

Variation in High-Sensitivity C-Reactive Protein Levels over 24 Hours

in Patients with Stable Coronary Artery Disease

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Limited, controversial data exist regarding changes in high-sensitivity C-reactive protein (hs-CRP) levels over short times and the importance of detecting these changes in patients who have coronary artery disease (CAD). We investigated the variation of hs-CRP levels and their association with the severity of CAD in patients with stable CAD.

We measured morning, midday, evening, and midnight hs-CRP levels in 124 patients (94 with CAD, 30 with normal coronary arteries), who were evaluated via coronary angiography and Gensini scoring. Patients were divided into 3 groups (normal coronary arteries, mild CAD, or severe CAD) according to Gensini score.

Temporal hs-CRP levels varied significantly—the highest mean concentrations were found in the morning, and the lowest concentrations at midday ($P < 0.001$). All temporal hs-CRP measurements and the absolute increase in hs-CRP levels were significantly higher in patients with severe CAD (both $P < 0.001$). The most significant predictors of CAD severity were age ($P = 0.005$), midday hs-CRP level ($P < 0.001$), and brain natriuretic peptide level ($P = 0.045$). Receiver operating characteristic curve analysis showed that cutoff values of hs-CRP taken at different times predicted severe CAD with similar sensitivity and specificity. Different cutoff values for temporal hs-CRP levels correlated with the severity of CAD. Serum levels of hs-CRP varied over 24 hours, whether patients had CAD or normal coronary arteries. (***Tex Heart Inst J 2010;37(1):42-8***)

Key words: Analysis of variance; biological markers/blood; C-reactive protein/analysis; coronary artery disease/blood; coronary stenosis; predictive value of tests; reference values; time factors

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High-sensitivity C-reactive protein (hs-CRP) is secreted from the liver in response to inflammation. Consequently, patients who have coronary artery disease (CAD) have elevated hs-CRP levels.^{1,2} Moreover, high baseline hs-CRP levels are associated with the presence, severity, and prognosis of coronary arteriosclerosis in patients with stable CAD.³⁻⁸ In 2003, the American Heart Association and the Centers for Disease Control (AHA/CDC) recommended that CRP be regarded as an element of global coronary risk assessment in adults without known cardiovascular disease. In that recommendation, a CRP cutoff value of 3 mg/L was considered to indicate high risk for CAD.⁹

Previous studies have shown elevated hs-CRP levels in patients who have unstable CAD, and the severity of this elevation has been correlated with the extent of coronary atherosclerosis, myocardial damage, and relative prognosis.^{5,7,8,10-12} One study¹³ reported diurnal hs-CRP variation in a middle-aged population, whereas other investigators¹⁴ observed no variation among healthy subjects. Limited and controversial data exist regarding changes in hs-CRP levels during the day and the significance of these changes in patients who have stable CAD.

We investigated the variation of hs-CRP levels at 6-hour intervals over a 24-hour period and the association of any variation with the severity of CAD in patients with stable CAD.

Patients and Methods

We enrolled 124 patients (mean age, 56.7 ± 8.9 yr; 84 men) in this cross-sectional study. Each patient had stable angina and ischemia induced by an exercise or chemical stress test. All were in stable overall condition and were undergoing optimal, individualized medical therapy for their cardiovascular conditions. Persons were excluded

from the study if they had renal disease (creatinine, >2 mg/dL), recent acute coronary syndrome, valvular heart disease, life-threatening arrhythmias, acute or chronic liver disease, infectious or noncoronary inflammatory disease, or symptomatic heart failure. Our local ethics committee approved the study, and written informed consent was obtained from all participants.

All patients were hospitalized for 36 hours and then underwent coronary angiography. We recorded their medical histories, including cardiovascular risk factors. Echocardiography was performed, and left ventricular ejection fractions were calculated by use of the modified Simpson method.¹⁵

Measurements of Biochemical Variables

On the day of the test, venous blood samples were taken from the antecubital vein every 6 hours: morning (6 AM), midday (12 PM), evening (6 PM), and midnight (12 AM). Each patient rested in a supine position for 20 minutes before blood was drawn. The samples were collected in tubes that contained EDTA. The hs-CRP levels were measured by means of immunonephelometric assay (BN ProSpec[®] System protein analyzer, Siemens Diagnostic Healthcare Inc.; Deerfield, Ill). Absolute change in hs-CRP (absolute Δ hs-CRP) over time was calculated as the hs-CRP level in the morning minus the hs-CRP level at midday. Relative change in hs-CRP (relative Δ hs-CRP) over time was calculated as absolute Δ hs-CRP divided by the hs-CRP level at midday. Levels of serum cholesterol, glucose, homocysteine, brain natriuretic peptide (BNP), cystatin C, and creatinine were measured by routine laboratory methods.

