THE ASSOCIATION BETWEEN MATRIX METALLOPROTEINASE-9 (MMP-9) WITH HIGH SENSITIVE TROPONIN T (hs-TnT) IN PATIENT WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Mechanism of acute myocardial infarction (AMI) is previously due to atherosclerotic plaque rupture with occurs because extra-cellular matrix of plaque fibrous cap destruction or degradation by protease enzyme matrix metalloproteinase-9 (MMP-9), which released by macrophage cell.Increased plasma MMP-9 is predisposition factor of atherosclerotic plaque rupture in AMI and followed by acute thrombosis inside coronary artery lumen which caused myocardial ischemic and clinical sign of AMI. If the ischemic process continuous and ongoing that can caused myocardial necrosis which can increased plasma troponin. High sensitive troponin T (hs-TnT) newly and more sensitive detection of plasma cTn-T than conventional.The aim of this study was to determined the association between plasma MMP-9 with hs-TnT in AMI patients.This study was a cross-sectional observational which performed in 62 patients with AMI which enrolled by consecutive sampling at Sanglah Hospital Denpasar from December 2011 until December 2012. MMP-9 and hs-TnT plasma level were measured 48 hours after onset IMA. Sixty two patients AMI were involved in this study consist of 35 STEMI patients (56.5%) and 27 NSTEMI patients (43.5%), the mean plasma MMP-9 was 23.9 (SD 0.42) ng/mL and hs-TnT was 464.7 (SD 39.3) ng/mL.The results of this study were positive correlation between MMP-9 and hs-TnT AMI patients (r= 0.507; Y= - 650.6 + 46.7(X_1); P<0.0001); plasma MMP-9 and onset of AMI were influenced to plasma hs-TnT with formulationY = - 815.0 + 46.5(X_1)+ 20.7(X_2); ($\hat{a}$ MMP-9=46.5(95%CI : 24.7 to 68.4); P<0.0001; $\hat{a}$ onset AMI=20.7(95%CI : 2.1 to 39.4); P=0.030) and there was more stronger correlation betweenMMP-9 and hs-TnT in STEMI group than NSTEMI. **[MEDICINA 2015;46:22-27].**

***Keywords**: MMP-9, hs-TnT, AMI, STEMI, NSTEMI*

HUBUNGAN KADAR *MATRIX METALLOPROTEINASE-9* (MMP-9) DENGAN *HIGH SENSITIVE TROPONIN T* (hs-TnT) PADA PENDERITA INFARK MIOKARD AKUT

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ABSTRAK

Mekanisme terjadinya infark miokard akut (IMA) didahului oleh proses ruptur plak aterosklerosis dan diawali dengan destruksi atau degradasi matriks ekstraseluler *fibrus cap* plak oleh enzim protease yang dihasilkan sel makrofag yaitu *matrix metalloproteinase-9* (MMP-9). Kadar MMP-9 yang meningkat merupakan faktor predisposisi terjadinya ruptur plak aterosklerosis pada IMA yang diikuti oleh proses trombosis akut pada lumen arteri koroner yang menyebabkan proses iskemia miokard dan gejala klinis IMA. Proses iskemia yang tidak teratasi akan mengakibatkan nekrosis miokard yang ditandai meningkatnya troponin jantung. Pemeriksaan *high sensitive troponin T* (hs-TnT) merupakan pemeriksaan kadar troponin yang terbaru dan memiliki kemampuan lebih baik dari pemeriksaan troponin konvensional. Tujuan dari penelitian ini untuk mengetahui hubungan kadar MMP-9 dengan hs-TnT plasma pada penderita IMA. Penelitian ini merupakan studi observasional potong lintang yang dilakukan pada 62 penderita IMA yang dikumpulkan secara *consecutive sampling* di RSUP Sanglah Denpasar dari Desember 2011 sampai Desember 2012. Kadar plasma MMP-9 dan hs-TnT diukur 48 jam setelah awitan IMA. Dari 62 sampel penelitian yang terdiri dari 35 pasien STEMI (56.5%) dan 27 pasien NSTEMI (43.5%) didapatkan rerata kadar MMP-9 plasma 23.9 (SB 0.42) ng/mL dan hs-TnT plasma 464.7 (SB 39.3) ng/mL.Hasil penelitian ini terdapat korelasi positif antara

