure (mmHg)	146.4 ± 30.4	142.0 ± 29.5	0.305
Diastolic blood pressure (mmHg)	79.9 ± 20.4	77.5 ± 19.0	0.489
Heart rate (beats/min)	87.7 ± 22.1	98.8 ± 25.5	**0.00266**
Shock index	0.63 ± 0.26	0.76 ± 0.42	**0.00892**
Laboratory marker			
Cardiac Troponin I (ng/ml)	0.14 ± 0.32	0.15 ± 0.30	**0.00670**
Creatinine kinase (U/l)	120.20 ± 290.05	73.08 ± 49.45	0.292
Creatinine (mg/dl)	1.03 ± 0.23	1.21 ± 0.46	**0.0257**
D-Dimer (mg/l)	2.82 ± 4.48	3.06 ± 3.52	**0.0720**
Echocardiography			
sPAP (mmHg)	16.17 ± 9.77	45.98 ± 11.33	
RVD	29.6%	80.0%	**<0.000001**

We performed logistic regression models to investigate the association between sPAP in general as well as sPAP > 30 mmHg and myocardial necrosis on the one hand and RVD on the other hand. Logistic regression models were computed uni-variate first. In case of significance, we also calculate a multi-variate logistic regression model to test, whether the significance still remains after adjustment for age and gender.

Receiver Operating Characteristic (ROC) curves with areas under the curves (AUC) and Youden Index were calculated to test the effectiveness of sPAP to predict myocardial necrosis as well as RVD in acute PE, if association was still significant in the multi-variant regression model. Wilcoxon-Mann-Whitney-test was used to test the deviation of the ROC curve from the angle bisector.

Commercially available software BIAS® (version 10.04) was used for the computerised analysis. *P* values of <0.05 were considered as statistically significant.

Results

Between May 2006 and June 2011, 182 patients with acute confirmed PE event were identified in the hospital information system database, but only 134 of these patients met the inclusion criteria and were included in the study. The other 48 PE patients had no accurate echocardiographic examination with assessment of sPAP.

Median age of the PE patients was 67.8 ± 15.2 years. 59.7% of the patients were of female gender. Two (1.5%) PE patients of the study sample of 134 patients died an in-hospital death after the PE event. Five patients revealed a high-risk PE stadium with systolic blood pressure of less than 90 mmHg. The mean sPAP value was 33.96 ± 18.14 mmHg. Fifty-four of the included patients (40.3%) had a sPAP of ≤ 30 mmHg, while 80 (59.7%) revealed sPAP of > 30 mmHg.

PE patients with sPAP > 30mmHg were significantly older (71.2 ± 13.8 vs. 62.7 ± 15.7 years, $P = 0.000489$), more frequently female (66.3% vs. 50.0%, $p = 0.0609$) and reported more often dyspnea (92.5% vs. 75.9%, $p = 0.00720$). Chest pain was more frequently present in PE patients with sPAP ≤ 30 mmHg (42.6% vs. 27.5%, $p = 0.071$). PE patients with sPAP > 30 mmHg showed higher heart rate (98.8 ± 25.5 vs. 87.7 ± 22.1 beats/min, $p = 0.00266$), shock index (0.76 ± 0.42 vs. 0.63 ± 0.26, $p = 0.00892$), cTnI (0.15 ± 0.30 vs. 0.14 ± 0.32 ng/ml, $p = 0.00670$), creatinine (1.21 ± 0.46 vs. 1.03 ± 0.23 mg/dl, $p = 0.0257$) and D-Dimer values (3.06 ± 3.52 vs. 2.82 ± 4.48 mg/l, $p = 0.0720$) as well as higher percentage of RVD (80.0% vs. 29.6%, $p < 0.000001$). The groups did not differ significantly in percentage of high-risk PE stadium and in-hospital death (Table 1).

