

## Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

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## Background

- 快速診斷出AMI對於及早開始有效治療相當重要
- ECG與troponin是目前診斷cornerstone
- Troponin與其他biomarker相比之下更有診斷AMI的價值
- Standard cardiac troponin assays: 太慢了!
- 更新,更敏感的cardiac troponin assays
  - Abbott-Architect Troponin I
  - Roche High-Sensitive Troponin T
  - Roche Troponin I
  - Siemens Troponin I Ultra

## Method

- 2006/4~2008/4, 786位呈現懷疑可能是AMI症狀的急診病人
- 症狀onset或peak要在來急診前12 hrs以內
- 病人data要經過五種assay檢驗
- 最後診斷由兩位獨立cardiologist判定
- 血液樣本: 當下, 1, 2, 3, 6 hrs
- 雙盲
- CK-MB/myoglobin用immunoassay測定
- Receiver-operating-characteristic(ROC) curves

## Result (I)

Characteristic	All Patients (n=786)	Patients who Had an Acute Myocardial Infarction (n=133)	Patients who Did Not Have an Acute Myocardial Infarction (n=653)	P Value
Age — yr	64	72	62	<0.001
Male sex — no. (%)	48 (6.1)	75 (56.4)	49 (7.5)	0.01
Diabetes	134 (17.2)	21 (15.8)	113 (17.3)	0.17
Current smoking	173 (22.0)	18 (13.5)	155 (23.7)	0.01
History of smoking	284 (36.1)	37 (27.8)	247 (37.9)	0.05
History — no. (%)				
Coronary artery disease	211 (26.9)	41 (30.8)	170 (26.1)	1.00
Previous myocardial infarction	181 (23.1)	11 (8.3)	170 (26.1)	0.001
Previous revascularization	202 (25.8)	19 (14.3)	183 (28.0)	0.02
Peripheral artery disease	147 (18.7)	13 (9.8)	134 (20.5)	0.006
Previous stroke	41 (5.2)	14 (10.5)	27 (4.1)	0.01
Other findings				
Heart rate — beats/min				0.18
Median	75	80	75	
Interquartile range	66-86	66-86	66-86	
Systolic blood pressure — mm Hg				0.006
Median	141	139	142	
Interquartile range	127-160	129-158	127-160	
Diastolic blood pressure — mm Hg				0.01
Median	86	86	86	
Interquartile range	79-95	79-95	79-95	
Body mass index*				0.04
Median	26.3	26.6	26.3	
Interquartile range	23.8-29.4	23.9-30.0	23.8-29.4	
Electrocardiographic findings — no. (%)				
ST-segment depression	17 (2.2)	11 (8.3)	6 (0.9)	<0.001
ST-segment elevation	11 (1.4)	15 (11.3)	6 (0.9)	<0.001
T-wave inversion	18 (2.3)	18 (13.6)	4 (0.6)	<0.001
No clinically significant abnormalities	124 (15.8)	14 (10.5)	110 (16.8)	<0.001
Electrocardiographic findings — no. (%)				
Median	93	83	94	<0.001
Interquartile range	76-109	67-104	76-111	

## Result (II)

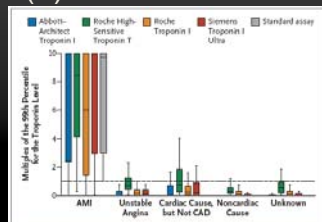
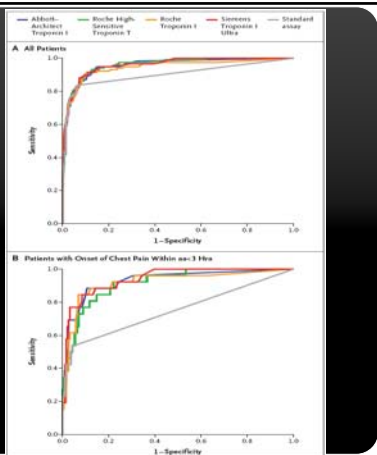


Figure 1. Levels of Cardiac Troponins at Presentation, as Assessed by Four Sensitive Assays and a Standard Assay, According to the Final Diagnosis. Troponin levels at the time of patients' presentation to the emergency department are shown as multiples of the 99th-percentile level, according to the adjudicated final diagnosis. The boxes represent interquartile ranges, the horizontal line in each box represents the median (the absence of a horizontal line indicates a median >10 times the 99th percentile), and the whiskers show the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box). AMI denotes acute myocardial infarction, and CAD coronary artery disease.

