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CLINICAL RESEARCH

Which high-sensitivity troponin variable best characterizes infarct size and microvascular obstruction?



Quelle type de troponine de haute sensibilité choisir pour caractériser au mieux la taille d'infarctus et l'obstruction microvasculaire?

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KEYWORDS

Acute myocardial infarction;
High-sensitivity troponin;

Summary

Background. – The link between hs-Tn and infarct size has already been proved in several articles. However few is known about the kinetic of the troponin and its link to the infarct characteristics, likewise MVO. Our primary objective was to study which hs-Tn characterizes the best infarction.

Abbreviations: AUC, Area Under the Curve; CE-CMR, Contrast-Enhanced Cardiac Magnetic Resonance; hs-TnI, high-sensitivity Troponin I; hs-TnT, high-sensitivity Troponin T; MVO, Microvascular Obstruction; PCI, Percutaneous Coronary Intervention; STEMIST-, Segment Elevation Myocardial Infarction; s-TnI, sensitive Troponin I.

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Ce-CMR;
Infarct
characterization;
Microvascular
obstruction

Methods and results. – We identified 29 consecutive STEMI patients to study. The kinetics of hs-TnT (Roche) and two different TnIs (hs-TnI from Abbott, s-TnI from Siemens) were evaluated for all patients. Area under curves (AUC), first peak (FP) and second peak (SP), for hs-TnT, were compared to IS and MVO size using contrast-enhanced cardiac magnetic resonance. For IS, statistically SP of hs-TnT presented the best correlation compared to other peak values [$r=0.9$ vs. 0.73 for FP hs-TnT; vs. 0.69 for hs-TnI; vs. 0.57 for s-TnI; respectively $P<0.01$, $P<0.01$, $P<0.01$]. For MVO size, statistically SP of hs-TnT presented the best correlation compared to other peak values [$r=0.84$ vs. 0.75 for FP hs-TnT; vs. 0.72 for hs-TnI; vs. 0.62 for s-TnI; respectively $P=0.01$, $P<0.01$, $P<0.01$]. The best AUC were archived by the hs-TnT (AUC = 0.95) but there were no statistical differences when compared to other hs-Tn AUC.

Conclusion. – The SP of hs-TnT had the greatest level of correlation and therefore seems to be the best biological parameter to evaluate and characterize infarct size.

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MOTS CLÉS

Infarctus du
myocarde aigu ;
Troponine sensible ;
IRM cardiaque ;
Taille de nécrose ;
Obstruction
micro-vasculaire

Résumé

Introduction. – La relation en troponine hypersensible et taille d'infarctus a été prouvée dans de nombreux articles. Cependant, peu de relations ont été établies entre cinétique de troponine et les caractéristiques de l'infarctus, notamment l'obstruction microvasculaire. Notre objectif principal était d'étudier quelle troponine de haute sensibilité caractérisait le mieux l'infarctus du myocarde.

Méthodes et résultats. – 29 patients ayant subi un infarctus du myocarde aigu ont été inclus consécutivement dans cette étude. Les cinétiques de la troponine T-hs (Roche) et deux troponines I (hs-TnI de chez Abbott, s-TnI de chez Siemens) ont été évaluées pour tous les patients. Les aires sous la courbe, la valeur du premier pic (PP) et du second pic (SP), pour la troponine T-hs, étaient comparées aux valeurs de taille d'infarctus et d'obstruction microvasculaire mesurées par IRM cardiaque. Concernant la taille de la nécrose, le second pic (SP) de troponine T-hs (hs-TnT) avait la meilleure corrélation en comparaison des autres valeurs de pic ($r=0,9$ vs 0,73 pour le PP de hs-TnT ; vs 0,69 pour le pic de hs-TnI ; vs 0,57 pour le pic de s-TnI ; respectivement $p<0,01$, $p<0,01$, $p<0,01$). Concernant la taille de l'obstruction microvasculaire, le SP de hs-TnT présentait la meilleure corrélation également en comparaison des autres valeurs de pics ($r=0,84$ vs 0,75 pour PP de hs-TnT ; vs 0,72 pour le pic de hs-TnI ; vs 0,62 pour le pic de s-TnI ; respectivement $p=0,01$, $p<0,01$, $p<0,01$). La meilleure aire sous la courbe de troponine était retrouvée avec la hs-TnT (AUC = 0,95), sans différence significative cependant comparativement aux autres troponines.

