Elevated levels of natriuretic peptides in patients with pulmonary thromboembolism

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Summary

Background: Pulmonary thromboembolism (PTE) occurs in a wide variety of clinical settings and presents a diagnostic challenge to clinicians, often requiring extensive imaging of the vascular bed. Management increasingly requires accurate risk stratification to rapidly identify those with massive and submassive PTE requiring different therapeutic strategies such as thrombolysis. Provision of a rapid blood test that improves diagnostic certainty and helps stratify risk could therefore bridge the gap between uncertainty and delivery of immediate early life-saving treatment.

Methods and results: One hundred and fourteen consecutive patients with suspected PTE underwent prospective evaluation. Venous blood samples were obtained from an unselected group referred for ventilation–perfusion scintigraphy. B-type natriuretic peptide (BNP), atrial natriuretic peptide (ANP) and N-terminal pro-ANP (N-ANP) were measured by radioimmunoassay using commercially available kits. The scans were classified into three groups according to standard criteria (PIOPED); normal scan (N) (n = 20), low/intermediate probability (L/I) of PTE (n = 77) and high probability (H) of PTE (n = 17). Comparisons were also made between patients with high probability scans who died (n = 3) and those who survived (n = 14). Values are quoted for the median and interquartile ranges. There were statistically significant differences between groups for levels of (a) BNP (P < 0.001): N = 6.7 pmol/l (5.6–11.9), L/I = 12.5 pmol/l (6.7–28.2) and H = 18.5 pmol/l (12.6–74.6); (b) ANP (P < 0.005): N = 12.6 pmol/l (7.1–16.0), L/I = 19.51 pmol/l (12.5–28.2) and H = 19.1 pmol/l (15.7–31.7) and (c) N-ANP

KEYWORDS
Natriuretic peptides; Pulmonary embolism and death; Sudden
Introduction

Pulmonary thromboembolism (PTE) occurs in a wide variety of clinical settings and presents a diagnostic challenge to clinicians often requiring extensive imaging of the vascular bed. Clinical signs are often non-specific, and early treatment relies on limited information pending definitive testing with the consequences are of a condition that is both over- and underdiagnosed.\(^1\)

Recently there has been much interest in a family of peptides known as natriuretic peptides in the diagnosis and risk stratification of conditions such as heart failure. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are hormones released by myocardial stretch\(^2\) and have been shown to be sensitive markers of left ventricular systolic dysfunction;\(^3,4\) an inactive N-terminal fragment (N-ANP) is also released. Their physiological role mediates natriuresis and vasodilatation through cGMP activation.\(^2\) The natriuretic peptides are also elevated in pulmonary disease with acute hypoxaemia\(^5\) or cor pulmonale, and increase in proportion to the degree of right ventricular dysfunction.

PTE can present as a life threatening illness typically with signs of right ventricular dysfunction or haemodynamic instability. Thrombolysis benefits this subgroup specifically,\(^6\) but an unacceptable risk of haemorrhage arises if thrombolysis is administered to patients with no evidence of massive or sub-massive PTE. There is a need to define the risk of pulmonary embolus early, and identify the subgroup of patients that may benefit from immediate thrombolysis or transfer to a higher level of care. Provision of a rapid blood test that improves diagnostic certainty and helps stratify risk could therefore bridge the gap between uncertainty and delivery of early life-saving treatment.

Thus there is a rationale within the natural history of acute PTE, that natriuretic peptides may be released with increasing right ventricular afterload, associated with significant territory occlusion of the vascular bed. This is supported by the finding of isolated case reports of elevated BNP levels in patients with PTE\(^7\) and the finding of increased mortality with raised BNP levels for those with acute pulmonary embolism.\(^8\) We hypothesised that natriuretic peptides may rise in PTE and in addition, provide a rapid, early indicator of the risk of associated right ventricular dysfunction and death.

