Heart Fatty Acid binding protein for the diagnosis of Myocardial Ischaemia and Infarction

Running title - Heart Fatty acid binding protein and myocardial injury

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Objective. To establish the analytical performance of a heart fatty acid binding protein (HFABP) method suitable for routine clinical use and examine its role for the diagnosis of myocardial ischaemia and myocardial infarction.

Methods. Analyses of HFABP were performed on an Advia 2400 (Siemens Healthcare Diagnostics). Imprecision, limit of detection (LOD), limit of blank (LOB) and linearity were assessed using standard methods. Stability was assessed at 4° C, -20° C and with 3 repeated freeze-thaw. Clinical diagnostic performance was assessed using chest pain patients with a final diagnosis using the universal definition of myocardial infarction with cardiac troponin I (cTnI) measured on the Siemens Advia Centaur (cTnI Ultra method, 99th percentile 50 ng/L, 10% CV 30 ng/L). The ability to detect ischaemia utilised sampling pre-and post angioplasty.

Results. LOD and analytical imprecision exceeded the manufacturers specification (LOD 1.128 µg/L, 20% CV 1.3 µg/L, 10% CV 2.75 µg/L). Clinical diagnostic efficiency was less than cTnI. Addition of HFABP to cTnI produced a modest increase in diagnostic sensitivity at a cost of significant loss of specificity.

Conclusion. Although the test had excellent analytical performance it did not contribute to the clinical diagnosis of patients with chest pain. HFABP appears to be a marker of myocardial infarction not myocardial ischaemia.

Introduction

Heart fatty acid binding protein (HFABP) is one of a number of fatty acid binding proteins (FABP’s) which act as intracellular chaperones responsible for intracellular uptake and buffering of free fatty acids. The low molecular weight (15 kDa), cytoplasmic location, early release following myocardial injury and relative cardiospecificity of HFABP have led to proposals to use HFABP as an early biomarker of myocardial damage(1). It has been proposed that HFABP might be an earlier marker than cardiac troponin (cTn) and measurement of both markers simultaneously might improve diagnostic sensitivity for the earlier diagnosis of acute myocardial infarction (AMI)(2). However, reports have been contradictory and the assay has only been available as a point of care test(3), a manual enzyme linked immunoabsorbent assay (ELISA) (4) or single sample semi-automated immunoassay(5;6). In order to achieve routine clinical use HFABP must be measurable on a routine high throughput automated analyser. A fully automated immuonoturbidometric assay has been developed suitable for implementation on analysers available in the routine clinical chemistry laboratory(7;8) There have also been interesting findings that even in patients where AMI is excluded, HFABP is a prognostic marker and might be a marker of myocardial ischaemia(9).An evaluation was performed of this fully automated immunoturbimetric assay for HFABP to assess routine analytical performance and clinical utility compared with cardiac troponin I (cTnI) for the assessment of patients admitted with chest pain and suspected AMI to the emergency Department and to explore the potential role as a marker of myocardial ischaemia using patients undergoing percutaneous coronary angioplasty and stent placement as a model of myocardial ischaemia.

Methods

*Ethical considerations.*

Residual samples were used for analytical evaluation from patients presenting with chest pain and suspected AMI. Ethical permission was obtained for the angioplasty component (14/YH/1008) via the national research ethics framework with the stipulation that additional venepuncture was not required. Data was extracted then rendered anonymous by agreement with the local Caldicott guardian and ethics committee. The entire study was conducted in concordance with the declaration of Helsinki.

*Sample material.*

All blood samples used in the study were collected into gel separator vacutainer tubes (Becton Dickinson, Plymouth, UK). Samples were allowed to fully clot then centrifuged prior to analysis. Samples were initially stored at 4° C and then at -20° C as required by the different stages of the analysis as described below.

