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RESEARCH ARTICLE

Increases in serum concentration of human heart-type fatty acid-binding protein following elective coronary intervention

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Abstract

Background: Heart-type fatty acid-binding protein (H-FABP) is considered a marker of myocardial necrosis but whether or not it is modified by myocardial ischemia is not clear. We sought to investigate if H-FABP serum levels increase following non-urgent coronary angioplasty.

Methods: We studied 31 patients undergoing coronary angioplasty. Peripheral venous samples were drawn immediately before angioplasty, 1 h after the first balloon inflation and 24 h after the procedure and assayed for H-FABP.

Results: Serum levels of H-FABP increased significantly at 1 h vs baseline from 2554 ± 1268 to 3322 ± 245 pg ml^{-1} ($p = 0.024$). However, no differences were observed between 1 h and 24 h after angioplasty (3268 ± 1861 vs 3322 ± 2459 pg ml^{-1}, $p = 0.87$). Moreover, no significant difference was observed when we compared 24 h after angioplasty with the baseline (3268 ± 1861 vs 2554 ± 1268 pg ml^{-1}, $p = 0.112$).

Conclusions: We conclude that H-FABP significantly increases after elective coronary angioplasty at 1 h compared with baseline values; whether or not this has any prognostic significance for future events, as it occurs with troponins, needs to be studied further.

Keywords: *Biomarkers; heart-type fatty acids; angioplasty*

Introduction

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight cytoplasmic protein involved in the uptake, transport and metabolism of free fatty acids in the myocytes and can therefore be regarded as the cytoplasmic counterpart of plasma albumin (Azzazy et al. 2006). H-FABP is an early marker of myocardial infarction (Kleine et al. 1992, Glatz et al. 1998, Okamoto et al. 2000, Seino et al. 2003) and increases sharply after successful reperfusion either with thrombolysis or primary percutaneous coronary intervention (PCI) (Ishii et al. 1997, de Lemos et al. 2000, de Groot et al. 2001). In addition, H-FABP carries prognostic significance in patients with acute coronary syndromes (O'Donoghue et al. 2006, Kilcullen et al. 2007). H-FABP is regarded as a marker of necrosis but whether or not it can perform as a marker of ischemia is not clear. This is the first study to examine if H-FABP serum levels increase following non-urgent coronary angioplasty.

Methods

We studied 31 consecutive patients undergoing non-urgent coronary angioplasty either ad hoc or electively between October 2007 and January 2008. The protocol was approved by the Ethics Committee of our Institution and all patients gave informed consent. Patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI were excluded. Because H-FABP is eliminated from the circulation predominantly by renal

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clearance, patients with chronic renal failure were also excluded (creatinine >1.8 mg dl^{-1}). The mean age of our patients was 63 ± 8 years and all but two were male. Twelve were diabetic, 21 hypertensive, 28 hypercholesterolemic, eight were smokers and 11 had a family history of coronary artery disease. The indication for intervention was effort angina with a positive exercise test in 13 patients, history of unstable angina–non-STEMI stabilized with medical therapy in 11 patients and a history of STEMI in seven. All patients with acute coronary syndromes were included at least 4 weeks after the index event. All patients were pretreated with aspirin, clopidogrel and statins and all but five were on β-blockers. The clinical characteristics of the study group are presented in Table 1. Twenty-seven patients underwent single-vessel angioplasty, three patients had two-vessel PCI and one three-vessel PCI, and therefore the index procedure achieved complete revascularization in only 12 patients. The treated vessel was the left anterior descending in 12, the circumflex in 11, the right coronary artery in 11 and a saphenous vein graft in two.

Peripheral venous samples were drawn immediately before angioplasty, 1 h after the first balloon inflation and 24 h after the procedure. All samples were centrifuged for 10 min at 3000 rpm within 15 min of sampling and stored at -70°C until assayed. The H-FABP was measured using an enzyme-linked immunosorbent assay (ELISA, HK401; Hycult Biotechnology, Uden, the Netherlands); this kit has a minimum detection level of 250 pg ml^{-1} and a measurable concentration range of 102–25 000 pg ml^{-1}.

Table 1. Baseline demographic and clinical characteristics of the study population.

	All patients(n = 31)
Age (years), mean ± SD	63 ± 8
Female/male, *n*	2/29
Cardiac risk factors, *n* (%)	
Hypertension	21 (67)
Hypercholesterolemia	28 (90)
Diabetes mellitus	12 (38)
Current smoking	8 (25)
Family history	11 (35)
Ejection fraction (%), mean ± SD	51 ± 9
Disease severity, *n* (%)	
Single-vessel disease	10 (32)
Two-vessel disease	11 (35)
Three-vessel disease	10 (32)
Current medications, *n* (%)	
ACE inhibitor or ARBs	28 (90)
β-Blockers	26 (84)
Calcium blockers	4 (13)
Antidiabetic drugs	12 (38)
Nitrates	27 (87)

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers.