Conclusion. – Le second pic de troponine T-hs semblait être le meilleur paramètre biologique d'évaluation des caractéristiques de l'infarctus du myocarde.

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Background

Prognosis after acute myocardial infarction is strongly related to the extent of the myocardial injury and the presence of microvascular obstruction (MVO) [1–4]. Contrast-enhanced cardiac magnetic resonance (CE-CMR) allows precise myocardial tissue characterization [5] at the acute phase of the myocardial infarction, and enables assessment of MVO and infarct size. CE-CMR is considered to be the gold standard for analysing myocardial injury and ventricular volumes [6–8]. However, the use of CE-CMR is limited by its availability in routine practice. Therefore, estimating infarct size from peripheral blood concentrations of cardiac biomarkers is a convenient alternative [6,9,10],

particularly when adapted to clinical research targeting a reduction in infarct size.

Repetitive evaluation of cardiac biomarkers is routinely used to assess myocardial damage when measured up to 72 hours after primary percutaneous coronary intervention (PCI). Several studies have shown that troponin measurements are highly correlated to infarct size, and can predict clinical outcomes [9,11,12]. Recently, new highly sensitive troponin assays (high-sensitivity troponin T [hs-TnT], sensitive troponin I [s-TnI] and high-sensitivity troponin I [hs-TnI]) have replaced the standard assays, with significantly improved sensitivity for the early detection of acute myocardial infarction [13].

There are various data on the correlation between the new generation of troponin assays and infarct size in patients with ST-segment elevation myocardial infarction (STEMI). In several studies, hs-TnT was associated with infarct size [8,14]. However, there are significant differences in the kinetics of hs-TnT, s-TnI and hs-TnI. Assays for hs-TnI have a similar linear decrease in the 48 hours after reperfusion, contrasting with a biphasic kinetic curve for hs-TnT [15,16]. It is not clear whether the peak, area under the curve (AUC) and second peak of hs-TnT provide equivalent information about the characteristics of infarcted tissue. The biological significance of the hs-TnT second peak is also unclear, although it has been suggested that it could be a reflection of MVO rather than infarct size.

The primary objective of our study was to assess and compare the levels of correlation between the new troponin assays (peak values and AUCs) with infarct size and MVO size assessed by CE-CMR in a reperfused STEMI population. The secondary objective was to assess the relationship between the hs-TnT second peak and MVO and infarct size.

Methods

The design and primary results of this study have been published [15]. This observational prospective study was conducted in a single tertiary referral centre: the University Hospital of Montpellier, France. All participants provided written informed consent, and the protocol was approved by the ethics committee of the University Hospital of Montpellier.

Study population

All patients from the initial study who had undergone a CE-CMR before discharge were included [15]. Between February and July 2014, consecutive patients admitted for STEMI who were treated successfully with primary PCI according to current guidelines [17] were included. The diagnosis of STEMI was based on chest pain onset < 12 hours, with ST-segment elevation of > 2 mm on a standard 12-lead electrocardiogram in two adjacent leads. Only patients with an initial occluded culprit coronary artery defined by a Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤ 1 on coronary angiography were included in the study.

Medical treatment

All patients were treated according to the updated international guidelines from the European Society of Cardiology [17] with a combination of dual antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors and statins, as appropriate.

Blood sampling

Venous blood samples were collected at admission, then twice daily for 5 days and then once daily until hospital discharge.

Measurement of hs-TnT

The hs-TnT assay was performed on the Cobas® 8000 e602 analyser (Roche Diagnostics, Meylan, France). The lowest concentration measurable at the 10% coefficient of variation level is 13 ng/L, and the 99th percentile among healthy individuals is 14 ng/L (confidence interval 12.7–24.9). The limit of detection is 5.0 ng/L [18].

