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Original Article

Comparing the value of Pregnancy Associated Plasma Protein A (PAPP-A) and ischemia modified albumin in the patients with chest pain

Göğüs ağrısı olan hastalarda gebelikle ilişkili Plazma Protein A (PAPP-A) ve iskemi modifiye albümin değerinin karşılaştırılması

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ABSTRACT

Aim: To evaluate the diagnostic value of PAPP-A and CK-MB in early diagnosis of ACS.

Material and Methods: It is a single-center, prospective, clinical study. There were totally 152 cases. At the end of the study the levels of troponin-T, CK-MB, PAPP-A and IMA in the different groups were compared.

Results: There were 13 patients with STEMI, 53 patients with NSTEMI/UAP and 80 patients with non-specific ECG findings. When we consider the definitive diagnosis; there were 8 patients with STEMI, 36 patients with NSTEMI, 23 patients with UAP, 17 patients with SAP and 68 patients with non-coroner chest pain. In our study, the most specific parameter at the highest sensitivity for the patients with the chest pain within the first hours (0-2 hour, 2-4 hour) was IMA. (Sensitivity/specificity; 100/30.7, 93.7/52.3 respectively).

Conclusion: According to our results, PAPP-A and IMA cannot be used as an diagnostic tool like troponin-T and CK-MB in ACS. Also IMA cannot be used as an ideal screening test in the diagnosis of ACS during the early period of chest pain. Still, IMA is more useful diagnostic biochemical marker than troponin-T, CK-MB and PAPP-A as a screening test in detecting ACS during the first hours.

Keywords: PAPP-A, IMA, chest pain, acute coronary syndrome

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ÖZ

Amaç: ÇAKS'un erken tanısında PAPP-A ve CK-MB'nin tanısal değerinin belirlenmesidir.

Gereç ve Yöntemler: Tek merkezli, prospektif, klinik bir çalışma 152 vaka incelendi. Çalışmanın sonunda troponin-T, CK-MB, PAPP-A ve IMA'nın farklı gruplardaki düzeyleri kıyaslandı.

Bulgular: 13 hastada STEMI tanısı kondu, 53 hastada NSTEMI/UAP ve 80 hastada non spesifik EKG bulguları mevcuttu. Kesin tanısına göre 8 hastada STEMI, 36 hastada NSTEMI, 23 hastada UAP (unstabil njina pektoris), 17 hastada SAP (stabil anjina pektoris) 68 hastada non koroner göğüs ağrısı mevcuttu. Göğüs ağrısının ilk saatlerinde (0-2 saat, 2-4 saat) en yüksek sensitivitedeki en spesifik parametre IMA idi. (Sensitivite/spesifite; 100/30.7, 93.7/52.3).

Sonuçlar: Sonuçlarımıza göre, PAPP-A ve IMA, AKS'de troponin-T ve CK-MB gibi bir tanı aracı olarak kullanılamaz. Sonuçlarımız, duyarlılık ve özgüllük özellikleriyle ilgili olarak IMA, göğüs ağrısı erken döneminde AKS tanısında ideal bir tarama testi olarak kullanılamaz. Yine de, IMA, ilk saatler boyunca AKS'yi saptamada bir tarama testi olarak troponin-T, CK-MB ve PAPP-A'ya kıyasla daha yararlı diagnostik biyokimyasal belirteçtir. Çalışma sonuçlarımız literatürde benzer bir çok araştırmanın aksine bir sonuç sergilemektedir ve bulguları daha kapsamlı bir dizi çalışma ile değerlendirilmelidir.

Anahtar kelimeler: PAPP-A, IMA, göğüs ağrısı, akut koroner sendromu

Introduction

Chest pain is a frequent cause of presentations to emergency departments [1]. Testing new biochemical markers in comparison with conventional biomarkers for ruling-in or ruling-out ACS is still an unresolved issue. The BACC study has recently evaluated this topic and demonstrated that a high-sensitivity troponin I test showed great accuracy in ruling out MI in patients with chest pain, with triage times reduced to 1 hour, and also showed better positive predictive ability than some other studies [2]. But, the time profile of the rise of troponins in the course of ACS is variable and the best cut-off for troponin assay as well as the other biomarkers are still to be validated.

Conventional tests have now largely been superseded by high-sensitivity cardiac troponin (hs-cTn) measurements. Recent research reports that this is useful in the early diagnosis of suspected acute myocardial infarction (AMI) [3]. However, because of problems with both sensitivity and specificity and delays in their elevations reaching to detectable level in blood, new and more practical biochemical parameters are needed. Several novel biochemical parameters are therefore being evaluated in the literature. pregnancy associated plasma protein A (PAPP-A) and ischemia modified albumin (IMA) are among the are among the potential biochemical parameters being investigated in terms of diagnostic sensitivity and specificity [4-9].