Cardiac enzymes – creatine kinase (CK), the MB isoenzyme of creatine kinase (CK-MB) and cardiac troponin I (Tn-I) were determined in the 24-h sample, as part of the standard care in our hospital. Reference normal values are as follows: CK <190 mU ml^{-1}, CK-MB <3.6 ng ml^{-1} and Tn-I <0.1 ng ml^{-1}. This is the 95th percentile of the reference control group for CK and CK-MB and the 99th percentile of the reference control group for Tn-I in our institution.

Statistical analysis was performed using SPSS software (version 14, SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD (range) and median. Although the distribution of H-FABP was found to be normal according to specific plots, data analysis was based on non-parametric statistical methods due to the small sample. In particular, to evaluate differences between mean values of H-FABP at the three time points, we applied the Friedman non-parametric criterion; post-hoc analysis was performed with the Wilcoxon test for pairwise comparisons; *p*-values were derived from two-sided hypotheses tests. However, due to the inflation of type I error because of multiple comparisons, all reported pairwise *p*-values were corrected according to Bonferroni's rule. Spearman's correlation was used for correlations between H-FABP at 1 and 24 h and cardiac enzymes at 24 h.

Results

Overall, there was no difference in H-FABP levels between the three prespecified time points (p = 0.16). Post-hoc analysis, however, showed that the H-FABP level increased significantly at 1 h vs baseline, from 2554 ± 1268 to 3322 ± 2459 pg ml^{-1} (p = 0.024). No difference was observed between 1 h and 24 h after angioplasty (3268 ± 1861 vs 3322 ± 2459 pg ml^{-1}, p = 0.87). Moreover, no significant difference was observed when we compared 24 h after angioplasty with the baseline (3268 ± 1861 vs 2554 ± 1268 pg ml^{-1}, p = 0.112) (Figure 1, Table 2). When we analysed our data according to troponin levels, we found that in troponin-positive patients (Tn-I >0.1 ng ml^{-1}, n = 14), the H-FABP level significantly increased at 1 h compared with the baseline (p = 0.016), with no significant difference between 1 h and 24 h and between baseline and 24 h (p = 0.73 and p = 0.43, respectively); conversely, troponin-negative patients (Tn-I <0.1 ng ml^{-1}, n = 17) showed no difference at all three time points (baseline vs 1 h, p = 0.35; 1 h vs 24 h, p = 0.96; and baseline vs 24 h, p = 0.21). CK was greater than 190 mU ml^{-1} in two patients, CK-MB was greater than 3.6 ng ml^{-1} in two patients and Tn-I was greater than 0.1 ng ml^{-1} in 14 patients, indicating minimal myocardial necrosis. No significant correlations between H-FABP levels at any time point following PCI and CK-MB and Tn-I at 24 h

Table 2. Heart-type fatty acid-binding protein (H-FABP) pre- and post-percutaneous coronary intervention.

	Baseline	1 h	24 h
H-FABP (pg ml^{-1})	2554 ± 1268 (387–5632); 2233	3322 ± 2459 (718–14 286); 2911*	3268 ± 1861 (664–7757); 2864

Data are presented as mean ± SD (range); median.
*p <0.05 vs baseline.

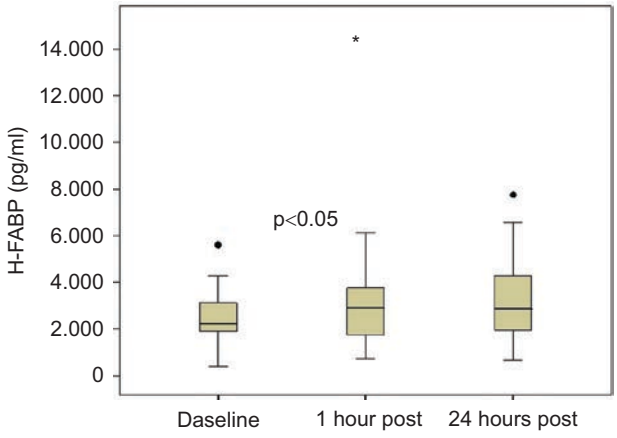

Figure 1. Box-plots of heart-type fatty acid-binding protein (H-FABP) levels throughout the study course (horizontal line represents the median and the top and bottom of the boxes represent the quartiles).

were observed. The clinical follow-up to 30 days was uneventful for all patients.

Discussion

We, for the first time, studied serum H-FABP levels in relation to elective coronary intervention and found that they significantly increase at 1 h compared with the baseline and return to initial values at 24 h; this is essentially due to changes in troponin-positive patients.