The uni-variate logistic regression models showed a significant association between sPAP and myocardial necrosis (OR 1.025, 95% CI 1.003–1.048, $p = 0.0235$) (Table 2) as well as sPAP and RVD (OR 1.091, 95% CI 1.058–1.125, $p < 0.000001$) and sPAP > 30 mmHg and RVD (OR 9.500, 95% CI 4.240–21.288, $p < 0.000001$) (Table 3). In the multivariant regression model, the association between sPAP and myocardial necrosis revealed still a borderline significance independently of gender and age (OR 1.021, 95% CI 0.998–1.045, $p = 0.0736$) (Table 4). sPAP and RVD (OR 1.100, 95% CI 1.064–1.136, $p < 0.000001$) (Table 5) as well as sPAP > 30 mmHg and RVD (OR 10.059, 95% CI 4.239–23.870, $p < 0.000001$) (Table 6) remain still significantly associated after adjustment for age and gender in the multi-variant logistic regression models.

The calculated ROC analysis for sPAP predicting myocardial necrosis showed an AUC of 0.628 with sPAP cut-off value of 41.00 mmHg and a $p = 0.0187$ for differentiation. The percentage of misclassification, sensitivity, specificity, positive and negative predictive values were calculated as 37.2%, 60.2%, 67.3%, 75.7% and 50.0% respectively (Fig. 1).

Table 2 – Uni-variate logistic regression to detect the coherence of myocardial necrosis and sPAP in general and the sPAP value of >30 mmHg, gender and age.

	OR (95% CI)	*P*-value
Gender	0.663 (0.308–1.427)	0.293
Age	1.021 (0.994–1.048)	0.120
sPAP (1 mmHg)	1.025 (1.003–1.048)	0.0235
sPAP > 30 mmHg	1.757 (0.810–3.809)	0.154

Table 3 – Multi-variate logistic regression to detect the coherence of myocardial necrosis and sPAP as well as gender and age.

	OR (95% CI)	*P*-value
Gender	0.878 (0.385–2.001)	0.757
Age	1.013 (0.985–1.041)	0.373
sPAP (1 mmHg)	1.021 (0.998–1.045)	0.0736

Table 4 – Uni-variate logistic regression to detect the coherence of RVD and sPAP in general and the sPAP value of >30 mmHg, gender and age.

	OR (95% CI)	*P*-value
Gender	0.970 (0.477–1.970)	0.932
Age	1.020 (0.997–1.044)	0.0896
sPAP (1 mmHg)	1.091 (1.058–1.125)	<0.000001
sPAP > 30 mmHg	9.500 (4.240–21.288)	<0.000001

Table 5 – Multi-variate logistic regression to detect the coherence of RVD and sPAP as well as gender and age.

	OR (95% CI)	*P*-value
Gender	2.405 (0.928–6.236)	0.0710
Age	1.000 (0.969–1.032)	0.990
sPAP (1 mmHg)	1.100 (1.064–1.136)	<0.000001

Table 6 – Multi-variate logistic regression to detect the coherence of RVD and sPAP > 30 mmHg as well as gender and age.

	OR (95% CI)	*P*-value
Gender	1.592 (0.663–3.821)	0.298
Age	1.005 (0.977–1.034)	0.722
sPAP (1 mmHg)	10.059 (4.239–23.870)	<0.000001

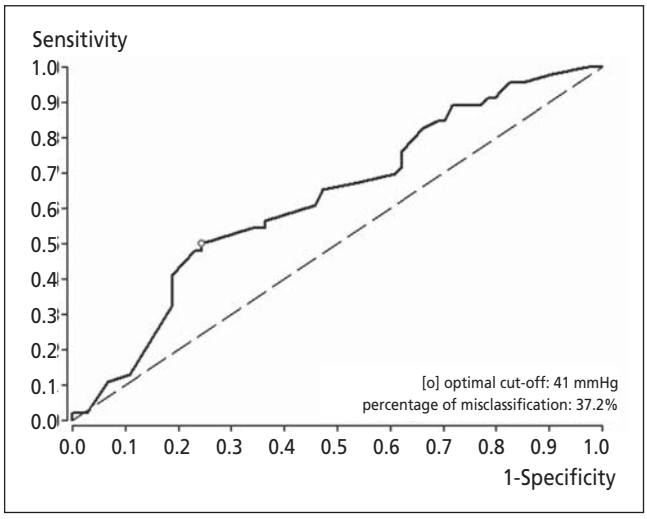

Fig. 1 – Receiver Operating Characteristic (ROC) curve with area under the curve (AUC) and Youden Index were calculated to test the effectiveness of sPAP to predict myocardial necrosis in acute PE.

