

Pulmonary embolism: role of echocardiography and of biological markers

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Echocardiography and biomarkers: what should be their place in the algorithms designed for pulmonary embolism (PE)? Our opinions on that continue to evolve. This manuscript attempts a snapshot reflecting the position of cardiac imaging and cardiac biomarkers in suspected and confirmed PE.

Comparing the prognostic performance of brain natriuretic peptide (BNP) and troponins, it seems that with thresholds set appropriately high, troponins could be more helpful in the identification of patients with adverse prognosis while low BNP levels are reliable markers of good prognosis. Because of the relatively short plasma half-life, BNP as well as NT-proBNP could be repeated to monitor evolution of the hemodynamic status of the patient and the results of implemented treatment. The role of echocardiography outside massive PE seems to be decreasing, although if considered together with information provided on potential alternative or additional cardiovascular diseases as well as intracardiac or intravascular thrombi, its place in a tentative management algorithm in PE seems still secured.

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Introduction

Echocardiography and biomarkers: what should be their place in the algorithms designed for pulmonary embolism (PE)? Do they provide complementary, redundant or overlapping information? How can they help to optimize therapeutic triage? Clearly our opinions on all that continue to evolve. This manuscript attempts a snapshot reflecting current and to some extent subjective opinions of the authors regarding the present and future of cardiac imaging and cardiac biomarkers in suspected and confirmed PE.

Echocardiography

The position of echocardiography in the diagnostic and prognostic workup of PE is not fully defined. As a diagnostic tool it has two different faces. While widely used in clinical practice^{1,2}, it stays outside the diagnostic algorithms recommended for hemodynamically stable patients. Indeed, a normal echogram does not rule out PE, just as it is the case with normal chest X-ray, arterial blood gases or ECG. Also, classical signs of right ventricular (RV) overload are of questionable specificity, when applied to

unselected patients, including those with concomitant cardiorespiratory diseases³.

However, two signs were claimed to be more specific for acute PE. "McConnell sign" defined as RV free wall hypokinesis in the presence of normal RV apical contractility was originally suggested mostly as a useful criterion to differentiate acute PE from chronic pulmonary hypertension^{3,4}. Of note, this specific pattern of abnormal regional RV contractility may occur also in acute RV infarction^{5,6}. Therefore a "true" McConnell sign requires concomitant echo-Doppler evidence of RV pressure overload, such as increased tricuspid jet velocity. Also, flow velocity pattern during RV ejection may provide useful information about its afterload. The short acceleration time and mid-systolic deceleration of flow velocity in the RV outflow tract reflecting increased pulmonary arterial input impedance and the premature return of reflected pressure waves, are seen in acute PE even with only mild to moderate increase in tricuspid jet velocity⁷. In fact, a prospective trial enrolling unselected symptomatic patients found acceleration time < 60 ms in the presence of tricuspid systolic gradient < 60 mmHg ("60/60 sign") highly specific for the diagnosis of acute PE³.

Despite being more specific, McConnell and 60/60 signs have low sensitivity in unselected population with PE. Therefore, echocardiography is not the best diagnostic choice in stable patients, when time permits to proceed according to practice guidelines in order to decide whether to start anticoagulant therapy⁸.

The situation is different in patients presenting with hypotension, i.e. with suspected massive PE. Despite paucity of published evidence echocardiography is almost universally considered very useful for emergency decision-making⁸. It permits bedside diagnosis of most of the alternative causes of acute clinical instability: aortic dissection, cardiac tamponade, left ventricular or valvular dysfunction, hypovolemia, etc. Moreover, when showing normal RV function echocardiography practically excludes massive PE as the cause of hemodynamic collapse. If signs of RV overload are present, and especially in the presence of McConnell and/or 60/60 signs, PE becomes very likely, but still not definitely confirmed. An immediate search for a venous clot with simplified venous compression test using vascular ultrasonic probe and – if still necessary – a search for emboli in the main pulmonary arteries with transesophageal probe often permits the final diagnosis⁹. Such comprehensive use of ultrasound at the patient's bedside is especially useful in the intensive care unit. In the meantime the patient is being stabilized and prepared for transport for further imaging tests, required in case any doubts regarding diagnosis remain to be resolved. Integrated ultrasound may be also rewording in pregnant women with suspected PE, sometimes allowing to make diagnosis without exposing the fetus to ionizing radiation.

