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Review Article

Role of Highly Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

Raymond Pranata[1], Nico Kusuma[2], Rachel Vania[1], Bambang Budi Siswanto[3]

[1]Faculty of Medicine, Universitas of Pelita Harapan, Banten, Indonesia
[2]Faculty of Medicine, Universitas Atmajaya, Jakarta, Indonesia
[3]Faculty of Medicine, Universitas Indonesia, Rumah Sakit Pusat Jantung Nasional Harapan Kita, Jakarta, Indonesia

Cardiac troponins (cTn) are the preferred biomarkers of myocardial necrosis, usually used for diagnosis and risk stratification in acute coronary syndromes. Highly sensitive troponin T (hs-cTnT) may be elevated in stable coronary artery disease (SCAD), in which subclinical plaque erosion or rupture and distal embolization and subclinical ischemic episode. hs-cTnT may be used as a prognostic marker in SCAD and can predict cardiovascular events and patient's mortality rate. In this article, plaque characteristic that is linked to hs-cTnT, it's used as prognostic biomarker and comparison to other indicators are the focus of discussion.

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Keywords: troponin – cardiac biomarkers – myocardial infarction

Tinjauan Pustaka

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Peran Pemeriksaan Troponin T Jantung Sensitivitas Tinggi pada Penyakit Jantung Koroner Stabil

Raymond Pranata[1], Nico Kusuma[2], Rachel Vania[1], Bambang Budi Siswanto[3]

Troponin adalah biomarker yang paling disukai untuk mendeteksi nekrosis miokardium dan untuk mendiagnosis dan stratifikasi risiko pada sindrom koroner akut. *Highly sensitive troponin T* (hs-cTnT) dapat meningkat pada penyakit jantung koroner stabil dimana terjadi ruptur plak atau erosi dan embolisasi distal sublklinis, dan episode iskemik subklinis. Sehingga biomarker tersebut dapat digunakan sebagai marker prognostik pada penyakit jantung koroner stabil dan dapat memprediksi angka kejadian kardiovaskular dan tingkat mortalitas pasien. Pada artikel ini akan dibahas mengenai karakteristik plak yang dihubungkan dengan peningkatan hs-cTnT, pengunaan sebagai biomarker prognostik dan serta perbandingan dengan indikator lainnya.

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Kata kunci: troponin – biomarker jantung– infark miokardium

Introduction

Cardiac Troponin T and I are components of cardiomyocyte contractile apparatus and the most widely used biomarker of cardiomyocyte necrosis Troponin measured in those with acute coronary syndrome. Studies had shown that even slight increase in cardiac troponin concentration is associated with worse prognosis in those with acute coronary syndrome.[1,2]

Elevation of cardiac troponin ≥0,01 µg/liter was associated with increased mortality in those with or without history of cardiovascular events (**Table 1**). Based on this finding, it is probable that increased level of troponin which does not pass the threshold concentration for positive test (below the limit for detection; very low plasma troponin level) may play a role as predictor of adverse cardiovascular events.[3,4,9]

Plasma cardiac troponin is a sensitive and specific biomarker which is commonly used to diagnose myocardial infarction. The advent of highly sensitive troponin T assay (hs-cTnT) enables not only early detection of myocardial infarction but also serves as a prognostication tool in stable coronary artery disease. It was able to detect the concentration of plasma cardiac troponin 10 times lower compared to conventional assay. Elevation of hs-cTnT above 99 percentiles was found in 1/3 patients with stable coronary artery

[1]Fakultas Kedokteran, Universitas of Pelita Harapan, Banten, Indonesia, [2]Fakultas Kedokteran, Universitas Atmajaya, Jakarta, Indonesia, [3]Fakultas Kedokteran, Universitas Indonesia, Rumah Sakit Pusat Jantung Nasional Harapan Kita, Jakarta, Indonesia

Correspondence:
dr. Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Banten, Indonesia.
E-mail: raymond_pranata@hotmail.com

Table 1. Association between *high-sensitive cardiac troponin* T and cardiovascular *outcomes*. From Omland et al, A sensitive cardiac troponin T assay in stable coronary artery disease.9

	Univariate Model		Multivariate Model 1†		Multivariate Model 2‡	
Outcome	Hazard Ratio (95% CI)§	P Value	Hazard Ratio (95% CI)§	P Value	Hazard Ratio (95% CI)§	P Value
Cardiovascular death	2.78 (2.24–3.45)	<0.001	2.39 (1.85–3.09)	<0.001	2.09 (1.60–2.74)	<0.001
Fatal or nonfatal CHF	3.08 (2.45–3.88)	<0.001	2.77 (2.12–3.60)	<0.001	2.20 (1.66–2.90)	<0.001
All cardiovascular deaths except those due to CHF	2.59 (2.05–3.27)	<0.001	2.21 (1.68–2.92)	<0.001	1.95 (1.46–2.61)	<0.001
Fatal or nonfatal MI	1.28 (1.08–1.52)	0.005	1.20 (1.00–1.45)	0.05	1.16 (0.97–1.40)	0.11