kadar MMP-9 dengan hs-TnT pada penderita IMA dengan kekuatan korelasi sedang dan secara statistik signifikan (r= 0.507; Y= - 650.6 + 46.7(X_1); P<0.0001); kadar MMP-9 plasma dan awitan IMA mempengaruhi kadar hs-TnT plasma pada penderita IMA dengan formula persamaan Y = - 815.0 + 46.5(X_1)+ 20.7(X_2); ($\hat{a}$ MMP-9=46.5(IK 95% : 24.7 sampai 68,4); P<0.0001; $\hat{a}$ awitan IMA=20.7(IK 95% : 2.1 sampai 39.4); P=0.030). dan kekuatan hubungan kadar MMP-9 dengan hs-TnT pada kelompok STEMI lebih besar daripada NSTEMI. **[MEDICINA 2015;46:22-27].**

***Kata kunci**: kadar MMP-9, hs-TnT, IMA, STEMI, NSTEMI*

INTRODUCTION

Coronary artery disease is leading cause of death in the world,[1] approximately 30% from all cause of death.[2]Acute coronary syndrome (ACS) is one of coronary heart disease manifestation and a serious cardiovascular emergency.[3]

Basic pathogenesis acute myocardial infarction is atherosclerotic plaque rupture with following thrombus formation in coronary artery. The process of atherosclerotic plaque rupture is caused by protease enzyme released from macrophage cell, such as matrix metalloproteinase-9 (MMP-9), that cause degradation and fibrous cap rupture and form thrombus with coagulation cascade activation. This thrombus formation will give clinical manifestation of ACS and increase of troponin levels.[4-7]

Cardiac troponin (cTn), cTnTand cTnI , is a gold standard for detection of myocardial necrosis.[5,8] Using high sensitive cardiac troponin (hs-cTn), hs-TnTand hs-TnI, will improve early diagnosis of acute myocardial infarction (AMI) significantly and hopefully will decrease false positive result.[5,9]

Several studies have been done to compare MMP-9 levels with hs-TnT in patients with ACS. Kobayashi et al[10] found MMP-9 levels increased in acute phase of ACS as reflection of plaque vulnerability and hs-TnT levels increased in later phase. Setianto et al[11] in 2011 compared MMP-9 levels MMP-9 and troponin-I (cTn-I) in ST Elevation Myocardial Infarction (STEMI) and Unstable Angina Pectoris (UAP)/ Non ST Elevation Myocardial Infarction (NSTEMI) with result a positive correlation between increase of MMP-9 levels and cTn-I mainly in STEMI group and stated MMP-9 role in myocardial damage severity with r=0.33 and P=0.003. There is no research that study correlation between increase of MMP-9 levels and hs-TnT in AMI patients.

METHODS

This study was a observational study with cross-sectional design to evaluate MMP-9 levels and hs-TnT levels in AMI patients at emergency unit and Intensive Cardiac Care Unit (ICCU) Cardiology Departement Udayana University Medical School/ Sanglah Hospital. This study was a research tree about ACS that has been held from December 2011 until December 2012 and the result became Joint Study of ACS. This study has been approved by Ethics Committee of Udayana University Medical School/Sanglah Hospital Denpasar. Subjects of this study were 62 patients with AMI that fulfilled inclusion and exclusion criteria. The inclusion criteria were: 1) all AMI patients age 30-80 years old and treated at emergency unit and ICCU Sanglah Hospital, 2) gave consent to participate in this study. The exclusion criteria were : 1) valvular heart diseases (VHD), 2) congestive heart failure (CHF), 3) acute or chronic liver disease, 4) chronic kidney disease (CKD) (creatinine clearance < 60 ml/1.73 m2/min), 5) chronic or acute infection, 6) sepsis, 7) malignancy, 8) treated with corticosteroid or non steroidal anti inflammatory or immunosuppresive drugs more than 1 weeks, and 9) stroke. This study using human MMP-9 ELISA kit and Roche Elycsys 2010 kit which measured 48 hours after onset AMI.

