CLINICAL UTILITY OF HFABP IN ACUTE MYOCARDIAL INFARCTION

GIULIA BIVONA[1], LUISA AGNELLO[1], DANIELA BUTERA[1], MARCELLO CIACCIO[1,2]
[1]Section of Clinical Biochemistry and Clinical Molecular Medicine, Department of Biopathology and Medical Biotechnologies, University of Palermo, Italy - [2]Department and U.O.C. Laboratory Medicine, University Hospital "Paolo Giaccone" of Palermo, Italy

ABSTRACT

Assessing chest pain patients presenting to the emergency area (EA) is still a clinical challenge, as acute myocardial infarction (AMI) diagnosis is not adjudicated in the majority of patients. New generation high sensitivity troponin assays (hs-cTn) still present some limitations, thus, novel biomarkers to early rule-in and rule- out myocardial infarction in chest pain patients presenting to the EA are sought after. Among all, heart- type fatty acid binding protein (h-FABP) has been largely investigated. Studies performed on HFABP in these patients present marked heterogeneity. However, it can be stated that HFABP is clearly not a reliable marker for AMI diagnosis, neither as a stand-alone test nor in combination with hs- cTn. More interventional trials are needed and more homogeneous studies are required to understand whether HFABP can add incremental value in rule- out AMI and risk stratify chest pain patients, however, available data may not encourage going on investigating.

Keywords*: AMI, HFABP, chest pain, diagnosis, rule-out.*

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Introduction

Assessing chest pain patients presenting to the emergency area (EA) is still a clinical challenge[(1)], as acute myocardial infarction (AMI) diagnosis is not adjudicated in the majority of patients[(2)]. Diagnostic tools include history, electrocardiography (ECG) and biomarkers. Cardiac Troponins (cTn) are deemed as a cornerstone for the diagnosis of AMI[(3)], and new generation high sensitivity c-Tn assays (hs-cTn) have been shown to outpace the standard one[(4)], albeit presenting some limitations[(5)]. Indeed, undetectable- hs-cTn in a single on admission-collected blood specimen does not allow safely discharge, thus serial measurements are required to correctly rule-in or safely rule-out AMI[(6)]. Major limitation of hs-cTn is a lag time in its rise, peaking at 10-13 hours after AMI[(5)]; secondarily, hs-cTn also presents suboptimal specificity[(7)], consequently leading to inappropriate hospitalization of untruly positive results.

This all leads to EA overcrowd and health-costs rise. Considering such hs-cTn disadvantages, novel biomarkers to early rule-in and rule-out AMI are required. Copeptin, brain natriuretic peptide (BNP), Galectin 3, growth differentiation factor 15 (GDF 15), ST2, IL16, ADMA, and heart- type fatty acid binding protein (h-FABP) have been considered as early markers of myocardial ischemic injury[(8-15)].

Among all, H-FABP has been largely investigated. It is a small (15kDa) soluble protein, present in cardiomyocites cytoplasm at high concentrations[(16)]. It is rapidly released into plasma after the onset of myocardial injury, with a peak at approximately 6-8 hours[(17)].

Studies performed on HFABP in chest pain patients reported controversial findings, mainly because most of the studies present some pitfalls. Firstly, there's a marked heterogeneity in terms of clinical features of the recruited patients, timing of presentation from the onset of pain and chosen

threshold for positivity. Then, observational studies have been mostly carried out[18-23], while randomized trials are the best suited to assess the clinical utility of any biomarker. Finally, it should be noted that the influence of demographic and clinical variables including age and renal function on HFABP plasma levels has not been fully investigated[19,24].

Further, it should be taken in count that HFABP is not fully cardio-specific, being expressed by other tissues as skeletal muscle, brain and kidney, albeit at lower concentrations than in myocardium[25].

Given such considerations, most relevant results can be summarized as follows.

Rule-in and rule-out AMI and risk stratification strategies

Collinson[26] measured cTnT, hs-TnT, Copeptin and HFABP biomarkers in 850 low- risk- chest pain- patients with non- diagnostic ECG. Samples for the analysis were drawn on admission and after 90 minutes from the presentation to the EA. The authors showed that simultaneous determination of HFABP and hs-cTnT on admission achieved lower sensitivity than that of presentation- and at 90 minutes- cTnT (AUC: 0.92 vs 0.94, respectively). Authors concluded that hs-cTnT shows superior diagnostic performance compared to HFABP. Even splitting patients into <3 and <6 hours- groups according to the duration of pain, the diagnostic accuracy of HFABP has been not demonstrated to outperform that of hs-cTnT (AUC: 0.84 vs 0.92, respectively). To note that Collinson population was a low-risk patients- cohort, which may be not a surrogate population of chest pain- patients presenting to the EA.