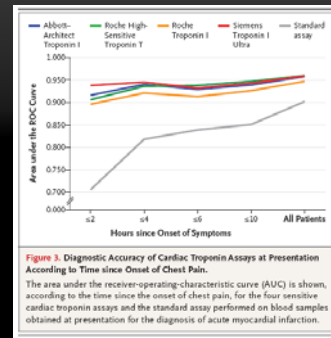
## Result (III)

Troponin Assay	Sensitivity	Specificity	Negative Predictive Value (95% confidence interval)	Positive Predictive Value
<b>Sensitive troponin assays</b>				
<b>Abbott-Architect Troponin I</b>				
Limit of detection, 0.012 µg/L	94 (93-97)	87 (84-90)	98 (97-99)	59 (52-66)
99th percentile, 0.028 µg/L	86 (79-92)	92 (90-94)	97 (95-98)	69 (61-76)
10% coefficient of variation, 0.012 µg/L	83 (77-90)	91 (90-95)	97 (95-98)	70 (62-78)
<b>Roche High-Sensitive Troponin T</b>				
Limit of detection, 0.002 µg/L	100 (97-100)	14 (12-18)	100 (96-100)	39 (34-43)
99th percentile, 0.014 µg/L*	93 (90-96)	80 (77-83)	99 (97-100)	50 (43-56)
<b>Roche Troponin I</b>				
Limit of detection, 0.100 µg/L	92 (86-96)	88 (86-91)	98 (97-99)	62 (55-69)
99th percentile, 0.140 µg/L	84 (76-90)	94 (91-95)	97 (95-98)	73 (65-80)
10% coefficient of variation, 0.100 µg/L	73 (66-82)	97 (95-98)	95 (93-97)	83 (75-89)
<b>Siemens Troponin I Ultra</b>				
Limit of detection, 0.004 µg/L	97 (91-99)	88 (84-92)	99 (97-100)	38 (31-44)
99th percentile, 0.040 µg/L*	89 (82-94)	92 (89-94)	98 (96-99)	68 (60-76)
<b>Standard assay</b>				
<b>Roche Troponin T 4th Generation</b>				
99th percentile, unknown				
Limit of detection, 0.010 µg/L	83 (76-90)	91 (91-95)	97 (95-98)	72 (64-79)
10% coefficient of variation, 0.010 µg/L	72 (64-80)	97 (96-98)	94 (92-94)	85 (76-91)

## Result (IV)



## Result (V)



**Figure 3. Diagnostic Accuracy of Cardiac Troponin Assays at Presentation According to Time since Onset of Chest Pain.**  
The area under the receiver-operating-characteristic curve (AUC) is shown, according to the time since the onset of chest pain, for the four sensitive cardiac troponin assays and the standard assay performed on blood samples obtained at presentation for the diagnosis of acute myocardial infarction.

## Result (Summary)

- 來急診當下的診斷accuracy: 4新>1舊
- 對NSTEMI和STEMI的診斷performance: 4新之間差不多
- 對不同性別,年紀,腎功能的診斷performance: 4新之間差不多
- 4新和1舊之間的差異在症狀產生後短時間內比較顯著
- 對4新而言,結合其他診斷marker並無幫助
- 症狀產生後時間 $\uparrow$ ,4新和1舊的AUC $\uparrow$

## Discussion (I)

- 4 major findings:
  - 4新在來診當下的診斷accuracy已經很高(AUC 0.94~0.96)
  - 4新的診斷accuracy明顯比1舊來的高
  - 4新的優勢在症狀產生後不久最明顯
  - 4新可以幫助D/D AMI

## Discussion (II)

- 4新還是需要和其他臨床細項評估做結合
- ECG還是不能不做
- 4新對於診斷unstable angina還是不太行

## Limitations

- 只評估了4種新的assays
- 未確切評估早期診斷的clinical effect
- 對於洗腎病人的診斷accuracy無法評估
- 對於final diagnosis的認定