Analysis of correlation between MMP-9 with hs-TnT using non-parametric analysis with Spearman test (P<0.05). Multivariate analysis with multiple linear regression the relationship of the functional predictive value MMP-9 and others confounding variable to plasma hs-TnT. The last we performed ANCOVA analysis to determine the difference of strength association between plasma MMP-9 and hs-TnT in STEMI or NSTEMI group. Data analysis using SPSS 17 with significant P<0.05.

RESULTS

A total of 62 samples were included in this study. Matrix metalloproteinase-9 (MMP-9) and hs-TnT plasma levels 48 hours after AMI onset were measured. The samples also got treatment based on ACS guideline from PERKI 2014.[12]

Subject characteristics

Total 62 patients with AMI were included, 50 males (80.6%) and 12 female (19.4%), with mean age 57.9 (SD 10.7) years. Thirty five patients were diagnosed with STEMI (56.5%) and 27 patients with NSTEMI (43.5%) with mean onset between 6.74 (SD 3.8) hours. Cholesterol levels were between 110-327 mg/dL, LDL levels were between 56.3-244.5 mg/dL, HDL

levels were between 22.23-78 mg/dL, and BMI were between 18.2-36.9 kg/m^2. There were 11 subjects with DM (17.78%), 55 subjects (88.7%) with dyslipidemia, 36 subjects (58.1%) with hypertension, and 32 subjects (51.6%) with obesity and smoking (**Table1**).

Table 1. Subject characteristics

Characteristics	n=62
Age (year), mean (SD)	57.9 (10.7)
Sex, male, n (%)	50 (80.6)
Diagnosis	
STEMI, n (%)	35 (56.5)
NSTEMI, n (%)	27 (43.5)
Diabetes Mellitus, n (%)	11 (17.7)
Dyslipidemia, n (%)	55 (88.7)
Cholesterol (mg/dl)	193.8 (46.3)
LDL (mg/dl)	134.2 (44.1)
HDL (mg/dl)	40.2 (11.8)
Triglyseride (mg/dl)	144.2 (85.5)
Hypertension, n (%)	36 (58,1)
Obesity, n (%)	32 (51.6)
BMI (kg/m^2), mean(SD)	24.8 (3.9)
Smoking, n (%)	32(51.6)
Onset AMI (hours), mean(SD)	6.74 (3.8)

Mean MMP-9 plasma levels was 23.9 (SD 0.42) ng/mL and mean hs-TnT plasma levels was 464.7 (SD 39.3) ng/mL.

Kolmogorov-Smirnov test was done to assess data normality. the data distribution of independent and dependent variables with result the data distribution was not normal (P=0.047). Therefore we assess with non-parametric Spearman correlation test and simple linear regression analysis with result scatter plot graphic correlation MMP-9 with hs-TnT. For every increase of MMP-9 was followed with increase of hs-TnT levels in the subjects. Correlation coefficient value (r)=0.507 which meant the corellation between MMP-9 and hs-TnT was moderate. Value R^2 (R square) = 0.247 which meant that variation of hs-TnT 24.7% was influenced by MMP-9 levels, and others 75.3% was influenced by another factors that were not studied (**Figure 1**). Coefficient â value MMP-9 ($\hat{a}_1$) 46.7 which meant for every 1 ng/dL increase of MMP-9 followed by increase of 46.7 ng/dL hs-TnT and statistically significant with P< 0.0001. With $\hat{a}_0$ = - 650.6, the equation formula simple regression analysis was: $Y= \hat{a}_0 + \hat{a}_1 X_1$ became $Y= - 650.6 + 46.7(X_1)$, where Y was hs-TnT plasma levels, X_1 was MMP-9 plasma levels.

Table 2. Analysis result of double linear regresion MMP-9 and confounding factors

Variables	β (95% CI)	Standard Error (SE)	P value
MMP-9	46.5(24.7 to 68.4)	10.9	<0.001
DM	-85.7 (-273.8 to 102.4)	93.7	0.365
Dyslipidemia	132.1(-102.7 to 367.0)	117.0	0.264
Hypertension	-39.4 (-194.8 to 116.1)	77.5	0.614
Obesiy	32.3 (-115.3 to 179.8)	73.5	0.663
Smoking	-46.7 (-193.8 to 100.4)	73.3	0.527
Age	3.7 (-3.4 to 10.8)	3.5	0.303
Sex	-82.0 (-316.6 to 198.4)	102.6	0.428
Onset AMI	20.7(2.1 to 39.4)	9.3	0.030