Angiographic Analyses

Coronary angiography was performed via standard Judkins techniques. Two experienced investigators (blinded to the clinical data) analyzed the angiograms. Coronary arteries were considered to be normal (0, for no stenosis), obstructed (25%, 50%, 75%, 90%, or 99% stenosis), or 100% occluded, according to the maximum obstruction that was observed in any projection. The severity of coronary atherosclerosis was classified according to Gensini score, which grades narrowing of the lumen as 1 for 1%–25% stenosis, 2 for 26%–50%, 4 for 51%–75%, 8 for 76%–90%, 16 for 91%–99%, and 32 for total occlusion.¹⁶ This score was multiplied by a factor that accounted for the importance of a lesion's position in the coronary arterial tree: 5 for the left main coronary artery; 2.5 for the proximal left anterior descending coronary artery (LAD) or proximal circumflex artery; 1.5 for the mid-LAD; 1 for the proximal right coronary artery, distal LAD, obtuse marginal artery, or posterior lateral artery; and 0.5 for other stenoses. The severity of disease was expressed as the sum of the scores for the individual lesions. The study population was then divided into 3 groups according to CAD-

severity score: normal coronary arteries (score, 0), mild CAD (score, 1–20), and severe CAD (score, >20).

Statistical Analyses

All analyses were performed with use of SPSS version 15.0 (SPSS, Inc.; Chicago, Ill). Categorical variables of the CAD groups were compared via the χ^2 test. Continuous variables were expressed as mean \pm SD. These variables were compared by 1-way analysis of variance, and, when indicated, by a post hoc Scheffé or Tamhane test. For the comparison of hs-CRP measurements that were taken at different times of the day, repeated-measures analysis of variance was applied. Correlations between continuous variables were evaluated by means of Pearson or Spearman rank correlation analysis. Multivariate logistic regression analyses were performed in order to determine significant predictors of CAD-severity scores above 20. Significant variables in univariate analysis at a $P < 0.1$ level were entered in logistic regression analysis. Linear regression analysis was also applied for determining CAD-severity score. A receiver operating characteristic (ROC) curve analysis was performed in order to identify the optimal cutoff points of hs-CRP levels that were taken at different times, and the BNP level was added to this ROC curve analysis (to determine maximal sensitivity and specificity) for predicting CAD-severity scores above 20. The area under the curve was calculated to determine the accuracy of the test. A P value of less than 0.05 was considered statistically significant. All data conformed to each test that was used to analyze them.

Results

Clinical Characteristics and Laboratory Variables According to Severity Score

Table I shows the clinical characteristics and laboratory variables of the study population. Of the patients, 94 had CAD (75.8%) and 30 had normal coronary arteries (24.2%). The severe-CAD group comprised more men, a higher mean age, a greater incidence of smoking, and higher levels of serum BNP and cystatin C than did the other groups. Except for BNP level, there was no significant difference between the normal-artery and mild-CAD groups in their comparative clinical and laboratory values.

Temporal Variation of High-Sensitivity C-Reactive Protein Levels

The hs-CRP measurements differed greatly throughout the day: the most significant difference was between the morning and midday measurements ($P < 0.001$) (Fig. 1). In all 3 groups, maximum mean hs-CRP levels were observed in the morning, and minimum mean levels were observed at midday. Accordingly, in the determination of absolute and relative Δ hs-CRP, the difference

TABLE I. Clinical and Laboratory Variables in Subgroups Defined by Severity of Coronary Artery Disease

