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THE DIAGNOSTIC VALUE OF HEART-TYPE FATTY ACID BINDING PROTEIN (h-FABP) RAPID TEST RELATED TO CARDIAC TROPONIN I IN NON ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

(Nilai Diagnostik Uji Cepat Heart Type Fatty Acid Binding (h-FABP) dihubungkan dengan Troponin I pada Non ST elevation Myocardial Infarction (NSTEMI))

F.R. Marpaung[1], Aryati[1], Sidarti Soehita SFHS[1], Yogiarto[2], Yusri[2]

ABSTRACT

Acute coronary syndrome (ACS) is caused by atherosclerotic plaque rupture and microembolization which lead to decreased oxygen supply into the myocardium. Generally, ACS includes an unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction. ACS may lead to ST elevation Myocardial Infarction (STEMI) and finally a sudden death. Cardiac troponin is used routinely for diagnosing acute coronary syndrome (ACS); however, troponin is not elevated in the initial hours of ACS—precluding their usefulness in the early diagnosis. The aim of this study is to determine the diagnostic value of h-FABP Rapid test in relation to Cardiac Troponin I in NSTEMI. Seventy five patients with ACS were enrolled in this study. All patients presented symptoms within six hours of the onset and suffered typical chest pain. Blood samples were obtained for rapid test h-FABP (cardiodetect) and Troponin I (tropospot). The h-FABP showed a 93.5% sensitivity, 95% CI: 81.1–98.3 and 82.8% specificity, 95% CI: 63.5–93.5, Positive Predictive Value 89.6%, 95% CI: 76.6–96.1, Negative Predictive Value 88.9%, 95% CI: 69.7–97.1, respectively in the first six hours. Troponin I had a 60.9% sensitivity, 95% CI: 45.4–74.5 and 96.6% specificity, 95% CI: 80.4–99.8, Positive Predictive Value 96.6%, 95% CI: 80.4–99.8, Negative Predictive Value 60.9%, 95% CI: 45.4–74.5, respectively in the first six hours. Based on this study result on patients with Non ST Elevation Myocardial Infarction (NSTEMI), it is suggested to determine the h-FABP as well. For this purpose, point-of-care h-FABP test can be utilized, as it has the advantage of highly sensitivity and specificity, beside it can carry on a bedside testing and show a rapid test results as well.

***Key wordS**: h-FABP, Troponin I, NSTEMI, UA*

ABSTRAK

Sindroma koroner akut (SKA) disebabkan oleh aterosklerosis akibat robekan (rupture) bercak (plak) dan mikroembolisasi yang menyebabkan asupan oksigen dalam miokardium menurun. Secara umum SKA terdiri atas tidak menetap/unstable angina (UA), dan jaringan mati otot jantung tanpa ST meninggi/non ST elevation myocardial infarction (NSTEMI). SKA dapat dapat berubah menjadi kematian jaringan otot jantung dengan ST meninggi/ ST elevation Myocardial Infarction (STEMI) dan menyebabkan kematian. *Cardiac troponin* telah digunakan secara lazim (rutin) untuk mendiagnosis SKA tetapi pada waktu awal timbulnya SKA troponin tidak meningkat, sehingga kegunaannya terbatas untuk diagnosis dini. Tujuan penelitian ini adalah untuk menentukan nilai diagnostik uji cepat (rapid test) H-FABP secara nisbi (relatif) terhadap *Cardiac Troponin* I di pasien Non ST Elevation Myocardial Infarction (NSTEMI). Penelitian ini melibatkan 75 pasien SKA. Semua pasien mengalami permulaan serangan (onset) nyeri dada kurang dari 6 jam dengan nyeri dada yang khas. Sampel darah diperiksa menggunakan alat uji cepat noktah penyelamatan/point-of-care rapid test h-FABP (*cardiodetect*) dan Troponin I (*tropospot I*). Kepekaan **h-FABP 93,5%, 95% CI: 81,1–98,3 dan kekhasan** h-FABP 82,8%, **95% CI:63,5–93,5, nilai peramalan positif (***positive predictive value*) 89,6%, 95% CI: 76,6–96,1, **nilai peramalan** negatif **88.9%, 95% CI: 69,7–97,1, pada 6 jam pertama permulaan serangan nyeri dada. Troponin I mempunyai kepekaan 60,9%,** 95% CI: 45,4–74,5 dan kekhasan 96,6%, 95% CI: 80,4–99,8, nilai peramalan positif 96,6%, 95% CI: 80,4–99,8, nilai peramalan negatif 60,9%, 95% CI: 45,4–74,5, pada 6 jam pertama permulaan serangan nyeri dada. Di pasien *Non ST Elevation Myocardial Infarction* (NSTEMI) disarankan pemeriksaan menggunakan H-FABP. Uji (tes) menggunakan uji cepat noktah penyelamatan (*point-of-care*) h-FABP memiliki keunggulan yaitu dapat dilakukan secara langsung disamping pasien, hasil kepekaan dan kekhasan yang tinggi selain itu hasilnya lebih cepat diperoleh.