Despite the information obtained from existing studies, no data pool to permit IMA and PAPP-A to enter routine use. The purpose of this study was to compare the diagnostic values of PAPP-A and IMA in the early period of ACS when levels of conventional biochemical parameters have not yet risen.

Material and Methods

Setting

This research, intended to compare the diagnostic values of PAPP-A and IMA in patients with chest pain, is one-center, prospective clinical study performed at an University Hospital following approval from the ethical committee.

Data collection process

Adult age group (>18 years) patients presenting to the ED in the first 8 h after chest pains of typical or atypical character between 01.01.2011 and 01.06.2011 were included in the study. Patients with advanced liver failure, end stage renal disease, decompensated heart failure, a history of major surgery or major trauma in the previous 3 months, known or suspected chronic inflammatory or neoplastic disease, acute mesenteric ischemia, cerebral ischemia or peripheral artery disease, or declining to take part in the study were excluded.

Establishment of the Study Groups

An initial screening examination was performed by the treating emergency physician with appropriate therapeutic measures and diagnostic studies initiated. All consecutive patients presenting to the ED with chest pain and meeting the inclusion criteria were categorized into four time periods on the basis of time of onset of chest pain (0-2 h, 2-4 h, 4-6 h, 6-8 h) by the same treating emergency physician as blind to the results of study markers.

They were then subdivided on the basis of definitive diagnoses. On the basis of definitive diagnosis, five subgroups were established in the light of definitive diagnoses following

additional diagnostic tests such as effort and angiography and measurement of cardiac enzymes based on the diagnostic algorithm established. These were;

a. ST elevation myocardial infarction (STEMI) group,

b. Non STEMI group,

c. Unstable angina pectoris (UAP) group,

d. Stable angina pectoris (SAP) group and

e. Non-coronary causes group.

Appropriate pictures were subsequently established by analyzing these groups' and subgroups' mean troponin-T, CKMB, PAPP-A and IMA levels at the time intervals determined. The biochemical markers of the patients in these groups and subgroups were then compared at the specific time intervals determined.

Age, gender, chest pain characteristics and duration, other accompanying symptoms, physical examination findings, risk factors and clinical and demographic characteristics of the patients included in the study were recorded by the maintenance of a data form from first application to the ED. All patients with chest pain were administered the diagnosis and treatment algorithm developed according to the American Health Association (AHA) guideline given in Figure 1 [10].

Blood specimens were collected at 0-2 h, 2-4 h, 4-6 h and 6-8 h since onset of pain from time of application. Relevant group membership, based on onset of chest pain, was considered in subsequent follow-ups. During this stage, a number of patients were discharged in the early period due to their clinical condition. Blood specimens were taken from these patients only in the time intervals up to discharge.

In collecting blood specimens, it was avoided from hemolysis as much as possible for each sample. Approximately 10 ml blood was placed a separator biochemistry tube, and since CKMB and troponin measurements are part of the routinely applied diagnostic approach, these were analyzed immediately. For PPAP and IMA measurements, specimens were kept at -80 C and analyzed at the same time for all the study groups (duration of storage at -80 C, min:1 day-max:60 days) by a biochemist as blind to patient's group or data.

Troponin measurement

Troponin-T levels were measured on an Elecsys 2010 (Roche Diagnostic, Tokyo, Japan) device and results were expressed as ng/mL. Values below <0.01 ng/mL were regarded as normal.

CK-MB measurement

CK-MB levels were measured on an Elecsys 2010 (Roche Diagnostic, Tokyo, Japan) device and the results were expressed as ng/mL. Normal value range was taken as 0-6.73 ng/mL for men and 0-3.77 ng/mL for women.

IMA measurement

The decrease in albumin-cobalt binding was evaluated using the rapid and colorimetric method described by Bar et al. and the results were expressed as absorbance units (ABSU) [10].

PAPP-A measurement

Serum PAPP-A levels were determined using enzyme-linked immunosorbent assay (ELISA) kits-DRG PAPP-A ELISA EIA:2397 (DRG Instruments GmbH, Marburg, Germany). Specimen absorbance was measured on a VERSA (Molecular Devices Corporation, California, USA) microplate reader at a wavelength of 450 nm. Results were given as µg/mL.

Patients were monitored for complications throughout their periods of hospitalization. Patients of their relatives were contacted by telephone 3 months after discharge, and any complications arising during that 3-month period were recorded.

Data analysis

Data were loaded onto the Statistical Package for the Social Sciences 13.0 program (SPSS Inc., IL, USA). Clinical and demographic characteristics, such as age, gender, risk factors and accompanying symptoms and descriptive statistics were produced. Normal distribution of biochemical measurements was evaluated using the Kolmogorov-Smirnov test. Comparisons among groups of normally distributed data were performed using Bonferroni-corrected one-way ANOVA, while Bonferroni-corrected Kruskal Wallis analysis of variance was used for non-normally distributed data. ROC analysis was performed for determining sensitivity, specificity, NPV and PPV of biochemical measurements for 0-2, 2-4, 4-6 and 6-8 h intervals for data grouped according to time for diagnosis of ACS on the basis of definitive diagnoses. Spearman's correlation analysis was used to determine the relationship between parameters for 0-2, 2-4, 4-6 and 6-8 h intervals. Significance was set at $P < 0.05$.