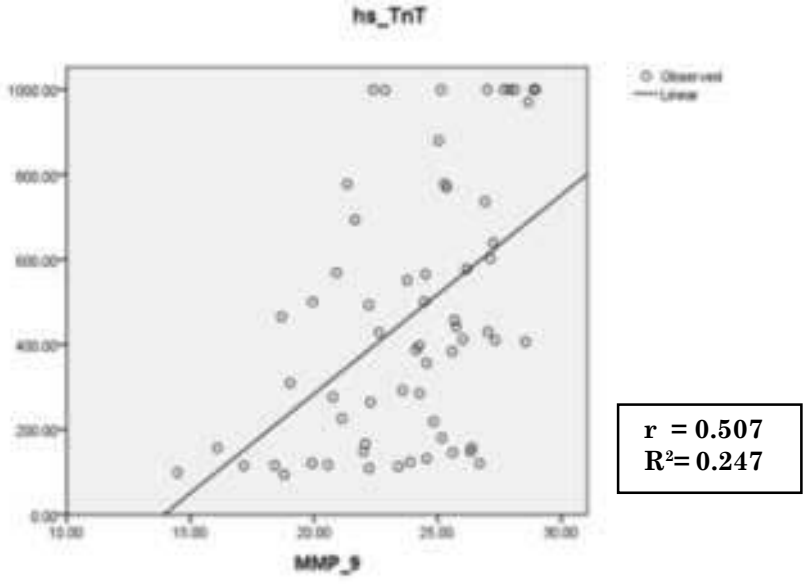
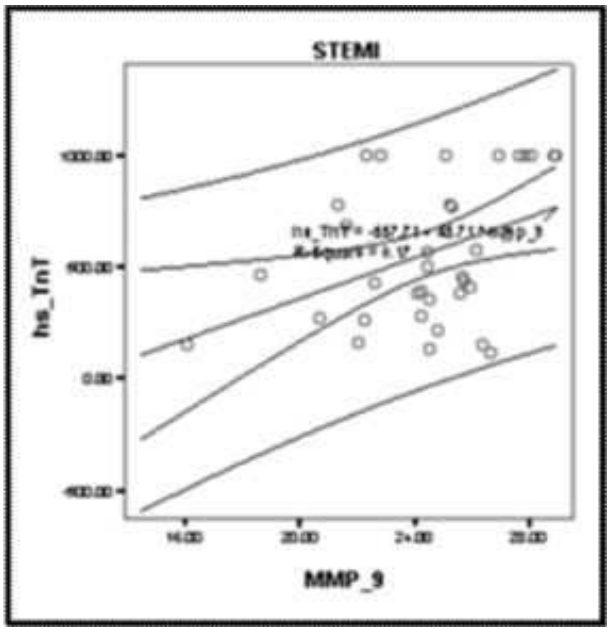


Figure 1. Scatter-Plot graphic correlationMMP-9 levels and hs-TnT levels.

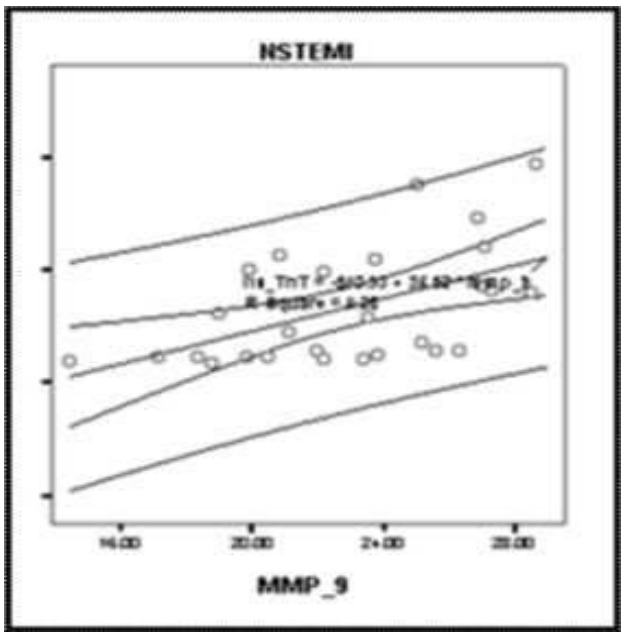
To assess effect of confounding factors such as DM, dyslipidemia, hypertension, smoking, obesity, sex, age, and onset AMI, to correlation between MMP-9 levels and hs-TnT levels, we did multivariate analysis (**Table 2**).

