Diagnostic and prognostic value of H-FABP in acute coronary syndrome: Still evidence to bring

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ABSTRACT

The assessment of chest pain patients presenting to the emergency area (EA) is still a clinical challenge, as the majority of patients are not diagnosed with acute coronary syndrome (ACS). New generation high sensitivity c-Tn (hs-cTn) assays have showed better performances compared to the standard c-Tn. However, hs-Tn still presents some limitations. Hence, novel, early biomarkers are needed in this setting. Among all, heart-type fatty acid binding protein (H-FABP) has been largely investigated. This article reviews the studies evaluating H-FABP performance in diagnosing acute myocardial infarction (AMI) and stratifying chest pain patients by risk. H-FABP optimal performances in ACS have been reported by studies that used low threshold for positivity, or compared the biomarker to cTn at 3–6 h, or by studies with small sample size. Literature review allows stating that H-FABP is clearly not a reliable marker in ACS, as it is unable to diagnose AMI, neither as a stand-alone test nor combined with hs-cTn. Few evidence supports its incremental value in ruling-out AMI and its risk stratification ability for chest pain patients presenting to EA. Thus, available data may not encourage going on investigating.

1. The state of the art

Acute coronary syndrome (ACS) is a clinical spectrum encompassing ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina (UA) and its main symptom is chest pain. The assessment of chest pain patients attending the emergency area (EA) is a clinical challenge [1], as the majority of patients are not diagnosed with ACS [2]. Diagnostic tools include history, electrocardiography (ECG) and biomarkers. Among these, cardiac Troponins (cTn) are considered as a cornerstone for the acute myocardial infarction (AMI) diagnosis [3]. New generation high sensitivity c-Tn (hs-cTn) assays have showed better performances compared to the standard c-Tn [4]. However, hs-Tn still presents some limitations [5]. Hence, novel, early biomarkers are needed in this setting.

Several biomarkers including brain natriuretic peptide (BNP), Copeptin, ST2, growth differentiation factor 15 (GDF 15), Adiponectine, Galactin-3, IL16, asymmetric dimethylarginine (ADMA), and heart-type fatty acid binding protein (H-FABP) have been considered as a potential aid to the diagnosis, either alone or combined with standard cTn and hs-cTn [6–13]. Among all these biomarkers, H-FABP has been largely investigated. It is a small (15 kDa) soluble protein, present at high concentrations in cardiomyocytes cytoplasm [14]. It is rapidly released into plasma after the onset of myocardial injury, with the peak occurring approximately 6–8 h later [15].

1.1. Hs-cTn diagnostic gaps

Actually, undetectable hs-cTn in a single blood specimen collected on presentation does not allow a safe discharge. Thus, recurrent tests are required to correctly rule-in or safely rule-out AMI [16]. Indeed, the first limitation of hs-cTn could be identified in its late rise, peaking at 10–13 h after AMI [5]. Secondly, hs-cTn also presents suboptimal specificity [17], leading to inappropriate hospitalization of patients with false-positive results. This causes the overcrowding of EA and the rising cost of healthcare.

In order to stratify chest pain patients by risk within EA, several accelerated diagnostic pathways (ADPs) [18–21] and risk assessment algorithms [22–24] have been developed, either using troponin alone [23,25–29] or combining it with other biomarkers, such as H-FABP and copeptin [7,22,24,30–32].

2. Studies addressing H-FABP in chest pain patients

2.1. Pitfalls in studying H-FABP

Although H-FABP has been deeply investigated in chest pain...
patients, results are controversial and complex to interpret, because of the pitfalls emerged from the studies evaluating H-FABP in these patients:

- Studies have shown heterogeneity in terms of clinical features of the enrolled patients, timing of presentation from the onset of pain and positivity thresholds.
- Observational studies have been predominantly carried out [33–38]. In order to assess the clinical utility of any biomarkers, randomized trials are needed, since these evaluate the real impact of measuring a biomarker instead of a conventional one within an established diagnostic pathway [39].
- The influence of some demographic and clinical variables, such as age and renal function, on H-FABP plasma levels has been not fully investigated [34,40]. With few exceptions [41], chest pain patients were mostly enrolled without considering their renal function, except for those who needed dialysis treatment.

Furthermore, it should be taken into consideration that H-FABP is not fully cardiac-specific, since other tissues such as skeletal muscle, brain and kidney produce it, although at a lower concentrations than in the myocardium [42]. Table 1 summarizes pros and cons of H-FABP in ACS.

Having said this, the most relevant studies can be summarized as follows.

