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par

Flavie MONDOUT

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Estimation par modélisation cinétique de la quantité de biomarqueurs de nécrose myocardique relarguée lors de l'infarctus du myocarde et association avec la taille de l'infarctus mesurée en IRM : étude pilote

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Professeur Dominique BABUTY, Cardiologie, Faculté de Médecine - Tours

Membres du Jury :

Professeur Denis ANGOULVANT, Cardiologie, Faculté de Médecine – Tours

Professeur Théodora BEJAN-ANGOULVANT, Pharmacologie clinique, Faculté de Médecine –Tours

Docteur David TERNANT, Pharmacologie fondamentale et clinique, MCU-PH, Faculté de Médecine – Tours

Directeur de Thèse : Docteur Fabrice IVANES, Physiologie, MCU-PH, Faculté de médecine - Tours

RÉSUMÉ

Introduction : La taille d'un infarctus du myocarde (IDM) est un facteur prédictif de la récurrence d'événements cardio-vasculaires et est idéalement mesurée par l'étude du rehaussement tardif en IRM cardiaque. Cependant, la disponibilité de cet examen est limitée en pratique courante et de nombreuses études estiment indirectement la taille de l'infarctus en mesurant le pic de concentration ou l'aire sous la courbe (AUC) de différents biomarqueurs de nécrose myocardique (CK, troponine). Ces méthodes, en ne tenant pas compte des paramètres cinétiques des différents biomarqueurs peuvent mésestimer la quantité totale réellement relarguée. Nous avons récemment développé un modèle cinétique permettant une estimation de la quantité totale de biomarqueurs relarguée après un IDM (appelée A_0) en tenant compte de leurs paramètres cinétiques. Le but de cette étude était de déterminer la corrélation entre les paramètres cinétiques obtenus par cette modélisation, et la taille de l'IDM en IRM cardiaque.

Méthodes : Nous avons inclus rétrospectivement les patients admis à l'hôpital de Tours entre février 2015 et septembre 2017 pour un IDM avec sus-décalage du segment ST, traités par angioplastie primaire, qui ont bénéficié d'une IRM cardiaque dans les jours suivant leur admission. Les concentrations de CK, de troponine I (cTnI) et de troponine T hyper-sensible (cTnT) ont été recueillies et la cinétique de ces biomarqueurs a été décrite selon le modèle cinétique utilisé dans notre précédente étude. Nous avons comparé la concentration maximale (Cmax), l'AUC et l'A_0 déterminés par modélisation cinétique pour chacun de ces biomarqueurs à la taille de l'infarctus mesurée en IRM cardiaque.

Résultats : Sur les 41 patients inclus dans notre étude, tous avaient des dosages de CK, 16 de cTnI (sous-groupe cTnI) et 25 de cTnT (sous-groupe cTnT). Le modèle décrivait avec une grande précision la cinétique de chacun des biomarqueurs, et ce avec seulement 3 mesures par marqueur. La taille de l'IDM était corrélée à chacun des paramètres (A_0, AUC et Cmax) des CK et de la cTnT. Le plus fort niveau de corrélation était obtenu pour la Cmax des CK (R^2=64,8%) et l'A_0 de la cTnT (R^2=67,1%). Pour la cTnI, il n'y avait pas d'association entre la Cmax et la taille de l'IDM (R^2=2%). De plus, dans le sous-groupe cTnI, la corrélation avec la taille d'IDM était meilleure avec les paramètres des CK qu'avec ceux de la cTnI.

Conclusion : Ce modèle permet de décrire avec une grande précision et peu de mesures la cinétique des biomarqueurs de nécrose après un IDM. Les paramètres estimés, en particulier le pic de concentration des CK et la quantité totale de cTnT relarguée par la lésion, sont corrélés à la taille d'IDM mesurée en IRM cardiaque et pourraient donc être utilisés en recherche clinique dans les études de cardioprotection.

Mots Clés : Infarctus du myocarde, modèle cinétique, troponine, créatine kinase, IRM cardiaque

ABSTRACT

Assessment of myocardial necrosis biomarker release after acute myocardial infarction determined by kinetic modeling and correlation with infarct size determined by magnetic resonance imaging: a pilot study

Introduction: Infarct size (IS) is a key determinant of subsequent cardiovascular events and is ideally assessed through the quantification of late gadolinium enhancement in cardiac MRI. However, MRI availability is limited and many studies used necrosis biomarkers (CK, troponin) as a surrogate marker of IS by determination of their peak concentration and/or their area under the concentration versus time curve (AUC). These biological methods, excluding biomarkers kinetic data such as absorption, distribution or elimination may provide inaccurate results. We recently developed a compartmental kinetic model allowing estimation of the total amount of necrosis biomarker released during ST-segment elevation myocardial infarction (STEMI), noted A_0. The aim of this study was to determine the correlation level between the amount of biomarkers released in STEMI patients obtained with this kinetic modeling and cardiac MRI measurements of IS.

Methods: We retrospectively included all patients admitted for STEMI in Tours University Hospital (France) from February 2015 to September 2017, that were treated by primary percutaneous coronary intervention and who had had a cardiac MRI in the days following their admission. CK, troponin I (cTnI) and troponin T (cTnT, using a high-sensitive assay) concentrations data were collected and kinetics of these biomarkers were described by our kinetic model. For each biomarker, we compared the maximum concentration (Cmax), AUC and A_0 determined by the model to cardiac MRI measurements of IS.

Results: Among the 41 patients included, all had CK assays available, 16 had cTnI assays (cTnI subgroup) and 25 had cTnT assays (cTnT subgroup) available. The model described satisfactorily biomarker kinetic data with only 3 values of each biomarker. IS was correlated with all CK and cTnT parameters, particularly with CK Cmax (R^2=64,8%) and cTnT A_0 (R^2=67,1%). For cTnI, there was no correlation between IS and cTnI Cmax (R^2=2%). Furthermore, in cTnI subgroup, IS correlation was stronger with CK parameters than with cTnI parameters.

Conclusion: This model allows an accurate description of necrosis biomarkers kinetics following STEMI, which only few measurements. Estimated parameters, particularly CK peak concentration and the total amount of cTnT released by the injured myocardium, were highly correlated to IS measured by cardiac MRI. This method may be used in future clinical trials on the assessment of therapies aiming to reduce IS, such as conditioning therapies.

