CLINICAL RESEARCH

Diagnostic accuracy of quantitative heart-fatty acid binding protein assays compared with Cardiodetect® in the early detection of acute coronary syndrome

Performance de l’heart-fatty acid binding protein quantitative comparée au Cardiodetect® pour le diagnostic précoce de syndrome coronaire aigu

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Summary

Background. — Heart-fatty acid binding protein (h-FABP) has been proposed as a cardiac marker for the early detection of acute coronary syndrome (ACS). In a study of 677 patients admitted to the emergency department (ED) for chest pain, we found that a semiquantitative point-of-care test that detects h-FABP (Cardiodetect® ) had low sensitivity for the prediction of ACS.

Objective. — The aim of this ancillary study was to analyze and compare the performance of h-FABP for early ACS diagnosis in this large cohort of unselected patients, using a quantitative immunoassay and Cardiodetect®.

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; cTnI, cardiac troponin I; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; h-FABP, heart-fatty acid binding protein; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; ROC, receiver operating characteristic; STEMI, ST-segment elevation myocardial infarction.

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h-FABP assays compared with Cardiodetect®

Background

The diagnosis of acute coronary syndrome (ACS) in unsolicited chest pain patients presenting to the emergency department (ED) remains challenging for physicians [1,2]. Besides the new highly sensitive troponin assays, very early biomarkers of cardiac damage, such heart-fatty acid binding protein (h-FABP), may prove to be diagnostically superior [3,4]. Point-of-care tests have been developed to make an early ACS diagnosis [5]. We recently reported that the semiquantitative assay of h-FABP (Cardiodetect®) predicted ACS diagnosis with high specificity (96.8%) but low sensitivity (13.5%) in a prospective study of 677 consecutive patients admitted to our ED for chest pain [6]. This test did not provide significant incremental information to a predictive model that included the usual tools for non-ST-segment elevation ACS management. A better h-FABP performance for ACS diagnosis was found with a quantitative assay in a selected population for ACS risk [4]. We hypothesize that the low performance of h-FABP found in our population was related to the semiquantitative assay used.

The aim of this study was, therefore, to analyze and compare the performance of h-FABP for early ACS diagnosis in this large cohort of unsolicited patients, using a quantitative immunoassay and the semiquantitative Cardiodetect® assay.

Methods

Study design

This was an ancillary study of a large, prospective, single-centre study of diagnostic accuracy, published recently [6].

References

This second analysis was done retrospectively. The institutional review board approved the study protocol.

**Study setting and population**

The study was carried out at a large urban university hospital as previously described [6]. Briefly, 677 patients admitted to the ED with chest pain evolving within 12 hours and suspected of having ACS were included by the emergency treating physician. Patients with ST-segment elevation on a 12-lead electrocardiogram were excluded. Patients signed informed written consent before inclusion in the main study, for the main study, for the serum bank and for analysis of the sample from the serum bank to study new biomarkers in the context of ACS.

**Study protocol**

After obtaining written consent, the clinical history, physical evaluation, serial 12-lead electrocardiogram, standard blood tests, cardiac troponin I (cTnI) measurements and chest X-rays were performed for all patients according to the usual procedures and reported on a case report form by the treating physician. After 1 month, major cardiac events, including death, admission to hospital for ACS and the results of the cardiovascular diagnostic tests carried out during the 30 days after ED discharge, were collected by the research assistant. The diagnosis of ACS, based on current international guidelines, was made by two independent experts as previously described [6]. Patients with ACS were classified as having non-ST-segment elevation myocardial infarction (NSTEMI) when the cTnI was above 0.1 μg/L on serial testing.

**Study measurements**

Serial plasma samples were collected shortly after ED admission, and were immediately centrifuged. cTnI concentrations were measured immediately on an Advia Centaur TnIc system (Bayer Diagnostics, Leverkusen, Germany) (99th percentile at 0.1 μg/L) at admission and after 6 hours.

Plasma samples at admission were frozen at −80°C and the h-FABP assays were performed a few months later. The h-FABP enzyme-linked immunosorbent assay (ELISA) test was based on the principle of a ready-to-use, solid-phase ELISA (HyCult Biotech, Uden, The Netherlands). The acute myocardial infarction (AMI) cut-off concentrations reported in other studies were between 5 and 7.3 ng/mL [7—9]. Measurement of the h-FABP ELISA test was performed by the biologist, who was blinded to the Cardiodetect® results and to the final diagnosis. Data analysis of the performance of the quantitative h-FABP was performed blinded to the performance of Cardiodetect®.

