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ORIGINAL ARTICLE

Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction

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ABSTRACT

Objective To investigate the relationship between circulating plasma copeptin values and infarct size as well as myocardial function at baseline and 4 months after mechanical reperfusion for ST segment elevation myocardial infarction (STEMI).

Design Prospective observational cohort study.

Setting University Hospital of Innsbruck.

Patients 54 patients with acute STEMI.

Main outcome measures Correlation of plasma copeptin with infarct size as well as left ventricular ejection fraction (LVEF) and remodelling.

Methods Participants underwent contrast enhanced cardiac MRI at baseline and 4 months thereafter. Blood samples were drawn 2 days after the onset of symptoms. Copeptin values were determined by an immunofluorescent assay.

Results Copeptin concentrations (median 10.4 pmol/l, IQR 6.0–14.4) were associated with early and chronic infarct size (r=0.388, p=0.004 at baseline; r=0.385, p=0.011 at follow-up) and inversely related to LVEF at both times (r=−0.484, p<0.001 at baseline; r=−0.461, p<0.001 at follow-up). Patients with adverse remodelling showed higher baseline copeptin values compared to patients without remodelling (p=0.02). Receiver operating characteristic analysis indicated a cut-off value of 16.7 pmol/l for copeptin to best identify patients with future adverse remodelling.

Conclusions Increased copeptin values 2 days after STEMI are associated with larger acute and chronic infarct sizes. Moreover, elevated copeptin concentrations at baseline were associated with myocardial function and remodelling 4 months post-STEMI. These findings strengthen the role of copeptin as a biomarker of adverse outcome after STEMI.

INTRODUCTION

Arginine vasopressin (AVP), or antidiuretic hormone, is secreted in response to acute illness.[1] The C-terminal portion of provasopressin (copeptin) is released in equimolar amounts to AVP and is easy to determine.[2] Thus, copeptin serves as a surrogate marker for AVP secretion. In recent years, copeptin gained attention as a potential prognostic biomarker in acute illness, such as lower respiratory tract infection, ischaemic stroke or heart failure.[1] After acute myocardial infarction (AMI), the AVP axis is activated and thought to have a causative role in the evolution of chronic heart failure.[3 4] Increased copeptin concentrations, measured 3–5 days post-AMI, were shown to correlate with left ventricular (LV) ejection fraction (EF) as well as remodelling 5 months after the acute event.[4] Furthermore, high copeptin values are a predictor of mortality and morbidity in patients with heart failure after AMI.[5]

In patients with ST segment elevation myocardial infarction (STEMI), infarct size is a stronger outcome predictor than LV function and volumes.[6] In addition, infarct size is related to LV remodelling,[6] which is associated with a significant worsening of prognosis after AMI.[7] Cardiac magnetic resonance (CMR) is the current gold standard for characterisation of cardiac structure, function, and scar.[8] These parameters are useful as surrogate end points in clinical trials of STEMI.[9]

We hypothesised that plasma copeptin values, determined early after STEMI, are related to myocardial infarct size and myocardial function both at baseline and 4 months follow-up as assessed by CMR. So far, this issue has not been investigated after successful primary percutaneous coronary intervention (PCI) for STEMI.

METHODS

Study population

We studied 54 STEMI patients admitted to the coronary care unit of Innsbruck Medical University. Inclusion criteria were diagnosis of STEMI according to the redefined European Society of Cardiology/American College of Cardiology (ESC/ACC) committee criteria[10] and successful reperfusion by primary PCI. Exclusion criteria were renal dysfunction with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, Killip class >2, pain-to-balloon time >24 h, and contraindications for CMR.

All STEMI patients underwent baseline CMR between April 2011 and March 2012 and 47 patients underwent a follow-up CMR 4 months after the acute event. Baseline CMR was performed 2 days (IQR 1–3 days) after the acute event. Follow-up scan was conducted within a median of 123 days (IQR 120–128) after the baseline scan. Seven patients were lost to follow-up (two patients refused follow-up scan, two patients were not contactable for follow-up, one patient missed

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follow-up due to illness, and two patients did not perform follow-up due to other reasons). The study was approved by the local ethics committee and written informed consent was obtained from each participant.