Regardless its admittedly limited role as a diagnostic tool echocardiography emerged as an important prognostic marker in confirmed PE. Several independent groups reported on excellent prognosis of heparin-treated patients with PE but no signs of RV overload or dysfunction at transthoracic echocardiography¹⁰⁻¹². Indeed, this seems an important criterion when considering patients with venous thromboembolism for outpatient treatment.

On the other hand there is accumulating evidence that RV dysfunction as detected by echocardiography indicates worse prognosis. In-hospital mortality was reported to be significantly higher in patients with RV dysfunction, ranging from 12.6 to 15.9%, as compared to those with preserved RV function (0-8%)^{1,10-12}. It should be noted, however, that echocardiographic criteria used across those trials varied significantly and were quite arbitrary. Also, most studies included patients with hypotension. A trial focusing on normotensive patients with confirmed PE showed a lower mortality (5%) than all the other studies¹², despite signs of RV dysfunction. However, 6 out of 65 (10%) patients with RV dysfunction presenting with normal blood pressure developed shock despite treatment with heparin, and 3 of them died due to PE. Based on those observations

the guidelines of the European Society of Cardiology formally labeled normotensive patients with PE but with echocardiographic signs of RV dysfunction as suffering from "submassive" PE⁸. However, no evidence-based recommendation regarding more aggressive treatment of this subgroup could be made. Interestingly, many clinical teams had already been treating patients with PE and echocardiographic signs of RV dysfunction with thrombolytics, regardless of their hemodynamic stability and despite the lack of definitive evidence of better outcome related to such an approach. On the contrary, a case-controlled retrospective trial comparing thrombolytic and heparin-only treatment in 128 patients with PE and RV dilation defined as a RV/left ventricular ratio > 0.6 called for caution¹³. It reported three intracranial bleedings in 64 patients treated with thrombolysis and no deaths related to PE regardless of the applied treatment. Although opponents of aggressive therapy often point at this trial as a strong evidence against thrombolysis in submassive PE it must be noted that all cerebral bleedings occurred in patients with relative contraindications to thrombolytic treatment: two in octogenarians and one in a patient with uncontrolled systemic hypertension. Moreover, the definition of RV dysfunction used in this trial was relatively liberal, probably explaining good outcome in heparin-only-treated patients. Interestingly, a larger, randomized prospective trial of normotensive patients with PE and RV overload, diagnosed either with echocardiography or right heart catheterization, revealed neither difference in mortality nor in major bleedings. However, patients treated with heparin alone had more often a complicated clinical course, requiring escalation of supportive therapy and/or rescue thrombolysis¹⁴.

Taken together, accumulated evidence points at excellent prognosis in patients with heparin-alone-treated PE in the absence of echocardiographic signs of RV overload or dysfunction. Patients with signs of RV overload at echocardiography, but also detected with other methods, such as right heart catheterization or spiral computed tomography, should be closely monitored as they often destabilize requiring emergency therapy, including rescue thrombolysis.

In addition to RV dysfunction, echocardiography can identify two more situations affecting prognosis in a patient with PE: patent foramen ovale and right heart thrombi.

Right heart failure due to an acute increase in afterload following pulmonary embolism may result in right-to-left shunt across the foramen ovale, which remains patent in about 20 to 30% of the adult population. The diagnosis can be made when contrast microbubbles appear in the left heart chambers within three cardiac cycles after opacification of the right atrium following peripheral vein injection of agitated saline or specific echocardiographic contrast medium. In-hospital mortality was significantly higher in pa-

tients with PE and evidence of such right-to-left shunt at the atrial level (33 vs 14%, $p < 0.015$). This was mostly due to episodes of ischemic stroke as well as a trend toward a higher rate of intracranial bleeding during antithrombotic therapy¹⁵. Although patent foramen ovale at contrast echocardiography seems to identify a subgroup of patients suffering from PE with worse prognosis no modification in management can be recommended at that time¹⁶.