## Conclusion

- 新式高敏感度 cardiac troponin assays 對診斷 AMI 來說有很棒的表現, 尤其對近期內發作的胸痛病人有更好的優勢

## High-Sensitivity Troponin T Concentrations in Acute Chest Pain Patients Evaluated With Cardiac Computed Tomography

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Presented by R1 錢逸群

## Background

- Troponin 是診斷 AMI 最重要的 biomarker
- 建議的 cutpoint 值為健康族群的 99th percentile
- 一般 assay 的 limit of detection 無法這麼低
- 新式高敏感度 troponin assay (hsTnT)

## Goal

- 檢視 hsTnT 的 diagnostic performance
  - Sensitivity? Specificity?
- 結合臨床症狀與 CTA 結果共同評估 hsTnT 的結果
  - Anatomic cause of elevated hsTnT?

## Method

- 2005/5~2007/5, 377 位呈現胸痛或懷疑是 ACS 症狀的急診來診病人 (MGH)
- 最後診斷由兩位醫師 retrospectively 判定
- 血液樣本在做 CTA 時同時取得 (4.2hrs)
- Cardiac biomarker testing:
  - hsTnT (13pg/ml)
  - cTnT (0.03ng/ml, 0.01ng/ml)
- CTA: 64 切 CT
- ROC curve, Kruskal-Wallis test, McNemar test

## Result (I)

Mean age: 53.7  
37(9.8%) have ACS  
25 have UA

Table 1. Characteristics of Study Population Categorized as a Function of ACS

Characteristic	ACS				P
	All (n=27)	MI (n=15)	UAF (n=20)	No ACS (n=340)	
Age, y	53.7 (12)	55.1 (10)	49.1 (12)	53.1 (12)	<0.001
Male sex, n (%)	19 (70)	9 (60)	12 (60)	273 (80)	0.002
Prior medical history, n (%)					
Diabetes mellitus	6 (22)	3 (20)	9 (45)	37 (11)	0.002
Hypertension	13 (48)	4 (27)	17 (85)	114 (33)	0.001
Hyperlipidemia	14 (52)	3 (20)	21 (105)	132 (39)	0.002
Family history of CAD	10 (37)	2 (13)	7 (35)	101 (30)	0.73
Previous history of CAD	12 (44)	1 (7)	11 (55)	101 (30)	<0.001
Prior MI	6 (22)	1 (7)	8 (40)	36 (10)	<0.001
Tobacco use	14 (52)	4 (27)	18 (90)	172 (51)	0.14
Medications at presentation, n (%)					
Aspirin	21 (78)	2 (13)	19 (95)	190 (56)	0.001
Statins	21 (78)	2 (13)	19 (95)	189 (56)	<0.001
Nitroglycerin	1 (4)	0 (0)	4 (20)	10 (3)	0.21
β-Blockers	10 (37)	2 (13)	18 (90)	81 (24)	0.001
Vital signs					
Systolic blood pressure, mm Hg	130 (22)	130 (14)	130 (23)	130 (12)	0.86
Diastolic blood pressure, mm Hg	73 (13)	63 (7)	71 (14)	68 (11)	0.002
Heart rate, beats/min	62 (11)	62 (7)	62 (11)	62 (7)	0.96
Body mass index, kg/m <sup>2</sup>	29 (5)	29 (3)	29 (5)	29 (3)	0.99
Coronary CT angiography					
Coronary with color flow Doppler	6 (22)	5 (33)	6 (30)	17 (5)	<0.001
Segments with nonoccluded plaque	3 (11)	4 (27)	3 (15)	8 (2)	<0.001
Segments with mixed plaque	2 (8)	3 (20)	2 (10)	8 (2)	<0.001
Segments with any plaque	7 (26)	6 (40)	7 (35)	21 (6)	<0.001
Segments with significant stenosis	1 (4)	1 (7)	1 (5)	1 (0)	<0.001
Vessels with any plaque	3 (11)	3 (20)	3 (15)	10 (3)	<0.001
Vessels with significant stenosis	1 (4)	1 (7)	1 (5)	1 (0)	<0.001
Cardiac chamber size and function					
Left atrial diameter, volume, mL	100 (2)	90 (3)	111 (3)	90 (2)	0.001
Left atrial systolic volume, mL	90 (2)	80 (3)	71 (3)	57 (2)	<0.001
Left ventricular volume, mL	120 (3)	120 (4)	120 (3)	110 (3)	0.17
Left ventricular ejection fraction, %	50 (2)	50 (3)	47 (2)	50 (2)	0.02
LV mass	100 (3)	100 (3)	100 (3)	100 (3)	0.14
Left ventricular wall thickness, %	100 (3)	100 (3)	100 (3)	100 (3)	0.001
Regional LV dysfunction, n (%)	27 (100)	8 (100)	19 (100)	82 (24)	<0.001
Nonischemic bundle branch block (BBB)	110 (23-420)	81 (35-143)	140 (23-420)	47 (24-110)	0.14
QTc (ms) (95% CI)	400 (10)	400 (10)	400 (10)	400 (10)	0.001
QTc (ms) (95% CI)	400 (10)	400 (10)	400 (10)	400 (10)	0.001

