Evaluation of Patients With Acute Chest Pain of Uncertain Origin by Means of Serial Measurements of High-Sensitivity C-Reactive Protein

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Introduction and objectives. We investigated the usefulness of taking two serial measurements of the high-sensitivity C-reactive protein (hs-CRP) level for evaluating acute chest pain in patients with non-diagnostic ECG findings and normal levels of markers of myocardial cell injury (ie, an inconclusive diagnosis). We hypothesized that the C-reactive protein concentration would be raised if symptoms were due to coronary endothelial damage or arteriosclerotic plaque rupture.

Methods. The study involved 468 consecutive patients who presented to the emergency department with acute chest pain, 191 of whom had an inconclusive diagnosis. In this patient group, we determined the hs-CRP level on emergency admission and at 24 hours. Standard guidelines on managing acute chest pain of suspected coronary origin were followed. Any increase in hs-CRP level between baseline and 24 hours was regarded as a positive result.

Results. In total, 38 (20%) patients were diagnosed with chest pain due to coronary disease. Measurement of the hs-CRP level differential (ie, the hs-CRP level at 24 hours minus the baseline level at emergency admission) had a sensitivity of 95% (95% confidence interval [CI] 81%-98%), a specificity of 40% (95% CI, 32%-47%), a positive likelihood ratio of 1.57 (95% CI, 1.33-1.83), a negative likelihood ratio of 0.13 (95% CI, 0.04-0.44), and an area under the receiver operating characteristic curve of 0.77 (95% CI, 0.69-0.85). By 30-day follow-up, no cardiac event had occurred in patients with a negative hs-CRP level differential.

Conclusions. Measurement of the hs-CRP level differential is diagnostically useful in patients with acute chest pain of likely coronary origin. A negative result is associated with a low risk of ischemic heart disease and would allow patients to be discharged safely from the emergency department.


Evaluación de los pacientes con dolor torácico agudo de origen incierto mediante la determinación seriada de los valores de proteína C reactiva de alta sensibilidad

Introducción y objetivos. Investigamos la utilidad de 2 medidas seriadas de proteína C reactiva de alta sensibilidad (PCR-as) para evaluar el dolor torácico en pacientes con electrocardiograma no diagnóstico y marcadores de daño miocárdico normales. Partimos de la hipótesis de que la concentración de PCR-as se incrementaría si los síntomas fueran causados por daño endotelial coronario o rotura de placa arteriosclerótica.

Métodos. Estudiábamos a 468 pacientes consecutivos atendidos en urgencias con dolor torácico, 191 con diagnóstico no concluyente. En esta población determinábamos la PCR-as en el momento del ingreso en urgencias y a las 24 h. Seguimos el protocolo de tratamiento del dolor torácico con sospecha de origen coronario. Cualquier incremento de la PCR-as a las 24 h en relación con la basal se consideró un resultado positivo.

Resultados. En total, 38 (20%) pacientes fueron diagnosticados de dolor torácico coronario. La diferencia de PCR-as (PCR-as a las 24 h menos PCR-as basal en urgencias) mostró una sensibilidad del 95% (intervalo de confianza [IC] del 95%, 81-98%), una especificidad del 40% (IC del 95%, 32-47%), una razón de probabilidad positiva de 1.57 (IC del 95%, 1.33-1.83), una razón de probabilidad negativa de 0.13 (IC del 95%, 0.04-0.44) y área bajo la curva receptor-operador de 0.77 (IC del 95%, 0.69-0.85). A los 30 días no hubo eventos cardiacos en los pacientes con diferencia negativa del valor de PCR-as.

Conclusiones. La diferencia de PCR-as resulta útil como herramienta diagnóstica en los pacientes con dolor.
torácico agudo de probable origen isquémico. Los resultados negativos se asocian con un bajo riesgo de isquemia coronaria significativa y permitirían dar de alta de forma segura a los pacientes desde el servicio de urgencias.


