N-terminal Pro-brain Natriuretic Peptide, High-sensitivity Troponin and Pulmonary Artery Clot Score as Predictors of Right Ventricular Dysfunction in Echocardiography

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Background	We investigated the ability of cardiac biomarkers and total pulmonary artery (PA) clot score to predict right ventricular dysfunction (RVD) on admission and at seven-month follow-up in subjects with acute pulmonary embolism (APE).
Methods	Sixty-three normotensive patients with APE were divided into two groups: patients with (n= 32, age 58 ± 19 years) and without (n=31, age 55 ± 16 years) echocardiographic RVD. Transthoracic echocardiography (TTE), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT) were assessed upon arrival and repeated at seven months. Total PA clot score was determined on admission.
Results	The age- and sex dependent NT-proBNP on admission, on day 5, and at seven months exhibited the best sensitivity (admission 94%, day 5 100%, seven months 100%) and negative predictive value (NPV) (89%, 100%, 100%) for detecting RVD. Six patients (10%) had persistent RVD at seven months. Total PA clot score showed only low to moderate sensitivity (77%) and PPV (7%) for detection of RVD at seven months.
Conclusions	Normal age- and sex dependent NT-proBNP on admission or measured five days later seems to be useful in exclusion of RVD at follow up. Total PA clot score shows only to be of modest benefit for predicting persistent RVD.
Keywords	Pulmonary embolism • Right ventricular dysfunction • Cardiac biomarkers • Pulmonary artery clot score

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Introduction

Acute pulmonary embolism (APE) is a potentially fatal disease with an average mortality rate of 10-15% during the first one to three months after diagnosis [1,2]. Acute pulmonary embolism displays a wide spectrum of clinical severity. Rapid risk stratification is crucial for the clinical management of patients with APE. Haemodynamic status on admission is considered the most important prognostic factor in terms of short-term mortality [3,4]. A challenging dilemma lies with the patient who is not haemodynamically compromised per se but in whom there appears to be a high risk of right ventricular dysfunction (RVD).

In haemodynamically stable patients, the presence of echocardiographically confirmed RVD has been associated with a short-term mortality of 10% in comparison to 3% in those without RVD [5]. Transthoracic echocardiography (TTE) has been used as a method of choice to identify patients with RVD [6]. So far, there is no consensus as to whether haemodynamically stable APE patients should be referred for TTE investigation. Furthermore, TTE is not readily available around-the-clock in several hospitals. Persistent RVD seems to be an independent predictor of long-term mortality and APE recurrence [7–9], suggesting that regular follow-up echocardiography after discharge would benefit patients with RVD.

Both the embolic burden and the size of right ventricle (RV) are rapidly assessed by computed tomography pulmonary angiography (CTPA), the method of choice for PE diagnosis. Recently, a meta-analysis showed that the localisation of emboli assessed at CT angiography is useful for risk stratification in patients with APE [10]. However, no study has found the clot size, location or total pulmonary artery (PA) obstruction to be significant independent predictors of mortality from APE in a model that includes clinical predictors and biomarkers [11–15].

Beyond echocardiographic signs, cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponins have been associated with an increased risk of mortality or complications during the acute phase of PE [16,17]. Emerging evidence suggests that high-sensitivity troponin T (hsTnT) may be capable of improving risk stratification of non-high risk APE [18–20].

Currently no uniformly established cut-off values of cardiac biomarkers exist for ruling out RVD. Furthermore, the data on prediction of persistent RVD and thus the risk of chronic thromboembolic pulmonary hypertension (CTEPH) is sparse. Therefore, the aim of the present study was to assess the ability of 1) NT-proBNP; 2) hsTnT; and 3) total PA clot score to predict RVD on admission and RVD at seven-month follow-up. Our second objective was to determine the correlation of total PA clot score, cardiac biomarkers, and echocardiographic parameters on admission.