Results

Seventeen thousand patients applied to the study center during the 5-month study period. During that time, the number of patients presenting to the ED with typical-atypical chest pain was 215 (1.26% of total patient number). Sixty-three of these 215 patients were excluded for meeting at least one of the exclusion criteria.

After evaluation of the exclusion criteria, 152 patients applying with typical or atypical chest pain were enrolled. Clinical and demographic characteristics of the patients included are shown in Table 1.

Patients were monitored with a diagnostic and therapeutic algorithm developed in line with the AHA guideline. At the end of this period, our patients were grouped according to their definitive diagnoses; 8 patients (5.26%) were diagnosed with STEMI, 36 (23.7%) with NSTEMI, 23 (15.1%) with UAP, 17 (11.18%) with SAP and 68 (44.73%) with non-coronary chest pain. Mean and compared troponin, CK-MB, PAPP-A and IMA levels identified as a result of biochemical analyses and groups formed on the basis of definitive diagnoses and initial duration of chest pain are shown in Table 2. According to definitive

Table 1. Clinical and demographic characteristics of the study group	
Age (Mean±SD)	50.66±18.13
Gender	n, (%)
Male	109 (71.7)
Female	43 (28.3)
Chest pain characteristics	n, (%)
Pain at rest lasting more than 20 min	98 (64.5)
New onset and activity restricting pain	45 (29.6)
Chest pain triggered by effort	66 (43.4)
Worsening angina pain	58 (38.2)
Pleurotic chest pain	32 (21.1)
Localizable pain	81 (53.3)
Mechanical-type pain	32 (21.1)
Accompanying symptoms	n, (%)
Cold sweat	23 (15.1)
Nausea	18 (11.8)
Palpitation	33 (21.7)
Syncope	9 (5.9)
Dyspnea	18 (11.8)
Cough	24 (15.8)
Fever	15 (9.9)
Risk factors	n, (%)
Previous history of CAD	41 (27.0)
Hypertension	62 (40.8)
Cigarette use	57 (37.5)
Previous history of MI	35 (23.0)
Diabetes	27 (17.8)
Obesity	29 (19.1)
Hyperlipidemia	26 (17.1)
Family history	35 (23.0)
Sedentary lifestyle	113 (74.3)
Renal disease	2 (1.3)
Systolic blood pressure (mean mm/Hg±SD)	134.5 ± 24.7
Diastolic blood pressure (mean mm/Hg±SD)	77.75 ± 14.3
HDL (mean mg/dl±SD)	50.44 ± 18.3
LDL (mean mg/dl±SD)	11.06 ± 38.7
Total cholesterol (mean mg/dl±SD)	186.85 ± 42.7
Cardiovascular events taking place during hospitalization	n, (%)
Death	1 (0.7)
New non-fatal MI	1 (0.7)
Repeat need for stent	1 (0.7)
Stroke	0 (0.0)
Malign arrhythmia	7 (4.6)
CPR required	7 (4.6)
MV required	14 (9.2)
Cardiovascular events taking place at 3-month follow-up after discharge	n, (%)
Death	0 (0.0)
Stroke	0 (0.0)
New application with chest pain	26 (17.1)
New hospitalization with chest pain	16 (10.5)
Repeat ACS	8 (5.3)
Stent	4 (2.6)
CABG opp	3 (2)
Malign arrhythmia	1 (0.7)
CAD: Coronary artery disease; ACS: Acute coronary syndrome; MV: Mechanical ventilation; CPR: Cardiopulmonary resuscitation; MI: Myocardial infarction; HDL: High density lipoprotein; LDL: Low density lipoprotein; SD: Standard deviation	

Table 2. Troponin-T, CK-MB, PAPP-A and IMA levels of patients grouped according to definitive diagnosis and chest pain