When Reiter[44] performed a prospective, multicentered study on 1074 consecutive patients presenting to the EA within 12 hours following acute chest pain, results showed that using HFABP did not increase the diagnostic accuracy of hs- cTnT (AUC: 0.88 combination vs 0.94 hs-cTnT alone).

Kilcullen[27] performed a prognostic study on 1448 high-risk, confirmed acute coronary syndrome (ACS) patients. The all-cause 12- months mortality was 2.1% in patients having HFABP < 5.8 μg/l, compared to 22.9% in those having HFABP > 5.8 μg/l (HR: 11.35). However, Kilcullen population is quite different from an EA- unknown origin- chest pain patients population, consequently making his findings difficult to compare to those of other studies. Further, Kilcullen maintains that HFABP provides additive information to that provided by the Global Registry of Acute Coronary Events (GRACE) risk score[28], but it should be observed that the GRACE score is a relatively old risk score and it is considered as not adequate to correctly identify patients suitable for discharge[29].

Body's group derived and validated in 2014 a clinical decision rule (the Manchester Acute Coronary Syndrome Rule- MACS rule), combining 6 clinical variables and 2 biomarkers (hs-TnT and HFABP)[30,31]. The MACS rule had an area under the curve (AUC) of 0.96 for diagnosing AMI; however, it should be noted that MACS population was recruited within 24 hours from the onset of pain, which is a very large time span when evaluating an early biomarker.

Dupuy[19] reported an overall diagnostic accuracy of HFABP in AMI lower than that of hs-TnT (AUC: 0.79 vs 0.85, respectively), showing HFABP to add small incremental value in rule- out AMI in combination with hs-TnT (AUC: 0.86 for combination vs 0.85 for hs-TnT alone). Moreover, the Authors pointed out that the best diagnostic performance of HFABP was reached at 3 to 6 hours following symptoms. Also Kitamura[32] analyzed their chest pain patients populations based on timing of presentation, finding that HFABP best performance over hs- cTnT was reached within 2 hours (AUC: 0.69 HFABP vs 0.48 hs-TnT). Conversely, after stratifying his population according to the time of presentation, Shoenenberger[33] documented HFABP to be not able to outperform hs-cTnT in the very early presenters (<1 hour) (0.83 for HFABP vs 0.90), as also Collinson[26] reported.

Two recent meta-analysis performed by Xu et al.[34] and Liou et al.[35], including, respectively, 22 studies on 6602 patients and 8 studies on 3395 patients, showed that HFABP does not improve the diagnostic accuracy of hs-cTn and demonstrated its incremental value over hs-cTn to be much small and of uncertain clinical significance. Both the studies concluded that HFABP should not be recommended as a biomarker either for diagnosis or rule out AMI into the clinical practice.

Generally, it can be stated that an optimal performance of HFABP in AMI has been reported by studies using low threshold for positivity (18,36-38), or comparing the biomarker to cTn at 3-6 hours and non-specific markers[23,32,39-48]), or by studies with small sample size[20,21,32,37,43,49,50], whose results should be confirmed on larger populations.

Finally, although HFABP has been shown to predict short- and long-term mortality[22,36,44,51,52] in both unknown origin-chest pain- and confirmed ACS-patients, such evidences on the prognostic value should be taken with a grain of salt, as HFAPB is actually deemed to be not a reliable prognostic marker in chest pain patients[53,54].

Conclusions

HFABP is clearly not a reliable marker in AMI, as it is unable to diagnosis AMI, neither as a stand-alone test nor in combination with hs- cTn. To better understand whether or not HFABP can risk stratify chest pain patients presenting to EA, more interventional trials are needed and more homogeneous studies are required in terms of clinical features and choice of timing between symptom onset and blood draw. However, available data may not encourage going on investigating.

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Corresponding author
Professor MARCELLO CIACCIO, MD, PhD
Department of Medical Biotechnologies and Biopathology
University of Palermo, Italy
Via del Vespro, 129
90127 Palermo
marcello.ciaccio@unipa.it
(Italy)