Key words: Acute myocardial infarction, kinetic model, troponin, creatine kinase, cardiac MRI

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TABLE DES MATIERES

ABBREVIATIONS

AUC: Area under the curve

CK: Creatine kinase

cTnI: cardiac Troponin I

cTnT: cardiac Troponin T

IS: Infarct size

LAD: Left anterior descending artery

LGE: Late gadolinium enhancement

LVEF: Left ventricular ejection fraction

MI: Myocardial infarction

MRI: Magnetic Resonance Imaging

PCI: Percutaneous coronary intervention

RCA: Right coronary artery

TTE: Transthoracic echocardiography

MVO: Microvascular obstruction

STEMI: ST-segment elevation myocardial infarction

INTRODUCTION

Infarct size (IS) is a key determinant of subsequent cardiovascular events [1,2] following ST-segment elevation myocardial infarction (STEMI) and a major endpoint in many clinical trials. It can be accurately assessed through the quantification of late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (MRI), which is the gold standard technique for IS determination [3–6]. However, MRI is not available in every center, and, when cardiac MRI is available, prompt and easy access to this technology is not always warranted.

Cardiac necrosis biomarkers, particularly troponins and creatine kinase (CK), are repeatedly measured in clinical practice from the diagnosis of myocardial infarction (MI) and are usually available on a 24/7 basis in most centers.

Troponin complex is a component of skeletal and cardiac muscle thin filaments. It is made of three subunits - troponin I, T, and C and its detection in blood samples is actually considered to be the gold standard for myocardial infarction definition [7,8]. Creatine kinase (CK) is an enzyme that is found primarily in the cardiac and skeletal muscles. Before the troponin era, it was used for MI diagnosis. It is now mainly used for the detection of early reinfarction [9].

These necrosis biomarkers may be used as a surrogate marker for IS determination. Indeed, estimation of the total amount of necrosis biomarker released by the injured myocardium, using the peak and/or the area under the concentration versus time curve (AUC) of CK and troponin have good correlation with IS measured by heterogeneous techniques [10–12] and mortality [13].

However, peak concentrations or AUC estimated by trapezoidal rules, are influenced not only by release, but also by distribution and elimination of biomarkers, and thus entails a risk of overprediction or underestimation of the real amount of released necrosis marker. Furthermore, determination of AUC requires repeated measures of biomarkers concentrations (usually 12 to 15) that necessitates human time, financial resources and increases the risk of iatrogenic anemia in patients [14].

We previously developed a kinetic model [15] allowing the estimation of the total amount of necrosis biomarker (CK, CK-MB, Troponin I) released during myocardial ischemia-reperfusion injury from its serum concentrations, in the context of STEMI. We showed not only a good descriptive performance of biomarkers' kinetics, but also that estimation of

this amount by kinetic modelling was a powerful approach to investigate the efficacy of given conditioning therapies.

However, at this stage, the association of the biomarker release amount determined by kinetic modelling with IS has not been investigated yet.

Therefore, the aim of our study was to determine the correlation level between the amounts of biomarkers released in STEMI patients, estimated by kinetic modelling, and cardiac MRI measurements of IS.

* * *

METHODS

Study population

We retrospectively included all patients admitted for STEMI in Tours University Hospital (France) from February 2015 to September 2017, that were treated by primary percutaneous coronary intervention (PCI) and who had had a cardiac MRI between 4 and 10 days after the onset of symptoms.

The diagnostic of STEMI was based on the occurrence of a chest pain lasting 30 minutes, associated with ST-segment elevation $\geq$ 2 mm on the ECG in two adjacent derivations. Only patients with a PCI performed within 12 hours after the onset of symptoms were included. Patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, priori ischemic heart disease or significant valvular disease were excluded.

Cardiac magnetic resonance imaging

Cardiac MRI examinations were performed on a 1.5T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) with a 32-channel cardiac phased array coil. Cardiac MRI protocol included cine imaging with steady-state free-precession, T2 weighted triple inversion recovery images and LGE images that were performed in short-axis orientation covering the entire left ventricle. LGE images were acquired 20 minutes after administration of 0.2 mmol/kg of Gadopentate Dimeglutime (Gadolinium DTPA, Magnevist Bayer, Germany) and obtained using of a segmented inversion recovery

technique. The inversion time was progressively optimized to null unaffected myocardium.

IS quantification

Infarcted myocardium displays a hypersignal on the LGE sequences and IS was quantified as hyperenhancement using a semi–automated validated method (5 SD-threshold) [16]. As described by Bondarenko et al., once epicardial and endocardial borders are manually traced, a visually healthy region of myocardium (without enhancement or edema) is selected and the area of enhanced myocardium, i.e infarcted tissue, is calculated automatically as the area with a signal intensity ≥ 5 standard deviation above the mean of heathy myocardium signal (Figure 1). Results were expressed in absolute values (g) and as the enhanced percentage of enhanced over total left ventricular myocardial mass (%LV).

Presence of microvascular obstruction (MVO) was also noted, defined as hypoenhanced area present within the hyperenhanced infarcted region on delayed contrast images.

Blood samples

Patients admitted for a STEMI had repeated blood samples to measure necrosis biomarkers (CK and troponin) concentrations every 4-6 hours, from admission and up to the peak concentration. From February 2015 to June 2016, our biochemistry lab routinely used troponin I subunit (cTnI) assays. Since July 2016, in order to detect low levels of troponin and to improve diagnostic efficiency in patients with suspected acute coronary syndrome, routine assessment was switched to the determination of cardiac troponin T (cTnT) concentrations with high-sensitive method, in accordance with the current guidelines [7].

Immunoenzymatic assays for cTnI concentrations were performed on Access2® analyzer (Beckman Coulter®). Limits of detection were 0.01 – 100 ng/mL. The 99th percentile for a population of apparently healthy adults [17] was 0.04 ng/mL (95% confidence interval (CI) 0.03-0.05)

cTnT concentrations were measured using the Cobas6000® analyzer (Roche Diagnostics®) with a high-sensitive immunoenzymatic method. The lower limit of

detection was 5 ng/L and the high reference value (99th percentile for a healthy population) was 14ng/L (95% CI 12.7-24.9).

Before July 2016, CK concentrations were quantified with AU2700® (Beckman Coulter®). After this period, it was performed on the Cobas6000® analyzer (Roche Diagnostics®). Determination of CK activity after activation by N-acetyl-cystein (37°C) was performed according to International Federation of Clinical Chemistry method, with a limit of detection of 7 UI/L. Reference values for healthy people (95th percentile) were 30-223 UI/L for the first analyzer, and 20-200 for the second.

Biomarker data analysis

The kinetics of biomarkers were described using models, similar to pharmacokinetic compartmental models [18], which describe biomarker release by injured tissue, distribution and elimination. The total amount of necrosis biomarker released during myocardial ischemia-reperfusion injury was the parameter of interest and was noted A_0. This amount was estimated for CK (A_{CK}), cTnI (A_{TnI}) and cTnT (A_{TnT}). IS was tested as a covariate and its association with A_0 was tested as a power model:

$A_0 = A_{0,pop}.(IS / med(IS))^{\beta}$, where med(IS) is the median value of IS in the population and β is the parameter quantifying the association between A_0 and IS.