Blood samples

Blood samples were drawn 2 days (IQR 1–3 days) after the onset of symptoms. They were collected in EDTA tubes and centrifuged for 10 min at 2000 *g* within 0.5 h. Plasma was stored at −80°C until analysis. Plasma copeptin concentrations were determined by a commercially available automated immunofluorescent assay (Thermo Fisher Scientific, B.R.A.H.M.S., Henningsdorf, Germany).[11] Detection limit of the assay was 4.8 pmol/l.

Creatine kinase (CK) activity and N-terminal pro B-type natriuretic peptide (NT-proBNP) values were determined by an enzymatic assay (Roche Diagnostics, Mannheim, Germany). Cardiac troponin T (cTnT) concentrations were measured by a fourth generation cTnT enzyme immunoassay (Roche Diagnostics, Mannheim, Germany).[12] To assess maximum CK, cTnT, NT-proBNP, and C reactive protein (CRP), blood samples were drawn before and every 6 h after primary PCI until 24 h thereafter, and then daily until discharge.[12]

CMR protocol

All scans were performed on a 1.5 Tesla Magnetom AVANTO scanner (Siemens, Erlangen, Germany). A detailed description of the CMR protocol was published previously.[13] Briefly, cine CMR images in short axis (11 slices) were acquired using breath hold, retrospective ECG triggered TrueFISP bright blood sequences. Evaluation of images was performed using standard software (ARGUS, Siemens, Erlangen, Germany) as described previously.[8] An increase in end diastolic volume (EDV)≥20% was defined as a surrogate marker of adverse remodelling.[14]

Ten minutes after an intravenous gadolinium bolus injection of 0.1 mmol/kg (Multihance, Bracco, Vienna, Austria), late enhancement (LE) CMR images were acquired by using an ECG triggered, phase sensitive inversion recovery single shot TrueFISP sequence with consecutive short axis slices as described in detail previously.[13] The area of LE was evaluated quantitatively as reported previously.[8]

Statistical analysis

Statistical analysis was performed with SPSS Statistics 19 (IBM, Armonk, New York, USA). The Kolmogorov–Smirnov test was used to test for normal distribution (ND), and Spearman-Rho for calculation of linear correlations for selected variables. Differences between baseline and follow-up values were compared using t test for paired variables. The Mann–Whitney U test was used to determine differences in continuous variables (not ND) between groups. A two tailed p value <0.05 was considered to indicate statistical significance. To calculate the predictive value of copeptin for future adverse remodelling after STEMI, receiver operating characteristic analyses were performed. Based on previous studies we estimated to require a sample size of approximately 50 STEMI patients to determine main outcomes of the proposed study.[15]

RESULTS

Baseline patient characteristics

Detailed demographic features of the study population are summarised in table 1. All patients were successfully treated with primary PCI (median pain-to-balloon time 209 min, IQR 130–466, range 60–1392). Median copeptin concentration was 10.4 pmol/l (IQR 6.0–14.4, range 5.0–42.5). There was no significant difference in copeptin concentrations between anterior or non-anterior STEMI (p=0.590) and one, two, or three vessel disease (p=0.816). Also acute and chronic infarct sizes were not significantly correlated with the number of diseased vessels (all p>0.05). Patients with adverse remodelling were more likely to have multivessel disease compared to patients without remodelling (p=0.048). Patients with microvascular obstruction on LE CMR displayed a trend for higher copeptin values (11.5 pmol/l, IQR 7.1–15.2 vs 7.4 pmol/l, IQR 5.8–11.3; p=0.108). Females had a lower median copeptin value than men (6.7 pmol/l, IQR 5.1–12.2 vs 10.6 pmol/l, IQR 6.3–15.9), but the difference did not reach significance (p=0.157).