Variable	Coronary Artery Disease Severity Score			P Value
	Normal (0) n=30	Mild (1–20) n=37	Severe (>20) n=57	
Age, yr	53 ± 7.4 ^a	54 ± 8.1 ^b	60 ± 8.9	<0.001
Men/women, n	14/16 ^a	25/12	45/12	0.003
Smoking, n (%)	6 (20) ^a	11 (29.7)	27 (47.3)	0.008
Hypertension, n (%)	19 (63.3)	25 (67.5)	32 (56.1)	0.42
Diabetes mellitus, n (%)	5 (16.6)	14 (37.8)	18 (31.6)	0.23
Hypercholesterolemia, n (%)	8 (26.6)	16 (43.2)	20 (35.1)	0.57
Family history of CAD, n (%)	8 (26.6)	11 (29.7)	10 (17.5)	0.26
Body mass index, kg/m ²	29 ± 5.2	28 ± 3.8	28 ± 4.3 ^c	0.299
Systolic blood pressure, mmHg	122 ± 10	121 ± 13	120 ± 12 ^c	0.969
Diastolic blood pressure, mmHg	78 ± 6.6	77 ± 9.1	78 ± 8.4	0.997
Heart rate, beats/min	76 ± 8.3	74 ± 11	75 ± 10	0.714
Medical/PCI/CABG treatment, n	30/0/0 ^{a,c}	18/13/6 ^b	8/12/37	<0.001
Left ventricular ejection fraction	0.62 ± 0.09	0.63 ± 0.06	0.58 ± 0.14	0.109
Glucose, mmol/L	102 ± 37	114 ± 49	119 ± 54	0.269
Creatinine, mg/dL	0.9 ± 0.2	1 ± 0.3	1.1 ± 0.3	0.07
Cystatin C, mg/L	0.8 ± 0.3 ^a	1 ± 0.4	1.1 ± 0.4	0.005
Total cholesterol, mmol/L	172 ± 42	178 ± 48	182 ± 40	0.064
Brain natriuretic peptide, pg/mL	20 ± 17 ^{a,c}	45 ± 57 ^b	119 ± 155	<0.001
Homocysteine, µg/dL	2 ± 0.7 ^a	2.4 ± 1.1	2.7 ± 0.9	0.008
Morning hs-CRP, mg/L	3.2 ± 2.3 ^a	5.3 ± 5.2 ^b	10.4 ± 8.7	<0.001
Midday hs-CRP, mg/L	1.9 ± 1.7 ^a	3.4 ± 3.5 ^b	7.1 ± 6.9	<0.001
Evening hs-CRP, mg/L	2.2 ± 1.9 ^a	3.7 ± 3.6 ^b	7.7 ± 6.8	<0.001
Midnight hs-CRP, mg/L	2.5 ± 1.9 ^a	4.3 ± 4.5 ^b	8.7 ± 7.3	<0.001
Absolute Δhs-CRP, mg/L	1.2 ± 1.3 ^a	1.8 ± 2.5	3.3 ± 4.6	0.017
Relative Δhs-CRP, %	86 ± 93	92 ± 143	82 ± 103	0.925

CABG = coronary artery bypass grafting; CAD = coronary artery disease; hs-CRP = high-sensitivity C-reactive protein; PCI = percutaneous coronary intervention

^a*P* < 0.05 between normal and severe score.

^b*P* < 0.05 between mild and severe score.

^c*P* < 0.05 between normal and mild score.

Values are expressed as number or as mean ± SD. *P* < 0.05 is considered statistically significant.

between the morning and midday hs-CRP measurements was used. Morning measurements were higher than other measurements in all of the study population, except for 3 patients in the mild-CAD group and 6 in the severe-CAD group. All 4 temporal hs-CRP levels and the absolute Δhs-CRP were significantly higher in the severe-CAD group, whereas no significant difference was observed for relative Δhs-CRP (Fig. 2 and Table I).

Correlation of High-Sensitivity C-Reactive Protein Levels with Clinical and Laboratory Variables

Table II shows the correlation of hs-CRP levels with the clinical and laboratory variables. All temporal hs-CRP measurements positively correlated with the CAD-severity score, patient age, and concentrations of serum creatinine, homocysteine, cystatin C, and BNP. Of the 4 temporal measurements, midnight