The estimation of individual (post-hoc) kinetic parameters was made using Bayesian models [19] which were designed from our previous biomarker kinetic models. Bayesian estimation consists in combining (i) prior information about the kinetics of a given compound (mean, interindividual variances and covariate effects), which include prior estimates of kinetic parameters, and (ii) concentration measurements of a given patient for whom individual kinetics has to be estimated.

The population parameters (i.e. structural, interindividual and residual estimates) were used as priors for Bayesian estimation of individual parameters, except for A_{CK}, A_{TnI} and A_{TnT}, the interindividual distributions of which were fully estimated. Kinetics of cTnT was described using a model derived from the model of cTnI. Early attempts showed that only three kinetic parameters were different between cTnI and cTnT: A_0, biomarker concentration at admission (C_0) and the proportion of biomarker released by the first release model (Fr). All other kinetic model parameters were similar between cTnI and

cTnT (supplemental figure 1). The interindividual distribution of these three parameters was therefore fully estimated.

Biomarker endpoints

For each biomarker, three endpoints were considered: (i) maximum concentration (Cmax), which was determined by graphical inspection, (ii) A_0, estimated by kinetic modelling, and (iii) area under the concentration curve up to 72 hours, which was computed from kinetic models [15]. The association between biomarkers and IS was assessed using a coefficient of determination (R^2).

Concentrations of CK were determined in all evaluable patients, but the patients had measurements of either cTnI (cTnI subgroup, before July 2016) or cTnT (cTnT subgroup, after July 2016). Therefore, strengths of IS association with biomarkers were compared within each subgroup by testing R^2 with a Student's t-test and comparing p-values.

* * *

RESULTS

Population

Among the 657 patients admitted in our center for STEMI between February 2015 and September 2017, 49 patients had a cardiac MRI in the early follow-up period. Among them, 8 patients were excluded because of incomplete MRI data (due to technical problem or low image quality).

All 41 remaining patients had blood CK concentrations assays available. Regarding troponin level assessment, 16 (39%) had cTnI concentration measures (cTnI subgroup) and 25 (61%) cTnT concentration measures (cTnT subgroup). No patient had both cTnI and cTnT measurements. (Figure 2).

Median (interquartile range) age was 57 (52-65) y.o and 21.9% were women (table 1). The culprit artery was the left anterior descending artery (LAD) in 36%, the right coronary artery (RCA) in 54% and circumflex artery in 10%. TIMI flow was 0–1 in all patients on admission. Median time from the onset of symptoms to reperfusion was 180 (136-240) minutes. In the acute phase, all patients were treated with intravenous

unfractioned heparin, aspirin, and ticagrelor following the current guidelines on the management of acute myocardial infarction in patients presenting with STEMI [5].

MRI data

Time from admission to imaging was 7 (6-9) days. A total of 429 slices with LGE were used. The median total infarct size was 21.2 (14.8-29.0) g, representing 17.1 (11.1-21.2) % of the left ventricular myocardial mass. 21 patients (51%) had MVO within the infarcted region. Median left ventricular ejection fraction (LVEF) measured by MRI was 50 (44-56) %.

Median IS (interquartile range) was significantly more important in the MVO subgroup: 21.3 (15.5-25.4) %LV compared to patients without MVO: 13.2 (7.4-17.4) %LV; p=0.005. LVEF was also significantly lower in patients with MVO: 44 (39-53) % compared to patients without MVO: 54(50-64) %; p=0.001.

Biomarker kinetics analysis

A total of 171, 95 and 120 measurements of CK, cTnI and cTnT concentrations were available for 41, 16 and 25 patients, respectively. Bayesian models described satisfactorily biomarker kinetic data (Figure 3). Of note, the best model fitting of kinetic data was obtained with cTnT (R^2=0.995). For CK and cTnI, correlations between observed and model-predicted concentrations were also excellent (respectively R^2=0.986 and R^2=0.988). The biomarker input parameters were estimated with good accuracy: A_{CK} = 4720 UI/L (precision coefficient of variation of 10%), A_{TnI} = 351 ng/mL (23%) and A_{TnT} = 30.4 ng/mL (8%).

Biomarker endpoints

For CK, IS was strongly associated with Cmax (R^2 = 64.8%), and similarly associated with A_{CK} (R^2 = 53.1%) and AUC_{CK} (R^2 = 52.3%). **For cTnI**, IS was not associated with Cmax (R^2 = 2%), and similarly associated with A_{TnI} (R^2 = 33.4%) and AUC_{TnI} (R^2 = 28.7%). **For cTnT**, IS was very highly associated with A_{TnT} (R^2 = 67.2%), and then with AUC_{TnT} (R2 = 48.7%) and Cmax (R2 = 38.9%) (Table 2, Figure 4).

In the cTnI subgroup, the strength of association of IS was higher with kinetics of CK compared to that of cTnI:

- for Cmax: R^2 = 67.1% (CK, p=0.00028) vs R^2=2% (cTnI, p=0.34)
- for A_0: R^2=50.5% (CK, p=0.002) vs. R^2=33.4% (cTnI, p=0.023)
- for AUC: R^2=40.6% (CK, p=0.010) vs. R^2=28.7% (cTnI, p=0.037).

In the cTnT subgroup, the strongest association with IS was found for A_{TnT} (R^2=67.2%, $p=6.0\times10^{-7}$). Similar strengths of association were found for A_{CK} (R^2=56.6%, $p=1.8\times10^{-5}$), AUC_{CK} (R^2=51%, $p=7.6\times10^{-5}$), CK Cmax (R^2=58.1%, $p=1.8\times10^{-5}$) and AUC_{TnT} (R^2=48.7%, $p=1.3\times10^{-4}$). Lowest association was with cTnT Cmax (R2=38.9%, p=0.0011).

Overall, the strongest association of IS with A_0 was obtained with A_{TNT} ($p = 6.3\times10^{-8}$), then with A_{CK} ($p = 4.1\times10^{-6}$) and A_{TnI} ($p = 0.028$).

* * *

DISCUSSION

Our study aimed to model kinetics of necrosis biomarkers in a real-life STEMI population and to compare the amounts of biomarkers released with IS measured with the gold standard method, i.e LGE assessment in cardiac MRI. To note, our study population matched a recent national French registry of STEMI patient [20], regarding age and sex ratio.

