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Central thromboembolism is a possible predictor of right heart dysfunction in normotensive patients with acute pulmonary embolism

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ABSTRACT

Background: Right heart dysfunction is a crucial factor in risk stratification of normotensive patients with pulmonary embolism. Apart from biomarkers, determinants of right heart dysfunction in this group of patients are not yet well established.
Aim and method: In order to identify such determinants, we analysed data of 252 patients with acute pulmonary embolism admitted to our hospital in 2008.
Results: 69 out of 140 patients showed right heart dysfunction by echocardiography within 24 hours after diagnosis, 71 did not. Right ventricular dysfunction was significantly more frequent in patients with central clots on computed tomography ($p=0.004$), a history of syncope ($p<0.001$) and among women on oral contraceptives ($p=0.003$). In multiple regression analysis, only central thromboembolism ($p<0.001$) was identified as individual predictor of right ventricular dysfunction. Age, gender, body mass index, idiopathic or recurrent thromboembolism, duration of symptoms, preceding surgery, room air oxygen saturation, carcinoma, hypertension, diabetes, renal disease, congestive left heart failure and concomitant lung disease were equally distributed. In comparison with NT-pro brain natriuretic peptide (PPV 67%, NPV 75%, $p=0.782$) and troponin I (PPV 76%, NPV 62%, $p=0.336$), central thromboembolism has shown to have a greater statistical power in predicting right heart dysfunction in normotensive patients with pulmonary embolism (PPV 78%, NPV 88%, $p<0.001$).
Conclusion: Among normotensive patients with acute pulmonary embolism, those with central clots seem to be at greater risk for echocardiographically evaluated right ventricular dysfunction.

Introduction

Echocardiographic findings suggesting right heart dysfunction occur in at least 25% of normotensive patients with acute pulmonary embolism [1]. Right ventricular pressure overload in these patients was related to an increase of short-term mortality and adverse events in several studies [2,3]. On the other hand, patients without right heart dysfunction had an excellent clinical outcome with a mortality related to pulmonary embolism less than 1 % [2,4]. Thus, right heart dysfunction assessed by echocardiography is a crucial factor in risk stratification of normotensive patients with acute pulmonary embolism and may influence further therapeutical strategies.

It is essential to identify patients at risk for an adverse outcome immediately, taking into consideration the impending life-threatening course of the disease. Unfortunately, diagnostic criteria for right heart dysfunction are not well standardised and echocardiography is not always rapidly available after admission to the hospital. Previous studies found that only a minority of emergency physicians at large, academic teaching hospitals in the U.S.A. reported the ability to obtain echocardiography within a few hours after admission [5,6]. Biomarkers like BNP or troponin indicating increased myocardial stretch or injury have gained more and more importance, because they are nowadays comprehensively available and may demonstrate right heart dysfunction shortly after admission. Biomarkers have shown to be able to predict a worse outcome, but their positive predictive value seems to be low [7]. On the other hand, risk stratification with biomarkers alone might not allow prediction of in-hospital complications and mortality due to an insufficient time span for secretion as a consequence of sudden right ventricular pressure overload [8].

Whereas several features are associated with a worse outcome of patients with pulmonary embolism [9], clinical determinants for right heart dysfunction in haemodynamically stable patients at the time of

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; CRP, C reactive protein; SD, standard deviation; NPV, negative predictive value; PPV, positive predictive value.

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Table 1
Characteristics of normotensive patients with acute pulmonary embolism with and without right heart dysfunction (RHD) by echocardiography on admission.