Materials and Methods

Study Population

We studied 63 consecutive patients (33 women, 30 men, mean age 55 years) with non-high risk APE confirmed by CTPA at the Emergency Department of Helsinki University Central Hospital. Exclusion criteria comprised clinically high risk APE (haemodynamically unstable patients), chronic pulmonary disease requiring regular medication, previous APE, non-stable angina pectoris, heart failure, patients on anticoagulation therapy, and terminal cancer (with estimated life expectancy of less than seven months). Medical records were reviewed at the time of admission for the presence of risk factors for venous thromboembolism such as age, gender, immobilisation in the preceding three months, hormone replacement or hormonal contraception therapy, family history of venous thromboembolism, active malignancy, and varicose veins. The subjects were divided into two groups based on the presence of RVD on TTE on admission: patients with RVD (n=32) versus patients without RVD (n=31).

Once PE was diagnosed, patients were treated in hospital by the clinician in charge according to the established contemporary guidelines [21]. Sixty patients received subcutaneous low molecular weight heparin, and three, systemic thrombolysis. Every patient continued with oral anticoagulants for at least six months. Seven months after discharge from hospital a follow-up visit was performed with clinical history and examination, blood sampling, and TTE.

Written informed consent was obtained from all participants, and the institutional ethics committee approved the study design.

Demographic Variables, Clinical and Biochemical Investigations

A 12-lead electrocardiogram (ECG) was recorded on admission. Criteria for right ventricular overload in ECG was defined by the presence of one or more of the following signs: T-wave inversion in leads V1 to V3, incomplete or complete right bundle branch block, S1Q3T3 pattern, and the signs of right atrial enlargement [22,23].

An arterial blood gas analysis was carried out on admission. NT-proBNP and hsTnT were quantified from a venous blood sample, which was drawn on admission and repeated seven months later. In addition, NT-proBNP was collected on day 5 after the diagnosis of APE. The biomarkers were analysed using commercial kits: NT-proBNP (Roche Diagnostics Elecsys) and hsTnT (Roche Diagnostics Elecsys). NT-proBNP was analysed consequently and plasma samples were stored in -80 °C. HsTnT was analysed from frozen samples. The age- and sex dependent NT-proBNP cut-off value according to Roche Diagnostics Elecsys was used. HsTnT concentration of 15 ng/L was regarded as elevated in congruence with our local laboratory reference values.

Echocardiographic Assessment of RVD

Transthoracic echocardiography was performed within 12 hours after the diagnosis of APE and repeated at the seven-month follow-up visit by one of three experienced cardiologists using two different ultrasound scanners (Vivid 5 or Vivid 7, GE Healthcare, Horten, Norway). The investigators were blinded to clinical data and to the results of biochemical assays. The standardised echocardiographic protocol

included apical two- and four-chamber views and parasternal long- and short axis views. The analyses and measurements were carried out from stored data on magneto-optic discs.

Right ventricular dysfunction was diagnosed in the presence of one or more of the following criteria: 1) right to left ventricular (RV/LV) end-diastolic ratio over 1.0 in the left parasternal long axis view; 2) wall-motion abnormality of the interventricular septum; and 3) mean peak velocity of tricuspid regurgitation >2.8 m/s [21,6].

Computed Tomography Pulmonary Angiography

Computed Tomography Pulmonary Angiography was performed as previously described [24,25]. The volume of contrast material varied between 90 and 120 ml and was injected with a power injector using bolus tracking. Slice thickness was 1 or 1.25 mm in the multi-slice scanners and 3 mm in the single-slice scanners. All angiograms were systematically read on a CT workstation after the study period by two senior radiologists. The investigators were blinded to echocardiographic and clinical data.

The mass of embolism was scored using the method of Mastora et al. [26], in which the percentage of obstructed surface of each artery is evaluated using a five-point scale. The score for the mass of embolism is 0-55 for central emboli (thrombus in mediastinal or lobar arteries) and 0-100 for peripheral (segmental) arteries. The sum of mediastinal, lobar, and segmental artery scores leads to a total clot score with a maximum of 155. If the embolism was only in subsegmental arteries, the count was 0. The total PA clot score was dichotomised based on the value 78 representing the 50% obstruction of the pulmonary artery tree.