Measurement of hs-TnI and s-TnI

Two different assays were used to assess TnI. The hs-TnI concentrations were measured on the ARCHITECT i1000SR® (Abbott Diagnostics, Lake Forest, IL, USA) using the ARCHITECT_{STAT}® hs-TnI assay (Abbott Laboratories, Abbott Park, IL), according to the manufacturer's instructions. With this assay, the dynamic range was 0.5–50,000 ng/L and the 10% coefficient of variation level was 3.9 ng/L. The 99th percentile among healthy individuals was set at 14 ng/L for men and 11 ng/L for women [19,20]. The ARCHITECT_{STAT} hs-TnI assay is a double immunoassay, using a capture antibody directed against amino acids 24–40 of the TnI protein, and a chimeric detection antibody directed against amino acids 41–49.

The s-TnI concentrations were measured on the ADVIA Centaur® Immunoassay Analyser (Siemens, Tarrytown, NY, USA) using the ADVIA Centaur® TnI-Ultra assay. This assay has a 10% coefficient of variation limit of 30 ng/L and a 99th percentile at 40 ng/L (confidence interval 20–60). The ADVIA Centaur® TnI-Ultra assay is a double chemiluminescent immunoassay using a capture antibody directed against amino acids 41–49 of the TnI protein, and a chimeric detection antibody directed against amino acids 27–40.

The troponin AUC (troponin concentration [in ng/L] over time) was calculated, which represents more precisely the amount of troponin released.

Acquisition of CE-CMR

All CE-CMR studies were performed on a 1.5 T MAGNETON® Avanto Tim system (Siemens, Erlangen, Germany) before discharge, using vectocardiogram monitoring and a phased-array cardiac receiver coil. Localizers and left ventricular functional assessment were performed using steady-state free-processing sequences in the three axes of the heart. In the short-axis orientation, the left ventricle was completely encompassed by contiguous slices. Delayed enhancement inversion recovery sequences were acquired 10 min after administration of 0.2 mmol/kg gadolinium-based contrast agent (Dotarem®, Guerbet, Roissy CdG, France) to assess infarct size and MVO. Inversion times were individually adjusted to optimize nulling of normal myocardium (typical value of 270–300 ms).

Image analysis

Images were analysed off-line by one experienced operator (MS) who was completely blinded to clinical and biological data. Left ventricular volumes, ejection fraction and mass measurements were performed with dedicated software (ARGUS; Siemen Medical Solutions, Malvern, PA, USA). All delayed enhanced images were transferred to a

Table 1 Baseline characteristics according to the presence of microvascular obstruction on contrast-enhanced cardiac magnetic resonance imaging.

	MVO+ (n = 16)	MVO– (n = 13)
Men	14 (87)	13 (100)
Age (years)	57 ± 14	53 ± 9
Diabetes mellitus	3 (18.75)	2 (15.38)
Current smoker	4 (25.00)	9 (69.23)
Hypertension	9 (56.20)	4 (30.77)
Family history of CAD	9 (56.25)	3 (23.08)
Dyslipidaemia	3 (18.75)	5 (38.46)
Culprit coronary artery		
LAD	10 (62.50)	6 (46.15)
LCx	1 (6.25)	4 (30.77)
RCA	5 (31.25)	3 (23.08)
Final TIMI flow	3 (3–3)	3 (3–3)
CE-CMR characteristics		
LVEDV (mL)	187.50 (161.00–198.50)	169.00 (156.00–195.00)
LVESV (mL)	112.00 (90.00–134.50)	83.00 (68.00–98.00)
LVEF (%)	36.50 (34.00–45.00)	53.00 (49.00–56.00)
MVO (g)	3.74 (1.37–7.67)	0.00 (0.00–0.00)
Infarct size (RT + MVO)	38.64 (25.78–55.05)	13.30 (4.76–22.73)