**Data analysis**

Baseline characteristics were assessed using Student’s t test or the Mann-Whitney U test for continuous variables and the Khi² test for categorical variables. P values less than 0.05 were taken as significant. Receiver operating characteristic (ROC) curves were used to evaluate the performance of the ELISA h-FABP assay for the final diagnosis of ACS and NSTEMI. The cut-off level of 7 ng/mL was used to assess clinical sensitivity and specificity. Classification agreement of the two tests (ELISA h-FABP and Cardiodetect®) for the cut-off value of 7 ng/mL was examined using the kappa test.

To assess if plasma h-FABP levels provided additional information beyond the criteria usually used for ACS diagnosis, we compared the model with the usual immediately available data for the diagnosis of ACS as described previously and a model with the h-FABP values in addition to the previous variables. The usual available data were: age, sex, cardiovascular risk factors (smoking status, hyperlipidaemia, diabetes, family history of ischaemic heart disease, hypertension), previous coronary artery syndrome, clinical presentation with persistent chest pain, ischaemic electrocardiogram abnormalities and cTnI measurement on admission. A likelihood ratio test was carried out between both models and the accuracy of each was calculated for a cut-off at 0.5.

**Results**

Among 677 consecutive patients (454 men, 223 women, mean age 57 ± 17 years) included in the study, non-ST-segment elevation ACS was diagnosed in 185 patients (27.3%) including 99 NSTEMIs (53.5%). The classification agreement between the experts for ACS status measured by the kappa test was 0.71. Baseline characteristics of the patients are reported Table 1.

The median h-FABP level was significantly higher in patients with ACS (1.36 μg/L, interquartile range [IQR] 0.59—3.55) and with NSTEMI (2.25 μg/L, IQR 0.74—7.36) than in patients with a diagnosis of non-ischaemic chest pain (0.58 μg/L, IQR 0.24—1.34; P < 0.01).

The area under the curve was 0.68 (95% confidence interval [CI] 0.63—0.73) and 0.74 (95% CI 0.69—0.80) for ACS and NSTEMI diagnosis, respectively (Fig. 1). For the cut-off level at 7 ng/mL, the performances of h-FABP for ACS and NSTEMI diagnoses were reported (Table 2). The h-FABP sensitivities were 15.7% (95% CI 12.9—18.4) and 26.3% (95% CI 22.9—29.6)

![Figure 1. Receiver operating characteristic (ROC) curves of heart-fatty acid binding protein (h-FABP) for acute coronary syndrome diagnosis. CI: confidence interval.](image-url)
Table 1  Baseline characteristics of the patient group based on the diagnosis of non-ST-segment elevation acute coronary syndrome.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute coronary syndrome</th>
<th>Non-ischaemic chest pain</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>185 (27.3)</td>
<td>492 (72.7)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.3 ± 15.3</td>
<td>53.7 ± 15.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Men</td>
<td>125 (67.6)</td>
<td>329 (66.9)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 (21.1)</td>
<td>46 (9.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>106 (57.3)</td>
<td>163 (33.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smokers</td>
<td>36 (19.6)</td>
<td>160 (32.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>71 (38.6)</td>
<td>132 (27.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>121 (65.8)</td>
<td>164 (33.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>63 (34.2)</td>
<td>147 (30.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>103 (55.7)</td>
<td>103 (20.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 ± 4.6</td>
<td>26.0 ± 4.9</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Delay from chest pain to management (minutes)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to inclusion</td>
<td>150 (90—230)</td>
<td>132 (84—240)</td>
<td>0.61</td>
</tr>
<tr>
<td>Time to blood taking</td>
<td>176 (104—260)</td>
<td>170 (104—270)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Total duration of chest pain (minutes)</strong></td>
<td>90 (45—180)</td>
<td>79.5 (30—180)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

**Admission presentation**

| Persistent chest pain           | 79 (47.3)               | 207 (47.5)               | 0.97  |
| ECG abnormalities               | 64 (34.6)               | 47 (9.6)                 | < 0.001 |
| Elevated troponin              | 55 (28.9)               | 8 (1.63)                 | < 0.001 |

**Markers**

| Quantitative h-FABP (μg/L)      | 1.36 (0.59—3.55)        | 0.58 (0.24—1.34)         | < 0.01 |
| Elevated quantitative h-FABP (cut-off 7 μg/L) | 29 (15.7)              | 14 (2.9)                 | < 0.001 |
| Elevated h-FABP (Cardiodetect®) | 25 (13.5)               | 16 (3.25)                | < 0.001 |

