Cardiac biomarkers levels predict pulmonary embolism extent on chest computed tomography and prognosis in non-massive pulmonary embolism

VUILLEUMIER, Nicolas, et al.
Cardiac biomarkers levels predict pulmonary embolism extent on chest computed tomography and prognosis in non-massive pulmonary embolism

Nicolas Vuilleumier1; Arnaud Perrier2; Jean-Charles Sanchez3; Natacha Turck3; Grégoire Le Gal4; Frank Verschuren5; Damien Gruson6; Noury Mensi1; Denis Hochstrasser1; Marc Righini7

1Division of Laboratory Medicine, Department of Genetics and Laboratory Medicine, Geneva University Hospitals and University of Geneva, Switzerland; 2Division of General internal Medicine, Department of Internal Medicine, Geneva University Hospitals and University of Geneva, Switzerland; 3Department of Structural Biology and Bioinformatics, Biomedical Proteomic Research Group, University Medical Centre of Geneva, Switzerland; 4Department of Medicine and Chest Diseases; EA 3878 (GETBO), Brest University Hospital, Brest, France; 5Emergency Department, Saint-Luc University Hospital, Brussels, Belgium; 6Department of Laboratory Medicine, Saint-Luc University Hospital, Brussels, Belgium; 7Division of Angiology and Haemostasis, Geneva University Hospitals and University of Geneva, Switzerland

Dear Sir,

Cardiac biomarkers, such as cardiac troponin I (cTnI), N-terminal proBrain Natriuretic Peptide (NT-proBNP), heart-type fatty acid binding protein (H-FABP) and myoglobin have all been described as emergent prognostic markers in pulmonary embolism (PE) (1–3), but, their potential association with anatomical PE clot localisation, a controversial prognostic feature in PE (4, 5), has not yet been reported. We also investigate whether combining the anatomical clot localisation with elevated levels of NT-proBNP and cTnI, recently reported as the most promising biomarkers for outcome prediction in non-massive PE (2), could yield incremental prognostic information in non-massive PE.

Data of the current study are derived from a subgroup analysis involving three out of five tertiary university hospitals involved in an international prospective multicentric study recently published elsewhere (6). Briefly, 166 patients had proven PE on multi-detector-row chest computed tomography (CT) or pathological lower limb ultrasonography. Herein, we studied only the 110 patients (48 men, 62 women, median age: 72 years, range: 21–92) with proven non-massive PE on multi-detector-row chest CT. All patients completed a three-months follow-up, and the composite outcome consisting in need for intensive care monitoring-operating curve (ROC) analyses were performed using Statistica™ software. A p-value <0.05 was considered as significant.

For continuous variables (expressed as median and range), Kruskal-Wallis rank test was used to assess differences between the three PE anatomical groups (central, lobar and segmental). Bilateral Fischer Exact test for proportion was performed for nominal variables. Univariate odds ratios (OR) with corresponding 95% confidence intervals (95%CI) were used to determine the association between three-months outcome and central PE localisation using logistic regression. Analyses were performed using Statistica™ software (StatSoft, Tulsa, OK, USA). Receiving-operating curve (ROC) analyses were performed using Analyse-It™ software. A p-value <0.05 was considered as significant.

Overall, median values of cardiac biomarkers were 0.02 ng/ml (range: 0–0.85) for cTnI, 527 pg/ml (5–18842) for NT-proBNP, 2.95 ng/ml (0.37–28.8) for H-FABP, and 27 ng/ml for myoglobin (6.3–133.3). Upon admission, 28 patients (26%) had central PE, 42 (38%) had lobar PE, and 40 (36%) had segmental PE. The composite outcome was met by 12 patients during three months follow-up (Deaths: 2, relapse TE event: 5, major haemorrhagic complication: 1, intensive care unit [ICU] monitoring upon admission: 2, admission for dyspnoea with or without chest pain: 2). Patients with central PE had significantly higher levels of cTnI, NT-proBNP and H-FABP, than patients with lobar, or segmental PE localisation, but no such difference was obtained for myoglobin (Table 1). Among patients with central PE (n=28), 86% (24/28) had elevated NT-proBNP values and 60% (17/28) had elevated cTnI values, whereas 5% (4/82) of patients with more distal PE had elevated NT-proBNP (<300 pg/ml) and 11% (9/82) elevated cTnI value. Those differences were significant (p<0.00001).

Spearman correlation showed a significant association between PE localisation and circulating levels of all cardiac biom-
Markers (the more proximal the lesion, the higher the plasmatic biomarker levels), but the strength of association was higher for cTnI and NT-proBNP (r=0.44, p<0.01; and r=0.40, p<0.01, respectively), than for myoglobin (r=0.22, p=0.05) and the association was not significant for H-FABP and r=0.18, p=0.05; respectively). ROC curve analyses showed that all cardiac biomarkers could significantly discriminate between central and non central PE, but cTnI and NT-proBNP were the most discriminatory tests with areas under the curve (AUC) of 0.81 (95%CI: 0.72–0.90; p<0.0001) and 0.77 (95%CI: 0.68–0.88; p<0.0001), respectively, compared to 0.69 (95%CI: 0.58–0.80; p=0.0003) for H-FABP and 0.62 (95%CI: 0.5–0.75; p=0.027) for myoglobin. The AUC were significantly different between myoglobin and cTnI (r=0.22, p<0.05) but not between the other biomarkers.