Patients and methods

Subjects

One hundred and fourteen unselected, consecutive patients (age range 20–91 years) undergoing investigation for suspected pulmonary embolism were recruited into the study over 3 months. The Tayside Committee for Medical Research Ethics approved the study and all patients gave informed written consent prior to inclusion. All eligible patients were referred by their primary physician with clinical suspicion of PTE for investigation at their local teaching hospital. Patients were not excluded from the study even with conditions known to independently increase natriuretic peptides such as left ventricular dysfunction. Many of these conditions are independent risk factors for PTE mortality and exclusion may therefore have introduced selection bias. Therefore, echocardiography was not performed in our patient population as a routine investigation primarily to prevent such selection bias and to include a representative cohort of patients referred with suspected PTE.

Patient characteristics are shown in Table 1.
Radionuclide scan

Each patient underwent radionuclide scanning in the investigation of PTE in addition to other diagnostic modalities. The same experienced radiologist, blinded to the values of natriuretic peptides, reported all radionuclide scans. On completion each scan was classified into one of three validated groups (normal, high, and a third group including patients with a low or intermediate probability of Pte) according to the findings of the PIOPED study.9,10

Natriuretic peptide assay

Venous blood was taken in the prone position at the same time as the perfusion scan was performed, prior to injection of Tc labelled MAA. ANP, brain natriuretic peptide (BNP) and N-terminal pro atrial natriuretic peptide (N-ANP) levels were assessed by radioimmunoassay (Peninsula Laboratories, St. Helens, UK).

Data analysis

The individual data points for levels of natriuretic peptides in patients with normal, high probability and low/intermediate probability scans are represented in dot plots. Comparisons between these groups were made using the non-parametric Kruskal–Wallis test. Comparisons between levels of natriuretic peptides in patients with high probability scans who were alive on discharge or died during their hospital admission were made using the non-parametric Mann–Whitney U-test. A two tailed probability of \( P < 0.05 \) was considered to be statistically significant. Values are quoted as median and interquartile ranges.

Results

The study group consisted of 114 consecutive patients who underwent radionuclide scanning. Of these, 20 were reported as normal, 77 as representing low or intermediate probability of pulmonary embolism and 17 representing a high probability of PTE. All patients with high probability scans according to PIOPED criteria also had a clinical diagnosis of PTE and were anticoagulated.

Figure 1 demonstrates the results of natriuretic peptide assay in patients with normal, intermediate and high probability scans. Values are quoted for the median and interquartile ranges. There were statistically significant differences between groups for levels of (a) BNP \( (P < 0.001) \): \( N = 6.7 \text{ pmol/l (5.6–11.9)} \), \( L/I = 12.5 \text{ pmol/l (6.7–28.2)} \) and \( H = 18.5 \text{ pmol/l (12.6–74.6)} \); (b) ANP \( (P < 0.005) \): \( N = 12.6 \text{ pmol/l (7.1–16.0)} \), \( L/I = 19.51 \text{ pmol/l (12.5–28.2)} \) and \( H = 19.1 \text{ pmol/l (15.7–31.7)} \) and (c) N-ANP \( (P < 0.05) \): \( N = 177 \text{ pmol/l (119–200)} \), \( L/I = 302 \text{ pmol/l (152–576)} \) and \( H = 322 \text{ pmol/l (223–563)} \).

There were three deaths in the study, each with a high probability radionuclide scan. Levels of BNP and ANP were significantly \( (P < 0.05) \) higher in patients with high probability scans who died from pulmonary embolism than in those who survived; BNP: 91.6 pmol/l (77.5–336.2) vs. 14.4 pmol/l (11.9–27.4) and ANP: 32.5 pmol/l (21.7–105.5) vs. 17.6 pmol/l (15.2–19.3) (Fig. 2).

Discussion

This study is the first to report elevated levels of the natriuretic peptides ANP, BNP and N-ANP in patients with high probability of PTE on radionuclide scanning. In addition, we have
demonstrated a significant relationship between elevated levels of ANP and BNP in patients with high probability scans and a clinical diagnosis of PTE who died compared to survivors.