Analytical methods - HFABP and cTnI

The HFABP assay (Randox Laboratories Ltd, Crumlin, Ireland) has been designed to be used on non-proprietary automated analysers and was assayed on the Advia 2400 (Siemens Healthcare Diagnostics, Frimley, Surrey, UK). The assay is immunoturbidimetric using latex particles coated with anti-HFABP antibodies and a 6-point calibration curve. Samples were run in batches with one calibration per batch. The formation of the antibody-antigen complex during the reaction is measured as a change in absorbance at 700nm. The manufacturers specifications for the assay are as follows: limit of detection (LOD) 0.747 µg/L and limit of quantitation 2.94 µg/L, range 2.94-123 µg/L. g/L. Analytical imprecision was 8.4-2.2% from 5.3-92.1 µg/L with the upper reference limit 6.3µg/L. Values exceeding the upper reference limit (97.5th percentile) were considered to be indicative of myocardial injury.

Measurement of cTnI was performed on the Siemens Advia Centaur XP (Siemens Healthcare Diagnostics, Frimley, Surrey, UK) using the TnI-Ultra assay. This method is a three-site sandwich immunoassay with a polyclonal goat anti-troponin I antibody labelled with acridinium ester and two biotinylated mouse anti-troponin I antibodies conjugated to the solid phase. The detection limit of the instrument is 17 ng/L and upper limit 50,000 ng/L. The 10% CV is 30 ng/L with a 99th percentile of 50 ng/L.

Analytical evaluation of HFABP

Limit of blank and limit of detection

Limit of blank (LOB) and LOD were determined with 15 replicates of the calibration blank and calculated as mean + 1.645\*SD (calibration blank). LOD was estimated using 20 replicates of a low concentration sample and calculated as LOB + 1.645\*SD (low concentration sample).

Linearity

For the linearity studies, a high pool was constructed from 3 patients with troponin I concentrations >200ng/L.Linearityof the method was assessed by dilutions of 3 high concentration pools to a total of 500uL using HFABP negative serum obtained from healthy volunteers to 100% 80%, 50%, 20% and 10% of its original concentration. Samples were then analysed in duplicate and results expressed as absolute value. The predicted values were calculated on the basis of the dilutions and the percentage difference from predicted value calculated.

Imprecision

For imprecision studies, 5 serum pools were prepared by pooling together 12 redundant patient serum samples with known cTnI values across the analytical range. Each serum pool was then centrifuged and 0.5mL aliquots stored at -20°C for imprecision testing.. Analytical imprecision was estimated in accordance with CLSI protocol EP5A. Aliquots from each serum pool were thawed, centrifuged then together with the low and high internal quality controls were analysed in duplicate twice a day over 5 days, with each run being separated by at least 2 hours.

Stability

For stability, 2 patient pools were created, a low pool (10 patients with cTnI <17 ng/L and high pool (8 patients with cTnI 50-200 ng/L). Aliquots of each pool were prepared within 12 hours of sample collection and analysed immediately. The remaining aliquots were then stored as follows prior to analysis: 4oC for 24, 48, 72 and 96 hours and -20° C for 48, 72 and 96 hours. An additional 2mL sample from the high and low sample pools was aliquoted to test the effects of 3 freeze/thaw cycles over 3 days between 20oC and -20oC with initial storage at -20° C for 48 hours prior to the first freeze thaw cycle with 24 h storage at -20oC between each cycle. All frozen samples were thawed to room temperature then centrifuged prior to analysis. The others were analysed at room temperature.

*Clinical evaluation*

*Patients with chest pain?MI.*

Serial patients presenting to the emergency department patients with chest pain with a minimum of two serial cTnI measurements were selected. The protocol in use at St George’s is measurement of cardiac troponin on admission and at 3 hours from admission with a further sample taken at 6-12 hours if considered clinically appropriate. Time of onset of chest pain is not formally recorded but time of admission is used as time zero. Measurement of cTnI occurred as part of routine clinical patient management. Samples for subsequent HFABP measurement were stored frozen at -20oC and analysed within 1 month from collection. All samples were analysed in batches. Aliquots were defrosted and thoroughly mixed then centrifuged prior to analysis for HFABP and cTnI. Samples were obtained from 217 admissions from mid December 2012 to mid August 2013. Full sample sets were obtained on a median of 2 patients per day (range 1-9) but samples where not obtained on every day over the entire period due to weekends and holidays. Median age was 71.8 years, range 18.6-102.2 years (Lower quartile 55.5 years, upper quartile 85.2 years) with 131 males (60.4%). Preliminary diagnoses are shown in supplementary table 3 with the final diagnosis in Table 1.