Data are expressed as number (%), mean ± standard deviation or median (interquartile range). CAD: coronary artery disease; CE-CMR: contrast-enhanced cardiac magnetic resonance; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MVO: microvascular obstruction; RCA: right coronary artery; RT: rheolytic thrombectomy; TIMI: thrombolysis in myocardial infarction.

dedicated OsiriX workstation (OsiriX Foundation, Geneva, Switzerland) for measurement with semiautomatic software CE-CMR tools. The full-width half-maximum algorithm was used to measure hyperintense myocardial areas in the infarct territory, and the hypoenhanced areas within the infarct area were defined as MVO. Infarct size and MVO extent were expressed in grams of tissue and percentage of left ventricular mass, assuming a myocardial specific density of 1.05 g/cm³.

Statistical analysis

Normally distributed data are shown as means ± standard deviations and non-normally distributed data as medians (interquartile ranges). Categorical data are presented as counts and percentages. Continuous variables concerning patient characteristics and treatment were compared using an unpaired *t* test or the Mann-Whitney *U* test according to the normality of the variables' distribution. Categorical variables were compared using the χ^2 test (or Fisher's exact test if the conditions for the χ^2 test were not reached). Spearman correlations and linear regressions were performed to analyse the relationship between CE-CMR infarct size and troponin peaks on the one hand, and troponin AUC on the other hand. Spearman correlations were also carried out to analyse the association between high-sensitivity troponin peaks and highly enhanced myocardial tissue or MVO, along with Steiger tests to compare the two correlations obtained for each peak. Furthermore, an analysis of sensibility via receiver operating characteristic curves was conducted to identify the high-sensitivity troponin peak with the best prognostic value for MVO as a binary variable.

Results

Study population

Between February and July 2014, 29 patients were included. Baseline characteristics are reported in Table 1. Twenty-seven (93%) patients were male, and the mean age was 55 ± 12 years. The left anterior descending coronary artery was the culprit artery in 16 (55%) patients. Optimal angiographic reperfusion was obtained in all patients. MVO was observed on CE-MRI in 16 (55%) patients. The CE-CMR analysis was performed 3 [2–6] days after admission.

Correlation between high-sensitivity troponin variables and CE-CMR infarct size

All analysed troponin variables were significantly highly correlated with infarct size. Correlation levels were good for both peak values and AUC (Figs. 1 and 2). For peak values, correlations with infarct size were significantly stronger with hs-TnT (Roche) ($R^2 = 0.62$) and hs-TnI (Abbott) ($R^2 = 0.57$) than with s-TnI (Siemens) ($R^2 = 0.53$) (Fig. 1). Results were similar using the AUC analysis. The strongest correlation was obtained with hs-TnT (Roche) ($R^2 = 0.53$) compared with hs-TnI (Abbott) ($R^2 = 0.51$) or s-TnI (Siemens) ($R^2 = 0.44$) (Fig. 2).

Correlation between high-sensitivity troponin variables and no reflow

There was good correlation between all the new troponin kinetic variables and MVO (Table 2), but they were not