Biomarker kinetics

Historically, Witteveen et al [21] developed a two-compartmental method to assess the elimination of different enzymes after myocardial infarction. This mathematical approach required data regarding extravascular volume, permeability constant, and catabolic rate constant for each enzyme, which was subject to interindividual variations (particularly for CK). The subsequent studies commonly used this method with α-hydroxybutyrate dehydrogenase assays because of its relatively constant catabolic rate [22–27]. For convenience, AUC method was later proposed to estimate myocardial damages [10,28].

Recently, we developed new compartmental models to describe the kinetics of the most common necrosis biomarkers (including troponin), with focus not only on the

distribution and elimination, but also on kinetics of release [15]. In addition, population approach allows the quantification of all interindividual distribution of kinetic parameters. Our results confirm, with this population, the strong correlation between observed and kinetic model-fitted concentrations of CK and cTnI. This correlation was also demonstrated for cTnT kinetics. Bayesian analysis is generally used to estimate individual pharmacokinetic parameters using small number of samples [19] provided that samples bear sufficient information on kinetic shapes, notably during absorption and early elimination phases. In our study, most of blood samples were collected within 24 hours, which totally covers biomarker release phase and probably explains the good predictive performance of our Bayesian estimators.

Biomarker endpoints

Priors studies showed the association of CK and troponin measurements, commonly using peak of concentration and/or and trapezoidal AUC, with subsequent cardiovascular events [29–32] and/or infarct size measured by cardiac MRI [33], left biplane ventriculography [34], scintigraphy [35,36] or estimated by enzymatic Witteveen's method [22–24]. Therefore, clinical trials commonly use these biological parameters to evaluate the efficacity of treatments on IS [37]. Considering that these previous methods exclude kinetics data such as absorption, distribution or elimination, the results obtained could be inaccurate and the conclusions misled. This could be corrected using our kinetic model, which showed a better assessment of conditioning therapies in cardioprotective clinical trials using A_0 rather than AUC [15]. However, in our previous study, the association between A_0 and infarct size could not be assessed because of the lack of MRI data available. Here, our results demonstrated that A_0 for of each necrosis biomarker necrosis (CK, cTnI and cTnT) was associated with infarct size measured by cardiac MRI, the highest correlation being with cTnT.

CK. For CK, the best correlation level was obtained for Cmax. The correlation was lower, but still significant considering AUC, in concordance with previous studies [38], and A_0. These results suggest that kinetics of CK could be strongly associated with prognosis in patients after a STEMI, which has already been demonstrated for CK peak [30,39].

Troponin I. Studies that investigated the relationships between cTnI concentrations, following primary PCI and IS are very heterogeneous, using either biological methods,

biplane ventriculography or MRI for IS assessment. Results mostly showed that late time point measurements of cTnI (up to 72h after admission) were correlated with IS [32,40–42]. In our study, cTnI assays were routinely performed until the peak concentration was obtained (generally within 12-16h following admission). Our results showed that IS measured by MRI was not associated with cTnI Cmax but was correlated with AUC_{TNI} and $A_{TNI.}$ These associations were significantly lower than those of CK kinetics parameters. cTnI kinetics, in line the clinical practices guidelines of the European Society of Cardiology, is part of the universal definition of myocardial infarction and an important parameter in acute coronary syndromes' diagnosis, but seems to be less correlated to prognosis in STEMI patients compared to CK, considering IS.

Troponin T. Similarly to cTnI, several studies showed a correlation between IS and delayed time point measurements of cTnT[43–46]. With our early time point samples, (within 24 hours) we obtained a good correlation between A_{TNT} and IS. The correlation was also significant when we considered AUC, but less with Cmax. Furthermore, in the cTnT subgroup, A_{TNT} was a stronger estimate of IS than $A_{CK,}$ AUC_{CK} and CK Cmax. Considering that IS is a major predictor of adverse outcomes, estimation of cTnT total release concentrations with this model could be of substantial help in assessing patients' prognosis, in concordance with a previous prospective study [47]. However, more studies are needed to understand how cardiac troponins and CK model-estimated infarct size may be integrated in prognosis and risk stratification.

Regarding LGE measurement in MRI, we compared the 5SD semi-automatic method assessed in this study to the autothreshold method, which automatically determine the percentage of enhanced myocardium by algorithms after endocardial and epicardial contouring (Figure 1). We obtained a good correlation between the two methods as a gauge of quality of our MRI data (R^2=0.92, Supplemental figure 2).

Study limitations

CK isoenzyme MB (CK-MB) values have been shown to reflect infarct size and clinical outcomes [29,31,48,49] and CK-MB kinetic modeling was showed more accuracy than CK or cTnI for the assessment of the cardioprotective effect of conditioning therapies in our previous study [15]. In the present study, CK-MB values were not available. In addition, direct comparisons between cTnI and cTnT were not possible.

A main limitation of our study could be the small number of patients, particularly in cTnI subgroup where correlations with IS were lower.

In addition, and a result of the retrospective nature of the study, sampling times and number of samples were heterogeneous. Yet, population approach may compensate these biases by quantification of all interindividual distribution of kinetic parameters

Several parameters assessed by cardiac MRI, with a known correlation with clinical outcomes in STEMI patients, such as edema or MVO [50,51], cannot be assessed by the mathematical kinetic model.

Lastly, only STEMI patients have been included. More studies are mandatory to assessed the correlation between biomarkers release described by this mathematical model and non-STEMI patients' outcomes.

* * *

CONCLUSION

This new kinetic model for myocardial necrosis biomarker's release estimation in the context of STEMI described accurately biomarkers' kinetics and showed good correlations with infarct size measurement. The strength of this approach stands in (i) the use of very common necrosis biomarkers (ii) obtained with only few measures, (iii) in the first 24 hours following patient admission (typically when the patient is still in the intensive care unit).

The total amount of cTnT released after a STEMI, estimated with our kinetic model, was best associated with IS assessed by MRI, more than all CK parameters, and probably more than troponin I parameters even if comparison between the 2 subunits of troponins could not be performed in the same group of patients.

This kinetic model may be used in assessment of therapies aiming to reduce IS, such as conditioning therapies, considering that reperfusion injury is an important contributor to final infarct size [52]. Clinical use for direct risk and prognosis stratification needs to be investigated.