## Result (II)

- Median hsTnT: 5.4 pg/ml
- 62人(16.4%)的hsTnT>13pg/ml
- hsTnT in AMI vs. unstable angina vs. no ACS:  
112.0 vs. 12.3 vs. 7.0
- AUC in hsTnT vs. cTnT: 0.79 vs. 0.74

## Result (III)

The optimal cutpoint of hsTnT:  
8.62 pg/ml

Table 2. Results of Troponin Testing for Diagnosis of ACS

Analyte, Cut Point	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Diagnostic accuracy for ACS in all patients (AUC <sub>hsTnT</sub> : 0.79)				
hsTnT, 13 pg/mL	62 (47-78)*	89 (85-92)	39 (26-50)	96 (93-98)
cTnT, 0.01 ng/mL	49 (33-65)	97 (96-99)†	67 (49-84)	95 (92-97)
cTnT, 0.03 ng/mL	35 (20-50)	99 (98-100)†	72 (52-83)	93 (90-95)
Diagnostic accuracy for MI in all patients (AUC <sub>hsTnT</sub> : 0.86)				
hsTnT, 13 pg/mL	88 (47-100)	85 (81-89)	11 (5-22)	100 (98-100)
cTnT, 0.01 ng/mL	88 (47-100)	94 (92-97)†	26 (11-46)	100 (98-100)
cTnT, 0.03 ng/mL	88 (47-100)	97 (95-98)†	39 (17-46)	100 (98-100)
Diagnostic accuracy for unstable angina pectoris in patients without MI (AUC <sub>hsTnT</sub> : 0.72)				
hsTnT, 13 pg/mL	55 (37-74)*	89 (85-92)	30 (16-44)	96 (93-98)
cTnT, 0.01 ng/mL	38 (21-58)	97 (95-99)†	55 (32-77)	95 (92-97)
cTnT, 0.03 ng/mL	21 (8-40)	99 (97-100)†	55 (32-80)	94 (90-96)

ACS indicates acute coronary syndrome; PPV, positive predictive value; NPV, negative predictive value; and AUC, area under the curve.  
\*P<0.001 vs cTnT; †P<0.001 vs hsTnT.

## Result (IV)

Independent predictors:  
Age  
Presence/extent of CAD  
Cardiac structure  
Cardiac function  
NT-proBNP

Characteristic	Univariable		Multivariable	
	Spearman Correlation	P	β	P
<b>Physical examination</b>				
Body mass index, kg/m <sup>2</sup>	0.05	0.39	...	...
Systolic blood pressure, mm Hg	0.09	0.87	...	...
Diastolic blood pressure, mm Hg	-0.075	0.14	...	...
Heart rate, beats	-0.09	0.68	...	...
<b>Coronary CT angiography</b>				
Segments with calcified plaque	0.31	<0.001	...	...
Segments with noncalcified plaque	0.25	<0.001	...	...
Segments with mixed plaque	0.25	<0.001	...	...
Segments with any plaque	0.32	<0.001	...	...
Segments with significant stenosis	0.20	0.005	-0.324	0.03
Vessels with significant stenosis	0.22	<0.001	0.834	0.004
Vessels with plaque	0.30	<0.001	...	...
<b>Cardiac chamber size and function</b>				
LA diastolic volume	0.20	0.001	...	...
LA systolic volume	0.20	0.001	...	...
LV end-diastolic volume	0.13	0.01	-0.012	0.06
LV end-systolic volume	0.16	0.003	0.028	0.06
LV mass	0.30	<0.001	0.008	<0.001
LV ejection fraction	-0.06	0.24	0.042	0.04
Regional LV dysfunction	0.30	0.001	0.669	<0.001
<b>Biomarkers besides troponin T</b>				
NT-proBNP	0.26	<0.001	0.001	0.003
Cystatin-C	0.13	0.009	...	...