Table 1 Baseline characteristics of the study cohort (n=54)

	Mean/median/number	SD/IQR/%
Age, years	57	10
Female, n (%)	8	14.8
Body mass index, kg/m^2	27	3
Hypertension, n (%)	43	79.6
Blood pressure, mmHg	131/77	24/13
Family history for AMI, n (%)	14	25.9
Smoking status, n (%)	23	42.6
Hyperlipidaemia, n (%)	40	74.1
Diabetes mellitus, n (%)	4	7.7
CKD, n (%)	2	3.7
eGFR, ml/min/1.73 m^2	88	17
Anterior STEMI, n (%)	22	40.7
Number of diseased vessels, n (%)		
1	24	44.4
2	25	46.3
3	5	9.3
Microvascular obstruction, n (%)	32	59.3
CK max, U/l	2521	1686
cTnT max, ng/l	6334	4209
NT-proBNP max, ng/l	1349	1186
Copeptin, pmol/l*	10.4	6.0–14.4

*Median+IQR.
AMI, acute myocardial infarction; CK max, creatine kinase maximum; CKD, chronic kidney disease; cTnT max, cardiac troponin T maximum; eGFR, estimated glomerular filtration rate; NT-proBNP max, N-terminal pro B-type natriuretic peptide maximum; STEMI, ST segment elevation myocardial infarction.

Baseline and follow-up CMR

Mean baseline infarct size was 23±13 g corresponding to 18±10% of LV myocardial mass. Infarct size decreased significantly to 14±9 g (p<0.001) after 4 months corresponding to 11±7% (p<0.001) of LV myocardial mass. Average LVEF was 55±10% at baseline and improved significantly up to 61±10% (p<0.001) at follow-up. Accordingly, mean stroke volume (SV) increased from 78±17 ml at baseline to 88±14 ml at follow-up (p<0.001). There was no significant difference in EDV and end systolic volumes (ESV) between baseline and follow-up scan (EDV: 144±27 ml vs 148±29 ml; ESV: 66±22 ml vs 60±25 ml; all p>0.05). Maximum cTnT concentration was significantly correlated with EF and infarct size at baseline and 4 months follow-up (EF: r=−0.407, p=0.002 at baseline; r=−0.331, p=0.023 at follow-up; infarct size: r=0.552, p<0.001 at baseline; r=0.694, p<0.001 at follow-up).

Table 2 Correlation between copeptin and CMR parameters at baseline and follow-up

	Baseline (BL)		Follow-up (FU)		ΔFU-BL	
	r	p Value	r	p Value	r	p Value
EF (%)	−0.484	<0.001	−0.461	0.001	0.110	0.462
EDV (ml)	0.077	0.581	0.305	0.037	0.243	0.100
ESV (ml)	0.334	0.014	0.453	0.001	0.103	0.493
SV (ml)	−0.345	0.011	−0.155	0.300	0.227	0.125
MMED (g)	0.090	0.516	0.153	0.306	−0.015	0.922
Infarct mass (% of MM)	0.388	0.004	0.385	0.011	−0.076	0.630

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; MM, myocardial mass; MMED, myocardial mass end diastolic; r, Spearman-rho correlation coefficient; SV, stroke volume; Δ, difference.

Correlations between copeptin and clinical as well as CMR characteristics

Correlations between plasma copeptin concentrations and CMR data at baseline and follow-up are summarised in table 2. Copeptin values were associated with maximum CK (r=0.290, p=0.033) and maximum cTnT (r=0.309, p=0.023). No significant correlation was observed between copeptin values and patient age (r=−0.029, p=0.837), body mass index (r=0.224, p=0.104), and eGFR (r=−0.204, p=0.139). Correlation between copeptin values and maximum NT-proBNP as well as maximum CRP was not significant (NT-proBNPmax: r=0.231, p=0.095; CRP max: r=0.144, p=0.298).

Copeptin values were positively associated with acute (r=0.388, p=0.004) and chronic (r=0.385, p=0.011) infarct size in percentage of LV myocardial mass (IS %). There was no correlation between copeptin values and end diastolic myocardial mass (MMED) (p>0.05 at baseline and follow-up). Baseline copeptin values were also significantly and inversely correlated with EF at baseline (r=−0.484, p<0.001) as well as at follow-up (r=−0.461, p<0.001). Furthermore, they correlated with SV at baseline (r=−0.345, p=0.011) but not with the improvement of EF between baseline and follow-up (r=0.110, p=0.462). There was a positive relationship between copeptin and ESV (r=0.334, p=0.014 at baseline; r=0.453, p=0.001 at follow-up) and EDV at follow-up (r=0.305, p=0.037) but not at baseline (r=0.077, p=0.581). Differences of IS %, MMED, EDV, ESV, and SV between baseline and follow-up imaging were not associated with copeptin (all p>0.05).