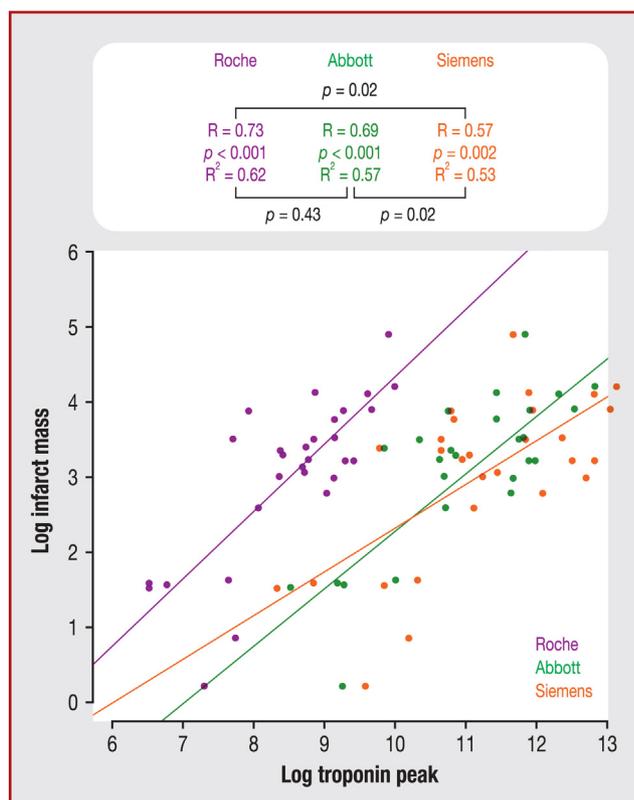


Figure 1. Correlation curves between infarct mass evaluated on cardiac magnetic resonance imaging and peak troponin levels using the Roche (in black), Abbott (in blue) and Siemens (in red) systems. R: coefficient of correlation.

more correlated with MVO than with infarct size (all P values > 0.05) (Table 2).

Prognostic value of high-sensitivity troponin variables

Patients with MVO had a significantly greater CE-CMR infarct size and lower left ventricular ejection fraction, but also a greater troponin peak and AUC (Table 3). The troponin peak had good sensitivity, specificity and an AUC in the receiver operating characteristic model to predict the presence of MVO (Table 4 and Fig. 3).

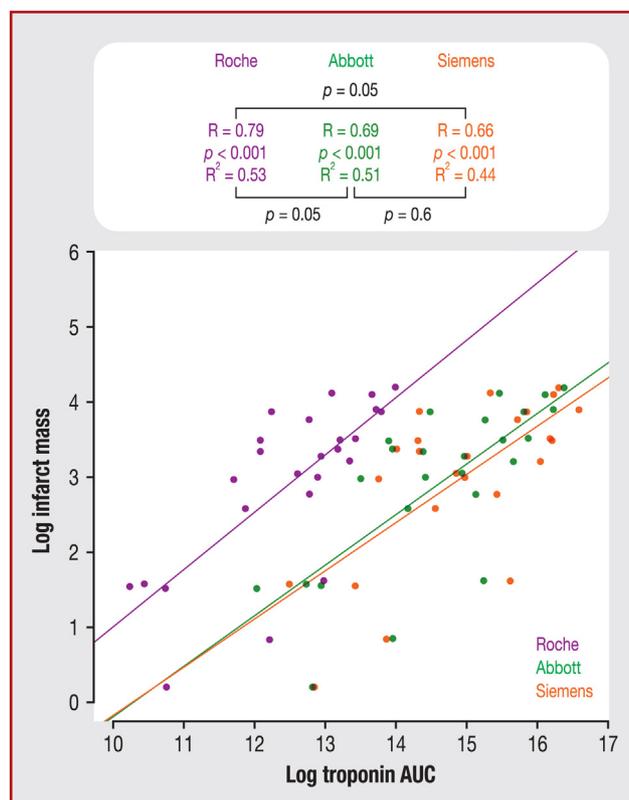


Figure 2. Correlation curves between infarct mass evaluated on cardiac magnetic resonance imaging and troponin area AUC levels using the Roche (in black), Abbott (in blue) and Siemens (in red) systems. R: coefficient of correlation; AUC: under the curve (AUC).

Specificities of the second peak of hs-TnT (Roche)

The second peak of hs-TnT (Roche) was achieved at a median time of 75 hours versus 77 hours in the entire population of the study by Laugaudin et al. [15]. Our results show that the second peak of hs-TnT (Roche) had extremely good correlation with infarct size ($r = 0.9$; $P < 0.0001$) (Table 2). This correlation was statistically greater than with the other high-sensitivity troponin variables ($r = 0.9$ vs. 0.73 for hs-TnT first peak [Roche], vs. 0.69 for hs-TnI peak [Abbott] and vs. 0.57 for s-TnI peak [Siemens]; $P < 0.01$, $P < 0.01$, $P < 0.01$, respectively).

