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Damien Logeart
Lucien Lecuyer
Gabriel Thabut
Jean-Yves Tabet
Jean-Michel Tartière
Christophe Chavelas
François Bonnin
Jean-Louis Stievenart
Alain Cohen Solal

Biomarker-based strategy for screening right ventricular dysfunction in patients with non-massive pulmonary embolism

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D. Logeart (✉) · J.-Y. Tabet
Hôpital Lariboisière,
Service de Cardiologie,
2 rue Ambroise Paré, 75010 Paris, France
e-mail: damien.logeart@lrb.ap-hop-paris.fr
Tel.: +33-1-49956607
Fax: +33-1-49958664

D. Logeart · L. Lecuyer · J.-M. Tartière · C. Chavelas · A. C. Solal
Hôpital Beaujon,
Department of Cardiology,
Assistance Publique-Hôpitaux de Paris,
Clichy, France

G. Thabut
Hôpital Beaujon, Department of Pneumology, Assistance Publique-Hôpitaux de Paris,
Clichy, France

F. Bonnin · J.-L. Stievenart
Hôpital Beaujon,
Laboratory of Nuclear Medicine,
Assistance Publique-Hôpitaux de Paris,
Clichy, France

Abstract *Objective:* To evaluate the usefulness of B-type natriuretic peptide and troponin I measurements in predicting right ventricular dysfunction (RVD) in non-massive pulmonary embolism. *Design:* Prospective observational study. *Setting:* University-affiliated emergency unit, cardiology and pneumology departments. *Patients:* Sixty-seven patients admitted because of acute pulmonary embolism, without shock on admission, completed the study. *Interventions:* Blood samples and echocardiography were obtained on admission for subsequent and independent assessment of B-type natriuretic peptide (BNP) and troponin I levels as well as RVD. *Measurements and results:* Echocardiographic RVD was diagnosed in 36 patients and was severe in 13 on admission. BNP and troponin I levels were higher in patients with RVD than in those with no RVD [62 (27–105) vs. 431 (289–556) pg/ml for BNP, $p < 0.001$; 0.01 (0–0.09) vs. 0.16 (0.03–0.32) μg/l for troponin I, $p = 0.005$]. The area under the receiving operating characteristic curve (AUC) for diagnosing RVD was 0.93 for BNP and 0.72 for troponin I. The troponin I level increased further when RVD was severe, compared with moderate, and the AUC was 0.91 for identifying severe RVD. Diagnoses of RVD and severe RVD were ruled out by BNP ≤ 100 pg/ml (30% of patients) and troponin I 0.10 μg/l (58% of patients), respectively. In-hospital death or circulatory failure occurred in nine patients; all had echographic RVD and level of BNP > 100 pg/ml and troponin I > 0.10 μg/l. *Conclusion:* In hemodynamically stable pulmonary embolism, BNP/troponin I measurement is helpful on admission, especially for ruling out RVD, i. e. patients with in-hospital high-risk.

Keywords Pulmonary embolism · Natriuretic peptide · Troponin · Right ventricle

Abbreviations *RVD:* right ventricular dysfunction · *BNP:* B-type natriuretic peptide · *ECG:* electrocardiographic · *AUC:* area under the receiving operating characteristic curve

Introduction

Although the death rate from acute pulmonary embolism (PE) is in general low, some subgroups of patients have high risk, especially patients with hemodynamic impairment – so-called massive PE – but also hemodynamically stable patients with right ventricular dysfunction (RVD) – so-called submassive PE [1, 2]. Indeed, RVD is the main determinant of the short-term course of pulmonary embolism [3, 4] and could guide early management of patients with PE. Some authors have suggested that thrombolytic therapy could be indicated for submassive

PE [5]. The assessment of RVD requires echocardiography [6, 7, 8]. However, echocardiographic examination is poorly available in most emergency units, results are largely operator-dependent, and echocardiographic criteria of RVD are not definitely established. In contrast, biomarkers, including natriuretic peptide (BNP and NproBNP) and troponin, can be easily obtained from all patients and biological analysis produces reliable results [9, 10]. BNP and troponin are released from overloaded and/or injured ventricles and have been shown to have prognostic value in various settings [9, 10].

The aim of this study was to compare the value of BNP and troponin levels as well as clinical and electrocardiographic characteristics for diagnosing RVD in patients with nonmassive PE.