ABBREVIATIONS
CI: confidence interval
ECG: electrocardiogram
hs-CRP: high-sensitivity C-reactive protein
ROC: receiver operating characteristic
TnI: troponin I

INTRODUCTION

A significant proportion of patients with acute chest pain have normal, equivocal, or non-diagnostic electrocardiograms, and normal serial measurements of myocardial-cell injury markers. According to current guidelines, this population requires further testing when there is a high clinical risk of significant ischemic heart disease. The standard of care mandates these patients to undergo a time consuming diagnostic study (exercise testing, stress echocardiography and, if indicated, coronary angiography).

Some alternatives to the standard of care include image testing or using additional biochemical markers. Multi-slice computed tomography scan or cardiac magnetic resonance image are costly and not fully available. Other than traditional specific biochemical markers for the identification of myocardial ischemia such as ischemia modified albumin requires a short frame period for sampling measurement (less than 3 hours). Assessing plasma levels of myeloperoxidase, another biochemical marker associated with culprit lesions prone to rupture, is not widely available in clinical practice.

C-reactive protein is an acute phase reactant that increases above the baseline after a lag period of 12 h. of tissue damage and is commonly used in clinical practice for other diagnostic purposes. We hypothesized that patients with chest pain would show an increase in C-reactive protein concentrations if symptoms were caused by coronary endothelial damage or plaque rupture. Therefore we compared the accuracy of this test with those considered the reference standard for the diagnosis of ischemic heart disease in daily clinical practice.

METHODS

Patients and Study Design

We prospectively studied consecutive patients with acute chest pain attending our emergency department between November 2003 and November 2005. The study was carried out according to the Standards for Reporting of Diagnostic Accuracy criteria (STARD Initiative).

Patients who met all the following criteria were selected for study: a) arrival at Emergency Department within 12 hours of acute chest pain episode, b) normal or non-diagnostic ECG, and c) negative serial cardiac troponin I results. Patients with “diagnostic” ECG, positive cardiac troponin I (cTnI), active inflammatory diseases, neoplasms, and those with a definite diagnosis of non-ischemic chest pain were excluded.

We collected clinical data with regard to cardiovascular risk factors, including smoking status, hypercholesterolemia, diabetes mellitus, hypertension, obesity, and previous history of coronary disease. In addition, we recorded patients’ medications with potential anti-inflammatory effects to decrease baseline C-reactive protein values (antiplatelet agents, lipid-lowering drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers).

All patients carried out their assessment according to standard clinical practice.

Setting

The Marina Baixa Hospital is a 280-bed institution that belongs to the National Health Service located in the east coast of Spain, and attends a population of 180 000 inhabitants. Patients with acute chest pain are evaluated by emergency doctors and those with a probable coronary origin are referred for further testing at the Cardiology Department.

Study Protocol

12-Lead ECG

All patients underwent standard 12-lead ECG at baseline, and at 6, and 12 hours. ECG were considered to be non-diagnostic or uninterpretable when at least 1 of the following criteria was present: a) none or <1 mm ST segment depression, b) absence of T wave inversion (excluding leads aVR, III, and V1), c) previously known left bundle branch block, d) ventricular pacing, and e) non-dynamic repolarization abnormalities due to several entities (left ventricular hypertrophy, digitalis effect, Wolff-Parkinson-White, right bundle branch block).

Blood Samples

Cardiac troponin I concentrations were measured in serum on admission and at 6-8 hours by a high-sensitivity
cTnI commercial assay (cTnI TestPak, Dade Behring Inc., Newark DE, USA). A cTnI concentration greater than 0.08 ng/mL was considered positive for myocardial damage according to the criteria in our institution. High sensitivity C-reactive protein (hs-CRP) concentrations were determined in serum by a high-sensitivity immunoassay, on admission and 24 hours after the onset of chest pain (CRP latex HS, Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was 0.03 mg/L. The interassay coefficient of variation was 3.62 percent at 2.48 mg/L. The day-to-day coefficient of variation was 1.09 percent at 2.40 mg/L according to internal controls.