LA indicates left atrial; LV, left ventricular; and NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

## Result (V)

Comparison among no ACS:  
Complex medical hx  
Cardiac abnormalities  
Prevalent and extensive CAD

Characteristic	No ACS		P
	hsTnT ≥13 pg/mL (n=38)	hsTnT <13 pg/mL (n=302)	
Age, y	61.5±14.0	52±11.0	<0.001
Male sex, n (%)	20 (53)	166 (55)	0.40
<b>Past medical history, n (%)</b>			
Diabetes mellitus	16 (20)	27 (9)	0.001
Hypertension	21 (55)	113 (37)	0.03
Hyperlipidemia	21 (55)	111 (37)	0.03
Family history of CAD	16 (20)	73 (24)	0.60
Personal history of CAD	16 (20)	25 (8)	<0.001
Prior MI	7 (18)	19 (6)	0.008
Tobacco use	15 (39)	157 (52)	0.10
<b>Medications at presentation, n (%)</b>			
Aspirin	17 (45)	99 (33)	0.10
Statins	17 (45)	84 (28)	0.03
Nitroglycerine	5 (13)	14 (5)	0.03
β-blocker	16 (42)	65 (21)	0.005
<b>Wrist signs</b>			
Systolic blood pressure, mm Hg	137±23.0	139±23.0	0.60
Diastolic blood pressure, mm Hg	77±18.0	81±13.0	0.20
Heart rate, bpm	65±7.0	67±10.0	0.30
Body mass index, kg/m <sup>2</sup>	29±6.0	29±6.0	0.40
<b>Coronary CT angiography</b>			
Segments with calcified plaque	4.4±4.0	1.5±3.0	<0.001
Segments with noncalcified plaque	1.8±3.0	0.8±2.0	0.05
Segments with mixed plaque	1.4±2.5	0.5±1.4	0.04
Segments with plaque	4.3±5.0	1.7±3.0	0.001
Segments with significant stenosis	0.4±1.0	0.06±0.3	0.04
Vessels with significant stenosis	0.2±0.5	0.05±0.3	0.09
Vessels with plaque	2±1.8	0.9±1.3	0.001
<b>Cardiac chamber size and function</b>			
LA diastolic volume, mL	107±33.0	95±24.0	0.02
LA systolic volume, mL	69±31.0	65 (17.0)	0.01
LV end-diastolic volume, mL	122±45.0	117±30.0	0.50
LV end-systolic volume, mL	48±41.0	38±16.0	0.20
LV mass	173±60.0	147±36.0	0.01
LV ejection fraction, %	60±14.0	68±9.0	0.20
Regional LV dysfunction, n (%)	8 (22)	24 (8)	0.008
<b>Biomarkers besides troponin T, median (IQR)</b>			
NT-proBNP, ng/mL	248 (69-492)	42 (23-86)	<0.001
Cystatin-C, mg/L	0.93 (0.75-1.07)	0.82 (0.73-0.92)	0.05

## Discussion

- Why 99<sup>th</sup> percentile?
- 除了ACS以外,hsTnT還跟很多因素相關
- 並不是所有ACS都有hsTnT升高的情形
- hsTnT的specificity(89%)較cTnT略低
- 可以靠hsTnT偵測MI without necrosis嗎?
- hsTnT升高對臨床醫師的意義? Not always AMI!
- hsTnT method: test for "myocardial injury", not for "MI"

## Limitations

- Cohort不夠大
- 所選病人ACS風險偏低
  - hsTnT prognostic value評估受影響
  - 無法將結果應用在複雜與高危險病人
- 抽血時機與hsTnT測量次數

## Conclusion

- 在低到中度風險的胸痛病人,hsTnT是有高敏感度與特異度診斷ACS的方法
- hsTnT提高代表有心肌受損或心臟結構問題,但這部一定代表有ACS的情況