Methods

Study population

Between January 2002 and March 2004, 100 consecutive out-patients admitted with a first diagnosis of symptomatic PE were screened in the emergency department or the intensive care unit. Patients with a history of heart failure or myocardial infarction or PE ($n = 11$) and those with evidence of hemodynamic impairment ($n = 8$) such as shock, systolic blood pressure < 90 mmHg or syncope were excluded. All patients had high probability of PE. The diagnosis of PE was confirmed on admission by lung scintigraphy (PIOPED criteria) [11], and/or spiral computed tomography [12]. The following data were systematically recorded on admission: blood pressure, heart rate, clinical evidence of RV failure, blood gas values before oxygen administration and electrocardiographic (ECG) recording; ECG criteria of acute RV overload were negative T waves in V_1–V_4, D_{III} and V_F leads. The study protocol has been approved by the local ethics committee (Beaujon Hospital) and informed consents was obtained from all patients.

Echocardiography, definition of RVD and exclusion criteria

Bedside echocardiographic examination was performed as soon as the diagnosis of PE was obtained or before its confirmation [median 8 h (range 2–19) after admission] and was recorded on admission on S-VHS videotapes for blinded analysis. The following measurements were obtained: left ventricular (LV) ejection fraction; RV and LV diameter at the base of the ventricles from the apical view; RV wall and interventricular septum motion analysis; assessment of tricuspid insufficiency and measurement of its velocity by continuous Doppler analysis; and inferior cava vena diameter during inspiration by subcostal view. RVD was defined by the presence of two or more of the following: RV/LV diameter ratio > 0.7, hypokinesis of the RV free wall, inferior cava vena diameter > 10 mm during inspiration, interventricular septum bulging in the LV, and tricuspid regurgitant jet velocity > 2.7 m/s. Moreover, RVD was qualified as moderate or severe. According to the literature [7] and in our experience, the presence of interventricular septum bulging in the LV was considered the most reliable criteria of severe RVD. Moderate RVD was defined by the presence of two or more criteria described above except the interventricular septum bulging in the LV; severe, by interventricular septum bulging in the LV and at least two other criteria described above.

Patients were excluded in whom echocardiographic examination showed evidence of chronic pulmonary hypertension, defined by tricuspid regurgitant velocity > 3.7 m/s.

BNP and troponin I assay

Blood samples were collected on admission into tubes containing potassium EDTA (1 mg/ml blood), and plasma was stored at –80 °C. BNP levels were measured by use of the Triage® BNP test (Biosite Diagnostics, San Diego, CA). Troponin I level was measured by use of the Access AcuTnI assay (Beckman Coulter, Villepinte, France); troponin I was considered significantly increased if above 0.06 μg/l. Physicians were blinded to BNP and troponin I results during the study.

Lung scintigraphy and quantitative perfusion score

Scintigraphy including 99m-Tc perfusion and ventilation imaging was obtained in all patients either on admission or during the first following days. Lung scans were interpreted according to the PIOPED criteria [11]. A perfusion score, derived from the Miller score [13], was assessed by two scintigraphists, blinded to other data. Lungs were divided into 18 segments (8 from the left lung and 10 from the right lung), and each segment was graded in terms of perfusion reduction. Finally, normal, hypoperfused and nonperfused segments corresponded to 5.55%, 2.78% and 0% of the total perfusion, respectively; the perfusion score was the sum of each segment. The perfusion score was established only when scintigraphy was performed in the first 3 days after inclusion in the study.

Statistical analysis

Categorical data are presented as numbers (percent), and continuous data as means ± SD. BNP and troponin I concentrations are presented as median and interquartile ranges because skewed distribution and log-transformed

BNP and troponin I values were used for statistical analysis. Student's *t*-test and Fisher's exact test were used as indicated. Group comparisons of BNP and troponin I values involved use of ANOVA with the Newman–Keuls post-hoc test; p values < 0.05 were considered significant. Area under the receiving operating characteristics curve (AUC) was computed to determine the diagnostic and prognostic value of BNP and troponin I and to determine optimal BNP and troponin I cut-offs. Sensitivity, specificity, negative and positive predictive values, and accuracy were determined for several relevant cut-offs; associated 95% confidence intervals (CI) were obtained by bootstrap resampling. The analyses involved use of STATA 8.0 for Windows (Stata Corporation, College Station, Texas).