Due to the lack of prospective controlled trials our knowledge regarding right heart thrombi in patients with PE comes mostly from case reports and registries. A European registry indicated that the risk of death related to right heart thrombi depended on their appearance. Mobile thrombi of venous origin, temporarily blocked in the right atrium while in-transit to the pulmonary arteries resulted in 42% early mortality¹⁷. This was in contrast to relatively benign clinical course of mural, *in situ* developing thrombi, usually found in patients with intracardiac catheters or electrodes. Analysis of the largest database reporting clinical presentation and outcome in unselected patients with PE (ICOPER) confirmed that the mortality of those with right heart thrombi is doubled at 14 days as well as at 3 months¹⁸. To what extent this difference could be attributed directly to the presence of right heart thrombi remained unclear since patients with right heart thrombi were also more hemodynamically compromised at presentation than those without right heart thrombi.

The optimal treatment in patients with mobile right heart thrombi also remains controversial. Two largest analyses questioned the strategy of heparin alone in this population. Rose et al.¹⁹ reported 28.6% mortality in patients treated with heparin alone, with 23.8 and 11.3% mortality among patients treated surgically and with thrombolysis, respectively. Also ICOPER patients with right heart thrombi treated with heparin alone had high 23.5% mortality at 14 days, contrasting with 8% in similarly compromised and identically treated patients free from intracardiac thrombi. In clinical practice the majority of patients with PE and right heart thrombi are treated with thrombolysis, although mortality seems to remain high – 20.8% according to ICOPER¹⁸. We feel that surgical embolectomy could be a good alternative in experienced hands and should be preferred to thrombolysis in cases with impending paradoxical embolism due to straddling of interatrial septum by a thrombus blocked in a patent foramen ovale. However, reliable comparative data are lacking.

Cardiac biomarkers

Cardiac biomarkers have a long history in the objective diagnosis of myocardial infarction. Recent years revolutionized the very definition of myocardial

infarction due to improvements in laboratory tests detecting circulating troponin, a cardiac-myocyte-specific intracellular contractile protein.

Also the brain natriuretic peptide (BNP) or its biologically inactive twin-brother NT-proBNP, both released in excess from the stretched myocytes of failing ventricles, were suggested as useful for differential diagnosis of cardiac vs non-cardiac causes of dyspnea. Interestingly, with time the major clinical role of troponin and BNP became more prognostic than diagnostic. This is true also in acute PE.

Troponins. Detectable troponin I and T concentrations reported both in acute and chronic pulmonary hypertension seem to support an old concept of diffused ischemia of the right ventricle resulting from a sequence of events beginning with elevated RV afterload, relative RV dysfunction and decreased output. This in turn leads to decreased aortic pressure and RV coronary perfusion gradient in the setting of increased oxygen demand due to high RV intramural tension and increased adrenergic drive. It should be underlined, that progressive, irreversible RV failure was reported to precipitate the fatal outcome in PE patients. Moreover, transmural RV infarctions were found at autopsy in patients who died because of massive PE. In the pivotal trial the prevalence of positive troponin T results defined as > 0.1 ng/ml was reported to increase from 0%, through 35 to 50% in subgroups of patients with non-massive, submassive and massive PE, respectively²⁰. More importantly positive troponin T was related to 44% in-hospital mortality, compared with 3%, translating to an odds ratio of 15.2 (95% confidence interval 1.22-190.37). Another trial in patients with confirmed PE reported on the correlation between the level of circulating troponin and prevalence of clinical endpoints, including deaths²¹. Nevertheless, in our experience already quite low troponin T concentrations, merely exceeding 0.01 ng/ml identify subgroups with increased risk of deaths among initially normotensive patients with PE (odds ratio 21, 95% confidence interval 1.2-389)²². Similarly to acute coronary syndromes, repeated sampling at 6 to 12 hours should be considered because initially negative results may revert to positive, with prognostic implications. This can be expected especially in patients admitted early after first symptoms or those who do not respond to initially applied treatment. Of note the potential role of myoglobin testing, based on rapid response of this marker to myocardial injury and its reported prognostic value also in acute PE²³.