Logistic regression showed a trend to an increased risk in patients with central PE, although not statistically significant (Table 1). On the other hand, having elevated NT-proBNP or cTnI increased the risk of three-months complications by 10.6- and 3.9-fold, respectively (Table 1). Combined with central PE localisation, elevated NT-proBNP and cTnI conferred a three-months risk of complications by 11.4- and 5.1-fold, respectively (Table 1).

The current study results support an association between the degree of vascular obstruction, elevation of cardiac biomarkers and poor prognosis in PE. We assume that the herein reported associations reflect the various degrees of right myocardial strain varying upon the importance of pulmonary blood flow obstruction, which in our study was significantly affected by the clot anatomical localisation. The reasons why those associations were stronger for cTnI and NT-proBNP compared with H-FABP and myoglobin are unclear. However, those results corroborate previous studies showing that mostly natriuretic peptides (and to a less extent cTnI) were correlated with right ventricular dysfunction (8, 9) and predictive of poor prognosis in PE (2). Altogether, these observations suggest that significant prognostic differences can be expected among the various cardiac biomarkers currently under investigation as risk stratification tool in PE. These findings extend to NT-proBNP and cTnI prior observations showing that D-dimer elevation reflected the degree of vascular obstruction and prognosis in PE (10–11).

Central PE localisation was not a significant prognostic factor in this study, although we did see a trend in that direction. This is most probably due to the small patient sample. Also, our results indicate that combining the anatomical clot localisation with an elevated level of NT-proBNP did not add any incremental prognostic value when compared to NT-proBNP alone. On the other hand, combining cTnI with central clot localisation provided a marginal increment of cTnI prognostic value. This may be due to the closer link between right ventricular dysfunction (RVD), clot burden (higher in central PE) and NT-proBNP elevation. Since NT-proBNP appears highly sensitive for RVD, it is not unexpected that clot localisation does not increase predictive accuracy.

Besides the small size of our study sample, one limitation is that we chose to use a simplified version of the CT pulmonary angiography (CTPA) index proposed by Ghanima (7), instead of

### Table 1: Median biomarker values according to pulmonary embolism (PE) localisation on chest CT.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Median Value</th>
<th>IQR</th>
<th>Range</th>
<th>Odds Ratio (univariate)</th>
<th>95% Confidence interval</th>
<th>**P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP; pg/ml</td>
<td>1380</td>
<td>552–6969</td>
<td>160–1884</td>
<td>Central vs Lobar</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cTnI; ng/ml</td>
<td>0.1</td>
<td>0.04–0.24</td>
<td>0.007–0.85</td>
<td>Central vs Lobar</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>H-FABP; ng/ml</td>
<td>4.2</td>
<td>2.3–6</td>
<td>0.4–29</td>
<td>Central vs Lobar</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Myoglobin; ng/ml</td>
<td>36</td>
<td>22–57</td>
<td>8–126</td>
<td>Central vs Lobar</td>
<td>0.38</td>
<td>0.08</td>
</tr>
</tbody>
</table>

## Outcome prediction according to PE clots localisation, elevation of cTnI and NT-proBNP, alone and in combination with PE clot localisation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (univariate)</th>
<th>95% Confidence interval</th>
<th>**P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central PE</td>
<td>3.5</td>
<td>1–11.8</td>
<td>0.07</td>
</tr>
<tr>
<td>NT-proBNP +</td>
<td>10.6</td>
<td>1.3–84.4</td>
<td>0.003</td>
</tr>
<tr>
<td>cTnI +</td>
<td>3.9</td>
<td>1.1–13.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Central PE and NT-proBNP +</td>
<td>4.4</td>
<td>1.3–15.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Central PE and cTnI +</td>
<td>5.1</td>
<td>1.4–18.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>
the other ones available to determine the clot burden (8–10). However, as all CTPA scoring systems are still under investigation and need to be validated (11), we chose the approach proposed by Ghanima, because of its more intuitive way of classifying the anatomical localisation of the clot (central, lobar or segmental) for non-radiologists. Furthermore this index has been shown to correlate with the degree of vascular obstruction (7) and RVD upon echocardiography (16).

In conclusion, our results combined with existing data in literature suggest that the elevation of cTnl and NT-proBNP in PE not only predicts the clinical severity of PE, but also its radiological severity. Furthermore, our results indicate that in presence of elevated NT-proBNP levels, the angiographic PE extent does not add any incremental prognostic information to the one obtained for NT-proBNP only, further suggesting that this peptide could be the strongest biochemical predictor in non-massive PE.

References