Natriuretic peptides are thought to be released as a consequence of a stretch coupling mechanism and are elevated in a number of conditions characterised by elevations in left and right atrial and ventricular pressures such as left ventricular failure, hypoxaemic cor pulmonale and primary pulmonary hypertension. It is also known that acute hypoxia is a potent stimulus to ANP but not BNP secretion and the hypoxaemia seen in patients with pulmonary embolism may have contributed to elevated levels of ANP. We have also shown that levels of the inactive N-terminal portion of the 126 amino acid prohormone of ANP, N-ANP are elevated. The natriuretic peptides may be released in an attempt to improve haemodynamic
function by triggering vasodilatation and natriuresis.\textsuperscript{15,16} Previously there have been reports of elevated plasma BNP associated with acute pulmonary embolism in patients with RV dysfunction;\textsuperscript{8,17} ANP and BNP levels are also elevated in asymptomatic patients with chronic right ventricular pressure overload caused by congenital heart disease.\textsuperscript{18}

As well as the finding of elevated levels of ANP, BNP and N-ANP in patients with high probability of PTE, there is a progressive incremental rise in natriuretic peptide levels with increasing degrees of ventilation-perfusion mismatch within the lung, suggestive of a direct relationship between perfusion defects and release of natriuretic peptide. The levels of ANP, BNP and N-ANP all correlate strongly together in subjects with suspected pulmonary embolism, supportive of the notion that the development of ventilation-perfusion defects stimulates natriuretic peptide release from the myocardium by cardiac myocyte stretch.

The patients who died with pulmonary embolus had significantly elevated levels of natriuretic peptides compared to survivors. Levels of BNP in patients with high probability scans who died were 15–100 times greater than the upper limit of normal. BNP release from the right ventricle\textsuperscript{5} in PTE may aid early risk stratification, given that BNP can be assayed rapidly in the emergency department\textsuperscript{19} and acute right ventricular dysfunction is a major determinant of outcome of acute PE in hospital.\textsuperscript{20} Indeed, RV dysfunction defined echocardiographically has recently identified a group of patients with an adverse prognostic risk likely to benefit from thrombolysis.\textsuperscript{6,21} The finding of a statistically significant increase in mortality associated with high BNP levels leads to the speculation that higher BNP levels are therefore associated with an increased risk of death though admittedly the numbers of deaths in the study group were small. For those with major pulmonary emboli and haemodynamic compromise mortality is greatly elevated with the majority of deaths occurring within the first hour of presentation requiring optimal diagnosis and therapy within one hour.\textsuperscript{22}

We speculate that since BNP measurement is rapidly available and non-invasive, it may be a useful tool in the risk stratification of patients with suspected pulmonary embolus.

This study is limited primarily by the diagnostic tool commonly used in the diagnosis of PTE namely, ventilation-perfusion (V/Q) scanning. It seems reasonable to suppose that in those with a high pre-test clinical probability of PTE, combined with a high probability V/Q scan had pulmonary emboli according to validated criteria from the PIOPED study. The PIOPED study demonstrated that for patients with normal or high probability lung scans, a diagnosis of PTE can be refuted or confirmed with a high degree of probability, and that these probabilities can be refined further by using clinical probabilities. In patients with low or intermediate probability lung scan results V/Q scanning is much less helpful and clinical probabilities become more useful, we have categorised this group as a single cohort “intermediate probability”. Due to inaccuracies in the phenotype of this group (who are likely to contain patients with and without PTE) due to assumptions regarding clinical diagnosis given by the individual clinicians for these patients, with or without performing further investigation, we have not tried to characterise these patients further. Fig. 1 demonstrates that for normal probability scans that there is a large spread of values suggesting that the test is not specific enough to obviate the need for additional investigation for PTE.

What are the possible clinical applications of our results? Measurement of natriuretic peptides such as BNP may aid clinical decision making in diagnosis and rapid risk stratification of PTE. Natriuretic peptide levels may also help identify differential diagnoses such as left ventricular failure\textsuperscript{3,4} in which there is an increased mortality associated with the development of acute PTE.\textsuperscript{23} This pilot study suggests that further work is required to establish the utility of this peptide family in PTE and whether it will help to reduce excess mortality in a previously unidentified high-risk group.

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References

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