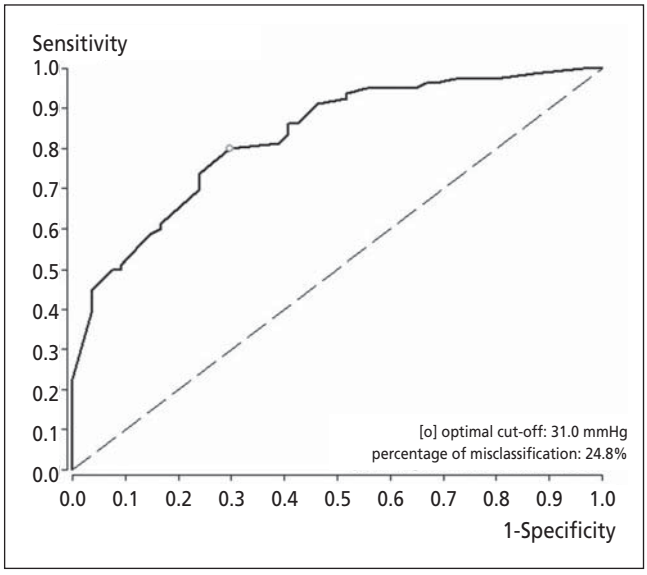

Fig. 2 – Receiver Operating Characteristic (ROC) curve with area under the curve (AUC) and Youden Index were calculated to test the effectiveness of sPAP to predict RVD in acute PE.

The ROC analysis for sPAP predicting RVD revealed an AUC of 0.829 with sPAP cut-off value of 31.00 mmHg and a $p < 0.000001$ for differentiation. The percentage of misclassification, sensitivity, specificity, positive and negative predictive values were calculated as 24.8%, 77.9%, 73.0%, 70.4% and 80.0% respectively (Fig. 2).

Discussion

An acute PE involves the risk of impairment of circulation, heart and lungs [1,10]. PE is associated with a varying degree of obstruction of the pulmonary artery bed that may lead to an increased pulmonary artery pressure [22]. If more than 30% of the pulmonary arterial bed is occluded by thrombus material, the acute PE event causes hemodynamic consequences [11]. Obstruction of blood flow to the lung by PE thrombus material could be followed by right heart failure with cardiac adaptations such as RVD and myocardial necrosis, cardiogenic shock and death [2,5,22,35]. The right ventricle under normal conditions has a narrow range to handle an acute increase of afterload [22]. An abrupt increase of afterload, seen in cases of acute PE event, lead to elevated right ventricular wall tension that could result in right ventricular dilatation, hypokinesis and secondary tricuspid regurgitation [22]. These acute cardiac adaptations caused by acute PE event were summed up as RVD. In acute PE, presence of RVD or myocardial necrosis is associated with increased mortality [1,2,6-14,16-22,36–39]. PE patients with an elevated cTn level showed 3.5–5.3-times increased mortality rate three months after acute PE event [7,9,11,24]. Rapid risk stratification in acute PE is crucial in deciding appropriate therapy management [3–5]. We investigated several different parameters for risk stratification in acute PE with different issues in already published analysis using this same patient population [23,40-49]. The main problem about RVD is, that there is still no generally accepted echocardiographic definition of RVD used for prognosis in acute PE [50]. Published studies have based their diagnosis of PE-induced RVD on a wide variable spectrum of RVD criteria [16,18,51]. The prognostic value of echocardiography in PE patients is reduced because of the poor standardization of echocardiographic RVD criteria [51]. Still, it remains unclear which criterion is the most sensitive indicator for patients' prognosis [18]. sPAP is in some definitions included in these RVD-criteria [2,22,50], but in most of the studies sPAP is not part of these RVD-criteria [19,37,52,53]. Therefore sPAP was also in our present analysis not included in the definition of RVD.

The objective of our study was to investigate sPAP as a single parameter for risk stratification and especially for prediction of myocardial necrosis and RVD in acute PE event.

