トロポニン：troponin T and I（060521、110214）

110214　参考文献 2～4 を追加

トロポニンはうまく利用すれば強力な武器になると思う。ただ単に陽性だから心筋梗塞、陰性だと心筋梗塞は否定的というような単純な判断では必ず痛い目にあうと思うので、十分に検査特性は理解しておくことが必要と思う。（むしろ、状況によってはトロポニンに頼らないという選択がベストなこともあると思う。）

H-FABP については以前の項目を参照のこと

「H-FABP の感度/特異度」
http://rockymuku.sakura.ne.jp/zyunnkannkinaika/H-FABP.pdf

トロポニンは CK-MB の動きと似ているが現在の検査では 4 時間までに 80%の人が上昇を認めるとされる。1） 地域の現場では、トロポニンが陰性でも早期の場合は ACS が否定できないことも多く、症状から ACS が否定できなければ、循環器内科や入院施設のある病院へ紹介したり（→ちょうど、紹介先へ到着したころに検査が陽性になることも多々ある・・・）、最低でも外来で経過観察することも多いのではないだろうか（→ST 変化を伴う MI では血液検査の結果如何にかかわらず治療を行うべきであるが、ST 上昇を伴わない患者では急速な再潅流療法は必ずしも重要でないという意見もあり、少なくとも 4-6 時間後に再評価をおこなう）。

トロポニンは中等度から重度の肺梗塞、心筋炎、心不全、蘇生後などの外傷後でも上昇するし、高度の腎不全、骨格筋障害でも上昇する可能性がある。トロポニン I はトロポニン T と異なり、溶血の影響は無く、陽性までの時間も比較的短い。いずれにしても、感度、特異度を下げうる様々な要因があることは理解しておく必要がある。1）

Test	Onset	Peak	Duration
Creatine kinase – total and MB	3-12 hours	18-24 hours	36-48 hours
Troponins	3-12 hours	18-24 hours	Up to 10 days
Myoglobin	1 -4 hours	6-7 hours	24 hours
Lactate dehydrogenase	6-12 hours	24-48 hours	6 to 8 days

Time course of serum markers in acute MI Time course of the major serum markers used to confirm the diagnosis of acute myocardial infarction. The early onset of elevations in creatinine kinase (CK), both total and MB fraction, and troponins permits early detection, while the short duration of the elevation in CK permits infarct extension to be identified by the detection of new elevations. On the other hand, the long duration of the troponin and lactate dehydrogenase permits the diagnosis to be established days after the acute event. Myoglobin is not routinely measured because it lacks specificity for the heart. However, it may be helpful when used in addition to these other markers.

（参考文献 1 より引用）

時間経過と検査特性には非常に大きな関係があって、特に感度は発症間もないとかなり低い。トロポニン T の陰性尤度比が 0.2 以下になるのは 6～8 時間後であり、トロポニン I でも 5 時間後である。この論文の結論には胸痛の発症後 8 時間以降に陰性であれば除外に特に有効としている。

Sensitivity increases for both troponin T and I from 10% to 45% within 1 hour of the onset of pain (depending on the cutoff) to more than 90% at 8 or more hours. Specificity declines gradually from 87% to 80% from 1 to 12 hours after the onset of chest pain for troponin T and is approximately 95% for troponin I.

Although troponin T and I values are useful tools for the diagnosis of AMI, they must be interpreted according to the number of hours from the onset of chest pain. The test is particularly useful at ruling out MI when the value is negative at 8 or more hours after the onset of chest pain.