All biochemical analyses were performed by technicians unaware of patients’ history. Caregivers and physicians evaluating diagnostic tests were not informed about hs-CRP results.

Ischemic Diagnostic Tests

All patients completed a chest pain unit protocol 24 hours after their arrival. According to patients’ characteristics we performed: ECG exercise stress testing, exercise, or pharmacologic stress echocardiography (dobutamine or dipyridamole), or coronary angiography. Patients were considered to have unstable angina in the presence of symptoms of acute cardiac ischemia and typical ischemic ECG changes or chest pain during exercise test, regional wall motion abnormality on stress echocardiography, or significant stenosis (≥70%) on coronary angiography. Non-ischemic chest pain was diagnosed when all the following situations were found: a) a non cardiac mechanism was documented as the cause of chest pain, b) negative cardiac troponin I results on serial sampling (over a 6-12 h interval), and c) no abnormalities in ischemic tests or coronary angiography were found.

Follow-Up

Follow-up data were obtained by telephone interview 1 month after hospital discharge and by review of hospital admission records. Recorded cardiac events included death, non-fatal infarction, or angina. Cause of death was further classified as cardiac or non-cardiac.

Sample Size Estimate

We tested the non-inferiority of hs-CRP differential compared with exercise stress test to diagnose coronary artery disease. We considered 0.75 as the average sensitivity of exercise stress test. For a unilateral type I error of 0.05, and 85% certainty in detecting a sensitivity of hs-CRP differential of at least 0.55 (0.20 difference below than that of exercise stress test), a total of 38 disease positive patients were needed.

Statistical Analysis

Results of normally distributed continuous variables are expressed as the mean value (standard deviation), and continuous variables with non-normal distribution are presented as median values and interquartile range. Categorical data are shown as number (percentage). Comparisons of continuous variables were performed using the independent samples t test, Mann-Whitney U test, or Wilcoxon test as appropriate. Proportions were compared with the χ² test or Fisher’s exact test. Hs-CRP levels were found to have non-normal distribution.

Receiver operator characteristic (ROC) curve analysis and calculation of the area under the curve and its 95% confidence interval was carried out to evaluate the ability of hs-CRP on admission, hs-CRP at 24 hours and hs-CRP differential to correctly discriminate between those with and without acute coronary syndrome. We a priori considered a test positive, if hs-CRP on admission or a hs-CRP at 24 hours ≥ 3 mg/L. These cut-off points were based on previous observations that related concentrations of hs-CRP above 3 mg/L with a greater risk of suffering cardiovascular events. To maximize sensitivity, we a priori selected as positive test hs-CRP differential (hs-CRP at 24 hours minus hs-CRP on admission) ≥ 0 mg/L. We calculated the sensitivity, specificity, positive, and negative predictive values, and positive and negative likelihood ratios. Multivariate analysis was used with logistic binary regression to assess independent predictors of acute coronary syndrome on admission. Differences were considered to be statistically significant if the null hypothesis could be rejected with >95% confidence (P<.05). The SPSS 10.0 statistical software package (SPSS, Illinois, USA) was used for all calculations.

RESULTS

Study Population

Between November 2003 and November 2005, a total of 468 patients attended our Emergency Department with potential cardiac ischemia symptoms. Two-hundred and seventeen patients were excluded due to positive ischemia markers or abnormal ECG on arrival, delayed arrival, concomitant inflammatory conditions or non-coronary chest pain. (Figure 1). Thus 251 patients fulfilled eligibility criteria. Among patients with eligibility criteria, hs-CRP differential was not performed in 29 patients because of technical problems (shortage in test availability), and 31 did not undergo an ischemic diagnostic test, as considered not feasible by the evaluating cardiologist. Thus, we analyzed 191 patients with complete information.
At entry, patients with chest pain due to acute coronary disease more often had a history of hypertension and documented coronary disease, but had similar proportions in the distribution of other cardiovascular risk factors. Patients with a final diagnosis of acute coronary syndrome had significantly greater proportion of cardiovascular drug treatments than those with non-ischemic chest pain (Table 1).