Statistical Analysis

All statistical analyses were performed with SPSS 19.0 for Windows (SPSS, Inc., Chicago, Illinois). Normality of continuous variables was checked by the Kolmogorov-Smirnov test. Data are presented as frequencies or percentages for categorical variables, as means ± SD for normally distributed continuous variables, and as medians (range) for skewed variables. Between-group differences were assessed by the Mann-Whitney U test or the unpaired t-test. Categorical data were compared by the chi-square test or Fisher's exact test. Sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) were determined for each parameter. Correlations were calculated by the univariate Spearman correlation coefficients. Receiver operating characteristics curves were plotted and area under the curve (AUC) was calculated with 95% confidence intervals (95% CI) to measure discrimination ability. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Clinical and biochemical characteristics and total PA clot score of the study groups are presented in Table 1. Age,

sex, predisposing conditions, blood pressure parameters, and heart-rate did not differ between the groups. Signs of RV overload on ECG as well as arterial hypoxaemia and hypocapnia were more common in patients with RVD.

Cardiac Biomarkers and Total Pulmonary Artery Clot Score in Prediction of RVD on Admission

On admission, the levels of hsTnT, NT-proBNP, and total PA clot score were higher in subjects with RVD compared to subjects without RVD. NT-proBNP on day 5 after initial treatment was also higher in the group with RVD on admission (Table 1). The AUC of NT-proBNP, hsTnT, and total PA score for predicting RVD on admission was 0.833 (95% CI, 0.732-0.933), 0.681 (95% CI, 0.545-0.818), and 0.844 (95% CI, 0.744-0.943), respectively.

A parallel dot plot showing the values of NT-proBNP value on admission and at follow-up is presented in Figure 1.

In univariate correlation analyses, total PA clot score showed significant correlation with RV/LV ratio, RV end-diastolic diameter, and peak velocity of tricuspid regurgitation. NT-proBNP correlated more strongly than hsTnT with total PA clot score. In addition, NT-proBNP correlated with echocardiographic signs of RVD. HsTnT correlated only with RV/LV ratio and RV end-diastolic diameter (Table 2). The ability of elevated cardiac biomarkers and a higher total PA clot score (total mass >78) to predict RVD on admission is given in Table 3. Age- and sex dependent NT-proBNP showed the highest sensitivity and NPV for prediction of RVD on admission. HsTnT revealed overall a moderate role for predicting RVD on admission. Total PA clot score showed a low sensitivity and NPV, but a high specificity and PPV for predicting RVD at admission.
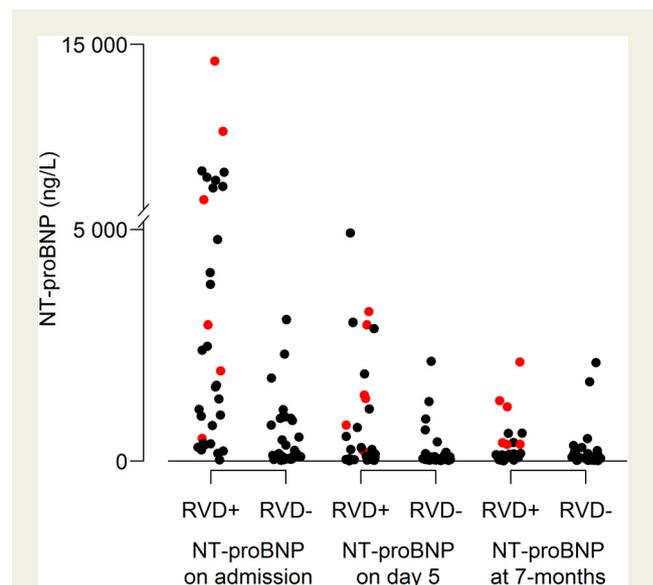

Figure 1 Individual NT-proBNP values on admission and at follow-up in the two study groups.
Points in red indicate subjects with persistent right ventricular dysfunction (RVD) after 7-month follow-up.