* CHF denotes congestive heart failure, and MI myocardial infarction.
† The model was adjusted for treatment assignment, age, sex, current smoking status, and American Heart Association–Centers for Disease Control and Prevention categories for high-sensitivity C-reactive protein (<1, 1 to 3, and >3 mg per liter).
‡ The model was adjusted as for model 1, with additional adjustment for sex-specific quartiles of the N-terminal pro–brain natriuretic peptide.
§ Hazard ratios are for each unit increase in the natural logarithm of the high-sensitivity cardiac troponin T level.

disease diagnosed through computed tomography angiography. [5,6,7]

Cardiac Troponin and Stable Coronary Artery Disease

Concentration of hs-cTnT is higher in those with stable coronary artery disease compared to a normal person. (**Figure 1**) Subclinical erosion or plaque rupture and distal embolization, subclinical ischemic episode, micro-small vessels occlusion, inflammatory process, cardiomyocyte apoptosis, reduced renal clearance and distention due to pressure or volume overload were hypothesized to be the underlying pathophysiology of increased troponin and worse outcome.[8]

A study by Torbjorn Omland, et al. conclude that increased concentration of plasma cardiac troponin T measured by hs-cTnT was significantly associated with increased adverse cardiovascular events and heart failure, but not myocardial infarction in patients with stable coronary artery disease. This study showed that very low plasma cardiac troponin T concentration was detectable in the majority of patients with stable coronary artery disease and preserved ejection fraction. After adjustment for other independent prognostic indicators, there was a strong and graded increase in the cumulative incidence of cardiovascular death and of heart failure in the study group. A study by Mirta Diez, et al showed that increased level of highly sensitive cardiac troponin (hs-cTn) was directly proportional to ventricular dysfunction and those with ejection fraction ≤ 45% had higher hs-cTn. Increased level of hs-cTn was associated with poor clinical outcome, low cardiac output, and cardiogenic shock. Cardiomyocyte damage was even more prominent during acute exacerbation of heart failure due to increase in pulmonary capillary pressure, reduced coronary perfusion pressure, increased catecholamine secretion, abnormal calcium metabolism, oxidative stress and inflammation. This study concluded that heart failure caused by coronary artery disease had high hs-cTn level compared with heart failure due to other etiology. The use of hs-cTn for risk stratification

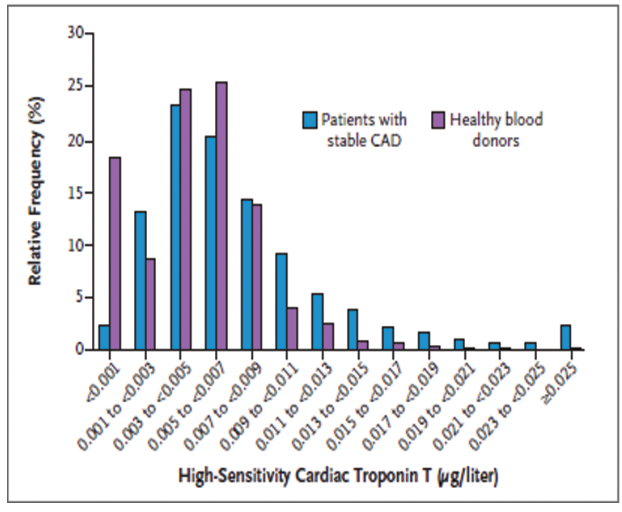

Figure 1. Distribution and determinants of cardiac troponin T concentration in stable coronary artery disease and apparently healthy blood donors. From: Omland et al. A sensitive cardiac troponin T assay in stable coronary artery disease.[9]

during admission helps in determining those at high risk of death and poor prognosis which helps in guiding a more aggressive and emergent therapy.[7,9]