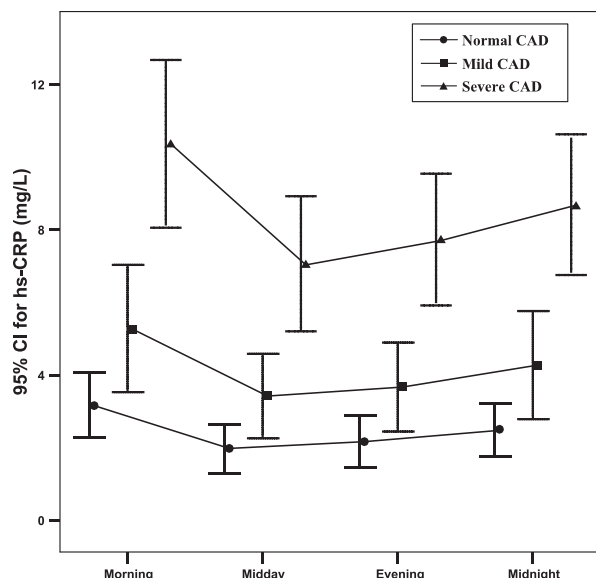


Fig. 1 Temporal variation of mean high-sensitivity C-reactive protein (hs-CRP) levels according to coronary artery disease (CAD) severity group.

CI = confidence interval

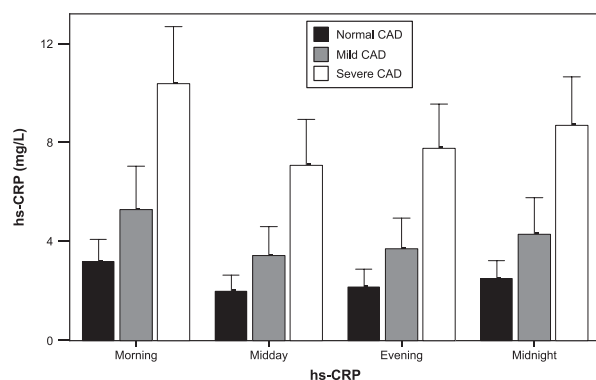


Fig. 2 High-sensitivity C-reactive protein (hs-CRP) levels (mean values \pm SD) taken at 6-hour intervals around the clock, according to coronary artery disease (CAD) severity group.

hs-CRP most significantly correlated with CAD-severity score. Although absolute Δ hs-CRP positively correlated with the CAD-severity score and with homocysteine concentration, no correlation was observed between relative Δ hs-CRP and these 2 variables.

Independent Predictors of Severity Score

Multivariate linear regression analysis showed that age ($\beta=0.234$, $P=0.005$), midnight hs-CRP ($\beta=0.3$, $P<0.001$), and BNP level ($\beta=0.165$, $P=0.045$) were the most important predictors of the CAD-severity score. The coefficient of determination (R^2) for the CAD-severity score was 0.28. Figure 3 shows the relationship between the midnight hs-CRP level and the severity score. Upon multivariate logistic regression analysis, independent predictors of a severity score above 20 were

age, midnight hs-CRP level, and BNP level; these were adjusted for sex, smoking, and homocysteine, and for morning, midday, and evening hs-CRP levels (Table III). Every 10-pg/mL increase in BNP, 1-mg/L increase in midnight hs-CRP, and 1-year increase in age caused corresponding increases of 10.5%, 20.1%, and 8.7% in the risk of having severe CAD.

Receiver Operating Characteristic Curve Analyses for Detecting Patients with Severe Coronary Artery Disease

We performed ROC analyses in order to estimate the predictive value of hs-CRP levels in the diagnosis of severe CAD (Table IV). Area-under-ROC curves for the 4 temporal hs-CRP levels and for BNP provided good discriminatory power, particularly for morning hs-CRP. These analyses also disclosed that different cutoff values of hs-CRP levels at particular measurement times revealed similar sensitivities and specificities for predicting severe CAD (Table IV).

Discussion

Our study shows significant temporal variation in hs-CRP levels over 24 hours, whether patients had CAD or normal coronary arteries. Morning hs-CRP was markedly higher than at other sampling times in all 3 groups. Moreover, different cutoff hs-CRP values for samples taken at different times had similar sensitivities and specificities for predicting severe CAD.

In our study, patients with stable CAD had significantly elevated hs-CRP levels regardless of the sampling time, which is in accordance with previous studies that reported high hs-CRP levels in stable and unstable patients alike.^{4,6,9,11,12} Our investigation of sampling time of hs-CRP revealed high hs-CRP at all measurement times in patients with mild and severe CAD.