According to median copeptin concentration (median: 10.4 pmol/l, IQR 6.0–14.4) patients were divided in two groups. Patients with copeptin values above the median displayed significantly larger infarct sizes (14.7±9.3% vs 20.5±9.8% at baseline, p=0.03; 8.3±4.5% vs 14.5±7.2% at follow-up, p=0.02), larger ESV (60±21 ml vs 71±23 ml at baseline, p=0.087; 52±17 ml vs 68±29 ml at follow-up, p=0.027) as well as lower EF (58±9% vs 51±10% at baseline, p=0.011; 64±7% vs 57±11% at follow-up, p=0.013) at baseline and follow-up than patients with copeptin values below the median (figure 1).

Plasma copeptin and adverse remodelling

A further distinction was made between patients with (n=6) and without (n=41) adverse remodelling 4 months after STEMI. In the group with remodelling, copeptin values were significantly higher compared to patients without remodelling (p=0.024). The area under the curve (AUC) of copeptin (0.79, 95% CI 0.59 to 0.98) with the optimal cut-off value of 16.7 pmol/l revealed 67% sensitivity and 88% specificity in the prediction of adverse remodelling at 4 months follow-up (figure 2). The negative and positive predictive value for the cut-off concentration calculated by cross tabulation was 95% (CI 82% to 99%) and 44% (CI 14% to 79%), respectively. The AUC of maximum NT-proBNP and maximum cTnT for prediction of remodelling 4 months after STEMI (NT-proBNP: 0.75, 95% CI 0.52 to 0.99; cTnT: 0.70, 95% CI 0.50 to 0.91) were comparable with the AUC of copeptin. The optimal cut-off value for NT-proBNP for prediction of adverse remodelling was 1916 ng/l (sensitivity 66%, specificity 83%). Interestingly, no patient with both biomarkers (copeptin and NT-proBNP) below the cut-off values developed adverse remodelling during follow-up. However, one of three patients with both biomarkers above the cut-off values showed no adverse remodelling at follow-up. The optimal cut-off value for maximum cTnT was 8783 ng/l (sensitivity 50%, specificity 88%). We further evaluated the utility of combining these three biomarkers in one model. All patients with three biomarker concentrations below (n=28) or above (n=2) cut-off values did not develop or developed adverse remodelling 4 months after STEMI.