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TABLES & FIGURES

Table 1. Baseline characteristics of the study population

Variables†	Study population n=41
Age, years	57 (52-64)
Gender (female), n (%)	9 (21.9)
BMI (kg/m^2)	25.4 (23.5-28.9)
Serum creatinine (μmol/L)	76 (63-85)
Creatinine clearance (MDRD, mL/min/1,73m^2)	94 (81-110)
Comorbidities, n (%)	
Hypertension	12 (29.3)
Diabetes mellitus	3 (7.3)
Smoking (actual or stopped in the last 3 years)	10 (24.4)
Dyslipidemia	7 (17.1)
Obesity (BMI ≥ 30 kg/m^2)	5 (12.2)
Overweight (BMI 25-30 kg/m^2)	16 (39.0)
Family history of premature cardiovascular disease	9 (21.9)
TIMI flow grade 0-1, n (%)	41 (100)
Time to reperfusion (minutes)	180 (136-240)
Culprit artery, n (%)	
LAD	15 (36.5)
RCA	22 (53.6)
Circumflex	4 (9.7)
Dominant coronary system, n (%)	
Right	35 (85.3)
Left	4 (9.7)
Balanced	2 (4.9)
LVEF before revascularization (TTE, %)	45 (40-50)
LVEF 3-10 days following revascularization (TTE, %) *	51 (45-55)
LVEF measured by MRI (%)	50 (44-56)

BMI: Body mass index, LAD: Left anterior descending artery, RCA: Right coronary artery, LVEF: Left ventricular ejection fraction, TTE: Transthoracic echocardiography, MRI: Magnetic resonance imaging

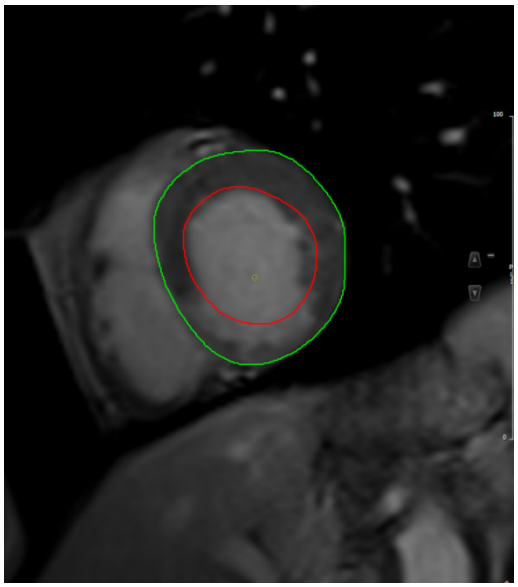
† continuous variables are expressed as median (interquartile range)

* data missing in 2 patients

Table 2. Coefficient of determination of IS association with biomarkers for each kinetic parameter

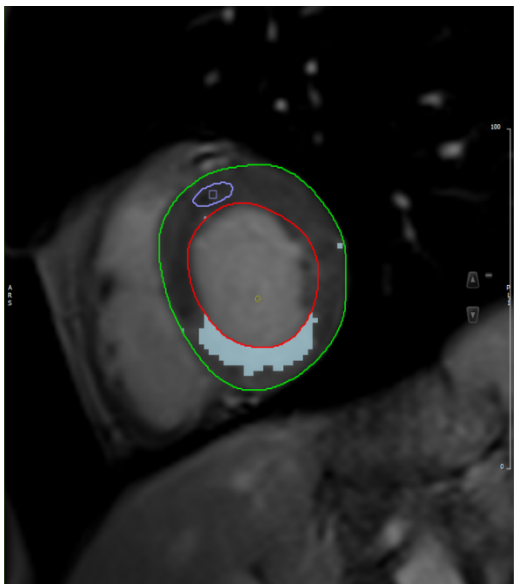
R^2	CK	cTnI	cTnT
Cmax	64,8	2,0	38,8
AUC	52,3	28,7	48,7
A_0	53,1	33,4	67,2

Figure 1. Methods of late gadolinium enhancement (LGE) measurement in cardiac MRI