After multivariate analysis with double linear regression between independent variable MMP-9 and confunding factors to evalute theirs effect to hs-TnT, it showed that variable MMP-9 and onset AMI were proven to influence hs-TnT levels. Coefficient â value MMP-9 levels = 46.5(95%CI : 24.7 to 68.4), onset AMI= 20.7(95%CI : 2.1 to 39.4);with P<0.0001 and 0.030 (statistically significant). Coefficient â MMP-9 ($\hat{a}_1$) 46.5,



R^2= 0.17
β_0 = -557.7
β_1 = 45.7

Figure 2. Graphic the strength of relationbetween MMP-9 levels and hs-TnT in STEMI group.



R^2= 0.26
β_0 = -503.9
β_1 = 36.5

Figure 3. Graphic the strength of relation between MMP-9 levels and hs-TnT in NSTEMI group.

which meant for every 1 ng/dL increase of MMP-9 followed by 46.5 ng/dL increase of hs-TnT. Coefficient â onset AMI ($\hat{a}_2$) 20.7, which meant for every 1 hour increase of onset AMI followed by 20.7 ng/dL increase of hs-TnT. From multivariate analysis result with double linear regression with $\hat{a}_0$ = - 815.0, the equation formula: $Y = \hat{a}_0 + \hat{a}_1X_1 + \hat{a}_2X_2$, so Y = - 815.0 + 46.5($X_1$)+ 20.7($X_2$), where Y was hs-TnT plasma levels, $\hat{a}_0$ was constanta; $\hat{a}_1$ was coefisient *â* MMP-9; $\hat{a}_2$ was coefisient *â* onset IMA, X_1 and X_2 were MMP-9 plasma levels.

To compare association between MMP-9 with hs-TnT in STEMI and NSTEMI, ANCOVA analysis was done.

In STEMI group, R^2 = 0.17 which meant value variation by MMP-9 in STEMI group was 17% and coefficient $\hat{a}_1$ = 45.7 which meant for every 1 ng/dL increase of MMP-9 levels in STEMI group followed with 45.7 ng/dL increase of hs-TnT; that statistically significant with P=0.019. With constanta ($\hat{a}_0$) = - 557.7; the equation formula: $Y = \hat{a}_0 + \hat{a}_1X_1$, became Y = - 557.7 + 45.7 (X_1); Y was hs-TnT plasma levels in STEMI, $\hat{a}_0$was constanta, $\hat{a}_1$ was coefficient â STEMI group, and X_1 was MMP-9 plasma levels in STEMI (**Figure 2**).

In NSTEMI group, R^2 = 0.26, which meant value variation of hs-TnT was influenced by MMP-9 in NSTEMI group was 26% and coefficient $\hat{a}_2$ = 36.5, which meant for every 1 ng/dL increase of MMP-9 in NSTEMI group followed by 36.5 ng/dL increase of hs-TnT levels; that statistically significant with P=0.019. With constanta ($\hat{a}_0$) = -503.9, the equation formula $Y = \hat{a}_0 + \hat{a}_2X_2$, became Y = -503.9 + 36.5 (X_2); where Y was hs-TnT plasma levels in NSTEMI group, $\hat{a}_0$ was constanta, $\hat{a}_2$ was coefficient â value NSTEMI group, and X_2 was MMP-9 plasma levels in NSTEMI group(**Figure 3**).