To the best of our knowledge, temporal hs-CRP variation in patients with CAD had not previously been investigated over a time frame such as ours. The available data on diurnal variations of hs-CRP levels in healthy subjects are few and controversial. A recent study¹³ of hs-CRP, D-dimer, tissue plasminogen activator, and von Willebrand factor in a middle-aged population showed diurnal variation as high as 34% in hs-CRP, with maximum hs-CRP levels observed at 3 PM. However, that study was limited in that hs-CRP was measured between 9 AM and 10 PM. In our study, we measured hs-CRP 4 times over 24 hours at 6-hour intervals, and we observed the highest levels of hs-CRP in the morning, with a variation of 86%. These results also held true for our 30 patients who had normal coronary arteries. Previously, Meier-Ewert and colleagues¹⁴ found no diurnal variation in hs-CRP samples that were taken hourly from 13 healthy subjects. The variation in our study could be due to cardiovascular factors in all patients—

TABLE II. Correlation Coefficients and *P* Values between hs-CRP Measurements and Clinical and Laboratory Variables

hs-CRP Measurement	CAD-Severity Score	Age	Cystatin C	Creatinine	Homocysteine	BNP
Morning						
Correlation coefficient	0.36	0.16	0.275	0.324	0.297	0.191
<i>P</i> value	<0.001	0.075	0.002	<0.001	0.001	0.033
Midday						
Correlation coefficient	0.353	0.182	0.284	0.323	0.217	0.208
<i>P</i> value	<0.001	0.043	0.001	<0.001	0.016	0.02
Evening						
Correlation coefficient	0.349	0.181	0.251	0.282	0.227	0.209
<i>P</i> value	<0.001	0.044	0.005	0.002	0.011	0.02
Midnight						
Correlation coefficient	0.372	0.168	0.245	0.266	0.253	0.201
<i>P</i> value	<0.001	0.063	0.006	0.003	0.005	0.026
Absolute Δhs-CRP						
Correlation coefficient	0.185	0.043	0.12	0.158	0.271	0.066
<i>P</i> value	0.04	0.635	0.184	0.079	0.002	0.468
Relative Δhs-CRP						
Correlation coefficient	-0.096	-0.061	-0.091	-0.054	0.012	-0.09
<i>P</i> value	0.288	0.5	0.315	0.552	0.896	0.32

BNP = brain natriuretic peptide; CAD = coronary artery disease; hs-CRP = high-sensitivity C-reactive protein

P < 0.05 is considered statistically significant.

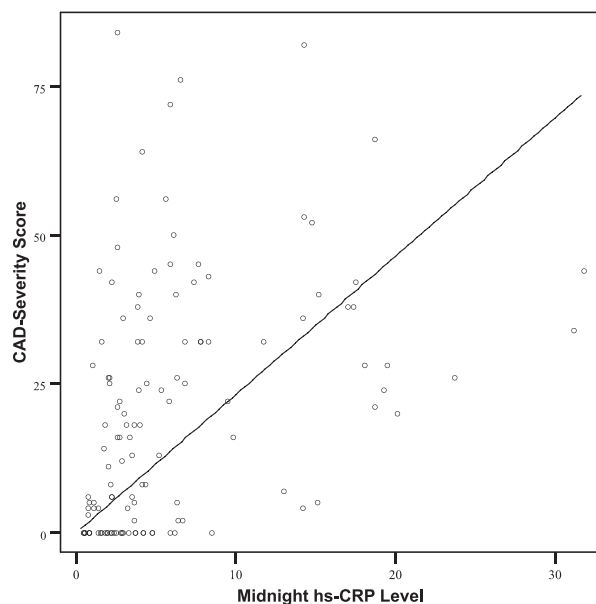


Fig. 3 The relationship between midnight levels of high-sensitivity C-reactive protein (hs-CRP) and coronary artery disease (CAD) severity score.

even in those with normal coronary arteries—because such risk factors as obesity, hypertension, diabetes mellitus, and smoking have been shown to induce hs-CRP secretion.⁶

A high baseline level of hs-CRP has been associated with the severity and prognosis of coronary atheroscle-

TABLE III. Multivariate Logistic Regression Analysis for Prediction of Severe Coronary Atherosclerosis