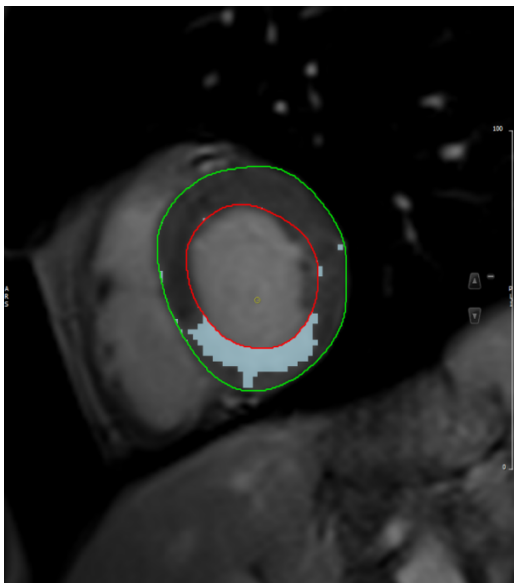
LGE in inferior myocardial infarction

Green: epicardial contour
Red: endocardial contour



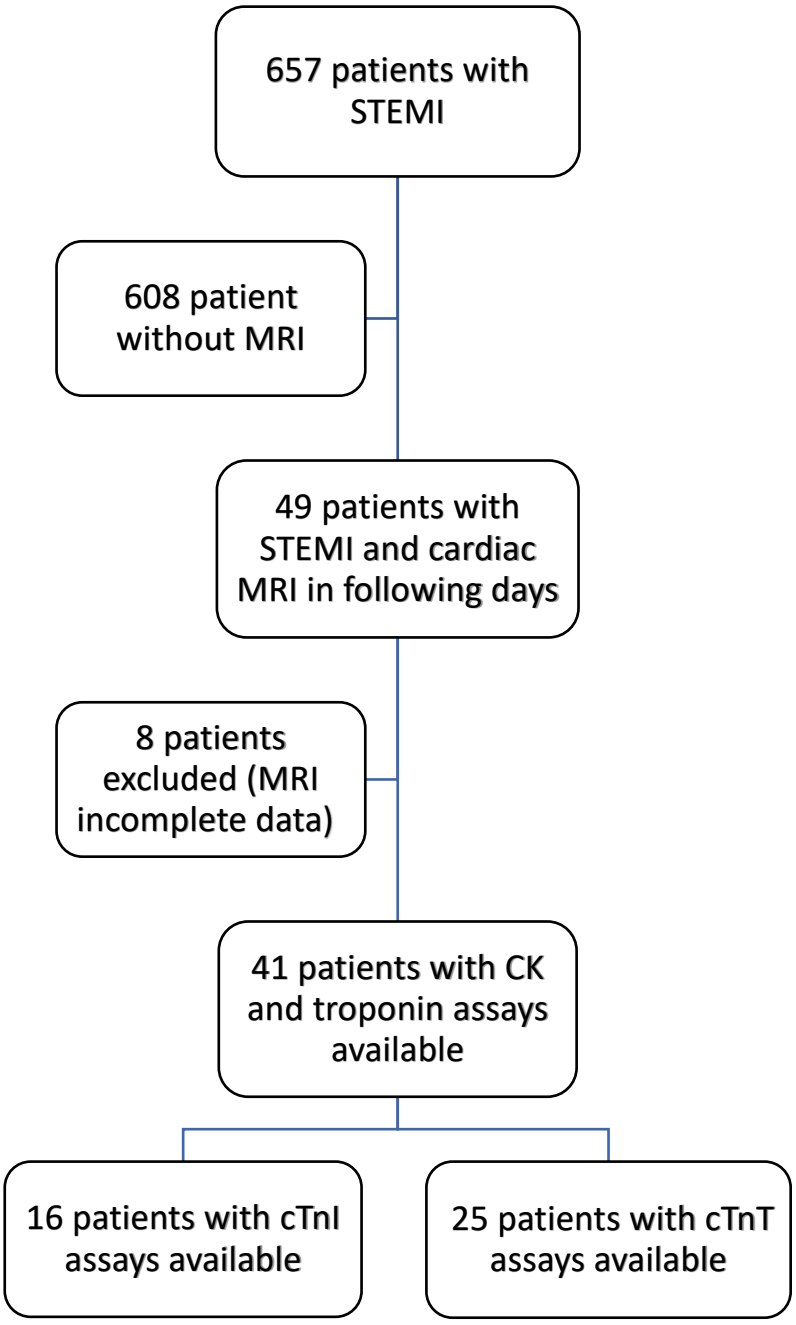
5SD-threshold measurement of LGE

Blue contour: selected healthy myocardium



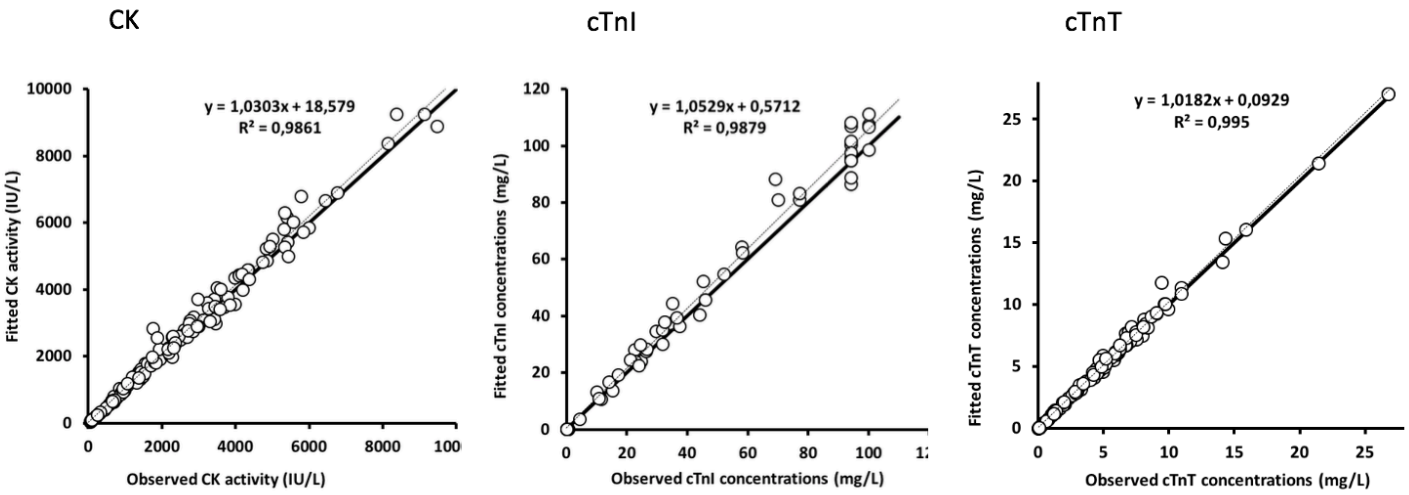
Autothreshold measurement of LGE

Figure 2. Flow chart



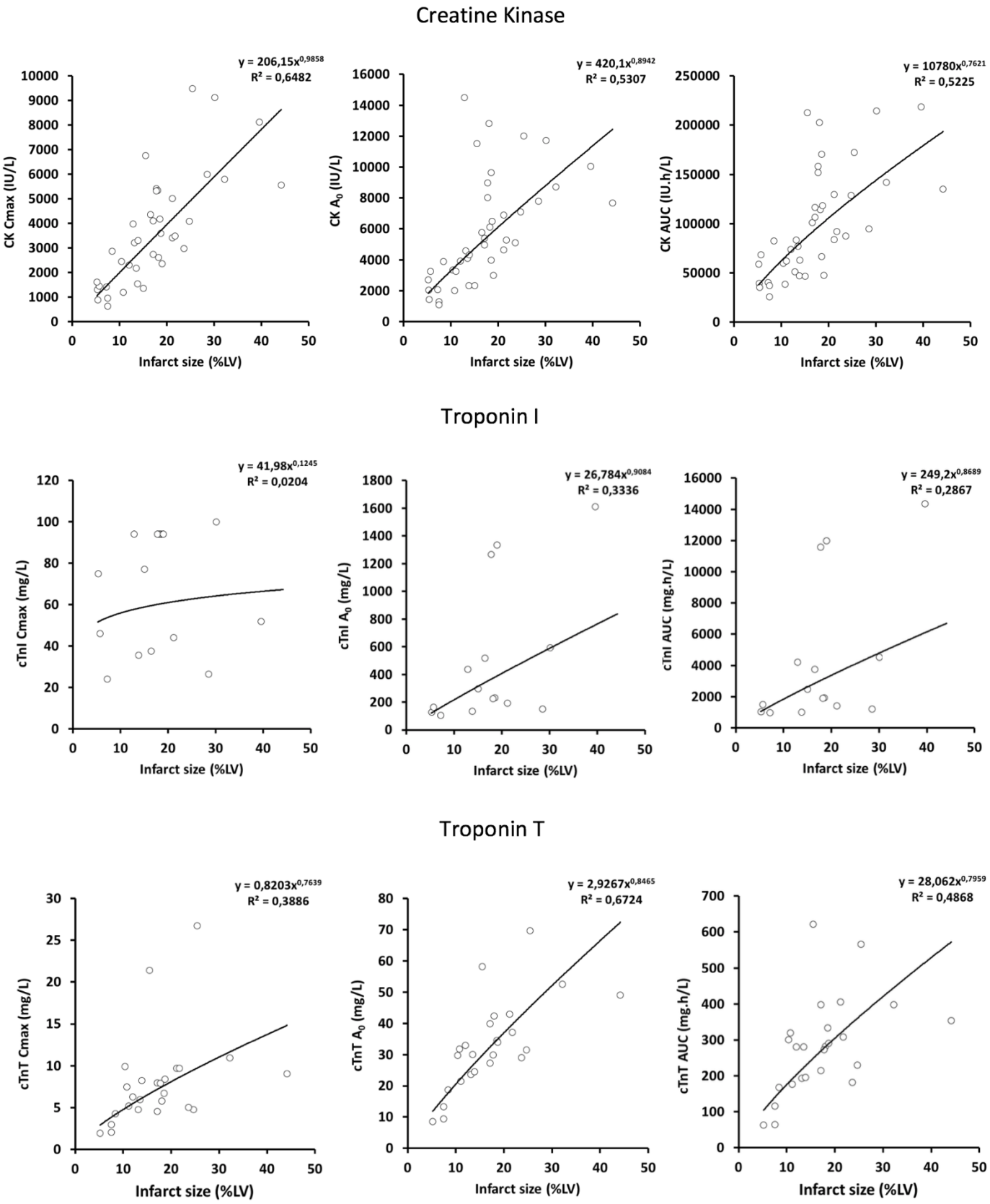
STEMI: ST-segment elevation myocardial infarction, MRI: Magnetic resonance imaging, CK: Creatine Kinase, cTnI: cardiac Troponin I, cTnT: cardiac Troponin T