Results

Characteristics of patients and RVD diagnosis

Among 81 enrolled patients, the diagnosis of PE was performed on admission using CT in 53 patients and lung scan in 23 patients. After echographic examination, 14 patients were excluded because of the lack of satisfactory echocardiographic data ($n = 9$) or because of evidence of chronic pulmonary hypertension ($n = 5$). RVD was observed in 36 of the remaining 67 patients. RV dilation, hypokinesis of RV free wall, tricuspid regurgitation velocity > 2.7 m/s, inferior vena cava diameter during inspiration > 10 mm and interventricular septum bulging into LV were observed in 54%, 37%, 58%, 48% and 24% of patients respectively. Finally, RVD was considered moderate in 23 patients and severe in 13 patients. Mild LV dysfunction was also observed in 7 patients [LV ejection fraction 0.40 (0.38–0.43)]. Table 1 shows the main characteristics of patients according to the RVD diagnosis. Compared with patients without RVD, those with RVD were older and more frequently had dyspnea at rest, and ECG analysis demonstrated more frequent signs of acute RV overload. BNP and troponin I levels were substantially higher in RVD patients (Table 1 and Fig. 1). Among the 59 patients with early lung scan, the hypoperfusion score was significantly higher in RVD patients.

During hospitalization, the following events were recorded in nine patients, between 4 hours and 8 days after

Table 1 Clinical, biochemical and scintigraphically determined characteristics according to the echocardiographic diagnosis of RVD. BP, Blood pressure; PaO_2, oxygen arterial pressure; BNP, B-type natriuretic peptide; ECG, electrocardiography; RBB, right bundle block. Because of skewed distribution, BNP and troponin I values are presented as median and interquartile ranges

	No RVD ($n = 31$)	RVD ($n = 36$)	p
Age (years)	59 ± 18	69 ± 15	0.01
Male gender	65%	56%	0.46
History of hypertension	16%	39%	0.04
Dyspnea at rest	16%	47%	0.007
Heart rate (beats/min)	97 ± 17	97 ± 19	0.85
Systolic BP (mmHg)	133 ± 23	132 ± 27	0.95
PaO_2 (mmHg)	64 ± 17	58 ± 8	0.09
Sinus rhythm	94%	92%	0.77
ECG RV ischemia	13%	61%	0.0001
RBB	13%	33%	0.04
BNP (pg/ml)	97 ± 109	497 ± 327	< 0.0001
Troponin I (μg/l)	0.05 ± 0.08	0.35 ± 0.58	0.005
Scintigraphic hypoperfusion score (%)	21 ± 7	31 ± 12	0.003
Number of hypoperfused / non-perfused segments	6.1 ± 2.5	7.7 ± 2.7	0.05