TABLE 2

Summary of Data for Troponin T and I Tests for Diagnosing AMI

	Hours from Onset of Chest Pain	Sensitivity	Specificity	LR+	LR-
Troponin T >0.1*					
	1	0.47	0.87	3.7	0.6
	2	0.53	0.87	3.9	0.5
	3	0.58	0.86	4.1	0.5
	4	0.64	0.85	4.2	0.4
	6	0.74	0.83	4.4	0.3
	8	0.84	0.81	4.5	0.2
	10	0.93	0.80	4.6	0.1
Troponin T >0.2†					
	1	0.14	0.87	1.1	1.0
	2	0.33	0.87	2.5	0.8
	3	0.50	0.86	3.5	0.6
	4	0.65	0.85	4.3	0.4
	6	0.86	0.83	5.1	0.2
	8	0.96	0.81	5.2	0.05
	10	0.96	0.80	4.7	0.05
Troponin I >0.1‡					
	1	0.13	0.95	2.7	0.9
	2	0.34	0.95	6.8	0.7
	3	0.52	0.95	10	0.5
	4	0.67	0.95	13	0.34
	5	0.80	0.95	16	0.2
	6	0.90	0.95	18	0.1

NOTE: \alues are calculated from the best-fit curves for sensitivity and specificity shown in Figure 1. \While troponin I appears to be more accurate, these data are based on the results of a single relatively small study and should be interpreted with caution.
AMI denotes acute myocardial infarction; LR+, positive likelihood ratio; LR-, negative likelihood ratio.
*Bakker, 1993; Bakker, 1995; Katz, 1998.
†Antman, 1995; Katz, 1998; Mair, 1996.
‡Mair, 1996.

（参考文献 2 より引用）

最近発表された高感度トロポニンの論文を読んでみる。参考文献 3 は高感度トロポニン I と従来のマーカーを比較した論文である。陽性の場合にはいずれの検査でも、かなり心筋梗塞の確率を上昇させる点は変わらない。従来の方法と比較して、発症早期（<3 時間）での感度が高く、陰性尤度比が低くなっている。

全患者	感度	特異度	陽性尤度比	陰性尤度比
高感度トロポニン I	90.7%	90.2%	**9.2**	**0.10**
トロポニン T	72.7%	94.1%	**12.3**	0.29

発症 6 時間以内	感度	特異度	陽性尤度比	陰性尤度比

高感度トロポニン I	86.8%	92.2%	11.1	0.14
トロポニン T	62.1%	94.9%	12.1	0.40

発症 3 時間以内	感度	特異度	陽性尤度比	陰性尤度比
高感度トロポニン I	84%	93.2%	12.4	0.17
トロポニン T	55.2%	95.7%	12.8	0.47

For samples obtained on admission, the diagnostic accuracy was highest with the sensitive troponin I assay (area under the receiver-operating-characteristic curve [AUC], 0.96), as compared with the troponin T assay (AUC, 0.85) and traditional myocardial necrosis markers. With the use of the sensitive troponin I assay (cutoff value, 0.04 ng per milliliter) on admission, the clinical sensitivity was 90.7%, and the specificity was 90.2%. The diagnostic accuracy was virtually identical in baseline and serial samples, regardless of the time of chest-pain onset. In patients presenting within 3 hours after chest-pain onset, a single sensitive troponin I assay had a negative predictive value of 84.1% and a positive predictive value of 86.7%; these findings predicted a 30% rise in the troponin I level within 6 hours. A troponin I level of more than 0.04 ng per milliliter was independently associated with an increased risk of an adverse outcome at 30 days (hazard ratio, 1.96; 95% confidence interval, 1.27 to 3.05; P=0.003).

Table 2. Discriminatory Value of Biomarkers for the Diagnosis of Acute Myocardial Infarction.*