Kata kunci: h-FABP, NSTEMI, UA, Troponin I

INTRUDUCTION

Acute coronary syndrome (ACS) is a clinical syndrome of coronary heart disease. It is caused by atherosclerotic plaque rupture and microembolization which lead to decreased supply of oxygen to the myocardium. Generally, the symptoms of ACS include an unstable angina (UA), and non ST elevation myocardial infarction (NSTEMI). ACS may lead to ST Elevation Myocardial Infarction (STEMI) and sudden

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death as well. The diagnosis of acute myocardial infarction (AMI) is generally made according to the WHO criteria which are characterized by the clinical history of chest pain, electrocardiography (ECG) changes, and serum enzyme findings.[1]

Sometimes it is difficult to diagnose the early stage of AMI because of the delayed liberation of serum cardiac markers, such as creatine kinase isoenzyme MB (CK-MB), cardiac Troponin (cTn) I and equivocal early ECG changes.[2–5] Cardiac markers are important tools in the diagnosis of ACS.[1-3] The ideal ACS marker should have a high sensitivity and specificity. Cardiac troponins fulfil these criteria to a large extent, because of their high sensitivity for minor myocardial injury and almost total specificity to the cardiac muscle that made it possible to redefine ACS in biochemical terms.[5] However, due to their delayed appearance in serum, there is still a need for certain reliable early markers. Thus, the detection of a rapidly appearing serum biochemical marker specific as 232 Okamoto *et al.* the human h-FABP for myocardial damage in AMI would facilitate a more appropriate diagnostic and therapeutic approach in patients with suspected AMI coincides with chest pain.[6]

Fatty-acid binding proteins (FABPs) are members of the cytosolic protein family. The name of FABP originates from their ability to adhere fatty acids noncovalently in a high-affinity manner. FABP is relatively tissue specific; liver, heart and intestinal FABPs origin are named as LFABP, h-FABP and I-FABP, respectively. They are most abundantly found in heart and liver tissue. h-FABP is an equivalent protein to albumin, in principle it is an extra cellular fatty-acid transporters, in regard to its function that is to transport fatty acids intracellularly.[7] Cardiac muscle contains FABP in amount 0.57 mg/g, and myoglobin's is 2.7 mg/g. Skeletal tissue contains 0.04–0.14 mg/g FABP and myoglobin 2.2–6.7 mg/g.[8–10] This difference helps one method to differentiate myocardial and skeletal muscle injury. Because of their high myocardial content, there is a reason for using h-FABP in early diagnosis of ACS, mainly presence in cytosole (unclear), low molecular weight, relative tissue specificity, and early (within two hours) appearance in plasma and urine after the AMI onset. Cardiac troponin I (cTnI) is more specific in myocardial injury, but lack of early sensitivity because their blood concentrations do not increase appreciably until 6–8 h after the onset of AMI.[11]

The present study was designed to assess the diagnostic value of h-FABP rapid test in relation to cardiac troponin I (cTnI) within NSTEMI Patients after 6 hours onset of a chest pain.

METHODS

Study population

This observational cross sectional study was conducted in 75 patients with a chief complaint of chest pain at the Emergency Department of the dr. Soetomo Hospital, Surabaya between the period of June 2010 until October 2010. The inclusion criteria of the subjects were as follows: patients presenting within six hours onset of typical chest pain, an episode of resting anginal pain lasting >10 minutes and at least one of the followings: ST-segment depression of at least 0.05 mV, T-wave inversion of at least 0.1 mV at least in two (2) contiguous leads

The exclusion criteria of the subjects: those suffering renal insufficiency or any renal disease impairing renal clearance, underwent percutaneous transluminal coronary angioplasty or coronary artery by pass grafting within 30 days, had prior AMI within 30 days, had chronic muscle disease, pulmonary thromboembolism or pericarditis, liver cirrhosis, anaemia, acute stroke ischemia. The protocol of this study has been approved by the local ethical committee, and from every subject participating in this study a written informed consent was obtained.

All patients underwent a comprehensive inquiry regarding the degree of angina pectoris, risk factors and past history. Subjects underwent serial ECG, and cardiac markers were measured every four hours. All subjects were managed medically in conformity with ACC/AHA ST elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina pectoris (USAP) guidelines.

The demographics and clinical data, including age, sex, diagnosis, and coronary risk factors were collected from the hospital medical records and addition from patient or family interviews.