Data are mean ± standard deviation, median (interquartile range) or number (%). The body mass index is the weight in kg divided by the square of the height in metres. ACS: acute coronary syndrome; CAD: coronary artery disease; ECG: electrocardiogram; h-FABP: heart-fatty acid binding protein.

and the specificities were 97.2% (95% CI 95.9–98.4) and 97.1% (95% CI 95.8–98.3) for the ACS and NSTEMI diagnoses, respectively. The initial cTnI sensitivity and specificity for NSTEMI diagnosis were 56.1% (95% CI 52.4–59.9) and 98.6% (95% CI 97.7–99.5), respectively. When added to the model that used the usual immediately available data in the ED for ACS or NSTEMI diagnosis, h-FABP did not significantly improve the performance of this model (odds ratio 0.92, 95% CI 0.32–2.70 for ACS; odds ratio 0.89, 95% CI 0.22–3.63 for NSTEMI).

The concordance of the results obtained with Cardiodetect® and the h-FABP quantitative assay using a cut-off level of 7 ng/mL was studied. We found that 611 patients (90.2%) were negative with both assays, 18 (2.7%) were positive with both assays and 48 (7.1%) were positive

Table 2  Performances of heart-fatty acid binding protein for diagnosis of acute coronary syndrome and non-ST-segment elevation myocardial infarction for a cut-off level at 7 ng/mL.

<table>
<thead>
<tr>
<th></th>
<th>ACS</th>
<th>NSTEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>15.7 (12.9—18.4)</td>
<td>26.3 (22.9—29.6)</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.2 (95.9–98.4)</td>
<td>97.1 (95.8–98.3)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>5.5</td>
<td>8.9</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.87</td>
<td>0.76</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>67.4 (63.9—71.0)</td>
<td>60.5 (56.8—64.2)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>75.4 (72.2—78.6)</td>
<td>88.5 (86.1—90.9)</td>
</tr>
</tbody>
</table>

Data are % (95% confidence interval), unless otherwise indicated. ACS: acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction.
onset but half of the AMI patients had STEMI [10]. In a recent publication, h-FABP sensitivity was measured at 64% for patients with chest pain within 3 hours of symptom onset but half of the AMI patients had STEMI [10]. In our study, only 14.6% of NSTEMI were diagnosed. Our patients had less myocardial damage and it is known that minor myocardial damage releases low amounts of h-FABP into the circulation and the sensitivity of the test is decreased in these situations [11,12]. Glatz et al. showed that h-FABP was a marker for the estimation of the size of a myocardial infarct in patients with STEMI diagnosis [12]. In a recent study, Haltern et al. confirmed that the discriminative value of h-FABP was poor in patients with NSTEMI and that the ROC curve was close to the diagonal [7].

Another explanation of the difference compared with other studies is the role of the reference standard used in previous studies. In a recent systematic review and meta-analysis of 16 studies, the overall sensitivity and specificity of h-FABP for AMI diagnosis were 84% (95% CI 76—90) and 84% (95% CI 76—89), respectively [13]. The authors reported in a covariate analysis that the use of troponin instead of creatine kinase as a reference standard for AMI had a significant impact on sensitivity. The sensitivity of h-FABP in studies using troponin (0.76 95% CI 0.67—0.84) was significantly lower than in those that did not use troponin as a reference standard (0.91 95% CI 0.84—0.95). The authors concluded that h-FABP used alone does not allow safe and early diagnosis of AMI. The use of a more highly sensitive troponin assay should further decrease the accuracy of h-FABP. A recent study showed that the area under the curve of sensitive troponin I (0.91) was higher than that of h-FABP (0.86) in the early hours of ACS [14].

Beyond the poor performance of h-FABP, we confirmed that h-FABP did not provide incremental information in addition to the clinical features used for ACS diagnosis in an ED.

**Study limitations**

The major limitations were reported in the previous article [6]. The classification agreement between the experts was not perfect because a diagnosis of unstable angina is difficult to make in an ED. However, the performance of h-FABP for the diagnosis of NSTEMI diagnosis was also poor.

**Conclusion**

In this study, we confirmed that the performance of h-FABP assays was insufficient for it to be used as a marker for the diagnosis of ACS and NSTEMI in an ED, whatever the analytical technique used. h-FABP did not provide useful information for ACS diagnosis in patients admitted to an ED with chest pain.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**Acknowledgments**

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**References**