Table 1 Clinical and biochemical characteristics and total pulmonary artery clot score of patients with acute pulmonary embolism with and without right ventricular dysfunction by echocardiography on admission

	RVD present (N=32)	RVD absent (N=31)	p
Age (years)	58 ± 19	55 ± 16	0.546
Sex (male/female)	17/15	13/18	0.262
Body mass index (kg/m^2)	27.7 (20.9-42.8)	27.7 (22.0-40.4)	0.768
Malignancy (N, %)	1 (3)	2 (6)	0.488
Current smokers (N, %)	3 (9)	8 (26)	0.082
Immobilisation (N, %)	16 (50)	16 (52)	0.549
Hormone therapy (N, %)	8 (25)	7 (23)	0.528
Family history of VTE (N, %)	3 (9)	2 (6)	0.515
History of VTE (N, %)	4 (12)	3 (10)	0.518
Varicose veins (N, %)	16 (50)	11(36)	0.182
Systolic blood pressure (mmHg)	139 ± 22	141 ± 21	0.743
Diastolic blood pressure (mmHg)	83 ± 14	84 ± 12	0.739
Heart-rate (beats per minute)	84 (56-160)	76 (55-113)	0.114
Right ventricular overload on ECG (N, %)	22 (69)	9 (29)	0.002
Arterial oxygen (PaO$_2$)	8.7 ± 1.7	9.7 ± 1.1	0.008
Arterial carbon dioxide (PaCO$_2$)	4.3 (3.5-7.3)	4.8 (3.1-6.1)	0.002
Serum creatinine (μmol/L)	86 ± 16	73 ± 16	<0.001
D-dimer, on admission (mg/L)	8.0 (0.7-31.8)	6.0 (0.8-30.1)	0.093
HsTnT, on admission (ng/L)	18.6 (4.0-240.7)	8.1 (5.1-57.4)	0.014
HsTnT, at 7-months (ng/L)	8.0 (3.6-20.3)	7.6 (3.7-114.9)	0.894
NT-proBNP, on admission (ng/L)	1795 (26-14438)	153 (16-3055)	<0.001
NT-proBNP, on day 5 (ng/L)	195 (7-4922)	81 (12-2156)	0.033
NT-proBNP, at 7-months (ng/L)	102 (7-2141)	85 (11-2126)	0.322
Total PA clot score	70 ± 23	32 ± 28	<0.001

Data are expressed as means (± SD), medians (range), or frequencies (%). PA, pulmonary artery; RVD, right ventricular dysfunction; VTE, venous thromboembolism; HsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECG, electrocardiogram.

Table 2 Univariate correlation analyses between total pulmonary artery clot score, cardiac biomarkers and echocardiographic indices of right ventricular dysfunction on admission

	Total PA clot score	NT-proBNP	HsTnT
RV/LV ratio	0.424 p=0.001	0.497 p<0.001	0.268 p=0.035
RV end-diastolic diameter	0.387 p=0.002	0.433 p<0.001	0.289 p=0.023
Tricuspid regurgitation	0.451 p<0.001	0.449 p<0.001	0.133 n.s.
HsTnT	0.285 p= 0.025	0.548 p<0.001	-
NT-proBNP	0.619 p<0.001	-	0.548 p<0.001

PA, pulmonary artery; RV, right ventricular; LV left ventricular; HsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Ability to predict right ventricular dysfunction on echocardiography on admission

	Sensitivity	Specificity	PPV	NPV
NT-proBNP ≥ age- & sex-dependent cut-off value[*]	94%	55%	68%	89%
HsTnT ≥ 15 ng/L	53%	79%	74%	59%
PA clot score (total mass >78)	44%	97%	93%	62%

HsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PPV, positive predictive value; NPV, negative predictive value.

[*]Age-sex dependent cut-off value: women <50 years: <155 ng/L, women 50-65 years: <222 ng/L, women >65 years: <352 ng/L, men <50 years: <84 ng/L, men 50-65 years: <194 ng/L, and men >65 years: <229 ng/L.

Table 4 Ability to predict right ventricular dysfunction on echocardiography at 7-month follow-up

	Sensitivity	Specificity	PPV	NPV
NT-proBNP ≥ age- & sex-dependent cut-off value[*] on admission	100%	33%	14%	100%
NT-proBNP ≥ age- & sex-dependent cut-off value[*] on day five	100%	72%	27%	100%
NT-proBNP ≥ age- & sex-dependent cut-off value[*] at 7 months	100%	86%	43%	100%
HsTnT ≥ 15 ng/L on admission	67%	65%	17%	95%
HsTnT ≥ 15 ng/L at 7 months	75%	88%	30%	98%
PA clot score (total mass >78), on admission	17%	75%	7%	90%

HsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PPV, positive predictive value; NPV, negative predictive value; RV, right ventricular; LV, left ventricular.