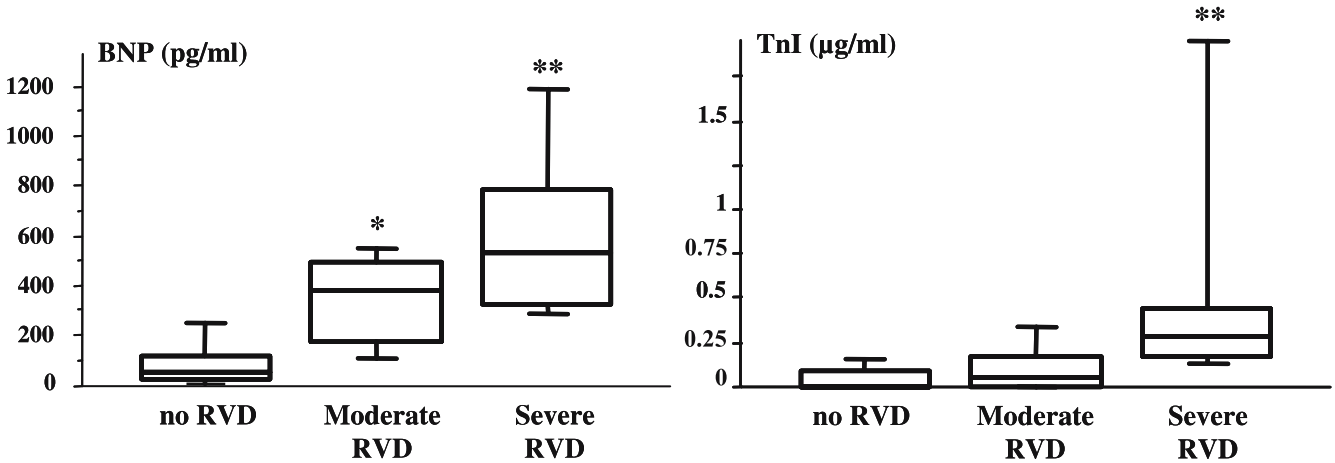

Fig. 1 BNP and troponin I (*TnI*) values according to the echocardiographic diagnosis of RVD. *Box plots* show median levels. *$p < 0.01$

admission: one PE-related death and seven circulatory failures requiring dobutamine infusion ($n = 5$) and/or rescue thrombolysis ($n = 6$). All these in-hospital events were observed in RVD patients, two with moderate RVD and seven with severe RVD.

Biomarkers and RVD diagnosis

To specify the value of biological markers for diagnosing RVD, receiving operating characteristics curves were established. AUC values were 0.93 (0.87–0.99) for BNP, with an optimal cut-off point of 200 pg/ml (sensitivity and specificity 85%), and 0.72 (061–0.87) for troponin I (Fig. 2). The combination of BNP and troponin I provided no additive diagnostic information compared with BNP alone (AUC 0.94). Table 2 gives the sensitivity, specificity, negative and positive predictive values, and accuracy of several cut-off points. For "ruling out" RVD, BNP $\leq$ 100 pg/ml had a negative predictive value of 100%.

When RVD was graded according to echocardiography as moderate or severe, the level of troponin I was significantly higher in severe RVD than in moderate RVD [0.28 (0.20–0.39) vs 0 (0–0.12) μg/l, $p = 0.029$, Fig. 1], whereas that of BNP was only slightly higher slightly [519 (318–769) vs 377 (152–486) pg/ml, $p = 0.055$]. The AUC was 0.91 (0.84–0.98) ($p < 0.001$) for troponin I for identifying severe RVD (0.85 for BNP). Among other parameters on admission, the proportion of overload-related abnormalities seen on ECG was slightly higher in severe RVD than in moderate RVD (85% vs 50%, $p = 0.059$).

Finally, BNP $\leq$ 100 pg/ml rules out the possibility of RVD, and troponin I $\leq$ 0.10 μg/l rules out the possibility of severe RVD. The combination of BNP > 100 pg/ml and troponin I > 0.10 μg/l on admission was associated with RVD in 80% of cases (severe RVD in 60%). None of the other clinical, ECG or biological parameters added further

Table 2 Diagnostic values (mean and range) of various BNP and troponin I cut-off points related to echocardiographic evidence of RVD on admission

	Sensitivity	Specificity	Negative predictive value	Positive predictive value	Accuracy
BNP 100 pg/ml ($n = 20$)	100% (92–100)	64% (47–80)	100% (86–100)	77% (64–88)	84% (75–93)
BNP 150 pg/ml ($n = 29$)	89% (78–97)	81% (93–97)	86% (71–97)	84% (72–95)	85% (75–93)
BNP 200 pg/ml ($n = 34$)	83% (71–94)	87% (74–97)	82% (68–94)	88% (76–97)	85% (76–93)
BNP 300 pg/ml ($n = 41$)	69% (55–84)	97% (89–100)	73% (59–86)	96% (88–100)	82% (73–91)
Troponin I 0.06 μg/l ($n = 32$)	69% (50–81)	65% (48–80)	65% (45–79)	69% (55–83)	67% (55–79)
Troponin I 0.10 μg/l ($n = 39$)	64% (44–76)	84% (69–97)	67% (50–79)	82% (65–96)	73% (63–84)
Troponin I 0.15 μg/l ($n = 44$)	56% (37–71)	90% (74–97)	64% (47–76)	87% (71–100)	72% (61–82)