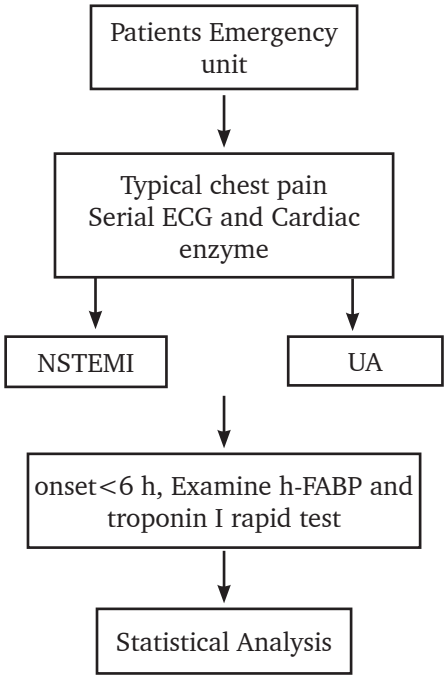
The Procedure

All of the eligible patients underwent cardiac markers h-FABP and Troponin I examination using qualitative Cardiodetect for h-FABP and Tropospot I for troponin I.

Troponin I (Tropospot I)

Tropospot I rapid test is an immunochromatography based on invitro test. It is designed for qualitative determination of cardiac troponin I (cTnI) in human serum. Rapid Tropospot I is designed to yield a positive result for cTnI concentrations at 1.0 ng/mL or greater. The time required for blood cTnl level to reach the upper limit of normal value has been found to be 4–6 hours after the onset of the symptoms. The

The Study Algorithm



cTnI level reaches the maximum concentration after 12–24 hours of the onset, and then remains elevated for 6–10 days in some cases.

The procedure of Troponin rapid test are as follows: 120–160 μL serum sample (2–3 drops using a pipette dropper provided or 150 μL using micropipette) is placed into the sample well (S) of the test card. The dropper should be held in a vertical position to ensure proper volume of each drop approximately. The results are then read within 15 minutes. A positive result is indicated by a coloured test line (T) and a coloured control line (C). A negative result is indicated by the presence of a coloured control line (C) and the absence of a test line (T). An invalid test result is indicated by the absence of a control line (C). If an invalid test result is obtained, the specimen should be retested.

h-FABP (cardiodetect)Test

The test contains of two different monoclonal antibodies specific to h-FABP, these are monoclonal anti-h-FABP antibodies (2.0 μL) and monoclonal anti-h-FABP antibodies (5.0 μL) which binding to a colloidal gold-labelled substance (40nm). The subject's blood sample (3–4 drops serum or 60–100 μL) will removes the gold-labelled h-FABP antibody from its matrix. This antibody forms an intermediary complex with h-FABP present in the sample. This complex passes through the detection zone. At the position named "T" the intermediary complex forms a sandwich complex with a second antibody. This sandwich complex shows up as a red line. A sample without h-FABP does not form such a sandwich complex and no red line appears (see Fig 2 below).

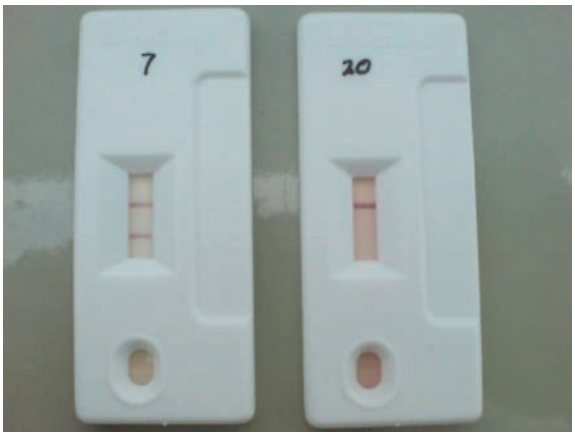


Figure 1. Positive result (left) and negative result (right) for h-FABP rapid test

It can detect serum h-FABP level to a sensitivity level of 7 ng/mL. An h-FABP level of >7ng/mL in a patient presenting chest pain within two hours of symptom onset was considered positive for an AMI. A negative test result was a level of <7 ng/mL (see Figure 1). The diagnostic window period for the test is in the first 20 minutes up to 24 hours after the symptom onset. This period may decrease to 16 hours if a medical intervention occurs.

The Statistical Analysis

The diagnostic test criteria included: sensitivity, specificity, negative and positive predictive values. These were calculated according to the related standard procedures. The respective 95% CIs are the test-based. For the measurement the researchers used Chi-square test, McNemar test, and measurement of Agreement Kappa. For the data processing, the researchers used MS Excel for Windows Vista; and for the statistical analysis, SPSS for Windows® version 15.0 statistical package with level of significance $p<0.05$ is used.