Variable	Sensitive Troponin I Assay*	Troponin T, Standard Assay†		Myoglobin‡	Myoglobin or Troponin T	
		99th Percentile	10% CV		99th Percentile	10% CV
	value (95% confidence interval)					
Presentation <3 hr after chest-pain onset						
Sensitivity	84.0 (77.5–89.3)	55.2 (47.2–62.9)	43.6 (35.9–51.6)	61.9 (52.5–70.6)	79.6 (72.2–85.8)	77.6 (69.9–84.2)
Specificity	93.2 (90.4–95.3)	95.7 (93.4–97.4)	98.0 (96.2–99.1)	88.0 (84.1–91.3)	83.5 (79.2–87.2)	86.2 (82.1–89.6)
Positive predictive value	82.0 (75.4–87.5)	82.7 (74.3–89.3)	88.9 (80.0–94.8)	64.0 (54.5–72.8)	66.9 (59.4–73.8)	69.8 (62.0–76.8)
Negative predictive value	94.0 (91.3–96.0)	85.2 (81.7–88.2)	82.4 (78.9–85.5)	87.0 (83.0–90.4)	90.7 (87.0–93.6)	90.3 (86.6–93.3)
Presentation <6 hr after chest-pain onset						
Sensitivity	86.8 (81.7–90.8)	62.1 (55.6–68.4)	50.6 (44.1–57.2)	62.4 (54.6–69.7)	83.8 (78.2–88.4)	80.0 (73.9–85.2)
Specificity	92.2 (90.0–94.1)	94.9 (93.0–96.4)	97.8 (96.4–98.8)	86.9 (83.7–89.6)	82.0 (78.6–85.2)	84.8 (81.5–87.7)
Positive predictive value	79.3 (73.8–84.1)	80.7 (74.1–86.1)	88.8 (82.2–93.6)	59.9 (52.3–67.2)	64.6 (58.7–70.2)	66.9 (60.7–72.7)
Negative predictive value	95.3 (93.4–96.8)	88.0 (85.5–90.3)	85.3 (82.7–87.7)	88.0 (84.9–90.6)	92.8 (90.1–94.9)	91.7 (88.9–93.9)
Presentation <12 hr after chest-pain onset						
Sensitivity	88.1 (83.7–91.6)	64.1 (58.3–69.7)	54.0 (48.1–59.9)	61.2 (54.1–67.9)	83.4 (78.4–87.7)	80.3 (74.9–85.0)
Specificity	92.1 (90.1–93.8)	95.4 (93.8–96.7)	97.9 (96.8–98.8)	86.9 (84.1–89.3)	82.6 (79.6–85.3)	85.0 (82.2–87.6)
Positive predictive value	78.7 (73.8–83.0)	82.1 (76.5–86.9)	89.6 (84.1–93.7)	58.3 (51.5–65.0)	64.4 (59.1–69.5)	66.7 (61.1–71.9)
Negative predictive value	95.9 (94.3–97.1)	89.0 (86.8–90.9)	86.6 (84.3–88.7)	88.2 (85.5–90.5)	92.9 (90.6–94.8)	92.1 (89.7–94.0)
All patients						
Sensitivity	90.7 (87.4–93.3)	72.7 (68.1–76.9)	63.7 (58.8–68.3)	61.3 (55.6–66.9)	87.1 (83.3–90.3)	84.1 (80.0–87.7)
Specificity	90.2 (88.3–91.9)	94.1 (92.6–95.4)	97.2 (96.0–98.0)	86.9 (84.6–89.0)	81.9 (79.3–84.4)	84.6 (82.1–86.9)
Positive predictive value	76.7 (72.7–80.4)	81.4 (77.1–85.3)	88.8 (84.6–92.1)	60.5 (54.8–66.1)	66.6 (62.3–70.7)	69.0 (64.5–73.2)
Negative predictive value	96.4 (95.2–97.5)	90.7 (88.9–92.3)	88.3 (86.4–90.0)	87.3 (85.0–89.4)	93.9 (92.0–95.4)	92.9 (91.0–94.5)

* A cutoff value of 0.04 ng per milliliter for the sensitive troponin I assay was determined to be the 99th percentile on the basis of analysis of samples obtained from 5000 subjects in the Gutenberg Heart Study. The 10% coefficient of variation (CV) was lower than the 99th percentile, so only the 99th percentile is presented.
† A troponin T level of 0.01 ng per milliliter represents the 99th percentile in the reference population. A troponin T level of 0.03 ng per milliliter represents the 10% coefficient of variation.
‡ The cutoff value for myoglobin was 107 ng per milliliter.