2.2. Ruling-in, ruling-out AMI and risk stratification strategies

In the sub-study of the POCT arm of the Randomized Assessment of Panel Assay of Cardiac Markers Trial (RATPAC Trial), Collinson et al. [43] measured cTnT, hs-TnT, Copeptin and H-FABP in 850 low-risk chest pain patients with non-diagnostic ECG. Samples have been collected on admission and 90 min later. The Authors concluded that on admission simultaneous determination of H-FABP and hs-cTnT achieved lower sensitivity compared to the one reached by cTnT at presentation and 90 min later. (Area Under the Curve [AUC]: 0.92 vs 0.94, respectively). Although the Authors found that on admission H-FABP was more accurate compared to its peak (AUC: 0.84 vs 0.82), they concluded that hs-cTnT showed higher diagnostic performance. Even classifying patients according to the duration of pain into < 3 and < 6 h groups, H-FABP diagnostic accuracy was lower as compared to hs-cTnT. (AUC: 0.84 vs 0.92, respectively). It is important to underline that the Authors stated that dividing patients according to the duration of pain improved H-FABP diagnostic performance. However, it should be noted that these were low-risk patients, which may be not representative of every chest pain patient attending EA.

In the same years, Reiter [44] carried out a prospective, multicenter study on 1074 consecutive patients attending the EA within 12 h following the onset of acute chest pain. The Authors found that H-FABP did not improve hs-cTnT diagnostic accuracy (AUC: 0.88 combined vs 0.94 hs-cTnT alone). Moreover, Reiter reported that H-FABP is not able to discriminate UA from non-cardiac causes of chest pain (AUC: 0.57).

Kilcullen obtained significant evidence [37] thanks to the prognostic study conducted on 1448 patients at high-risk of ACS. The all-cause 1-year mortality was 2.1% in patients having H-FABP < 5.8 µg/L, compared to 22.9% in those having H-FABP > 5.8 µg/L (HR: 11.35). Clearly, Kilcullen cohort is quite different from a patient population attending EA with chest pain of unknown origin, which makes it difficult to compare findings. Furthermore, Kilcullen suggests that H-FABP provides additional information to the Global Registry of Acute Coronary Events (GRACE) risk score [45], but it should be noted that GRACE score is a nearly outdated risk score that may not be proper to identify patients suitable for discharge [46].

In 2014 Body et al. derived and validated a clinical decision rule (CDR) including 6 clinical variables and 2 biomarkers (hs-TnT and H-FABP) [22,23]. The Manchester Acute Coronary Syndrome (MACS) rule had an AUC of 0.96 for the diagnosis of AMI and it showed 0.0% missing AMI among patients classed as “very low-risk”. However, MACS re-derivation algorithm only included hs-TnT, as the result of H-FABP assays reduced availability. It should be noted that patients were believed having chest pain of cardiac origin by the treating physician up to 24 h before the presentation to the EA. It is right to consider that these are not representative of chest pain patients attending the EA; moreover, it is difficult to evaluate an early biomarker at 24 h after the onset of pain.

Dupuy [34] showed that H-FABP made a small contribution in ruling-out AMI combined with hs-TnT (AUC: 0.86 combined vs 0.85 hs-TnT alone), and its diagnostic accuracy was lower than hs-TnT (AUC: 0.79 vs 0.85, respectively). All these aspects led Dupuy to state that H-FABP is not a reliable marker for AMI diagnosis. Moreover, the Authors pointed out that H-FABP best diagnostic performance was reached at 3–6 h following symptoms. Kitamura [47] also analysed chest pain patients population based on the time of presentation to EA, finding out that H-FABP best performance over hs-cTnT was reached within 2 h (AUC: 0.69 [H-FABP vs 0.48 hs-TnT]). Conversely, after having stratified his population according to the time of presentation, Shoenenberger [48] documented that H-FABP was not able to outperform hs-cTnT in those who attended the EA earlier (< 1 h) (0.83 for H-FABP vs 0.90), as Collinson [43] reported too.

In 2016 Young assessed whether H-FABP can contribute to correctly identify low-risk patients better than hs-cTn [33]. The Authors determined the optimum combination of H-FABP, hs-cTn and ECG, in order to maximize low-risk patients proportion whilst maintaining a minimum sensitivity of 99%. The best reported combination of H-FABP, troponins and ECG was obtained using a ROC-derived threshold at 3.0 µg/L and reached 98% sensitivity, while an acceptable adverse event rate < 1% for clinicians has been reported [49]. However, Young underlined that her population was a high cardiovascular risk population, since the study was carried out in New Zealand, whose healthcare system implies that low-risk patients do not attend the EA. Thus, the comparison between her findings and others obtained by chest pain patient populations attending the EA is not easy.

Some review studies [50–54] also examined H-FABP role in chest pain patients. In the early stage of investigations, H-FABP showed best diagnostic performances when blood samples are collected and processed within 4 h from the onset of pain [50,51]. Unfortunately, there are few studies involving patients who attended the EA within 3 h from the onset of pain. Two recent meta-analyses performed by Xu et al. and Liu et al., including, respectively, 22 studies on 6602 patients and 8 studies on 3395 patients, have shown that H-FABP does not improve hs-cTn diagnostic accuracy and have proved that its incremental value over hs-cTn had uncertain clinical significance. Both studies concluded that H-FABP cannot be recommended as a biomarker in the clinical practice neither to diagnose neither to rule-out AMI [53,54].