### Final Diagnosis and Follow-Up

A total of 38 (17%) patients had a final diagnosis of chest pain due to acute coronary artery disease, diagnosed by means of significant stenosis in coronary angiography (n=14), positive exercise test (n=13), positive pharmacologic echocardiography (n=6), or positive exercise echocardiography (n=5). A total of 153 patients had as a final diagnosis chest pain not due to coronary artery disease, these patients underwent coronary angiography (n=24), exercise test (n=75), pharmacologic echocardiography (n=33), or exercise echocardiography (n=21). There were no patients who suffered major cardiac events or sudden death at 30 day of follow-up.

### High-Sensitivity C-Reactive Protein Measurements

Results for hs-CRP at baseline did not show significant differences between patients with chest pain due to coronary artery disease or patients with non-ischemic chest pain (Table 2), and had a poor discriminative value for the diagnosis of coronary artery disease with an estimated area under the curve of 0.51 (Table 3). Hs-CRP at 24 hours showed a marked increase in patients with a final diagnosis of coronary artery disease compared with those with chest pain not attributable to cardiac ischemia (8.64 mg/L vs 2.59 mg/L, P<.000) (Table 2). Hs-CRP at 24 hours had an estimated area under the curve of 0.68 (Table 3). Hs-CRP differential showed greater discriminant values compared to hs-CRP at 24.
Clinical Characteristics of Patients

At 24 h 8.64 (2.38-19.90) 2.59 (1.41-7.45) .000

Differential (Hs-CRP at 24 h. Minus Hs-CRP on Admission)

TABLE 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Non-Ischemic Chest Pain</th>
<th>Acute Coronary Syndrome</th>
<th>( \text{P} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>61 (14)</td>
<td>64 (13)</td>
<td>.360</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>81 (52.9)</td>
<td>27 (71)</td>
<td>.610</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>92 (60.1)</td>
<td>32 (84)</td>
<td>.005</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>36 (23.5)</td>
<td>14 (37)</td>
<td>.095</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>96 (62.7)</td>
<td>27 (70)</td>
<td>.338</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>54 (34.7)</td>
<td>16 (42)</td>
<td>.435</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>21 (13.7)</td>
<td>3 (8)</td>
<td>.329</td>
</tr>
<tr>
<td>Previous CAD, %</td>
<td>43 (28.1)</td>
<td>19 (50)</td>
<td>.010</td>
</tr>
</tbody>
</table>

Medications

Aspirin, % 40 (26.1) 21 (55) .001
Clopidogrel, % 18 (11.8) 10 (26.3) .023
Betablockers, % 36 (23.5) 20 (52.6) .000
Statins, % 50 (32.7) 16 (42) .274
ACEI, % 25 (16.3) 13 (34.2) .144
ARB, % 17 (11.0) 12 (31.6) .002
CCB, % 25 (16.3) 8 (21) .492
Nitrites, % 27 (17.6) 14 (38.6) .010
Diuretics, % 20 (13.0) 12 (31.6) .001
Fibrates, % 4 (2.6) 2 (5.26) .342
Any therapy, % 93 (60.8) 30 (78.9) .036

TABLE 2. Median (Interquartile Range) of Hs-CRP at Baseline, Hs-CRP at 24 Hours, and Hs-CRP Differential (Hs-CRP at 24 h. Minus Hs-CRP at Baseline)

<table>
<thead>
<tr>
<th>Hs-CRP, mg/L</th>
<th>Coronary Artery Disease</th>
<th>Coronary Artery Disease</th>
<th>( \text{P} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=38)</td>
<td>No (n=153)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.26 (1.31-3.58)</td>
<td>2.27 (1.09-4.34)</td>
<td>.853</td>
</tr>
<tr>
<td>At 24 h</td>
<td>8.64 (2.38-19.90)</td>
<td>2.59 (1.41-7.45)</td>
<td>.000</td>
</tr>
<tr>
<td>Differential</td>
<td>6.40 (0.68-14.40)</td>
<td>0.24 (0.17 to 1.54)</td>
<td>.000</td>
</tr>
</tbody>
</table>