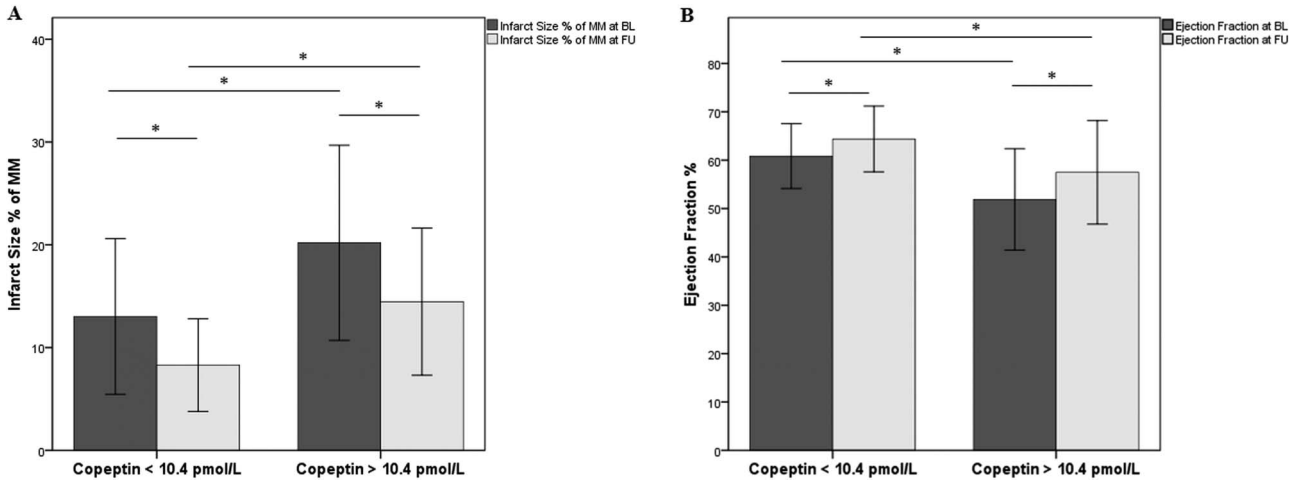

Figure 1 Patients with copeptin values above the median showed (A) higher infarct sizes and (B) lower ejection fractions at baseline and follow-up. *p<0.05. BL, baseline; FU, follow-up; MM, myocardial mass.

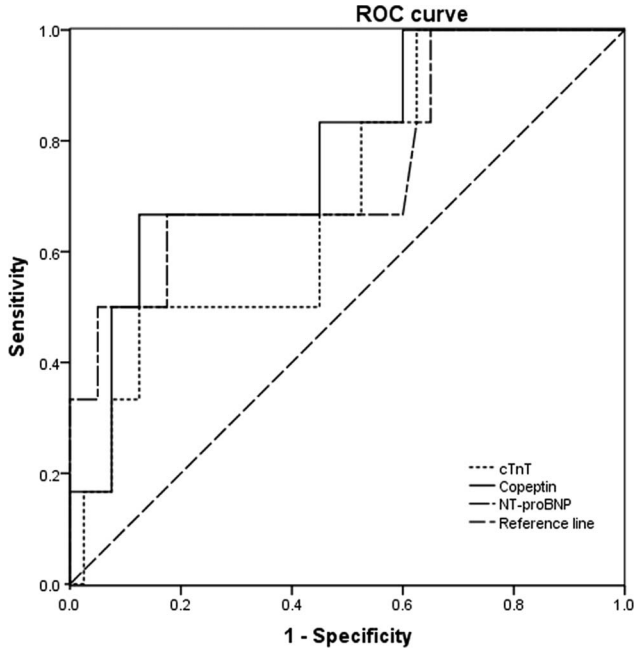

Figure 2 Receiver operating characteristic (ROC) analysis to identify the optimum cut-off value for prediction of adverse remodelling with maximum N-terminal pro B-type natriuretic peptide (NT-proBNP) values, maximum cardiac troponin T (cTnT) values, and copeptin values assessed 2 days after ST elevation myocardial infarction (STEMI). The area under the curve (AUC) of copeptin (0.79, 95% CI 0.59 to 0.98) with the optimal cut-off value of 16.7 pmol/l revealed 66.7% sensitivity and 87.8% specificity in the prediction of adverse remodelling and was comparable with the AUC of maximum NT-proBNP (AUC 0.75, 95% CI 0.52 to 0.99) and maximum cTnT (AUC 0.70, 95% CI 0.50 to 0.91).

DISCUSSION

In the present study we demonstrate that plasma copeptin concentrations measured 2 days after STEMI are significantly correlated with CMR determined acute and chronic infarct size. Moreover, copeptin was inversely associated with LV myocardial function at baseline and 4 months follow-up. Our results also indicate the potential of plasma copeptin to predict the likelihood of adverse remodelling.

The extent of myocardial necrosis is one of the most important outcome parameters following AMI.[16] CK and cTnT are established estimators for acute and chronic infarct size.[17] Besides these classical parameters, novel markers of myocardial injury were also recently studied.[18 19] Nevertheless, contrast enhanced CMR is the most accurate imaging modality to measure myocardial infarct size in vivo.[8 17] In our study, copeptin values quantified in the acute phase after STEMI were associated with acute and chronic infarct size assessed by contrast enhanced CMR. Furthermore, copeptin values were significantly correlated with biomarkers of myocardial necrosis (CK max and cTnT max). Patients with copeptin values above the median copeptin concentration displayed significantly larger infarct sizes. This is the first report showing that copeptin values predict infarct size at baseline and 4 months after STEMI. Release of copeptin is stimulated by various stressors,[1] such as cardiac ischaemia.[11] A larger infarct may augment stress response and therefore lead to increased copeptin secretion.[1] In an animal study, Hupf *et al*[20] provide strong evidence for the expression of vasopressin in cardiac tissue. Therefore, it has already been speculated that myocardial necrosis leads also to a direct release of copeptin from the heart independently of neurohypophysis release.[21] This hypothesis might also explain the higher values of copeptin in patients with larger myocardial injury.