Figure 3. Correlation between observed and model-predicted concentrations for each biomarker



CK: Creatine kinase, cTnI: cardiac Troponin I, cTnT: cardiac Troponin T

Figure 4. Correlation between biomarkers parameters determined by kinetic modeling and infarct size determined by MRI



%LV: % of left ventricular myocardial mass, CK: Creatine Kinase, cTnI: cardiac Troponin I, cTnT: cardiac troponin T

SUPPLEMENTAL DATA

Kinetic models

Kinetic models were previously described [15]. Being delayed in time, biomarker release is described using transit absorption models. For each patient, the origin of time is considered as the first blood sample. The function of biomarker release f(t) is written as a gamma law model, where the number of transit compartments (n, not necessary integer) and the transit rate (k_{tr}, $hours^{-1}$). For creatine phosphokinase (CK) and troponin I (cTnI) and T (cTnT), a combination of two transit release flows were used, which describe two release kinetics (release flows 1 and 2) that occur at different rates for flows 1 and 2. Therefore, a couple of number of transit compartments (n_1 and n_2), and transit rates (k_{tr1} and k_{tr2}) were estimated. Since a given biomarker molecule is supposed to be released by only one flow, the proportion of biomarker amount released following each of the two release models (Fr) had to be estimated. The main parameter A_0, which is the total input of released biomarker, was the sum of biomarker already released before and after the first blood sample.

Biomarker distribution and elimination was described using one and two-compartment models routinely used in pharmacokinetic modelling. Kinetics of CK and troponins (cTnI and cTnT) were described using one and two compartment models, respectively.

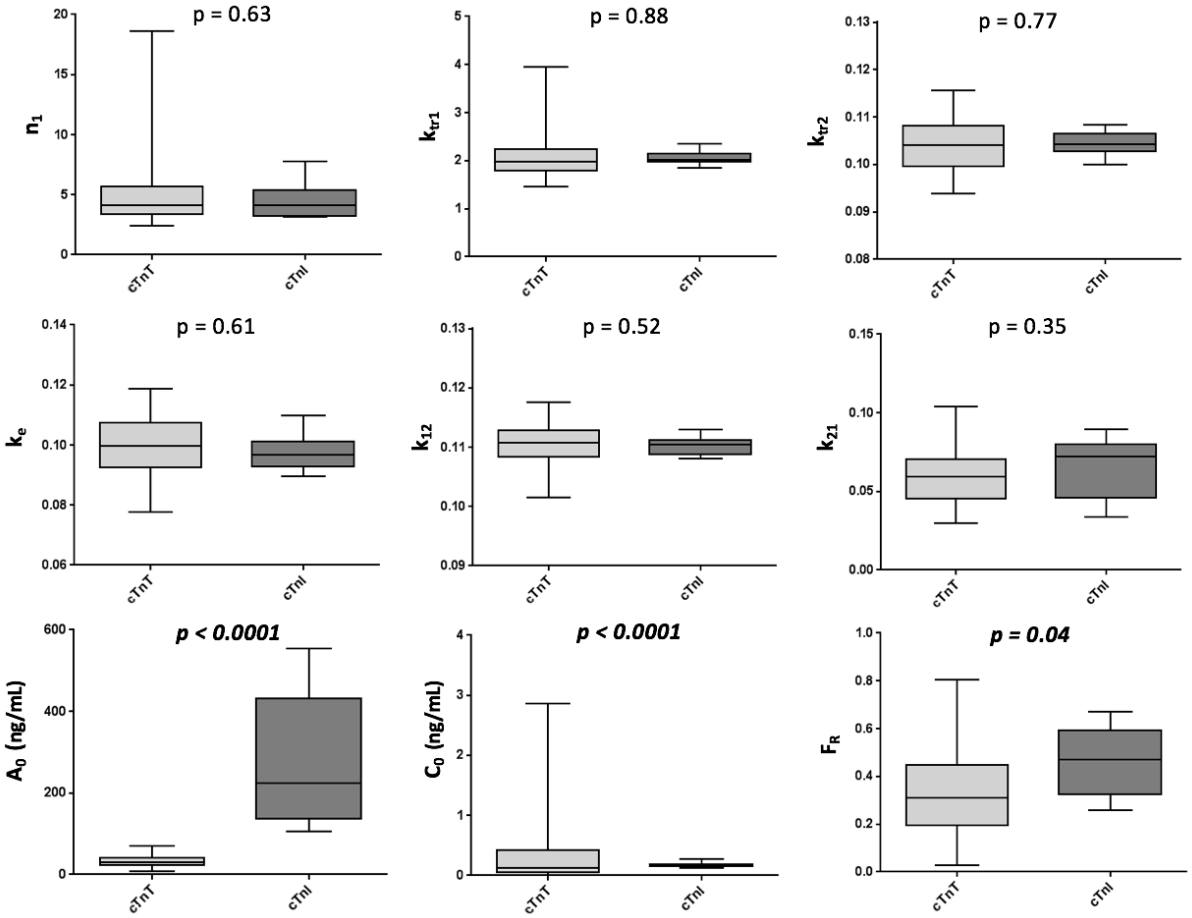
Kinetic modelling

Population approach was used to estimate kinetic parameters. Using this approach, data from all individuals were computed simultaneously; the interindividual distribution allows the estimation of the "mean" value of each kinetic parameter and corresponding interindividual variance. In addition, population approach allowed to test and to quantify the association of infarct size (IS) with A_0. This association is described using a power function as follows: $A_{0,i} = A_{0,pop} \cdot (IS / med(IS))^{\beta}$,where $A_{0,i}$ is A_0 for the i^{th} patient, $A_{0,pop}$ the mean value of A_0, med(IS) the median value of IS, and β is the power coefficient of IS association with A_0. The significance of this association was tested using likelihood ratio test.