Table 2 Correlations between troponin peak, infarct size and microvascular obstruction.

	Infarct size	MVO	P
hs-TnT first peak (Roche)	0.73 (0.60–0.89)	0.75 (0.45–0.85)	0.57
hs-TnT second peak (Roche)	0.90 (0.72–0.99)	0.84 (0.61–0.99)	0.31
s-TnI (Siemens)	0.57 (0.40–0.73)	0.62 (0.49–0.79)	0.63
hs-TnI (Abbott)	0.69 (0.55–0.88)	0.72 (0.58–0.94)	0.52

Data are expressed as Spearman's rank correlation coefficient, r (95% confidence interval). MVO: microvascular obstruction.

Table 3 Troponin kinetic variables according to the presence of microvascular obstruction on contrast-enhanced cardiac magnetic resonance imaging.

	No reflow		P
	No	Yes	
hs-TnT (Roche)			
AUC (ng/L)	176,960 (46,880–301,200)	558,021 (429,324–836,779)	< 0.001
First peak (ng/L)	2301 (1466–5889)	9286 (6593–13482)	< 0.001
Second peak (ng/L)	1032 (482–1674)	5153 (4396–7262)	0.005
s-TnI (Siemens)			
AUC (ng/L)	1,640,424 (677,124–2,653,296)	6,820,848 (3,250,056–10,875,090)	< 0.001
Peak (ng/L)	29,973 (14,301–56,336)	147,857 (69,021–315,126)	< 0.001
hs-TnI (Abbott)			
AUC (ng/L)	908,758 (357,550–1,601,321)	5,374,669 (3,182,050–7,878,012)	< 0.001
Peak (ng/L)	26,233 (10,364–44,418)	129,653 (71,339–152,586)	< 0.001

Data are expressed as median (interquartile range). AUC: area under the curve; hs-TnI: high-sensitivity troponin I; hs-TnT: high-sensitivity troponin T; s-TnI: sensitive troponin I.

Table 4 Sensitivity and specificity of troponin peaks in detecting microvascular obstruction.

	Cut-off (ng/L)	Sensitivity ^a	Specificity ^a	PLR	NLR
hs-TnT first peak (Roche)	6676	75 (50–94)	92 (77–100)	9.4	0.27
hs-TnT second peak (Roche)	4168	90 (70–100)	88 (67–100)	7.5	0.11
s-TnI peak (Siemens)	45,445	94 (81–100)	69 (46–92)	3.0	0.09
hs-TnI peak (Abbott)	49,908	81 (62–100)	85 (61–100)	5.4	0.22

hs-TnI: high-sensitivity troponin I; hs-TnT: high-sensitivity troponin T; NLR: negative likelihood ratio; PLR: positive likelihood ratio; s-TnI: sensitive troponin I.

^a Data are expressed as % (95% confidence interval).

Considering the prognostic value of the second peak, patients with MVO had a greater hs-TnT second peak (Roche) (Table 3). Correlations with MVO size were statistically greater with the hs-TnT second peak (Roche) than with the other troponin peaks (Fig. 4). The AUC to predict MVO for the hs-TnT second peak (Roche) was very good, but was not statistically different to the AUCs for the other troponin peaks (Fig. 3 and Table 4). The greatest sensitivity (94%) to predict MVO was reached with the hs-TnT second peak (Roche), whereas the greatest specificity (92%) was reached with the hs-TnT first peak (Roche) (Table 4).

Discussion

Despite a limited number of included patients, our findings can be summarized as follows:

- there are excellent levels of correlation between the peaks and AUCs of different high-sensitivity troponins and infarct size assessed by CE-CMR;
- the second peak of hs-TnT (Roche) is the best biological variable to evaluate infarct size.