	Patients applying with chest pain at 0-2 h					Patients applying with chest pain at 2-4 h					Patients applying with chest pain at 4-6 h					Patients applying with chest pain at 6-8 h				
	STEMI n=2	NSTEMI n=4	UAP n=4	SAP n=2	Non-cardiac n=25	STEMI n=2	NSTEMI n=8	UAP n=6	SAP n=5	Non-cardiac n=6	STEMI n=2	NSTEMI n=11	UAP n=4	SAP n=5	Non-cardiac n=18	STEMI n=2	NSTEMI n=13	UAP n=9	SAP n=5	Non-cardiac n=19
Troponin-Tng/ml (Ort.± SD)	0.010 ± .00	0.029 ± .025a	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00a	0.1 ± 0.09 b	0.14 ± 0.21c	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00b,c	0.19 ± 0.26	0.18 ± 0.22 h	0.01 ± 0.00	0.0 ± 0.00	0.05 ± 0.18h	10.61 ± 1.88 d,e	1.23 ± 2.71 f,g,i	0.01 ± 0.00 d,f,g	0.01 ± 0.00	0.05 ± 0.2 e,i
CK-MB ng/ml (Ort.± SD)	3.61 ± 0.71	3.47 ± 0.67	3.31 ± 0.54	2.81 ± 0.0	3.42 ± 0.52	7.35 ± 3.74	5.66 ± 2.93l	3.26 ± 0.71	2.74 ± 0.37	3.06± 0.55l	10.1 ± 11.5	16.5 ± 22.1	2.77 ± 0.25	2.8 ± 0.48	5.29 ± 8.34	273.0 ± 8.48	66.7 ± 112 j,k,m	3.15 ± 0.68j	3.11 ± 0.54k	5.42 ± 8.51 m
PAPP-A µg/ml (Ort.± SD)	1.55 ± 0.17	1.47 ± 0.16	1.66 ± 0.13	1.79 ± 0.0	1.60 ± 0.15	1.86 ± 0.07	1.51 ± 0.31	1.27 ± 0.14	1.46 ± 0.24	1.49 ± 0.32	1.31± 0.24	1.53 ± 0.23	1.56 ± 0.31	1.58 ± 0.15	1.51 ± 0.14	2.41 ± 1.19	1.49 ± 0.27	1.71 ± 0.91	1.23 ± 0.21	1.37 ± 0.23
IMA ABSU (Ort.±SD)	0.41 ± 0.03	0.51 ± 0.11	0.48 ± 0.08	0.29 ± 0.0	0.44 ± 0.08	0.54 ± 0.04	0.51 ± 0.19	0.52 ± 0.04	0.43 ± 0.1	0.45 ± 0.12	0.5 ± 0.01	0.5 ± 0.09	0.59 ± 0.08	0.5 ± 0.16	0.49 ± 0.09	0.58 ± 0.0	0.57 ± 0.09	0.59 ± 0.08	0.51 ± 0.16	0.49 ± 0.09

Significant results at comparisons in the same column and similar time intervals are indicated a,b,f,h,i,j,m P < 0.0001; c,e, P = 0.001; d,k, P = 0.002; g, P = 0.003; l, P = 0.005

diagnosis analysis findings (Table 3), which permit a more accurate picture of the diagnostic value of the biochemical parameters, CK-MB and troponin-T levels were more functional compared to IMA and PAPP-A in the differential diagnosis of chest pain.

STEMI and NSTEMI/UAP patients were regarded as ACS and other patients as non-ACS. Sensitivity, specificity, NPV and PPV values from ROC analysis performed for biochemical parameters measured between 0-2, 2-4, 4-6 and 6-8 h from the onset of chest pain are shown in Table 3.

Table 3. Sensitivity, Specificity, NPV and PPV Values from ROC Analysis

		AUC (95%CI)	Optimal cut-off point	Sensitivity (%); (95%CI)	Specificity (%); (95%CI)	NPV (%); (95%CI)	PPV (%); (%95CI)
Troponin-T ng/ml	0-2 h	0.600; (0.426-0.757)	>0.01	20.0; (2.5-55.6)	100.0; (87.2-100.0)	77.1; (59.9-89.6)	100.0; (15.8-100.0)
	2-4 h	0.719; (0.547-0.854)	>0.01	43.7; (19.8-70.1)	100; (83.9-100.0)	70.0; (50.6-85.3)	100.0; (59.0-100.0)
	4-6 h	0.760; (0.599-0.880)	>0.01	58.8; (32.9-81.6)	95.6; (78.1-99.9)	75.9; (56.5-89.7)	90.9; (56.6-99.8)
	6-8 h	0.748; (0.602-0.862)	>0.014	58.3; (36.6-77.9)	91.6; (73.0-99.0)	68.7; (50.0-83.9)	87.5; (61.7-98.4)
CK-MB ng/ml	0-2 h	0.533; (0.359-0.700)	≤3.1	50.0; (18.7-81.3)	76.9; (56.4-91.0)	80.0; (59.3-93.2)	45.5; (15.6-78.0)
	2-4 h	0.807; (0.644-0.917)	>3.1	81.2; (54.4-96.0)	71.4; (47.8-88.7)	83.3; (57.7-96.6)	68.4; (42.7-87.8)
	4-6 h	0.633; (0.466-0.779)	>4.1	52.9; (27.8-77.0)	91.3; (72.0-98.9)	72.4; (52.4-87.5)	81.8; (48.2-97.7)
	6-8 h	0.729; (0.583-0.846)	>3.8	66.6; (44.7-84.4)	80.0; (59.3-93.2)	71.4; (51.3-86.8)	76.2; (52.2-92.1)
PAPP-A µg/ml	0-2 h	0.573; (0.398-0.736)	≤1.38	20.0; (2.5-55.6)	100.0; (86.8-100.0)	76.5; (58.8-89.3)	100.0; (15.8-100.0)
	2-4 h	0.500; (0.332-0.668)	≤1.25	18.7; (4.0-45.6)	100.0; (83.9-100.0)	61.8; (43.6-77.8)	100.0; (29.2-100.0)
	4-6 h	0.504; (0.342-0.666)	≤1.36	35.3; (14.2-61.7)	91.3; (72.0-98.9)	65.6; (46.5-81.7)	75.0; (34.9-96.8)
	6-8 h	0.663; (0.512-0.793)	>1.72	30.4; (13.2-52.9)	100.0; (86.3-100.0)	61.0; (44.3-76.0)	100.0; (59.0-100.0)
IMA ABSU	0-2 h	0.604; (0.428-0.762)	>0.363	100.0; (69.2-100.0)	30.77; (14.3-51.8)	100.0; (63.1-100.0)	35.7; (18.6-55.9)
	2-4 h	0.786; (0.620-0.903)	>0.444	93.7; (69.8-99.8)	52.3; (29.8-74.3)	91.7; (61.5-99.8)	60.0; (38.2-79.2)
	4-6 h	0.577; (0.409-0.734)	>0.501	68.7; (41.3-89.0)	60.8; (38.5-80.3)	73.7; (48.8-90.9)	55.0; (31.5-76.9)
	6-8 h	0.742; (0.592-0.859)	>0.527	76.2; (52.8-91.8)	64.0; (42.5-82.0)	76.2; (52.8-91.8)	64.0; (42.0-82.4)