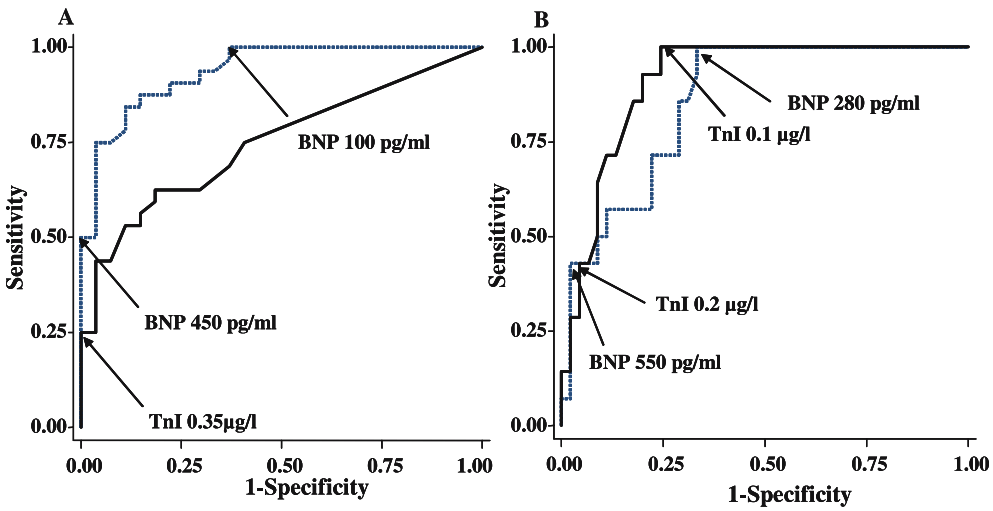

Fig. 2 Receiving operating characteristic curves for BNP and troponin I (*TnI*) cut-off values and diagnosis of: **A** any RVD, **B** only severe RVD

information over biomarkers. Moreover, in-hospital events occurred only in patients with both BNP > 100 pg/ml and troponin I > 0.10 μg/l on admission.

Discussion

We show that biomarkers are useful for stratifying hemodynamically stable patients with PE according to echographic RVD or no RVD. The usual clinical and ECG parameters add no relevant information. Our results show that biomarkers could aid in early management, mainly by identifying patients without RVD.

In agreement with previous studies [1, 2], we observed a high proportion of patients with echocardiographic evidence of RVD (one-half) with neither hypotension nor evidence of heart failure. No reliable clinical parameter could differentiate patients with RVD from the others. This subgroup of patients with "silent" RVD, so-called submassive PE, has a high risk of death or hemodynamic instability during the first days of admission [1, 3]. In our study, we observed such events in 8 of 33 patients with RVD. Thus, prompt and accurate identification of submassive PE is an important issue.

A number of echocardiographic parameters have been proposed to analyze right ventricular function. Some of them are difficult to obtain and/or are missing. In our study, RV echocardiographic analysis was insufficient in more than 10% of patients. Tricuspid and pulmonary insufficiencies are inconstant, and motion of the RV free wall is more difficult to study than motion of the LV walls because of the RV location in the chest as well as the particular RV shape. RV dilation is the most common criterion, but different thresholds have been proposed (RV/LV diameter ratio between 0.6 and 1.0) [14, 15, 16], which could explain discrepancies regarding RVD-related prognosis among studies. Others used ventricular area ratio, which can assess change in the apical shape [7]. In order to reduce diagnostic inaccuracy, we required at least two criteria. Because the severity of RVD is inhomogeneous, we graded RVD as moderate or severe according to the presence of interventricular septum bulging in The LV, rather than to the severity of RV dilation. In fact, such interventricular dyskinesia is a specific criteria of RVD in this setting, and others authors have defined RVD as the combination of both RV dilation and interventricular septum bulging in the LV [18]. Indeed, interventricular septum dyskinesia is associated with RV dilation but is less frequent (24% vs 54% of PE in our study); it is due to systolic RV overload and results in LV filling impairment, while RV dilation is mainly due to the increase in RV filling pressures [7].

In contrast with echography, biochemical markers can be promptly obtained in all patients and could be more suitable in this setting. A biomarkers-based stratification is relevant mainly in hemodynamically stable patients whose adverse outcome cannot be easily predicted by clinical examination. In contrast with previous studies, we excluded any patients with clinical evidence of massive PE, including syncope. BNP/NproBNP is mainly released by the LV when ventricular wall stress increases. The RV can also release natriuretic peptides, but subsequent BNP blood levels are low compared with those of the LV because of differences in muscular mass. Nagaya et al. demonstrated a strong positive relation between BNP level and pulmonary vascular resistance, as well as RV end-diastolic pressure, in patients with primary pulmonary hypertension [19]. In agreement with previous studies [20, 21, 22], natriuretic peptides are related to RV function and increase gradually according to the severity of RVD in our study. Recently, Kruger et al. [20] settled on a threshold BNP of 75 pg/ml for ruling out RVD, which is close to our results, according to slight differences in respective echographic parameters.