Correlation between troponin and infarct size

Having a biomarker that is extremely sensitive and perfectly correlated with infarct size is mandatory in the

management of patients with STEMI. Indeed, infarct size is the strongest independent predictor of outcome in this population. This is also of importance for clinical research, as troponins are used routinely as surrogate endpoints for infarct size assessment. Many studies have investigated the correlation between “standard” troponin and infarct size. Good correlations were found between infarct size assessed by single-photon emission computed tomography (SPECT) [21,22] or by CE-CMR [8,11,12] and these standard troponins ($r=0.45$ and $r=0.55$, respectively).

Surprisingly, until now, and despite their widespread use for this purpose, little was known about high-sensitivity troponins. Furthermore, the various assays are used irrespective of their intrinsic properties. Our study is the only one to assess and compare the levels of correlation between the peaks and AUCs of the different new-generation troponin assays and infarct size by CE-CMR. The levels of correlation that we achieved with all variables from these new troponin assays were excellent. For hs-TnT (Roche) we saw similar correlations to those reported by Nguyen et al. [14]. However, we have shown that all troponin assays are not equivalent. Indeed, in our study, s-TnI (Siemens) achieved a lower level of correlation with infarct size than hs-TnT (Roche) and hs-TnI (Abbott), whereas hs-TnT (Roche) showed the highest correlation with infarct size.

In practice, therefore, all of these assays could be considered as robust surrogate endpoints in clinical research, and

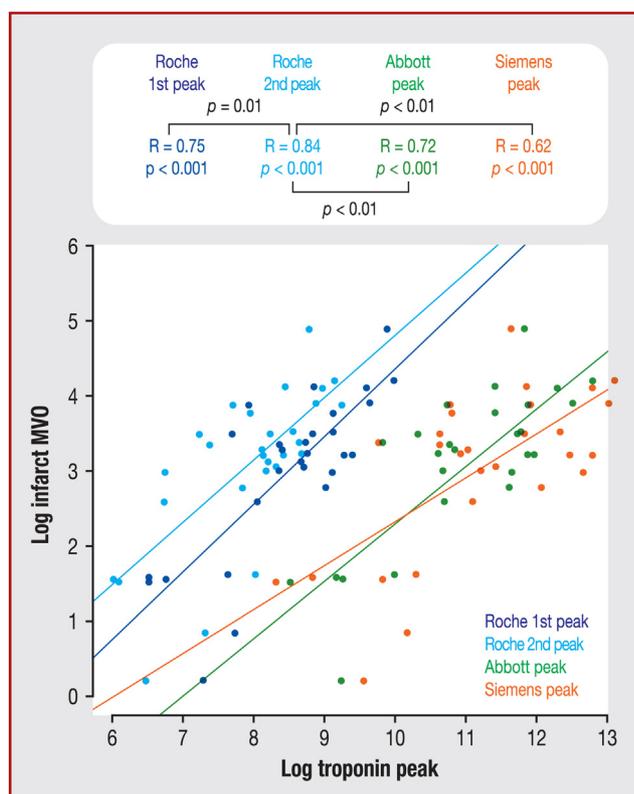


Figure 3. AUC in the receiver operating characteristic model to predict the presence of microvascular obstruction. AUC: area under the curve.

preferably hs-TnT (Roche) when available in clinical routine practice. Importantly, in the case of multicentre studies, homogeneity among assays seems to be important.

hs-Tn to predict MVO

We found good correlation between MVO size and troponin peak and AUC. Similar results have been published with “traditional” troponin assays [23,24]. We have also confirmed the results of Nguyen et al. for the peak of hs-TnT (Roche) [14]. However, it is well-known that MVO size correlates with infarct size. The more global myocardial tissue is damaged, the more MVO is important.

With good sensitivity and specificity, all troponin variables could be used to predict the presence of MVO. Our data enabled identification of a cut-off for all variables in the identification of a patient with MVO. This is important to establish the prognosis of a patient with STEMI. Indeed, the presence of late MVO is a strong and independent prognostic factor after STEMI [3]. Several studies have shown that MVO is associated with more heart failure [25] and a higher mortality rate [26]. In patients with MVO, mortality has been reported to increase by 75% at 1 month [27], 67% at 1 year [28] and 50% at 5 years [26].