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In order to determine the ideal screening test so that almost no patient with ACS presenting to hospital with chest pain at 0-2 and 2-4 h intervals should be missed, we investigated the parameters with the highest sensitivity (100%). PAPP-A had 100% sensitivity for ACS at 0-2 h and specificity of 15.4% (4.4%-34.9%). Specificity of IMA value was 30.8% (14.3%-51.8%). At 2-4 h, sensitivity of PAPP-A value for ACS was 100% while specificity was 9.5% (1.2%-30.4%). Specificity of IMA value was 42.9% (21.8%-66.0%). Specificity of Troponin-T and CK-MB values was lower. On the basis of these results, in contrast to biochemical markers (CK-MB and Troponin-T) in standard use and that do not rise in the early stage of chest pain (0-2 and 2-4 h), IMA having higher specificity at values at which it is 100% sensitive for ACS mean it can be used as a more ideal screening test than PAPP-A. IMA and PAPP-A ROC curves for these periods are shown in Figures 1 and 2.

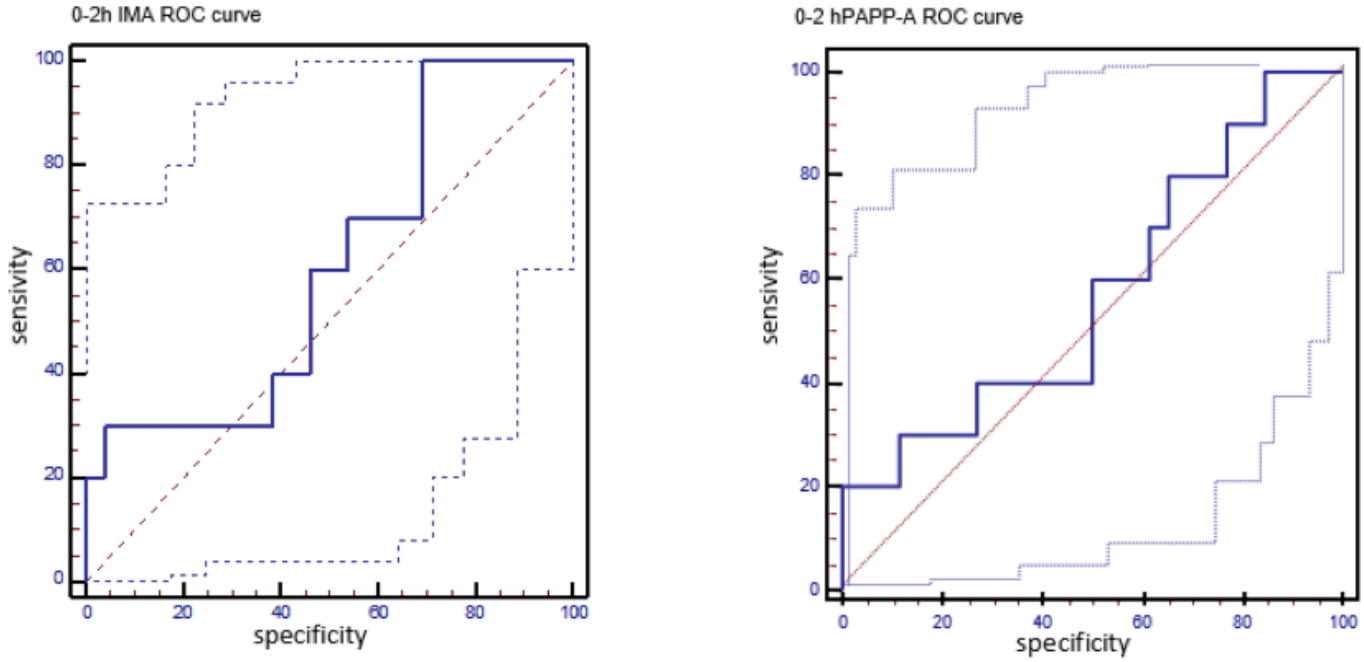

Figure 1. 0-2 h IMA and PAPP-A ROC curves

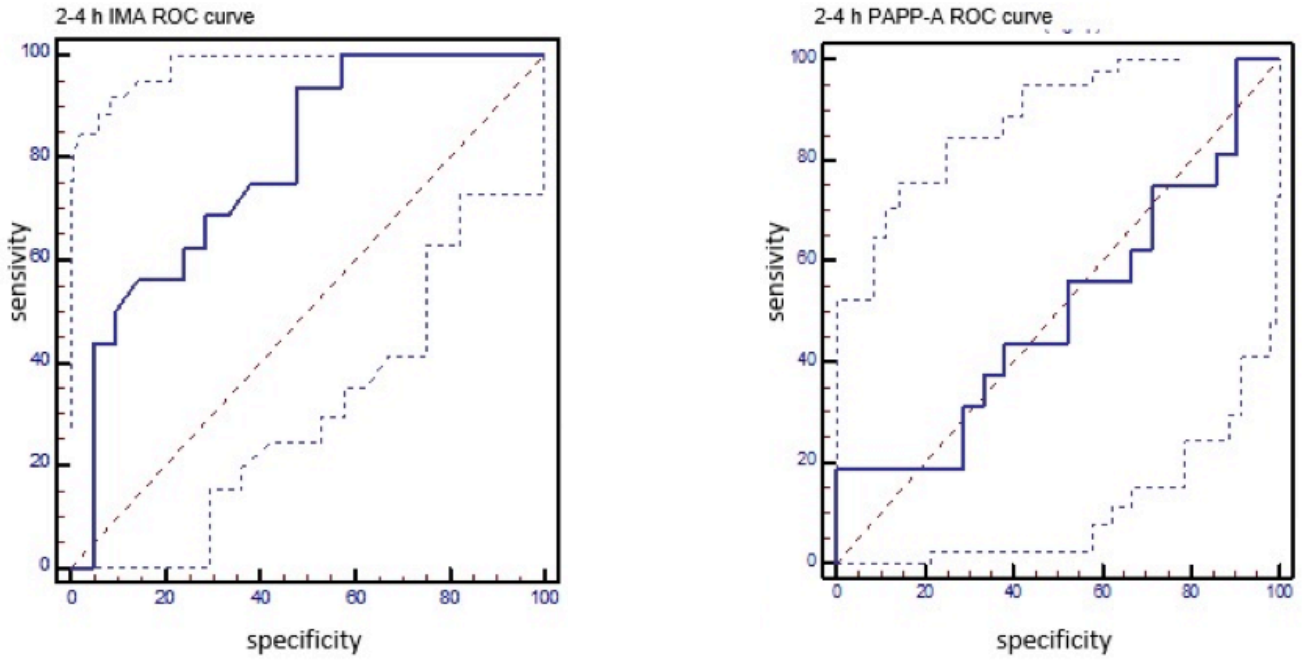

Figure 2. 2-4 h IMA and PAPP-A ROC curves

Spearman's correlation analysis performed for biochemical parameters measured between 1-2, 2-4, 4-6 and 6-8 h from the onset of chest pain. Accordingly, none of the parameters had any significant correlation in the 0-2 h period. For the period of 2-4 hours, there were significant positive correlations between troponin T and IMA, PAPP-A and CK-MB levels ($r = 0.326$, $P = 0.049$; $r = 0.325$, $P = 0.05$; $r = 0.677$, $P < 0.001$; respectively). For the periods of 4-6 and 6-8 hours, there were significant positive correlations only for CK-MB and Troponin-T ($r = 0.648$, $P < 0.001$; $r = 0.716$, $P < 0.001$; respectively).

Discussion

Chest pain is one of the most frequent causes of application to the ED. One of the most important points here, particularly for the emergency physician, is to perform differential diagnosis of the chest pain and make an early and accurate diagnosis. Various biochemical parameters are used in this differentiation. Early diagnosis is very important in terms of prompt and accurate treatment, especially in conditions with high mortality such as ACS. Several invasive and non-invasive techniques are currently used to investigate the etiology of chest pain, and biochemical analyses continue to represent an important diagnostic test assisting the physician with diagnosis.

Several studies have evaluated IMA and PAPP-A levels in patients with ACS. To the best of our knowledge, however, none have evaluated these two biochemical parameters together with standard contemporary cardiac biomarkers. Ours is an original study in that it is the first to compare PAPP-A, IMA, troponin-T and CK-MB values together.