The degree of adverse remodelling is strongly related to infarct size.[22] Patients with adverse remodelling 4 months after the acute event displayed significantly higher baseline copeptin concentrations. In our cohort, a copeptin concentration of 16.7 pmol/l was the optimal cut-off to predict adverse remodelling after STEMI. Compared to copeptin, the AUC for NT proBNP for prediction of remodelling 4 months after STEMI was similar. Interestingly, no patient with both biomarkers below the cut-off values developed adverse remodelling during follow-up. This is in line with previous reports indicating that the prognostic information of both biomarkers is at least in part complementary.[3] Our results also indicate that copeptin might be useful for the prediction of remodelling beyond cTnT. This finding fits nicely with the results of another trial which showed that copeptin improves risk stratification beyond cTnT in patients with symptoms suggestive for AMI but without ST segment elevations in the ECG.[23] We conclude that a multimarker approach with copeptin, NT-proBNP, and cTnT might provide additional information regarding adverse remodelling compared to each marker alone.

Patients with adverse remodelling following STEMI display progressive worsening of functional (SV, EF) and morphological (EDV, ESV) parameters.[24] In our study, copeptin was significantly associated with these remodelling indices. The strongest correlation was observed for EF. Although the association with EF was similar at both times of assessment, correlations with EDV and ESV were stronger at follow-up. These data support the hypothesis of Kelly *et al* that AVP might play a pathophysiological role in chronic remodelling processes after AMI.[4] AVP has been shown to increase afterload and ventricular wall stress.[25–27] Enhanced wall stress is known to be a major promoter of LV remodelling.[7 28] Furthermore, activation of the AVP axis is thought to increase water reabsorption,[29] which increases preload. Additional studies with a larger cohort, a longer follow-up and with determination of copeptin values at follow-up might help to confirm the validity of this suggestion. Our observations regarding functional and morphological parameters are in line with previously reported results.[4] Nevertheless, it must be mentioned that our study has some distinct features. This is the first study describing this association in a homogeneous STEMI population optimally treated with primary PCI. Moreover, myocardial function and volumes were assessed by CMR. CMR is superior to echocardiography for the measurement of volume, function, and morphology.[30] These differences most likely account for the considerably higher correlation coefficients observed in our study, despite the smaller number of patients investigated.

This study has some important limitations. First, it is limited by the fact that we measured copeptin at different time points (in median 2 days[1–3]) and relatively late after STEMI. However, studies describing the prognostic value of copeptin for clinical outcome determined copeptin values between day 3 and 5 after AMI.[3 4] The median values of copeptin in these studies were even slightly lower compared to ours. Therefore, copeptin measurement during the first days after STEMI seems useful, but studies with earlier and more exact time points for the measurement of copeptin are warranted to determine the most appropriate time point for assessing circulating copeptin concentrations.

Second, the sample size of our study is relatively small and females represent only 14.8% of the total study population.

Conclusions regarding gender related differences, such as different cut-off values for prediction of remodelling, cannot be drawn from this study. Therefore, large multicentre studies with an adequate percentage of women are necessary to confirm our data and to characterise possible gender differences in detail.

Third, our study cohort consisted of patients presenting with Killip class I or II, which were exclusively treated with primary PCI within the first 24 h after symptom onset. If the results of this study hold true for patients with Killip class III–IV (~10–20% of STEMI patients[31]), longer treatment delays or other treatment strategies remain to be clarified in future studies.

In conclusion, increased copeptin values at day 2 after STEMI are associated with larger acute and chronic infarct size. Moreover, copeptin is a potential predictor of myocardial function at baseline and 4 months after STEMI. Our study indicates that copeptin values <16.7 pmol/l potentially identify patients at very low risk for adverse remodelling. These findings highlight the possible role of copeptin as a robust biomarker predicting adverse outcome after reperfused STEMI. However, further evidence is needed to implement the biomarker into clinical routine.

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Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction

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Notes