Plaque Characteristic and Highly Sensitive Cardiac Troponin T

Elevated hs-cTnT was not associated with type or severity of chest pain and degree of stenosis but has a relationship between plaque composition especially remodeling in area without calcification and smooth or mixed plaque. A study investigated about plaque characteristic in non-culprit coronary artery with the result showing association between segmental plaque volume and virtual histology-derived thin-cap fibroatheroma (VH-TCFA) with elevated concentration of hs-cTnT in patients with stable coronary artery disease.[8] VH-TCFA was found in 49% of the patients with hs-cTnT concentration ≥14 pg/mL which means that there was 2 times more frequent compared to those with hs-cTnT <14 pg/mL (adjusted OR 2.35, 95% CI: 1.12-4.91, p = 0.024). VH-TCFA with high lesional plaque volume (lesional plaque volume above the median of all lesions classified as VH-TCFA) was three times more prevalent in those with hs-cTnT concentration ≥14 pg/mL (adjusted OR 3.36, 95% CI: 1.44 – 7.84, p = 0.005). Normalized segmental plaque volume and normalized segmental vessel volume were positively correlated with the level of hs-cTnT while there is no association between plaque burden and hs-cTnT concentration.[8] (**Table 2**)

A study also showed that elevated pre-procedural hs-cTnT concentration ≥14 pg/mL was found in 26% of patients with stable coronary disease undergoing percutaneous coronary intervention and is associated with increased risk of death. It was also an independent predictor of all-cause mortality within one year (HR 5.73; 95% confidence intervals 3.34–9.83; P<0.001; adjusted HR 2.08; 95% confidence interval 1.10–3.92; P=0.024, after adjustment to relevant risk factors including age, gender, and chronic kidney disease).[6] Elevated hs-cTnT was found to be related to cardiac-cause mortality (HR 4.68; 95% confidence interval 2.12–10.31; P<0.001).[6] (**Table 3**)

Highly Sensitive Cardiac Troponin T compared to other indicators

Heart and Soul Study compared traditional risk factors (age, gender, body mass index, hypertension, dyslipidemia, and diabetes) and biomarkers (NT-proBNP, hs-cTnT and urine albumin:creatinine ratio) in predicting risk of secondary events (secondary events in those with coronary heart disease) in patient with stable coronary artery disease. The top four indicators were NT-proBNP, hs-cTnT, urine albumin:creatinine ratio, and smoking.[10] From traditional and novel biomarker risk factors, elevated hs-cTnT was the second most powerful predictor of cardiovascular

Table 2. Association between high-sensitivity cardiac troponin T and plaque characteristics in non-culprit stable coronary artery disease. From: Oemrawsingh RM et al. High-sensitivity troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study.[8]

	Total study population	hsTnT <14 pg/mL (N = 186)	hsTnT ≥14 pg/mL (N = 45)	Adjusted P-value
Segmental plaque characteristics	***Median [IQR]***			
Normalised vessel volume (mm^3)	563.9 [439.2–755.0]	545.5 [421.2–691.3]	733.6 [494.8–917.5]	0.001
Normalised plaque volume (mm^3)	234.0 [149.9–340.6]	215.2 [140.8–311.2]	271.1 [192.4–413.7]	0.008
Plaque burden (%)	40.4 [32.2–47.7]	39.8 [31.9–47.1]	43.2 [33.8–50.2]	0.41
Plaque composition	***Median [IQR]***			
Fibrous (%)	56.3 [49.4–63.8]	56.0 [49.5–65.1]	56.6 [48.6–60.3]	0.49
Fibro-fatty (%)	9.5 [6.3–13.4]	9.3 [5.8–13.4]	11.2 [8.1–14.2]	0.18
Dense calcium (%)	11.0 [5.9–16.1]	10.9 [5.7–16.1]	11.4 [6.3–17.1]	0.79
Necrotic core (%)	21.5 [17.2–25.3]	21.5 [16.7–25.7]	21.5 [18.4–24.9]	0.82
Lesion morphology	***N (%)***			
VH-TCFA	86 (37.2)	64 (34.4)	22 (48.9)	0.024
VH-TCFA with high lesional plaque volume	43 (18.6)	28 (15.1)	15 (33.3)	0.005
MLA ≤ 4.0 mm^2	80 (34.6)	67 (36.0)	13 (28.9)	0.66
Plaque burden ≥ 70%	56 (24.2)	41 (22.0)	15 (33.3)	0.064

VH-TCFAs were classified as having a high lesional plaque volume in case the plaque volume of that particular VH-TCFA was above the median of all lesions classified as VH-TCFA. Multivariable analyses accounted for confounding by age, gender, hypercholesterolemia, diabetes, glomerular filtration rate, hypertension, smoking status, family history of CAD, history of MI, prior PCI, coronary artery bypass grafting, stroke and peripheral artery disease (PAD).
HsTnT = high-sensitivity Troponin T; VH-TCFA = Virtual histology-derived Thin-cap fibroatheroma; MLA = minimal luminal area.