*Diagnostic criteria*

Final diagnosis was made by the attending clinician on the basis of clinical features, laboratory testing and imaging as clinically appropriate and was independent of the investigators. The universal definition of myocardial infarction was used with serial measurement of cTnI as cardiac biomarker and a rise to greater than 50 ng/L with appropriate clinical and ECG changes required for confirmation. Diagnosis was taken from the discharge summary coding recorded in the hospital electronic patient record.

*Angioplasty samples*

50 patients undergoing percutaneous intervention (PCI) were prospectively recruited. Inclusion criteria were; patients undergoing elective (non-acute) PCI, age >18 years and male and female patients. Exclusion criteria were; patients undergoing emergency PCI, age 18 years or less and patients with communication difficulties due to ethnic, social or educational factors. After patient consent was obtained, three samples were collected: before balloon inflation, post balloon inflation and 3 hours after the percutaneous coronary intervention (PCI) procedure. Total time in the cardiac catheter suite was typically 30-60 minutes (from entry until transfer from the recovery area to the ward) with the first sample taken within 5 minutes of entering the laboratory. There was therefore always at least 25 minutes from pre-catheterisation to post catheterisation sample and the follow up sample was therefore a minimum of 3 hours from the commencement of the procedure but in practice could be up to 5 hours. Serum was separated and stored at -20° C until analysis. All samples were analysed in batches. Aliquots were defrosted and thoroughly mixed then centrifuged prior to analysis for HFABP and cTnI.

Statistical analysis

Statistical analysis was performed using the analyse-It ([www.analyse-it](http://www.analyse-it)) add in for excel. Non parametric statistics were used throughout. Linearity was assessed by graphical analysis and by calculation based on the method of Kroll and Emancipator. For the imprecision profile, imprecision and confidence intervals were calculated for each pool and plotted. 10% CV and 20% imprecision were calculated from the imprecision data using a power fit curve to the plotted data with interpolation. Sample stability under different storage conditions was assessed by 1 and 2 way ANOVA.

Diagnostic efficiency was estimated by construction of receiver operator characteristic (ROC) curves, calculating area under the curve (AUC) with comparison of the AUC using final diagnosis of MI as the dichotomous variable. In addition sensitivity and specificity of single marker and dual marker strategies were calculated and diagnostic classifications compared by construction of 2 x 2 tables and then by Fishers exact probability test. HFABP samples were considered positive myocardial injury if they exceeded the 97.5th percentile and cTnI samples as positive for myocardial injury if they exceeded the 99th percentile. Serial samples were compared using the Wilcoxon’s signed rank test and compared with total ischaemia time using the Spearman correlation coefficient.

**Results**

LOB was calculated as 0.701 µg/L (mean 0.36 µg/, SD 0.207) and LOD as 1.218 µg/L (mean of sample 3.293, µg/L, SD 0.314) . The assay was found to be linear to 107.4 µg/L. R2 for all three dilution experiments was 1.00 with the equation of the lines (for the raw data) respectively (pool 1) actual =1.002 expected +0.759, (pool 2) actual = 0.9997 expected + 0.258, (pool 3) actual = 0.9937 expected + 0.880) with no statistically significant differences between the polynomial and linear plots with mean recoveries that were within +/- 1-2% of the expected value for all dilutions (percentage recovery plots and linearity plots supplementary figures 1 and 2).

Precision

The precision profile of HFABP is shown in figure 1 and supplementary figure 3 with the original data in supplementary table 1. For total imprecision (between run variation) the 10% CV was 4 µg/L with 20% CV 1.3 µg/L and for within run (repeatability) 10% CV was 2.75 µg/L and 20% CV 1.22 µg/L.

Stability

Storage for up to 96 hours at both 4°C and -20°C showed no impact on the values of HFABP in either the low or high serum pools in comparison the concentration obtained at 0 hours. The low and high pools that were subjected to three freeze thaw cycles also showed no significant change in measurable HFABP (supplementary table 2) .