TABLE 3. Performance Characteristics of High-Sensitivity C-Reactive Protein (Hs-CRP) on Admission, at 24 Hours and Differential Hs-CRP (Hs-CRP at 24 Hours Minus Hs-CRP on Admission) for the Diagnosis of Coronary Artery Disease in Patients With Acute Chest Pain of Possible Coronary Origin

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>Total</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-C Reactive protein on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-CRP Yes No</td>
<td>Sensitivity 0.34 0.20-0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 mg/L 13 60 73 Specificity 0.61 0.53-0.68</td>
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<tr>
<td>&lt;3 mg/L 25 93 118 LR+ 0.87 0.52-1.35</td>
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</tr>
<tr>
<td>Total 191 LR- 1.08 0.80-1.37 AUC 0.51 0.42-0.60</td>
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<tr>
<td>Hs-C Reactive protein at 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-CRP Yes No</td>
<td>Sensitivity 0.71 0.54-0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 mg/L 27 70 97 Specificity 0.54 0.46-0.62</td>
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<td></td>
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</tr>
<tr>
<td>&lt;3 mg/L 11 83 94 LR+ 1.55 1.15-1.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total 191 LR- 0.53 0.31-0.85 AUC 0.68 0.59-0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-C Reactive protein differential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-CRP Yes No</td>
<td>Sensitivity 0.95 0.81-0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0 mg/L 36 92 128 Specificity 0.40 0.32-0.47</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;0 mg/L 2 61 63 LR+ 1.57 1.33-1.83</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total 191 LR- 0.13 0.04-0.44 AUC 0.77 0.69-0.85</td>
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*Hs-CRP indicates high-sensitivity C-reactive protein.

Acute coronary syndrome showed an area under the curve of 0.77 (95% CI, 0.69-0.85).

Two (1%) patients had false negative hs-CRP differential values. These patients had confirmed coronary disease by angiography but null increase in hs-CRP differential. Both of them had a previous diagnosis of vasospastic angina and their symptoms could be attributed to coronary spasm, thus, not reflecting an underlying inflammatory process due to an atherosclerotic coronary plaque rupture. A total of 92 (48%) patients had false positive results of hs-CRP differential. The false positive results may be related to intra- or inter-assay variations.

In our sample, patients treated with cardiovascular drugs with anti-inflammatory effect had similar hs-CRP values (median interquartile range) to those who did not receive cardiovascular drugs, both at baseline (2.42 mg/L [1.21-4.56] vs 2.10 mg/L [0.95-3.50], \( \text{P}=0.09 \)), at 24 hours (3.19 mg/L [1.64-8.89] vs 2.58 mg/L [1.40-9.69], \( \text{P}=0.528 \)) and its differential (0.39 mg/dL [-0.11 to -4.22] vs 0.44 mg/L [-0.018 to 4.03], \( \text{P}=0.643 \)).

In a logistic regression analysis that included those variables that were significant in univariate analysis (history of hypertension, previous coronary artery disease, and current treatment with medications with potential anti-inflammatory effect), hs-CRP protein proved to be
the strongest independent determinant associated with chest pain of ischemic origin (Table 4).