The biochemical markers recommended for use in the diagnosis of ACS are cardiac troponin and CK-MB [11]. These markers show myocardial necrosis and rise in association with necrosis. However, they do not rise in the early period and in UAP. Since they begin to rise 4-6 h after myocardial necrosis and onset of symptoms, a certain period of time needs to pass for them to rise significantly in the blood. This may lead to a delay in diagnosis [12-14]. Therefore, a marker that rises before the development of myocardial necrosis will both improve the effectiveness of treatment and also prevent unnucessary hospitalizations. In particular, since these classic markers are not determined at high elevations, there is a need for a biochemical parameter that can be used in the fist 4 h. Our study evaluated both the classic biochemical markers CK-MB and Troponin-T, and also PAPP-A and IMA, modern parameters recommended for the first 4-h period. In agreement with the literature, CK-MB and Troponin-T exhibited no significant elevation in ACS patients in the first 4 h. In the first diagnostically uncertain 4-h period, the first stage of evaluation of patients with chest pain in the ED and in which classical biochemical prameters have not yet risen, the most important diagnostic tool to guide the emergency physician to a correct diagnosis is still ECG. None of the biochemical parameters we analyzed in patients with suspected ACS on the basis of ECG findings were at diagnostically adequate levels in the first 4 h. However, after the first 4-h period both CK-MB and Troponin-T levels rose significantly in ACS patients in line with ECG findings and guided diagnosis of ACS. PAPP-A and IMA values did not rise sufficiently to act as diagnostic guides in this period.

ECG is an important diagnostic tool in the evaluation of patients with chest pain. However, in order to achieve definitive diagnosis a rather complex algorithm and advanced diagnostic tools (angio, effort, etc.) are required. From that perspective, the most important part of the data we obtained are those based on definitive diagnoses established after following this algorithm and using advanced diagnostic tools. There is exact agreement between the results we obtained from analysis based on definitive diagnosis of patients with chest pain and those obtained from ECG findings at time of application. In other words, the biochemical parameters we examined in the first 4-h period are not differential for ACS patients. Troponin-T and CK-MB levels after the 4th h, and particularly after the 6th h, were determined as biochemical parameters in the diagnosis of ACS patients, as also agreed in the literature. As shown in detail in tables 3 and 4, almost none of the parameters we analyzed had the desired levels of sensitivity and specificity in the first 4 h for diagnosis of ACS. A biochemical marker with the potential to be used as a screening test in the ED, and especially for such a vitally significant disease group as ACS, must have a specificity higher than the highest sensitivity value. From that perspective, CK-MB, Troponin-T and PAPP-A levels are inadequate. However, the sensitivity and specificity values for IMA levels investigated at 0-2 h before onset of chest pain, and particularly at 2-4 h, are relatively more satisfactory (sensitivity and specificity for 0-2 h and 2-4 h, 100/30.7 and 93.7/52.3, respectively)

IMA is a contemporary biochemical parameter. Studies in recent years have shown that serum IMA levels rise in acute ischemic conditions. Albumin's binding to metal capacity in the N-terminus region decreases in acute ischemic conditions and a metabolic protein forms. This change can be measured, and is known as IMA [15]. Measurement of the albumin species that form with the changes in albumin's binding to metal capacity is important and practical in the diagnosis of several ischemic diseases. Bar et al. reported that IMA concentrations in the blood of patients with temporary ischemia established with angiography rose within a few minutes. Blood IMA concentrations then began returning to the levls in insidivudlas with no ischemia approximately 6 h after perfusion with angiography [11]. Vasrious studies have shown elevated IMA levels in acute ischemic events such as pulmonary embolism, peripheral arterial occlusion, deep vein thrombosis, stroke, seziure and acute cardiac arrest. It is

therefore considered suitable as a diagnostic marker [16-19].

IMA measurement is recommended in the early diagnosis of myocardial ischemia in patients with chest pain [20]. Many studies have detertmined IMA to be a very valuable biochemical parameter. In one such study, Sinha et al. examined 208 patients presenting to the ED with chest pain, within 3 h of onset of pain. They determined that IMA had high sensitivity in the early stage of myocardial ischemia (82%), and that sensitivity rose even higher when this was analyzed together with troponin and ECG (95%). That study suggested that IMA can be used as a diagnostic parameter in the early stage of myocardial ischemia [21].

One recent study determined that IMA had a high negative predictive value (NPV) of 90% for excluding acute coronary syndrome, and that when used together with cardiac troponins and non-diagnostic ECG the NPV rose to 97.1% [22]. In a study of patients with retrosternal symptoms in the previous 3 h, typical and atypical findings at ECG but with negative troponin levels, Roy et al. showed that IMA is an independent marker [23]. Another study involved 121 patients with retrosternal chest pain over the previous 20 min. Fifty-eight patients were diagnosed with NSTEMI and 62 with UAP. IMA values were significantly elevated at the normal cutoff point (85 U/ml) in both groups. However, IMA had no diagnostic superiority at comparison of UAP and NSTEMI. In other words, IMA was valuable in the diagnosis of ACS types but inadequate in differentiating between types of ACS [24].