Diagnostic accuracy

Measurement of HFABP on the admission sample was diagnostically inferior to cTnI, with AUC’s (confidence intervals in parentheses) for cTnI and HFABP respectively of 0.81(0.72-0.89) and 0.67 (0.57-0.76) difference 0.14, p 0.0013 (figure 2). Combination of HFABP with cTnI improved diagnostic sensitivity as an additional 3 case of MI were detected, sensitivity for 80.6% cTnI alone and 90.3% for cTnI exceeding the 99th percentile or HFABP exceeding the 97.5th percentile in the admission sample. The increase in case detection was not statistically significant and came at the cost of a statistically significant fall in specificity, 58.1% to 33.9% (p <0.0001). For rule out, a cTnI below the 99th percentile had a sensitivity of 58.1% but rule out based on both cTnI and HFABP below the 99th percentile was only 33.9% sensitive (p <0.0001). ROC data for the second sample is shown in supplementary figure 4.

In the angioplasty study, paired samples were obtained from 50 patients, 36 males (72%) median age 67 years (range 34-94 years, Lower quartile 55.9 years, upper quartile 80.1 years). The follow-up 3 hour sample was obtained in 23/50 patients as the rest were day cases and did not have indwelling venous access post procedure. There was no difference in age and gender distribution between the two groups. Angioplasty was performed on a median of 1 artery (range 1-3) with median placement of 1 stent (range 1-5) with a median of 6.5 inflations (range 1-10). The median duration of ischaemia was 105.5 seconds (range 8.0-251.0 seconds). The risk factor profile of the patients is shown in supplementary table 3. Indications for angioplasty were: ST elevation myocardial infarction (STEMI) 5; non-ST elevation myocardial infarction (NSTEMI) 9; angina 36. Prior to angioplasty, HFABP levels were not markedly elevated (median 6.5 µg/L, range 2.0-33.4 g/L). There was no statistically significant differences between the pre, post angioplasty and the 3 hour sample values for HFABP and or cTnI in the whole cohort in any combination. In patients with STEMI, baseline cTnI values were already very high which significantly skewed the data distribution. The analysis was therefore repeated excluding patients with STEMI. There was still no statistically significant increase between pre and post angioplasty samples for HFABP and, cTnI. However,when patients with STEMI were excluded from the group, there was

a statistically significant increase in HFABP and cTnI between the 3 hour sample and both the pre and post angioplasty sample. For HFABP; (pre angioplasty vs 3 hour sample) median 6.8 µ/L vs 12.0 µg/L (p <0.0001) and (post angioplasty vs 3 hour sample) median 6.4 µg/L vs 12.0 µg/L (p = 0.0002). For cTnI (pre angioplasty vs 3 hour sample) median 17.0 vs 362.0 (p = 0.0134) and (post angioplasty vs 3 hour sample) 25.0 vs 362.0 (p = 0.0107). This data is summarised in supplementary figures 5 and 6.There was no correlation between any of the biomarker values measured at any of the time points, including and excluding patients with STEMI and total duration of ischaemia. **Discussion**.

There were three principal findings from this study. First, the analytical performance of the HFABP test on a routine laboratory platform exceeded the manufacturers specification. Second, the additional measurement of HFABP did not demonstrate clinical utility when added to measurement of cTnI either to rule in or rule out myocardial infarction. Finally, HFABP appears to be a marker of myocardial necrosis rather than myocardial ischaemia.

In order to be useful as a cardiac biomarker HFABP needs to be measured as part of a routine cardiac profile using existing equipment already available within the laboratory. The original HFABP assay ran on a specialist immunoassay platform (5). The use of a single dedicated analyser would not only interrupt workflow but have significant additional staffing requirements for provision of a 24-hour service. The reformulation of the assay as an immunoturbidimetric method running on a routine clinical chemistry analyser obviates this need. The analytical performance exceeded the manufacturers specifications with limit of detection and 10% CV below the 99th percentile for the assay and an acceptable imprecision profile. The results obtained in this study are in agreement with the original ELISA test(4) and previous studies which have evaluated the analytical performance on comparable Siemens and Roche equipment(7;8). In terms of analytical performance and laboratory organisation therefore the assay is eminently suitable for routine clinical use as part of a cardiac profile.