Table 3. One year outcome in patients with and without elevated hs-cTnT
From: Zanchin T, et al. Preprocedural high-sensitivity cardiac troponin T and clinical outcomes in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention.[6]

Outcome	Elevated hs-cTnT, n=527	Normal hs-cTnT, n=1502	HR (95% CI)	*P* Value
Death	39 (7.7)	20 (1.4)	5.73 (3.34–9.83)	<0.001
Cardiac death	16 (3.2)	10 (0.7)	4.68 (2.12–10.31)	<0.001
MI	20 (4.0)	50 (3.4)	1.15 (0.68–1.93)	0.60
Q-wave MI	7 (1.4)	8 (0.5)	2.52 (0.92–6.96)	0.074
Non–Q-wave MI	13 (2.6)	42 (2.8)	0.89 (0.48–1.65)	0.71
Death or MI	54 (10.6)	67 (4.5)	2.33 (1.63–3.34)	<0.001
Any revascularization	37 (7.5)	93 (6.5)	1.18 (0.81–1.73)	0.39
TLR	22 (4.5)	49 (3.4)	1.32 (0.80–2.19)	0.28
TVR	26 (5.3)	59 (4.1)	1.30 (0.82–2.06)	0.26
Stroke	4 (0.8)	7 (0.5)	1.67 (0.49–5.71)	0.41
Stent thrombosis (definite)	7 (1.4)	9 (0.6)	2.24 (0.83–6.01)	0.11
BARC 3–5 bleeding	15 (3.0)	22 (1.5)	2.00 (1.04–3.86)	0.038
TIMI bleeding	22 (4.4)	33 (2.3)	1.97 (1.15–3.37)	0.014

Depicted are first events (% from Kaplan–Meier estimate), hazard ratios (with 95% CI) from Cox's regression comparing elevated vs normal baseline hs-cTnT. BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; and TVR, target vessel revascularization.

events (adjusted HR 1.47, 95% CI 1.18-1.84); p = 0.001) behind smoking.

Prognostic value of hs-cTnT measurement is also influenced by various factors. A study by Carda et al showed that elevated hs-cTnT was associated with increased risk of the primary outcome (RR 2.360; p = 0.001) and heart failure (RR 5.932; p < 0.001) but not with acute ischemic events, however, it's significance is lost after controlling with age. Its significance is also affected by ejection fraction <40%, use of anticoagulant and ACE inhibitor. Carda et al also stated that other studies did not include patients with EF <40% as study sample which means that it's clinical significance are questionable in those with heart failure reduced ejection fraction. (Table 4) Carda et al also stated that their study is in agreement with ESC guideline for management of stable coronary artery disease in which troponin assay has prognostic value but is not enough to be recommended as routine systematic examination in stable coronary artery disease at outpatient settings.[10,11]

Conclusion

Subclinical erosion or plaque rupture and distal embolization, subclinical ischemic episode, micro-small vessels occlusion, inflammatory process, cardiomyocyte apoptosis, reduced renal clearance and distention due to pressure or volume overload were hypothesized to be the underlying pathophysiology of increased troponin and worse outcome. Highly sensitive cardiac troponin T is one of the best prognostication tools among traditional and novel risk factors to predict of adverse. It helps in gradation and risk stratification of those with stable coronary artery disease because of its proportionality with degree and complexity of coronary atherosclerosis, adverse cardiovascular event, and mortality rate.[12] Hs-cTnT is also able to predict acute coronary

Table 4. Adjusted multivariable for myocardial infarction, stroke or cardiovascular death in Heart and Soul Risk Model.
From: Beatty AL, et al. Traditional risk factors versus biomarkers for prediction of secondary events in patients with stable coronary heart disease: from the heart and soul study.[10]

	Derivation Cohort		Validation Cohort	
Variable	Adjusted* HR (95% CI)	*P* Value	Adjusted* HR (95% CI)	*P* Value
NT-proBNP†	1.40 (1.24, 1.58)	<0.001	1.38 (1.23, 1.55)	<0.001
hs-cTnT†	1.65 (1.32, 2.06)	<0.001	1.47 (1.18, 1.84)	0.001
uACR†	1.18 (1.08, 1.28)	<0.001	1.11 (1.02, 1.21)	0.01
Current smoking	1.57 (1.11, 2.22)	0.01	1.66 (1.25, 2.20)	<0.001

CV indicates cardiovascular; HR, hazard ratios; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; NT-proBNP, N-terminal pro-type brain natriuretic peptide; uACR, urine albumin to creatinine ratio.
*Adjusted for other variables in the model.
†Per standard-deviation increase in log variable.

syndrome, myocardial infarction and mortality in those with stable coronary artery disease due to its presence in the majority of patients including those who are at low risk. Albeit the promising prospect of hs-cTnT as a prognostication and risk stratification tool for patients with stable coronary artery disease, the evidence is still lacking to be recommended in the guideline and used routinely in clinical practice.

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