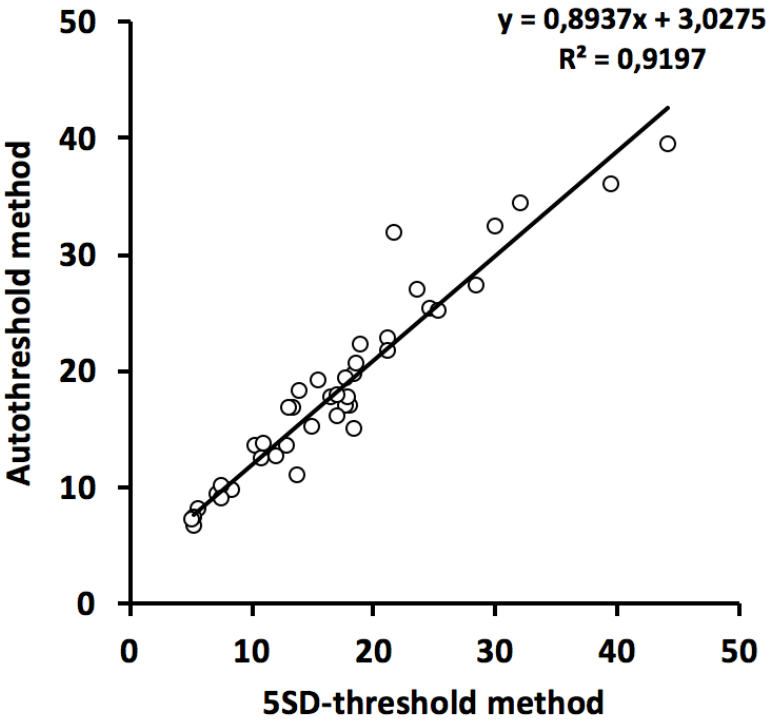
Since a limited number of observations were available, Bayesian analysis was used to estimate most of kinetic parameters, i.e. population parameters for CK and cTnI estimated

in our previous study [15] as priors to provide individual parameter estimates. However, the distribution of A_0 for CK and cTnI was fully estimated to provide unbiased description of the A_0 – IS association. Since no kinetic model of cTnT was previously described, a Bayesian model for cTnT kinetics was derived from cTnI kinetic model. Each cTnT kinetic parameter that was found to be different from cTnI kinetic parameters had their interindividual distribution fully estimated. These parameters were A_0, Fr and C_0, the concentration of troponin in central distribution compartment at the first blood sample (supplemental figure).

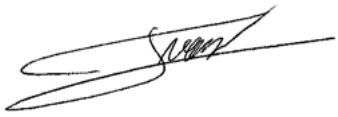
Supplemental figure 1: comparison of kinetic parameters between cardiac troponin I (cTnI) and cardiac troponin T (cTnT)



Supplemental Figure 2: correlation between 5SD-threshold method and autothreshold method for quantification of late gadolinium enhancement in MRI



Vu, le Directeur de Thèse



Vu, le Doyen
De la Faculté de Médecine de Tours

Flavie MONDOUT
40 pages – 2 tableaux – 4 figures – 1 texte supplémentaire – 2 figures supplémentaires

Introduction : La taille d'un infarctus du myocarde (IDM) est un facteur prédictif de la récurrence d'événements cardio-vasculaires et est idéalement mesurée par l'étude du rehaussement tardif en IRM cardiaque. Cependant, la disponibilité de cet examen est limitée en pratique courante et de nombreuses études estiment indirectement la taille de l'infarctus en mesurant le pic de concentration ou l'aire sous la courbe (AUC) de différents biomarqueurs de nécrose myocardique (CK, troponine). Ces méthodes, en ne tenant pas compte des paramètres cinétiques des différents biomarqueurs peuvent mésestimer la quantité totale réellement relarguée. Nous avons récemment développé un modèle cinétique permettant une estimation de la quantité totale de biomarqueurs relarguée après un IDM (appelée A_0) en tenant compte de leurs paramètres cinétiques. Le but de cette étude était de déterminer la corrélation entre les paramètres cinétiques obtenus par cette modélisation, et la taille de l'IDM en IRM cardiaque.

Méthodes : Nous avons inclus rétrospectivement les patients admis à l'hôpital de Tours entre février 2015 et septembre 2017 pour un IDM avec sus-décalage du segment ST, traités par angioplastie primaire, qui ont bénéficié d'une IRM cardiaque dans les jours suivant leur admission. Les concentrations de CK, de troponine I (cTnI) et de troponine T hyper-sensible (cTnT) ont été recueillies et la cinétique de ces biomarqueurs a été décrite selon le modèle cinétique utilisé dans notre précédente étude. Nous avons comparé la concentration maximale (Cmax), l'AUC et l'A_0 déterminés par modélisation cinétique pour chacun de ces biomarqueurs à la taille de l'infarctus mesurée en IRM cardiaque.

Résultats : Sur les 41 patients inclus dans notre étude, tous avaient des dosages de CK, 16 de cTnI (sous-groupe cTnI) et 25 de cTnT (sous-groupe cTnT). Le modèle décrivait avec une grande précision la cinétique de chacun des biomarqueurs, et ce avec seulement 3 mesures par marqueur. La taille de l'IDM était corrélée à chacun des paramètres (A_0, AUC et Cmax) des CK et de la cTnT. Le plus fort niveau de corrélation était obtenu pour la Cmax des CK (R^2=64,8%) et l'A_0 de la cTnT (R^2=67,1%). Pour la cTnI, il n'y avait pas d'association entre la Cmax et la taille de l'IDM (R^2=2%). De plus, dans le sous-groupe cTnI, la corrélation avec la taille d'IDM était meilleure avec les paramètres des CK qu'avec ceux de la cTnI.

Conclusion : Ce modèle permet de décrire avec une grande précision et peu de mesures la cinétique des biomarqueurs de nécrose après un IDM. Les paramètres estimés, en particulier le pic de concentration des CK et la quantité totale de cTnT relarguée par la lésion, sont corrélés à la taille d'IDM mesurée en IRM cardiaque et pourraient donc être utilisés en recherche clinique dans les études de cardioprotection.

Mots Clés : Infarctus du myocarde, modèle cinétique, troponine, créatine kinase, IRM cardiaque

Jury :

Président du Jury : Professeur Dominique BABUTY

Directeur de thèse : Docteur Fabrice IVANES

Membres du Jury : Professeur Denis ANGOULVANT
Professeur Théodora BEJAN-ANGOULVANT
Docteur David TERNANT

Date de soutenance : 26 octobre 2018