The question whether circulating troponins provide additional prognostic information beyond that provided by echocardiography was addressed by Kucher et al.²⁴. They analyzed troponin I and echocardiography in 91 patients with acute PE. As expected when both tests were normal 3-month survival was excellent (98%). Positive predictive value for complicated in-hospital

clinical course was 41% for echocardiographic signs of RV overload, 64% for positive troponin I (> 0.06 ng/ml) and 75% for both²⁴.

These data seem rather to question the role of echocardiography, considering the relative complexity and costs of this test and relatively small incremental prognostic value on top of that provided by assessment of troponin.

As it is the case with echocardiography optimal threshold for troponin has not been settled. Table I^{20-23,25-29} reports prognostic significance of cut-off levels used in the published literature.

Brain natriuretic peptides. The position of biomarkers in cardiovascular medicine was reinforced after quick and reliable tests assessing circulating BNP (NT-proBNP) were introduced into clinical practice. As mentioned before RV dysfunction can be detected by echocardiography in approximately 50% of acute PE patients. The significant RV distension and elevated RV systolic and end-diastolic pressures observed in acute PE lead to increased stretching of the RV wall, and may therefore result in the release of BNP.

Tulevski et al.³⁰ were the first to show increased BNP levels in those patients with PE who had echocardiographic signs of RV dysfunction, a finding repeatedly confirmed thereafter. Moreover, their 2 patients with the highest BNP values died within 30 days of BNP assessment.

In acute PE, BNP as well as NT-proBNP seem to be useful both for identification of patients with good prognosis and those with high probability of complicated clinical course^{25,26}. Because in contrast to troponins, BNP as well as NT-proBNP can always be detected in the plasma and show a correlation with several echocardiographic indices of RV overload, deciding upon the prognostic thresholds is of even greater importance. The reported cut-off values and resulting positive and negative predicted values for in-hospital mortality can be found in table I. In contrast to troponins, BNP as well as NT-proBNP have relatively short plasma half-lives (20 min and 2 hours respectively). This could make repeated testing a tempting approach, providing useful information regarding evolution of hemodynamic status of the patient and the results of implemented treatment (Fig. 1).

Combined use of troponins, brain natriuretic peptide and echocardiography

In a very recent trial by Kostrubiec et al.³¹ involving 100 consecutive initially normotensive PE patients in whom serum NT-proBNP and cardiac troponin T levels were assessed and echocardiography was performed at admission, the latter did not improve group selection according to prognosis. Receiver-operating character-

Table I. Selected reports on the prognostic value of cardiac biomarkers in acute pulmonary embolism.

Author	No. patients	Biomarker/test applied	Threshold	Positive (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Giannitsis et al. ²⁰	56	cTnT Troponin T (Roche Pharmaceuticals)	0.10 ng/ml	32	89	79	97	44
Konstantinides et al. ²¹	106	cTnI Centaur (Bayer)	0.07 ng/ml	41	86	63	98	14
Konstantinides et al. ²¹	106	cTnT Elecsys (Roche Pharmaceuticals)	0.04 ng/ml	37	71	66	97	12
Pruszczyk et al. ²²	64	cTnT Elecsys (Roche Pharmaceuticals)	0.01 ng/ml	50	100	57	100	25
Pruszczyk et al. ²³	46	Myoglobin Elecsys (Roche Diagnostics)	F: 58 ng/ml M: 72 ng/ml	46	100	64	100	33
ten Wolde et al. ²⁵	110	BNP Shionoria (CIS Bio International)	21.7 pmol/l	33	86	73	99	18
Pruszczyk et al. ²⁶	79	NT-proBNP Elecsys (Roche Diagnostics)	600 pg/ml	27	100	33	100	26
Janata et al. ²⁷	106	cTnT Elecsys (Roche Diagnostics)	0.09 ng/ml	11	80	92	99	34
Kucher et al. ²⁸	73	NT-proBNP Elecsys (Roche Pharmaceuticals)	500 pg/ml	58	NA	NA	100	12
Kucher et al. ²⁹	73	BNP Triage (Biosite Technologies)	50 pg/ml	58	NA	NA	100	12