	All	with RHD	without RHD	p
Number	140	69	71	
Female	80 (57.1)	46 (66.7)	34 (47.9)	NS
Male	60 (42.9)	23 (33.3)	37 (52.1)	NS
Women on oral contraceptives	8 (10.0) *	7 (15.2)*	1 (2.9)*	0.003
Age (years)	62.2 ± 19.1	64.2 ± 19.7	60.2 ± 18.3	NS
BMI (kg/m²)	28.7 ± 6.2	29.9 ± 4.3	27.5 ± 4.8	NS
Idiopathic	68 (48.6)	38 (55.1)	30 (42.3)	NS
Recurrent thromboembolism	25 (17.9)	14 (20.3)	11 (15.5)	NS
Duration of symptoms	2.9 ± 2.5	2.97 ± 2.70	2.80 ± 2.35	NS
History of syncope	18 (12.9)	12 (17.4)	6 (8.5)	<0.001
Concomitant lung disease	17 (12.1)	8 (11.6)	9 (12.7)	NS
LV-EF<40%	27 (19.3)	13 (18.8)	14 (19.7)	NS
Hypertension	81 (57.9)	42 (60.9)	39 (54.9)	NS
Renal disease	12 (8.6)	7 (10.1)	5 (7.0)	NS
Diabetes	19 (13.6)	10 (14.5)	9 (12.7)	NS
Carcinoma	18 (12.9)	9 (13.0)	10 (14.1)	NS
Surgery***	26 (18.6)	11 (15.9)	15 (21.1)	NS
Heart rate (beats/min.)	97.0 ± 17.1	100.4 ± 17.8	93.6 ± 15.7	0.02
Systolic blood pressure (mmHg)	124.0 ± 18.4	120.6 ± 18.7	127.3 ± 17.4	0.03
Diastolic blood pressure (mmHg)	71.2 ± 11.7	69.7 ± 11.7	72.8 ± 11.5	NS
Room air oxygen saturation (%)	90.8 ± 7.1	89.4 ± 6.0	92.0 ± 7.8	NS
Elevated NT-proBNP	70 (85.3)**	47 (94.0)**	23 (71.9)**	<0.001
Elevated troponin I	42 (30.0)**	32 (29.9)**	10 (9.4)**	<0.001
Thrombolysis	27 (19.3)	24 (34.8)	3 (4.2)	<0.001
Central thrombus	80 (57.1)	62 (89.9)	18 (25.4)	0.004
In-hospital mortality	4 (2.9)	3 (4.4)	1 (1.4)	NS

Nominal variables are shown as n (% of total number); continuous values as mean ± 1 SD.
*: percentage of all female patients only.
**: total numbers differ (see Table 2).
***: within 4 weeks before diagnosis.
NS: not significant.
LV-EF: left ventricular ejection fraction.

diagnosis are not yet established. Therefore, our study addresses the question, if clinical markers allow us to early identify a subgroup of normotensive patients, who are at increased risk for right heart dysfunction and therefore should be quickly guided to further evaluation by echocardiography.

Methods

In this single centre study at a tertiary, academic teaching hospital, 252 patients with newly diagnosed pulmonary embolism were retrospectively analysed from January through December 2008. Diagnosis was confirmed by multi-detector CT angiography. Pulmonary embolism was considered central, when the main pulmonary stem or the right or left main pulmonary branch were affected [10]. We excluded patients with a systolic arterial pressure less than 90 mmHg and those, who did not undergo echocardiography within 24 hours after diagnosis according to earlier studies [3]. Emergency physicians and ultrasonographers were not blinded to patients` data. Right heart dysfunction was assessed according to current guidelines [11] in the presence of one of the following criteria: right ventricular dilatation >30 mm, right ventricular hypokinesis, right ventricular / left ventricular diameter ratio >1, paradoxical septal motion or velocity of the tricuspid regurgitation jet >2.8 m/s. Blood samples were collected immediately before or within 6 hour after diagnosis. NT-proBNP measurements were considered when blood was drawn within 48 hours after time of diagnosis in regard of the longer pharmacological stability of NT-proBNP in contrast to BNP levels [12,13]. Troponin I>0.09 ng/ml and NT-proBNP>125 pg/ml were considered as elevated [14,15].

Statistical analysis was performed with SPSS software for Windows version 10.0 (SPSS, Inc., Chicago, Illinois, U.S.A.). Continuous variables are shown as means ± one standard deviation or as medians with range, when widely distributed. Student´s t-test was used for the comparison of continuous variables and the χ^2 test for the comparison of nominal variables. Multiple linear regression analysis was performed to investigate predictors for right ventricular dysfunction individually and to detect potential confounding effects between the covariates. A probability value of less than 0.05 was considered statistically significant, all reported p values are two-tailed.

Results

A total of 140 patients could be included into the study. Patients´ characteristics are given in Tables 1 and 2. Slightly more women (57.1%) than men were enrolled with a mean body mass index of 28.7 ± 6.2 kg/m^2 and an average age of 62.2 ± 19.1 years. 48.6% of pulmonary

Table 2
Laboratory data of normotensive patients with acute pulmonary embolism with (RHD +) and without (RHD -) right heart dysfunction by echocardiography on admission.

	N	All median (range)	n	RHD + median (range)	n	RHD - median (range)	p
D-Dimer (ng/ml)	138	3997 (156 - 35636)	68	5210 (292 - 35200)	70	3021 (156 - 35636)	0.02
CRP (mg/dl)	140	3.0 (0.09 - 30.9)	69	2.43 (0.11 - 24.4)	71	3.75 (0.09 - 30.9)	NS
NT-proBNP (pg/ml)	82	2037 (17 - 20896)	50	2923 (17 - 20896)	32	315 (29 - 20229)	0.04
Troponin I (ng/ml)	107	0.06 (0 - 7.54)	57	0.15 (0 - 7.45)	50	0.01 (0 - 1.58)	0.015

NS: not significant.