Some general aspects arise by critically reviewing all the studies performed on H-FABP in suspected and confirmed ACS patients:

- At least 2 different thresholds have been defined as the 99th percentile of a healthy population [55,56] and several cut-off values for

### Table 1

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tr>
<td><strong>Peaks early after myocardial injury</strong></td>
<td>Not fully cardiac-specific;</td>
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<td><strong>Easily measurable by immunoenzymatic assays</strong></td>
<td>Few data about the influence of age and renal function on circulating H-FABP levels;</td>
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<td></td>
<td><strong>No univocal cut-off for positivity</strong></td>
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<td></td>
<td><strong>No standardization of units of reporting</strong></td>
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<td></td>
<td><strong>Controversial diagnostic accuracy</strong></td>
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Table 2

Cut-offs for H-FABP positivity proposed by Literature.

<table>
<thead>
<tr>
<th>Authors</th>
<th>H-FABP cut-offs</th>
<th>References</th>
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<tbody>
<tr>
<td>Dupuy et al.</td>
<td>5.8 ng/mL</td>
<td>34</td>
</tr>
<tr>
<td>Kilicullu et al.</td>
<td>5.6 ng/mL</td>
<td>37</td>
</tr>
<tr>
<td>Body et al.</td>
<td>5.8 ng/mL</td>
<td>58</td>
</tr>
<tr>
<td>Cappellini et al.</td>
<td>3.49 μg/L</td>
<td>35</td>
</tr>
<tr>
<td>Inoue et al.</td>
<td>6.2 μg/L</td>
<td>41</td>
</tr>
<tr>
<td>Kitamura et al.</td>
<td>5.7 μg/L</td>
<td>44</td>
</tr>
<tr>
<td>Garcia-Vildecasas et al.</td>
<td>5.09 ng/mL</td>
<td>68</td>
</tr>
<tr>
<td>McMahon CG et al.</td>
<td>2.54 μg/L</td>
<td>68</td>
</tr>
<tr>
<td>Collinson et al.</td>
<td>3.6 μg/L</td>
<td>33</td>
</tr>
<tr>
<td>Young et al.</td>
<td>3.6 μg/L</td>
<td>33</td>
</tr>
<tr>
<td>Reiter et al.</td>
<td>5.7 μg/L</td>
<td>44</td>
</tr>
<tr>
<td>Gami et al.</td>
<td>0.19 μg/mL</td>
<td>69</td>
</tr>
<tr>
<td>Schernthaner et al.</td>
<td>3.2 μg/L</td>
<td>64</td>
</tr>
<tr>
<td>Freund et al.</td>
<td>5.6 ng/mL</td>
<td>60</td>
</tr>
<tr>
<td>Daly et al.</td>
<td>5.3 ng/mL</td>
<td>57</td>
</tr>
<tr>
<td>Willemsen et al.</td>
<td>7 μg/mL</td>
<td>61</td>
</tr>
<tr>
<td>Schoenenberger et al.</td>
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</table>

H-FABP positivity have been used (Table 2). The lower the positivity threshold, the better the H-FABP performance, thus, optimal sensitivity has been mostly reported [33,44,56,57] at decreased cut-offs (4 μg/L).

- Studies [31,38,58,59] showing H-FABP optimal performance often compared the biomarker to cTn at 3–6 h (leading to overestimate H-FABP sensitivity and negative predictive value (NPV), since standard cTn is still negative in the early hours of ACS) or to non-specific markers [31,38,47,60–66];
- Studies with small sample size have documented H-FABP optimal sensitivity compared to cTn and hs-cTn [35,36,47,61,67,68], but results should be confirmed on larger populations;
- Studies [69,70] carried out with weak methods or performed on patients whose clinical features are not well described have shown H-FABP optimal performance as well.

2.3. H-FABP prognostic value in chest pain patients

Based on previously reported evidence, it could be claimed that H-FABP is able to predict short- and long-term mortality [37,44,62,71,72] both in patients with suspected ACS both in patients with confirmed ACS. Nevertheless, such piece of evidence of the prognostic value of H-FABP is not considered to be a reliable prognostic marker in chest pain patients [73,74]. Moreover, interventional studies are needed in order to evaluate whether there is a clinical benefit associated with biomarkers use [39,44,46].

3. Conclusions

Although there is a marked heterogeneity among the studies performed, it can be affirmed that H-FABP is clearly not a reliable marker in ACS, since it is unable to diagnose AMI, neither as a stand-alone test nor combined with hs-cTn. Few evidence supports its incremental value in ruling-out AMI. Weak data is available on its risk stratification ability for chest pain patients presenting to EA. In order to better understand whether H-FABP improves early ruling-out of myocardial infarction, more interventional trials and homogeneous studies are needed as far as clinical features and choice of timing between symptom onset and blood collection are concerned. However, available data may not encourage further research.

References

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