Variable	Odds Ratio	95% CI	<i>P</i> Value
Midnight hs-CRP, mg/L	1.217	1.072–1.383	0.002
BNP (for each 10 pg/mL)	1.085	1.023–1.195	0.039
Age, yr	1.115	1.042–1.162	0.001
Sex (men/women)	1.763	0.6–5.182	0.302
Smoking	0.27	0.09–0.81	0.054
Homocysteine, μg/dL	0.927	0.562–1.529	0.766

BNP = brain natriuretic peptide; CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein

P < 0.05 is considered statistically significant.

rosis in patients who have stable CAD.⁵⁻⁸ To indicate a high risk of CAD in adults without known cardiovascular disease, the AHA/CDC recommended a CRP cutoff value of 3 mg/L.⁹ Likewise, Sabatine and associates⁶ showed that an hs-CRP cutoff value of more than 3 mg/L predicted a 78% increased risk of adverse cardiovascular events in patients with stable CAD. Another study¹⁷ showed that hs-CRP is an independent predictor of CAD in patients with diabetes, and the cutoff value

TABLE IV. Diagnostic Performance of hs-CRP and BNP Levels for Severe Coronary Atherosclerosis

Variable	Area Under Curve (95% CI) No. (Range)	P Value	Cutoff	Sensitivity (%)	Specificity (%)
Morning hs-CRP	0.779 (0.698–0.86)	<0.001	5.5 mg/L	66.4	79.1
Midday hs-CRP	0.749 (0.663–0.835)	<0.001	3 mg/L	68.4	73.1
Evening hs-CRP	0.771 (0.689–0.864)	<0.001	3.5 mg/L	68.4	74.6
Midnight hs-CRP	0.775 (0.693–0.857)	<0.001	4.5 mg/L	64.9	79.1
Absolute Δ hs-CRP	0.654 (0.553–0.755)	<0.001	1.5 mg/L	63.2	64.2
BNP	0.752 (0.664–0.841)	<0.001	40 pg/mL	66.7	80.1

BNP = brain natriuretic peptide; CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein

$P < 0.05$ is considered statistically significant.

was determined to be 5.2 mg/L. In our study, our respective cutoff values of 5.5 mg/L, 3 mg/L, 3.5 mg/L, and 4.5 mg/L for morning, midday, evening, and midnight samplings strongly predicted severe CAD.

The number of angiographically detected critical coronary artery stenoses is a predictor of unfavorable events in patients with CAD.¹⁸ In previous studies,^{11,19} no significant association was reported between baseline serum CRP levels and CAD severity or the extent of disease in patients with unstable CAD. This may be related to lesion morphology and vulnerability. Conversely, in a large study of patients with stable CAD, Zebrack and colleagues⁵ reported a weak but significant correlation between hs-CRP and CAD severity. Our results similarly showed an independent relationship between midnight hs-CRP levels and severe CAD. Furthermore, all cutoff values of our temporal hs-CRP measurements predicted severe CAD with similar sensitivity and specificity.

Limitations of the Study

Our study is limited in several ways. The sample population was relatively small, considering the prevalence of CAD in any community. Whereas we measured hs-CRP 4 times during a 24-hour period, hourly measurements may more precisely disclose round-the-clock variations in hs-CRP levels. (Of note, hourly or more frequent sampling would be more costly, and arguably unethical because of frequent venipunctures.) In support of our quadripartite testing over 1 day, almost all of our patients had consistent hs-CRP measurements during a particular sampling time, so we conclude that our approach was sufficient and not of major concern. All of our patients were in stable overall condition, and all were on optimal medical regimens for their cardiovascular conditions. The individualized therapy involved different medications and dosages, which may have influenced hs-CRP levels,⁶ and we did not consider medications in our analyses. Furthermore, our CAD-

severity groups differed greatly regarding age, sex, and treatment. Although these factors were adjusted in the analyses, it is a major concern that the severity groups were unmatched for these variables. Finally, because stable CAD and acute coronary syndromes have different pathogeneses, it remains to be determined whether our results would apply to patients with unstable angina pectoris and acute myocardial infarction.

Conclusions

This is the 1st study to show variation of hs-CRP levels in patients with stable CAD at 6-hour intervals over a 24-hour period. We have shown that the sampling time of hs-CRP is important, because only midnight hs-CRP measurements predicted severe CAD in our study population. This aside, when different cutoff values were applied to particular sampling times, severe CAD was predicted with similar sensitivity and specificity. Whether our results apply to other forms of CAD needs to be confirmed in future study populations.

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