DISCUSSION

Sixty two sample were included in this study, 35 STEMI samples and 27 NSTEMI samples. Range of age was between 39 until 80 years old and range of onset AMI was between 1 hour until 16 hour. Most of the samples were male, similar with several studies tht showed male had higher risk factors and mortality because of coronary artery disease, such as ONTARGET and TRANSCEND studies.[13]

Almost all subjects had dyslipidemia. Study The Effect of Potentially Modifiable Risk Factors associated with Myocardial Infarction (INTERHEART) that held in 52 countries found dyslipidemia was risk factor in 50% samples.[14]

The hypothesis of this study was proven, there was positive correlation with moderate strength between MMP-9 levels and hs-TnT plasma levels in AMI with coefficient correlation value 0.507; P<0.0001. From linear regression analysis, it was found that functional predictive relation between MMP-9 and hs-TnT plasma levels could be shown with

formula hs-TnT plasma level prediction: (Y) = - 650.6 + 46.7 (X_1), where we could predict the increase of hs-TnT levels by adding constanta ($\hat{a}_0$) with coefficient $\hat{a}$ timed MMP-9 plasma levels. In other word, for every increase of MMP-9 plasma levels influenced to increase of hs-TnT plasma levels in AMI patients.

Similar result was found in Margina et al study in 2005 that found relation between MMP-9 and I (cTn-I) with r=0.29; P=0.004, and study by Setianto et al[11] that found there was correlation between MMP-9 levels with troponin I (cTn-I) with weak magnitude in AMI patients, with r=0.33; P=0.003.

MMP-9 is an protease enzyme, gelatinase-B class, that has capability to degrade collagen type IV in basal membrane of fibrous cap, mainly contributes in plaque instability until plaque rupture. Capability MMP-9 in degrade collagen in fibrous cap was a predisposition factor of atherosclerotic plaque rupture, followed by thrombus formation in coronary artery lumen, activates couagulation cascade, and becomes AMI.[4,6,7] Increase of MMP-9 levels in circulation of AMI patients shows increase of MMP-9 production affects mechanism and pathophysiology AMI.[15] In AMI mechanisms, acute thrombotic process in coronary artery will be followed by myocardial necrosis and signed by increase of troponin plasma levels. Increase of troponin levels relates with severity of thrombotic process, indirectly showed extent of myocardial necrosis.[4,5]

Multivariate analysis was done to independent variable MMP-9 levels and confounding factors such as DM, dyslipidemia, hypertension, smoking, obesity, sex, age, and onset AMI to hs-TnT plasma levels. It showed MMP-9 and onset AMI affect hs-TnT plasma levels. From formula : Y = - 815.0 + 46.5(X_1)+ 20.7(X_2) increase of hs-TnT levels in AMI patients was influenced by magnitude of MMP-9 levels and duration of onset AMI.

This founding was similar with another studies that stated role of MMP-9 increased levels influenced atherosclerotic plaque rupture process until acute thrombotic process and indirectly influenced increase of troponin plasma levels.[4,5]Whereas onset AMI took effect to hs-TnT levels in accordance with motto "time is muscles", because the longer onset AMI the longer ischemia process caused by acute thrombotic in coronary artery lumen. This caused extention of myocardial necrosis.[5]

To test the strength difference between groups, ANCOVA analysis was done with result that in STEMI group had stronger difference of strength relation than NSTEMI, with higher â value (45.7 vs 36.5). But there was controversy if it looked from formula to predict hs-TnT levels between those groups (Y = - 557.7 + 45.7 (X_1) vs Y = -503.9 + 36.5 (X_2)) determine by R^2 value STEMI and NSTEMI (0.17(17%) vs 0.26(26%)). That might be caused by many factors that influenced hs-TnT levels in STEMI which indirectly showed extention of myocardial necrosis, besides MMP-9 plasma levels was not analyzed. Those factors were occlusion location in coronary artery where the more proximal the thrombosis location the more extended myocardial necrosis, collaterals or ischemic preconditioning, less or absence of them will cause increase of necrosis and both of those factors only could be seen with angiography.[16]

Clinical implication of this study is hoped as consideration management of increase MMP-9 plasma levels in acute phase of STEMI that followed by increase of hs-TnT plasma levels, indirectly showed extention of myocardial necrosis. Some MMP-9 inhibitor in AMI patients got permission from Food and Drug Administration (FDA) United States of America, such as doxycyclin and salviolic acid, selective MMP-9 inhibitor, that was still in animal study. Another study stated station use, fluvastatin, could decrease MMP-9 levels in AMI patients.[17]

CONCLUSION

There was a positive correlation between MMP-9 levels with hs-TnT plasma levels in AMI patients; MMP-9 plasma levels and onset AMI could influenced hs-TnT plasma levels, and there was there was stronger correlation between MMP-9 and hs-TnT in STEMI group than NSTEMI.

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