RESULTS AND DISCUSSION

Tabel 1. Patients baseline characteristics (n=75)

Characteristics	Number (%)
Demographics	
Age (years, mean±SD)	55.8±10.5
Sex	
Male	49 (65.3)
Female	26 (34.7)
BW (kg, mean±SD)	62.2±10.0
Risk factors	
Obesity	7 (9.3)
Hypertension	57 (76.0)
DM	31 (41.3)
Current smoking	37 (49.3)
Dyslipidemia	6 (8.0)
Family history	5 (6.7)
CHD history	5 (6.7)

Table 1 showed patients baseline characteristics including demographics and risk factor. Table 2 showed comparison of patients characteristics between NSTEMI and UA; where there were no significant different of age and onset of chest pain, but sex, body weight and duration of chest pain were significantly different ($p<0.05$).

The h-FABP showed a 93.5% sensitivity, 95% CI: 81.1–98.3 and 82.8% specificity, 95% CI: 63.5–93.5, Positive Predictive Value 89.6%, 95% CI: 76.6–96.1, Negative Predictive Value 88.9%, 95% CI: 69.7–97.1, respectively in the first six hours. Troponin I had a 60.9% sensitivity, 95% CI: 45.4–74.5 and 96.6% specificity, 95% CI: 80.4–99.8, Positive Predictive Value 96.6%, 95% CI: 80.4–99.8, Negative Predictive Value 60.9%, 95% CI: 45.4–74.5, respectively in the first six hours (table 3).

The diagnostic performance of h-FABP showed the highest sensitivity and specificity in those who presented<6 hours after symptom onset. Our findings are almost the same with the other trials. Cavus et al analysed the same test panel in an emergency setting and showed an overall sensitivity of 80%.[12]

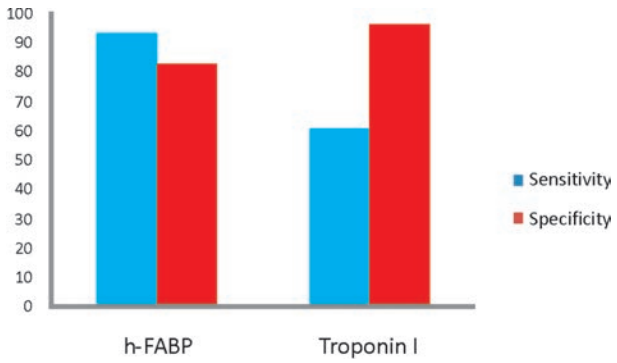


Figure 2. The diagnostic value of h-FABP and Troponin I on Acute Coronary Syndrome (ACS) patients within 6 hours onset of chest pain

The Troponin I showed a lower sensitivity but higher specificity compared to h-FABP, this finding also the same with Mad et al[13] findings.

Coloured line positive test is not always found straightforward; despite this being a substantial problem of such qualitative tests. In this study, colour bands of definite positive tests became visible within 5–15 minutes, but some colour bands were blurred.

In the researchers knowledge, this is the first study in Surabaya as well as in Indonesia, which is designed to assess the diagnostic value of h-FABP rapid test in relation to cardiac troponin I (cTnI) on NSTEMI within 6 hours onset of chest pain.

Table 2. Comparison of patient characteristics between NSTEMI and UA

	NSTEMI (n=46)	UA (n=29)	P value
Demographics			
Age (years, mean ±SD)	54.8±10.5	57.2±10.7	0.358
Sex			
Male	36	13	0.007
Female	10	16	0.003
BW (kg, mean±SD)	64.1	59.4	0.047
Risk factors			
Obesity (n, %)	6 (13.0)	1 (3.4)	0.238
Hypertension (n,%)	33 (71.7)	24 (82.8)	0.418
DM (n, %)	22 (47.8)	9 (31)	0.231
Current smoking (n,%)	26 (56.5)	11 (37.9)	0.183
Dyslipidemia (n, %)	5 (10.9)	1 (3.4)	0.396
Family history (n, %)	3 (6.5)	2 (6.9)	1.000
CHD history (n, %)	3 (6.5)	2 (6.9)	1.000
Symptoms			
Onset of chest pain (hour, mean)	4.00	3.65	0.338
Duration of chest pain (hour, mean)	2.78	0.98	0.001

CONCLUSIONS

It can be suggested that in patients with Non ST Elevation Myocardial Infarction (NSTEMI), POCT h-FABP test should be measured because of the high sensitivity and specificity, beside the advantage of bedside testing as well as the rapid test results. This study should be continued with a quantitative test and patient's 6 hours follow up to know the cut-off value of both h-FABP and Troponin I rapid test.

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