**DISCUSSION**

In our study 20 percent of patients admitted to a chest pain unit with normal biochemical cardiac ischemic markers and non-diagnostic ECG had a final diagnosis of coronary heart disease. In this population, serial sampling of hs-CRP proved to be a simple bedside diagnostic test to rule out acute coronary syndrome. According to our inclusion criteria, patients had to attend the emergency department within 12 hours of symptoms onset. This time frame was selected based on CRP kinetics that shows a delayed rise with exponential increase at 12-hours in patients with acute coronary syndromes. A null increase between hs-CRP on admission and at 24 hours significantly decreases the pre-test probability (negative predictive value: 97 percent, negative likelihood ratio: 0.13). In our study, a total of 61 patients without ischemic heart disease (30% of the total population) had a negative hs-CRP differential, thus allowing discharge without any other diagnostic test. Hs-CRP differential proved to be a better screening test than standard exercise test due to its greater sensitivity. However, significant increases of hs-CRP were less informative to ruling in...
acute coronary syndrome. A single determination of hs-CRP at 24 hours of admission was less informative than hs-CRP differential. Hs-CRP on admission had a very poor discriminant power to diagnose acute coronary syndrome. According to current guidelines, patients with acute chest pain and normal biochemical and non-diagnostic ECG require further diagnostic tests. These patients must follow a protocol that includes exercise stress test or stress echocardiography. Our data suggest that by using hs-CRP differential a significant number of ischemic tests could have been saved. In our population, should hs-CRP serial measurement have been used it would have saved 33 percent of ischemic diagnostic tests and unnecessary prolonged hospitalization. Only 2 (3.2%) out of 63 patients had false negative hs-CRP differential values and would have erroneously discharged from the emergency department. However, we did not observe any cardiac events at 30-day follow-up in the studied patients. Hs-CRP differential testing could be specially useful and cost-saving in centers with limited resources or in periods of time where chest pain units were not available.

Currently it is mandatory to pursue an earlier and more accurate management decision for patients suspected of having acute coronary syndromes. Another biochemical marker of ischemia that has been tested is ischemia-modified albumin. Ischemia modified albumin is generated as a result of structural changes in the N-terminus of the serum albumin caused by ischemia, which reduces its binding capacity for cobalt cations, and it can be detected even before myocardial necrosis occurs. Values of ischemia modified albumin lower than 85 U/mL have a negative predictive value of 82%, allowing cardiac ischemia to be ruled out. However, its use is limited to the first 6 hours after the onset of pain, and it is also an expensive assay, available only in a small number of centers. Other non-specific indicators of inflammation, endothelial damage or thrombotic status have been evaluated as prognostic, but not diagnostic markers, most of them being independent predictors of ischemic endpoints; these include myeloperoxidase, fibrinogen, homocysteine, leukocyte count, interleukins, neopterin, soluble CD40 ligand, interferon, B-natriuretic peptide, D-dimer, and others with a low specificity for acute coronary syndrome diagnosis.

Our study has some limitations. Firstly, a gold standard test such as coronary angiography was not performed in all patients, leading to a possible classification bias. However, this gold standard is an expensive and invasive test, not indicated according to current guidelines in the management of patients with low risk profile. Nevertheless, in low risk profile patients we used other non-invasive test and assessed the follow-up at 30 days. Secondly, hs-CRP differential proved to be a test with high sensitivity but low specificity. That means that in clinical practice it should be used as a screening test to rule out coronary artery disease, but patients with a positive hs-CRP differential should undergo the standard protocol after admission. Nevertheless, a negative hs-CRP differential could save performing a significant number of time consuming procedures. Thirdly, hs-CRP differential has an intrinsically inter- and intra-assay variation that limits its accuracy. However, we “a priori” selected a cut-off value that maximized the sensitivity of the test (sensitivity 95%) reducing the proportion of false negative results. Compared with other ischemia tests, hs-CRP has several advantages such as its widespread availability, low cost, and greater timeframe interval for its determination (from 8 to 48 hours). Sample size is 1 of the most important limitations, as is the fact that this is a single center study, all of which could compromise the external validity of the results. Further investigations with a large number of patients could confirm our findings.

CONCLUSIONS

Our study shows that hs-CRP differential may constitute a good screening test to add to current emergency room protocols in the management of chest pain of possible coronary origin. A null increase between hs-CRP at 24 hours and hs-CRP on admission can rule out significant coronary disease, thus allowing safe discharge.

REFERENCES