（参考文献 3 より引用）

参考文献 4 は各社の高感度トロポニンの検査特性を比較している。ロシュの超高感度は感度が相当高く、特異度が低いのでかなり特徴的な結果だが、それ以外の高感度検査はいずれも従来の物と比較してかなり優れていることが分かる。

	感度	特異度	陽性尤度比	陰性尤度比
Abbott-Architect Troponin I	94%	87%	**7.2**	**0.07**
Roche High-Sensitive Troponin T	100%	14%	1.16	**0**
Roche Troponin I	92%	88%	**7.6**	**0.09**
Siemens Troponin I Ultra	97%	68%	3.03	**0.04**
（Roche Troponin T 4th Generation）	83%	93%	**11.9**	**0.18**

注：Roche Troponin T 4th Generation は標準的なトロポニン検査

The diagnostic accuracy of measurements obtained at presentation, as quantified by the area under the receiver-operating-characteristic curve (AUC), was significantly higher with the four sensitive cardiac troponin assays than with the standard assay (AUC for Abbott-Architect Troponin I, 0.96; 95% confidence interval [CI], 0.94 to 0.98; for Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98; for Roche Troponin I, 0.95; 95% CI, 0.92 to 0.97; and for Siemens Troponin I Ultra, 0.96; 95% CI, 0.94 to 0.98; vs. AUC for the standard assay, 0.90; 95% CI, 0.86 to 0.94). Among patients who presented within 3 hours after the onset of chest pain, the AUCs were 0.93 (95% CI, 0.88 to 0.99), 0.92 (95% CI, 0.87 to 0.97), 0.92 (95% CI, 0.86 to 0.99), and 0.94 (95% CI, 0.90 to 0.98) for the sensitive assays, respectively, and 0.76 (95% CI, 0.64 to 0.88) for the standard assay. We did not assess the effect of the sensitive troponin assays on clinical management.

Table 2. Diagnostic Performance of Cardiac Troponin Assays at Presentation.

Troponin Assay	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
		percent (95% confidence interval)		
Sensitive troponin assays				
Abbott–Architect Troponin I				
Limit of detection, 0.010 μg/liter	94 (88–97)	87 (84–89)	98 (97–99)	59 (52–66)
99th percentile, 0.028 μg/liter	86 (79–92)	92 (90–94)	97 (95–98)	69 (61–76)
10% coefficient of variation, 0.032 μg/liter	85 (77–90)	93 (90–95)	97 (95–98)	70 (62–78)
Roche High-Sensitive Troponin T				
Limit of detection, 0.002 μg/liter	100 (97–100)	14 (12–18)	100 (96–100)	19 (16–23)
99th percentile, 0.014 μg/liter*	95 (90–98)	80 (77–83)	99 (97–100)	50 (43–56)
Roche Troponin I				
Limit of detection, 0.100 μg/liter	92 (86–96)	88 (86–91)	98 (97–99)	62 (55–69)
99th percentile, 0.160 μg/liter	84 (76–90)	94 (91–95)	97 (95–98)	73 (65–80)
10% coefficient of variation, 0.300 μg/liter	75 (66–82)	97 (95–98)	95 (93–97)	83 (75–89)
Siemens Troponin I Ultra				
Limit of detection, 0.006 μg/liter	97 (91–99)	68 (64–72)	99 (97–100)	38 (32–44)
99th percentile, 0.040 μg/liter*	89 (82–94)	92 (89–94)	98 (96–99)	68 (60–76)
Standard assay				
Roche Troponin T 4th Generation				
99th percentile, unknown				
Limit of detection, 0.010 μg/liter	83 (76–90)	93 (91–95)	97 (95–98)	72 (64–79)
10% coefficient of variation, 0.035 μg/liter	72 (64–80)	97 (96–98)	94 (92–96)	85 (76–91)

* The criterion of 10% coefficient of variation was fulfilled at the 99th percentile.

（参考文献 4 より引用）

高感度トロポニン検査が、従来のトロポニン検査と比較して、かなり有用な検査であることが分かった。ただし、心筋梗塞という重大イベントの判断をする場合にはより保守的な対応が望まれることも多いと思う。事前確率の見積もりも検査と同様に重要で、時間経過を注意深く利用することも重要である点は変わらないと思う。完璧な検査では無く、たとえ 99%正しいとしても、1%の間違い（つまり 100 回に 1 回）心筋梗塞を誤診するようなことがあったら、やっぱり凹むと思う・・・。

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