In a study involving diagnosis of ischemic heart disease Dawie J et al. investigated CK-MB, troponin I and IMA levels [25]. Mean IMA values in patients with ACS were significantly higher than those of the healthy control group. In that study, IMA levels were 100% sensitive for ACS patients and 85.3% specific [AUC 0.948 (95% CI 0.914-0.983)]. They evaluated IMA as a rapid and simple method and a biochemical parameter that can be used in myocardial ischemia and infarct.

Other studies in the literature suggest the opposite, however. In one such, Kim JS et al. studied 390 patients with chest pain for the previous 6 h and applying to the ED for that reason. They compared patients with ischemic and non-ischemic chest pain. According to their findings, IMA levels in patients with non-ischemic chest pain and those with ischemic chest pain were significantly different [26]. Similarly, Worster et al. reported that IMA was of no diagnostic value in myocardial ischemia in a study of patients with ischemic-type chest pain synmptoms in the previous 6 h [27].

We determined no significant IMA elevation in either the early or late stages in ACS patients. The fact that other researchers have reported similar results to ours heightens the doubts about the use of IMA in the diagnosis of ACS and reveals the need for further studies before IMA is used routinely as a marker in the early diagnosis of ACS.

Proteins involved in the process of conversion of a stable atherosclerotic plaque into a sensitive plaque are today being intensively studied as potential markers. At autopsies following death from heart diseases, levels of PAPP-A, a matrix metalloprotein, have been reported to be higher in patients with eroded atherosclerotic plaques and a torn fibrous capsule compared to patients with stable plaques [28]. PAPP-A is a biomarker that shows inflammation and plaque instability and that can be detected in the sera of patients with ACS [6, 28]. Contemporary research is taking place into ACS diagnosis and subsequent PAPP-A levels.

In one such study, Bayes-Genis et al. investigated a study group consisting of AMI, UAP, SAP and healthy individuals, and reported higher serum PAPP-A levels in patients with AMI and UAP than in those with SAP and the healthy individuals [28]. Lund et al. showed that PAPP-A measured in troponin-negative patients hospitalized with a diagnosis of UAP is an early marker of ischemic cardiac events [29]. Various other studies involving ACS patients have shown that elevated serum PAPP-A concentrations are a powerful marker for mortality at long- and short-term monitoring. To summarize, since PAPP-A is a marker of plaque instability, not of myocardial damage, high PAPP-A levels are reported to be of use in the determination of future cardiovascular events. Findings from other research suggest that PAPP-A levels are no value in ACS patients, however. Dominguez-Rodriguez et al. compared PAPP-A levels in 80 patients with a diagnosis of acute STEMI and an 80-member control group and determined no difference between the groups [30]. In another study, markers that might be significant in the early diagnosis of and risk evaluation for ACS were investigated, including PAPP-A as well as Troponin T, heart fatty acid binding protein (H-FABP), glycogen phosphorylase-BB, high-sensitivity C-reactive protein, myeloperoxidase, matrix metalloproteinase 9, D-Dimer, Soluble CD40 ligand and N-terminal pro-brain natriuretic peptide (NT-proBNP). In that study, only H-FABP sensitivity was high for patients with ACS in the first 4 h of chest pain. Additionally, in terms of potential risk of death from myocardial infarct within 1 year, in addition to Troponin T, H-FABP and NT-proBNP also emerged as independent markers [31]. In this study, PAPP-A levels determed in UAP, NSTEMI and also acute STEMI patients were no different to those of the SAP and non-coronary patient groups. Similarly to IMA, this increases the doubts about the use of PAPP-A in the diagnosis of ACS. These inconcistent results make it essential for more comprehensive research on the subject to be performed before PAPP-A also enters into routine use.

Limitations of our study; Our comparison of the diagnostic value of two novel biochemical parameters in the diagnosis of ACS was performed in a limited time frame and with a limited number of patients. In addition, although the most up to date

approach for treating patients with suspected ACS at the time the study was performed was adopted, it should be borne in mind that various subsidiary advances have been made on the subject since.

The revised STEMI guidelines now consider high-sensitivity troponin tests to be better than all alternative cardiac markers, such as myoglobin, CK-MB, H-FABP, and conventional troponin assays. However, since high-sensitivity troponin measurement was not possible in the center where the research was performed at the time of the study, all our analyses were based on conventional troponin measurements.

In conclusion, the biochemical parameters we analyzed in the first 4 h period are not reliable for diagnosis of ACS. IMA had the highest sensitivity and specificity in this period, being relatively more than Troponin-T, CK-MB and PAPP-A, but still not satisfactory for an ideal marker.

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