Second peak of hs-TnT (Roche) and characterization of infarcted tissue

Our first study showed that the kinetics of the different troponins differed significantly in patients admitted with STEMI

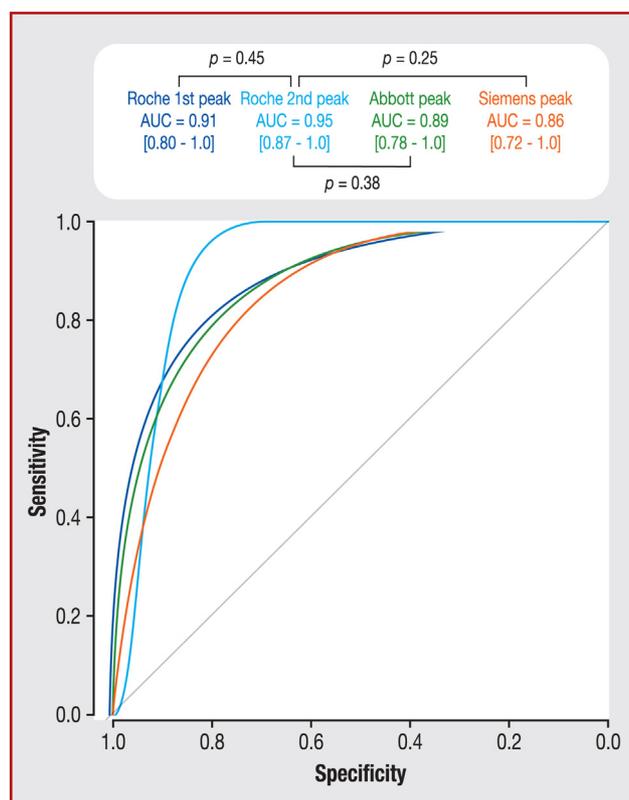


Figure 4. Correlation curves between microvascular obstruction evaluated on cardiac magnetic resonance imaging and troponin peak levels using the Roche (in black), Abbott (in blue) and Siemens (in red) systems. R: coefficient of correlation.

and treated by PCI. hs-TnI (Abbott) and s-TnI (Siemens) exhibit an early peak in the first 24 hours followed by a rapid log linear decrease. By contrast, hs-TnT has a short decrease then a rebound phenomenon, following a biphasic curve [15,16]. The pathophysiological explanations and clinical implications of this biphasic shape have not been established. We know that 94% of troponin T is bound to myofibrils, and is released more slowly, especially in the case of irreversible injury. Even if the second peak of hs-TnT achieves better correlations with MVO and infarct size, it cannot help to characterize microvascular dysfunction more specifically. However, our data show that, with better correlation, the second peak of hs-TnT is the best biological variable to evaluate both infarct and MVO size.

As the second peak of hs-TnT (Roche) occurs around 77 hours after the acute myocardial infarction, the assessment of this surrogate biological endpoint could be of value on days 2–3, rather than the AUCs of repeated assays. In a recent article, our team demonstrated retrospectively that the combination of a second troponin peak and a high C-reactive protein concentration were associated with increased prevalence of MVO evaluated by magnetic resonance imaging [29]. These correlations are not easy to explain. The second peak could be less dependent on compounding factors, such as the quality of reperfusion or the inflammation reaction of myocardial tissue. These hypotheses should be investigated in dedicated studies.

Study limitations

First, and importantly, our study had a small sample size, which means that all cut-off values should be tested in larger studies. From a clinical point of view, it would be useful to investigate the ability of only one assay at day 2 or 3 to provide information about infarct size and prognosis.

Conclusions

High cardiac troponin peaks and AUCs achieved excellent correlation with infarct size assessed by CE-CMR. Statistically, the second peak of hs-TnT (Roche) had the greatest correlation levels, and therefore seems to be the best biological variable for evaluating and characterizing infarct size. Of course, these results need to be confirmed in a larger patient population.

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Disclosure of interest

The authors declare that they have no competing interest.

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