Troponin leak is due to myocardial injury, whose mechanisms probably resemble those causing the increase in BNP level. Indeed, the main mechanism of PE-related RV injury is an acute increase in RV wall stress. Such a mechanism had been demonstrated in acute LV heart failure regardless of coronary artery integrity [23, 24]. In contrast to BNP, an increase in troponin I level occurred only in patients with severe echographic PE-related RVD in our study. Thus, an increase in troponin I level was more specific to severe RVD when an increase in BNP level was sensitive to any RV overload.

Using these differences in pathophysiological significance between BNP and troponin I levels, a biomarkers-based screening could be suggested. Biomarkers-based screening allows for ruling out RVD and severe RVD with a negative predictive value of 100% with BNP ≤ 100 pg/ml and troponin I ≤ 0.1 μg/l; in these cases, bedside echocardiography is unnecessary. The association of BNP > 100 pg/ml and troponin I > 0.10 μg/l predicts RVD, with a positive predictive value of 85%, which is severe in two-thirds of cases. Despite this high diagnostic value of biomarkers, echographic examination remains necessary in patients with history of heart failure as well as in cases of uncertainty regarding the diagnosis of PE, because BNP and troponin I blood levels increase in LV dysfunction as well as in acute coronary syndrome or sepsis [17]. Interestingly, clinical parameters as well as abnormalities seen on ECG (i. e. signs of RV overload) or scintigraphic score provided no additional information over biomarkers.

Finally, the clinical relevance of such biomarkers-based screening also depends on its ability to identify high-risk patients in order to manage them perhaps more intensively. Previous studies or surveys [1, 2] reported that in-hospital prognosis of patients with RVD was worse than that of patients without RVD. Consequently, aggressive treatment such as thrombolysis has been proposed in these patients [5]. Because of their ability to identify RVD, it has been suggested that measurement of natriuretic peptides

or troponin could be used for stratifying patients with PE [25]. Several studies demonstrated that an increase in level of the natriuretic peptides BNP [25, 26, 27] or NproBNP [21, 28, 29], as well as in levels of troponin I or troponin T [5, 29], predicted early complications. Recently, Kostrubiek et al. [16] underlined that combining both natriuretic peptide and troponin measurements improved the risk stratification; low NT-proBNP level indicated excellent prognosis, while high levels of both NT-proBNP and troponin T indicated high risk. In our study, the incidence of early events was low, but events were also observed in patients with an increase in both BNP (> 100 pg/ml) and troponin I (> 0.10 μg/l). Kucher et al. [25] proposed a lower BNP threshold (50 pg/ml), which could be due to very early BNP measurements after the onset of symptoms (< 6 h) in a few patients; such "false negatives" have been also observed in the acute heart failure setting because of flash pulmonary edema [30]. Interestingly, the echographic stratification could be less powerful than that by biomarkers. Indeed, echographic criteria lacked prognostic relevance compared with biomarkers in the recent study by Kostrubiek et al. [16], when age as well as comorbidity remained of prognostic importance. In a more severely ill population, Vieillard-Baron et al. also underlined the lack of prognostic relevance of echographic parameters in multivariate analysis compared with biological tests such as metabolic acidosis [18]. However, it should again be emphasized that biomarker-based stratification requires that there is no evidence of any other cause of increased levels of biomarkers; echographic examination should be promptly performed if not. Regarding thrombolytic therapy, its relevance in such hemodynamically stable patients is still debated because of the lack of large randomized studies [31, 32, 33]; the relevance of biomarker-based stratification could be tested in such studies.

Conclusion

Biomarkers can provide prompt and useful information in hemodynamically stable patients with acute PE. Normal BNP levels rule out patients with RVD, i. e. potential high-risk patients. On the other hand, when both BNP and troponin I levels are increased, severe RVD is strongly suspected. The usefulness of this strategy for subsequent treatment, including thrombolysis, needs further study.

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