In accordance with the results of Pruszczyk et al., we found a mean sPAP value of brief beyond 30 mmHg (33.96 ± 18.14 mmHg) in acute PE event [50]. In contrast Park et al. reported a higher mean sPAP of 71 ± 16 mmHg in their study sample of patients with acute PE [54]. Nearly 60% of our PE patients showed a sPAP of more than 30 mmHg. Ribeiro et al. reported a higher percentage of 92.3% of their included PE patients [22].

In our present analysis PE patients with higher sPAP were older, had higher cTnI values and more often RVD in echocardiography. sPAP was strongly associated with myocardial necrosis and RVD. An increase of sPAP within 1 mmHg leads to an increase of the risk for myocardial necrosis of 2.1% and of the risk of presence of RVD of 10.1%.

The effectiveness of sPAP to predict myocardial necrosis with cut-off value of 41.00 mmHg was moderate (AUC 0.628), while that of sPAP predicting RVD with cut-off value of 31.00 mmHg was excellent (AUC 0.829).

Pruszczyk et al. reported a significant higher sPAP value in PE patients, who died or needed a thrombolysis, than in those without both [50]. The study of Ribeiro et al. failed briefly to reveal a significant higher percentage of mortality in patients with sPAP > 30 mmHg than in those with ≤ 30 mmHg [22]. Five-year survival was in the

study of Ribeiro et al. 9.2-times higher if the sPAP at acute PE event was ≤ 35 mmHg [55].

The prognostic value of echocardiography examination for risk stratification in acute PE was confirmed in several studies [16–20,37,51]. Echocardiography is currently the mainstay examination for assessment of RVD in acute PE [18]. In various studies, RVD was connected with higher rates of death, recurrent PE events and complications [2,11,16–20].

Although, transthoracic echocardiography with sPAP is used as a standard screening method to detect pulmonary hypertension after PE in follow-up examinations, results about accuracy of this method are inconsistent [30–32]. While some studies revealed a high accuracy [32], other studies reported limitations in accuracy of echocardiography in hemodynamic assessment of pulmonary hypertension [30,31]. Lafitte et al. found a strong correlation between Doppler sPAP values and measurements in right heart catheterization [32]. In contrast, Fisher et al. reported, that the Doppler echocardiography is frequently inaccurate in estimating sPAP in comparison to the results of the invasive measurements in patients being evaluated for pulmonary embolism [30].

Furthermore, it is important to be aware that sPAP is dependent on age and body mass index [31]. Age related increases in sPAP are more prevalent in patients with diabetes [31]. Beside all these limitations, higher sPAP was connected with an increased mortality [31]. In addition, studies have emphasized that the intensity of sPAP elevation at acute PE event had an impact on the development of pulmonary hypertension in long-term [33,34].

The results of our study reveal that sPAP as a single parameter for risk stratification is not powerful enough, but the strong association between sPAP and RVD is a good argument to include sPAP as a further criterion to RVD criteria. sPAP as a single parameter for risk stratification may be useful in patients without preexisting sPAP elevation, but preexisting pulmonary hypertension could preexist especially in patients with chronic lung diseases and valve disorders and mostly this sPAP elevation is not known [56,57]. The sPAP cut-off value of 31 mmHg to predict RVD suggests that the afterload criterion of sPAP 30 mmHg may be a good cut-off to differentiate between PE patients with and those without RVD.

Limitations

Important study limitations are the small number of included PE patients, the single center study design and the retrospective study character. Moreover, we assessed the sPAP only in the acute phase of the PE event and we did not know how high the sPAP was before PE event. Several diseases, especially chronic lung diseases and heart valve diseases, could lead to a pulmonary hypertension. Therefore, we have to suggest a bias in this point.

Conclusions

sPAP and RVD as well as sPAP and myocardial necrosis are both associated. sPAP is effective to predict RVD in acute PE. sPAP values > 31 mmHg indicate for RVD.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
The research was conducted according to Declaration of Helsinki. Studies in Germany involving the retrospective analysis of diagnostic standard data do not require an ethics statement.

Informed consent
The authors declare that informed consent requirements do not apply to this manuscript. This is a retrospective study.

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