BNP = brain natriuretic peptide; cTnI = cardiac troponin I; cTnT = cardiac troponin T; F = females; M = males; NA = not available; NPV = negative predictive value; PPV = positive predictive value.

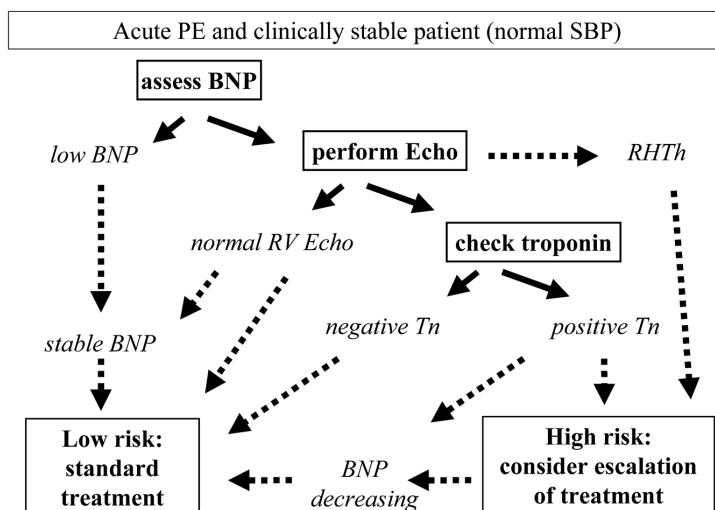


Figure 1. Suggested role of echocardiography and biomarkers in the prognostic assessment of patients with submassive pulmonary embolism (PE). BNP = brain natriuretic peptide or NT-proBNP; RHTth = mobile right heart thrombus; RV = right ventricular; SBP = systolic blood pressure; Tn = troponin I or troponin T.

istic (ROC) analysis was performed to assess the optimal cut-off values of serum NT-proBNP and cardiac troponin T for death and serious adverse event selection.

Multivariate and ROC analyses revealed that cardiac troponin T > 0.07 ng/ml was the most significant independent predictor, whereas NT-proBNP and systemic systolic blood pressure as well as the echocardiographic parameters were non-significant. At univariate analysis, cardiac troponin T > 0.07 ng/ml as well as NT-proBNP > 7600 ng/l predicted all-cause and PE-related mortalities. Mortality due to PE in patients with NT-proBNP \geq 600 ng/l and cardiac troponin T \geq 0.07 ng/ml reached 33% but if NT-proBNP > 600 ng/l and troponin remained < 0.07 ng/ml PE-related mortality was only 3.7%.

Comparing the prognostic performance of BNP and troponin it seems that with thresholds set appropriately high, troponin could be more helpful in the identification of patients with adverse prognosis while low BNP levels are reliable markers of good prognosis. On the other hand, because of relatively short plasma half-life, BNP as well as NT-proBNP could be repeated to monitor evolution of the hemodynamic status of the patient and the results of implemented treatment. The role of echocardiography outside massive PE seems to be decreasing, although if considered together with information provided especially on potential additional cardiovascular diseases as well as intracardiac or intravascular thrombi, its place in a tentative management algorithm in PE seems still secured (Fig. 1). In fact, a protocol of a long due trial comparing thrombolysis with heparin alone in patients with submassive PE will enroll patients who have both positive troponin result and echocardiographic signs of RV overload. Hopefully the thresholds have been optimally selected.

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