[*]Age-sex dependent cut-off value: women <50 years: <155 ng/L, women 50-65 years: <222 ng/L, women >65 years: <352 ng/L, men <50 years: <84 ng/L, men 50-65 years: <194 ng/L, and men >65 years: <229 ng/L.

Cardiac Biomarkers and Total Pulmonary Artery Clot Score in Prediction of RVD at Seven-month Follow-up

Six patients (10%) had signs of persistent RVD assessed by TTE at seven-month follow-up. Baseline characteristics of these patients are presented in Supplementary Table 1. There were no fatal adverse events during the seven-month follow-up period. The AUC for predicting residual RVD revealed 0.830 (95% CI, 0.668-0.933) for NT-proBNP, 0.693 (95% CI, 0.561-0.826) for hsTnT, and 0.499 (95% CI, 0.256-0.747) for total PA score.

Age- and sex-dependent NT-proBNP both on admission, five days later, and at seven months showed high sensitivity and NPV for predicting RVD at seven-month follow-up. Age- and sex dependent NT-proBNP at seven months showed the best specificity for predicting RVD at seven-month follow-up. HsTnT on admission and at seven months revealed a moderate sensitivity and specificity, but a high NPV for excluding RVD. Total PA clot score on admission showed a low to moderate sensitivity and NPV in excluding RVD at seven-month follow-up (Table 4).

Discussion

Our findings in a seven-month follow-up study of 63 haemodynamically stable patients with APE showed that, high total PA clot score predicted RVD with high PPV on admission, whereas the PPV in predicting RVD at seven months was low. Among cardiac biomarkers the age- and sex-dependent NT-proBNP cut-off value on admission, five days later, and at seven-months was better than hsTnT in exclusion of RVD. Among echocardiographic parameters RV/LV ratio and tricuspid regurgitation demonstrated the best correlation with PA clot score and the level of NT-proBNP.

One of the most burning problems related to APE is currently the best strategy to identify patients ultimately developing CTEPH. Previous studies demonstrate an association between echocardiographic parameters of RVD and long-term mortality and APE recurrence [7–9]. Nevertheless, the prognostic value of TTE in haemodynamically stable patients appears at best moderate [5]. Moreover, TTE is not always available in all emergency departments and the reliability of TTE largely depends on the experience of the operator.

Nowadays, CTPA has been established as the first-line imaging technique for the diagnosis of PE. The development

of multi-slice scanners allows the visualisation and measurement of the heart chambers, and CTPA is therefore a proper alternative to echocardiography for the assessment of RVD. In fact, RVD assessed by CTPA has recently been shown to associate with an increased risk of mortality in subjects with haemodynamically stable PE [27,28]. However, one meta-analysis [27] showed only a small increase in the ability of CT-assessed RVD to classify risk suggesting that basing therapeutic decision-making solely on CT results is not warranted. Moreover, a limitation of the CT approach is that it does not allow functional assessments of the RV concerning pulmonary hypertension, RV hypokinesis and tricuspid motion, which are all evaluated by echocardiography [28]. Another drawback of CTPA includes significant radiation exposure to the patient making it an impractical tool for assessment of RVD during the long-term follow-up of subjects with APE.

In contrast to echocardiographic examination, cardiac biomarkers, such as NT-proBNP and troponins, are readily available at any time without operator-dependent variability. NT-proBNP levels have been associated with an increased risk of early death and a complicated in-hospital course, even in haemodynamically stable patients with APE [16]. However, the main limitation of cardiac biomarkers in routine clinical practice is the use of different biomarker thresholds and various outcome definitions in most studies.

Our results may aid in creating follow-up strategies for detecting CTEPH after APE. Among 63 patients only 10% had RVD at seven-months follow-up. Notably, as we have reported previously, none of the patients without RVD at baseline developed RVD during the follow-up [24]. One can however argue, that the follow-up period was too short. In a prospective study by Pengo et al. [29], 3.8% of patients developed symptomatic CTEPH within two years of first PE. Our study clearly demonstrates that among biomarkers the age-and sex dependent cut-off value of NT-proBNP was the most useful in ruling out the probability of RVD also at seven months. Interestingly, NT-proBNP below cut-off at five days from admission had 100% NPV for excluding RVD after seven months. As far as we know this has not been previously published. All the study patients survived throughout the follow-up time, and therefore, the role of NT-proBNP for predicting mortality could not be evaluated in the present study.