The initial reports on HFABP suggested that it was an early marker of myocardial injury(1). Subsequent studies suggested that it was an earlier, more sensitive marker than cardiac troponin(2;10), although not all of the early reports were consistent(11), and added additional prognostic information(12). In this study we found that the combination of HFABP with cTnI did improve diagnostic sensitivity slightly but at the cost of a significant reduction specificity, consistent with a previous study and confirmed by meta-analysis of HFABP studies(13). Previous studies combined HFABP with less sensitive troponin assays and demonstrated a significant improvements in sensitivity(6;14-16). In this study a contemporary sensitive assay was used. Studies that have used a high sensitivity cardiac troponin T assay have concluded that HFABP (using the semi automated method) does not add significantly to diagnostic efficiency(6;17-19). The other study which has used the automated assay showed an increased diagnostic sensitivity when HFABP was added to a high sensitivity troponin(20).

Coronary angiography with balloon inflation and stent placement provides a relatively straightforward model of induced myocardial ischaemia. Previous studies of ischaemia markers have shown detectable changes in value over this time frame(21). Elevation of HFABP in patients who did not show elevation of troponin has been shown to be of prognostic significance(9). The speculation was that this might be due to detection of ischaemia. In this study the kinetic pattern of marker release of HFABP and troponin were identical. If HFABP were a marker of ischaemia it would be expected to rise significantly earlier than that of a known biomarker of cardiac necrosis, cardiac troponin. As the 3 hour sample was taken after completion of the procedure (and often slightly later) a significant change due to necrosis could be expected to be seen. Similarly, there was no correlation between HFABP and duration of myocardial ischaemia. One other study has examined HFABP following angioplasty and showed an increase at 1 h post angioplasty but only in patients who showed an increase in troponin(22). It would therefore seem likely that HFABP is a necrosis marker rather than a combined marker of ischaemia and necrosis.

A potential limitation of the study is the time of onset of chest pain and time of presentation. In theory, if HFABP was a significantly earlier marker then it would add to the diagnostic utility at first presentation. This might account for some of the discordance between the published literature with some populations containing a larger number of patients who present early. However, the study represented a typical population presenting to our hospital. In addition, in a study where time of onset of infarction has been reliably documented in patients with STEMI (where time of chest pain onset is more reliable in contrast to non-STEMI patients), segmentation of the data according to time of onset of chest pain showed no benefit of HFABP measurement(19).

 In conclusion, the immunoturbidimetric HFABP assay is entirely suitable for routine clinical use from an analytical perspective. However, clinically although there is some improvement in sensitivity on addition of admission measurement of HFABP to cardiac troponin, the additional benefit is small and comes at the expense of a significant loss in specificity both as a rule in and rule out test. The use of rapid diagnostic protocols for cardiac troponin based on high sensitivity assays is likely to render the additional measurement of HFABP unnecessary(23). Finally, HFABP does not appear to be a useful marker of myocardial ischaemia.

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Figure 1 Total imprecision

Figure 2 Receiver operator characteristic curves for admission measurement of cTnI and hFABP.

Table 1 Final diagnosis (CVA = cardiovascular accident, NSTEMI = non-ST elevation myocardial infarction, STEMI = ST elevation myocardial infarction)

|  |  |
| --- | --- |
| Final diagnosis  | n (%) |
| Unstable angina | 10 (4.6) |
| Chest infection | 15 (6.9) |
| Chest pain | 44 (20.3) |
| Chronic obstructive pulmonary disease | 3 (1.4) |
| CVA | 3 (1.4) |
| Dysrythmia | 20 (9.2) |
| Gastrointestinal disorder | 11 (5.1) |
| Heart failure | 10 (4.6) |
| Musculoskeletal | 2 (0.9) |
| Myocarditis | 4 (1.8) |
| NSTEMI | 29 (13.4) |
| Other | 25 (11.5) |
| Pulmonary embolus | 2 (0.9) |
| Sepsis | 11 (5.1) |
| STEMI | 2 (0.9) |
| Trauma | 26 (12.0) |