The H-FABP level increases within 3 h after acute myocardial infarction and returns to reference values within 12–24 h; if reperfusion is successful the H-FABP level peaks at 4 h and normalizes within 12–20 h, whereas if no reperfusion therapy is given, it peaks at 8 h and returns to baseline values within 36 h (Azzazy et al. 2006). H-FABP peaks earlier than troponins, following myocardial injury (Okamoto et al. 2000, Seino et al. 2003) as well as reperfusion (Ishii et al. 1997, Hayashida et al. 2000, Petzold et al. 2001, Hasegawa et al. 2004). In a dog model of reperfusion, H-FABP has been reported to increase immediately after reperfusion and reach a peak by 20–40 min (Sohmiya et al. 1993). We found that serum H-FABP level increases significantly at 1 h compared with the baseline following balloon inflation and the 24 h levels are back to initial values. Whether H-FABP increases in myocardial ischemia as it does following myocyte necrosis is not clear; in a rat model, it was observed that as early as 15 min after ischemia, the depletion of H-FABP could be detected and with the ischemic time prolonged, the depletion of H-FABP was more and more evident; in further detail, at 15 min after myocardial ischemia, the concentration of H-FABP was four times higher than that of the baseline level and with the continuation of ischemic time, the concentration of H-FABP increased, peaked at 4 h and then decreased (Meng et al. 2006). In our patients, however, we found a significant increase in H-FABP only at 1 h in troponin-positive patients.

Unbound free fatty acids – the free fraction of serum free fatty acids which is not bound to albumin – is considered to be an early marker of myocardial ischemia and has been shown to increase at 30 min post-PCI compared with 5 min pre-PCI levels in 22 patients undergoing elective angioplasty; in this study unbound free fatty acids levels were higher in those patients that developed electrocardiographic changes during PCI compared with those without such changes (Kleinfeld et al. 1996).

In conclusion, H-FABP significantly increases after elective PCI at 1 h compared with the baseline values, essentially due to changes in troponin-positive patients; whether or not this has any prognostic significance for future events, as it occurs with troponins, needs to be further studied.

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References

Azzazy H, Pelsers M, Christenson R. (2006). Unbound free fatty acids and heart-type fatty acid-binding protein: diagnostic assays and clinical applications. *Clin Chem* 52:19–29.

de Groot MJ, Muijtjens AM, Simoons ML, Hermens WT, Glatz JF. (2001). Assessment of coronary reperfusion in patients with myocardial infarction using fatty acid binding protein concentrations in plasma. *Heart* 85:278–85.

de Lemos JA, Antman EM, Morrow DA, *et al.* (2000). Heart-type fatty acid binding protein as a marker of reperfusion after thrombolytic therapy. *Clin Chim Acta* 298:85–97.

Glatz JF, van der Vusse GJ, Simoons ML, Kragten JA, van Dieijen-Visser MP,Hermens WT. (1998). Fatty acid-binding protein and the early detection of acute myocardial infarction. *Clin Chim Acta* 272:87–92.

Hasegawa T, Yoshimura N, Oka S, Ootaki Y, Toyoda Y, Yamaguchi M. (2004). Evaluation of heart fatty acid-binding protein as a rapid indicator for assessment of myocardial damage in pediatric surgery. *J Thorac Cardiovasc Surg* 127:1697–702.

Hayashida N, Chihara S, Akasu K, *et al.* (2000). Plasma and urinary levels of heart fatty acid-binding protein in patients undergoing cardiac surgery. *Jpn Circ* 64:18–22.

Ishii J, Nagamura Y, Nomura M, *et al.* (1997). Early detection of successful coronary reperfusion based on serum concentration of human heart-type cytoplasmic fatty acid-binding protein. *Clin Chim Acta* 262:13–27.

Kilcullen N, Viswanathan K, Das R, *et al.* (2007). Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. *J Am Coll Cardiol* 50:2061–7.

Kleine AH, Galtz JF, Van Nieuwenhoven FA, Van der Vusse GJ. (1992). Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man. *Mol Cell Biochem* 116:155–62.

Kleinfeld AM, Prothro D, Brown DL, Davis RC, Richieri GV, DeMaria A. (1996). Increases in serum unbound free fatty acid levels following coronary angioplasty. *Am J Cardiol* 78:1350–4.

Meng X, Ming M, Wang E. (2006). Heart fatty acid binding protein as a marker for postmortem detection of early myocardial damage. *Forensic Sci Int* 160:11–16.

O'Donoghue M, de Lemos JA, Morrow DA, *et al.* (2006). Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. *Circulation* 114:550–7.

Okamoto F, Sohmiya K, Ohkaru Y, *et al.* (2000). Human heart-type cytoplasmic fatty acid-binding protein (H-FABP) for the diagnosis of myocardial infarction: clinical evaluation of H-FABP in comparison with myoglobin and creatine kinase isoenzyme MB. *Clin Chem Lab Med* 38:231–8.

Petzold T, Feindt P, Sunderdiek U, Boeken U, Fischer Y, Gams E. (2001). Heart-type fatty acid protein (hFABP) in the diagnosis of myocardial damage in coronary artery bypass grafting. *Eur J Cardothorac Surg* 19:859–64.

Seino Y, Ogata K, Takano T, *et al.* (2003). Use of a whole blood rapid, panel test for heart-type fatty acid-binding protein in patients with acute chest pain: comparison with rapid troponin T and myoglobin tests. *Am J Med* 115:185–90.

Sohmiya K, Tanaka T, Tsuji R, *et al.* (1993). Plasma and urinary heart-type cytoplasmic fatty acid-binding protein in coronary occlusion and reperfusion induced myocardial injury model. *J Mol Cell Cardiol* 25:1413–26.