Elevated troponin levels have been associated with an increased risk of death and major adverse event in the acute phase of PE, but the results from large meta-analysis have been incongruous [17,30]. Recently developed hs-troponin assays have shown a 100% sensitivity and NPV with regard to the 30-day risk of mortality or major complications in stable patients with APE [18]. However, it has also been argued that hsTnT does not have sufficient sensitivity or specificity as a single test [31]. In the present study the hsTnT cut-off level of 15 ng/L showed only moderate sensitivity and NPV in prediction of RVD on admission, but clearly higher NPV for excluding RVD on TTE at seven-months follow-up. In fact, over-all, the usefulness of NT-proBNP

was better than that of hsTnT in our study population. The reason for this may be that, the stretch and dilation of RV induces invariably the secretion of NT-proBNP, whereas dilatation of RV does not lead to injury of cardiomyocytes and consequent hsTnT elevation in all cases.

Initial PA clot score showed only low to moderate sensitivity and PPV for excluding RVD at seven months. The factors affecting PE resolution, and the pathophysiology of persistent RVD and CTEPH are not fully understood. It has been shown that complete PE resolution occurs in >80% of patients during six months [32], but that neither median PA obstruction index at baseline nor the frequency of obstruction index >50% at baseline predict the presence of residual PE. Therefore other possible factors, such as individual variation of fibrinolytic potential or hypercoagulability may affect the persistence of PE. Moreover, persistent signs of RV enlargement and the development of CTEPH are not obvious consequences of incomplete PE resolution [32]. Our study extends previous findings of the role of initial PA clot score on long-term RVD. More studies are still needed to understand the complex interplay between PA clot resolution and changes in PA pressure.

So far, the estimation of embolic load in patients with APE by CT is still mainly experimental and not an essential part of the diagnostic work-up in every emergency department.

Clinical Implications

We found that none of the patients without RVD at baseline developed RVD at seven-months follow-up. The age- and sex dependent cut-off value of NT-proBNP on admission, before discharge from hospital, and at seven months seems to be helpful in risk stratifying patients with APE and for targeting diagnostic imaging of RVD during the follow-up period.

Limitations

Our study has certain limitations. First, the number of patients is relatively small as well as the number of patients with residual RVD reflecting a lower risk cohort and potentially affecting the statistical power of the study. Second, signs of RVD assessed by TTE, which was performed six hours later than CTPA and blood collection for cardiac biomarkers, might have been influenced by management during the delay [33]. We assume, however, that since patients with clinically high-risk APE were excluded from the study and only three patients received thrombolysis, the haemodynamic changes within 12 hours after the time of diagnosis were minimal. Third, the RV has a complex morphology, and most two dimensional echocardiographic methods are at best used as determinants of RV dysfunction, in a qualitative (by visual estimation of RV contractility and indirectly by septal flattening and RV dilation) manner. It is possible that emerging echocardiographic parameters derived from Doppler tissue imaging and wall strain assessment would have been better in the study of RV function. Fourth, each TTE was performed only by one operator and this may have

influenced the interpretation of RV function. Fifth, there were no reference TTE available for comparison prior to diagnosis of RV dysfunction and, therefore, we could not be confident that the RVD observed at baseline had occurred de novo. Finally, no multivariate analyses were performed due to a low event rate.

Conclusions

NT-proBNP was superior to hsTnT in the prediction of RVD. NT-proBNP above age- and sex dependent cut-off value on admission and at seven months distinguished patients with RVD at respective points of time. Normal age- and sex-dependent NT-proBNP measured five days after admission seems to be useful in exclusion of RVD at long-term follow-up. Total PA clot score showed a strong correlation with elevated levels of NT-proBNP and echocardiographic indices of RVD on admission. However, early phase total PA clot score showed only low PPV for the presence of persistent RVD at seven-month follow-up.

Disclosure Statement

There are no conflicts of interest to be declared by any of the authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2015.12.004.

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