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Ischémie myocardique

Myocardial ischaemia

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Inhibition of TREM-1 limits reperfusion injury and improves systolic function during experimental myocardial infarction in pigs

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Introduction: The widespread use of reperfusion therapy have led to an important improvement in short-term mortality after acute myocardial infarction (MI), but long-term mortality remains high and prevalence of chronic heart failure is currently increasing dramatically. The "double-edged sword" of Ischemia/Reperfusion (IR) injury could account for up to 50% of the final infarct size and limitation of this lethal insult appears more and more as a major therapeutic target. Among the numerous mechanisms involved in lethal reperfusion injury, the involvement of the innate immune system has gradually emerged as a critical component. There is especially a growing body of evidence linking Toll-like receptors (TLRs) engagement to the deleterious inflammatory effects seen in IR injury. The Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) belongs to the immunoreceptors superfamily and acts as an amplifier of the inflammatory response triggered by TLRs engagement during both infectious and aseptic inflammatory diseases. We hypothesized that administration of LR12, a synthetic peptide able to inhibit TREM-1 activation, could be beneficial at the acute phase of MI, in a clinically relevant model of experimental MI in pigs.

Material and methods: MI was induced in fifteen anesthetized and mechanically ventilated pigs weighing 45-55 kg, by inflation of an angioplasty balloon in the proximal left anterior descending (LAD) coronary artery cannulated under X-ray guidance, during 60 minutes. An angiogram was performed after inflation and deflation to verify complete occlusion and then restoration of LAD blood flow. Fifteen minutes before deflation, animals were randomized to receive either LR12 (n = 7) or LR12-scramble (n = 8), a placebo peptide. Complete hemodynamic and functional parameters were monitored through arterial line, swan-ganz and intraventricular conductance catheters. Resuscitation was conducted by experienced intensivists according to standard protocols used in clinical practice (fluid administration, vasopressors and/or inotropes). Blood samples were sequentially drawn for biological analyses. The monitoring was prolonged until H18, then survivors were euthanized.

Results: Final results will be available in late 2013. Preliminary results are as follows. The decrease in mean arterial pressure (MAP) was significantly limited during the monitoring period from H12 to the end (-22.1% vs -3.9%, $p < 0.01$). Cardiac power index, one of the strongest hemodynamic correlate of mortality in cardiogenic shock, was preserved under LR12 regimen (72% vs 45% from baseline value, $p < 0.05$). The compromise circulation was compensated by an increased organ oxygen extraction evidenced by a difference in SvO2 value (74% vs 62%, $p < 0.05$). The parameters of systolic function, achieved by conductance catheter at steady state and during transient occlusion of the inferior vena cava (inflation of a Fogarty catheter) revealed a less alteration after MI : dP/dtmax (96% vs 85% from baseline value, $p < 0.05$) and PRSW (91% vs 51% from baseline, $p < 0.03$). No differences in parameters of diastolic function were noted.

Discussion: Experimental inhibition of inflammation at the acute phase of MI is often surprisingly effective but this effectiveness has not been confirmed in the clinical area, probably because inflammatory response is mandatory for the natural healing process. Inhibition of TREM-1 by LR12 does not inhibit inflammation but modulates the amplification of this necessary process. This approach appears promising and seems to be supported by this work, using a clinically relevant large animal experimental model of MI.

Conclusion: TREM-1 inhibition by LR12 at the acute phase of myocardial infarction in invasively monitored pigs limits reperfusion injury and alteration of ventricular contractility.

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Landmark analysis of long-term outcome in early survivors of cardiogenic shock at the acute stage of myocardial infarction. Insights from the FAST-MI Registry

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Introduction: Patients with cardiogenic shock (CS) have high in-hospital and 30-day mortality, but there are little data about those who survive beyond the acute phase. The aim of this study was to assess long-term (5-year) mortality among early survivors of AMI, according to the presence of CS at the acute stage.

Patients and methods: We analyzed 5-year follow-up data from the FAST-MI 2005 registry, a nationwide French survey which included consecutive patients admitted for acute ST or non-ST-elevation myocardial infarction at the end of 2005 in 223 institutions.

Results: Of 3670 patients enrolled in this registry, shock occurred in 224 (6.1%), and 3414 survived beyond 30 days or hospital discharge, including 99 (2.9%) who had developed shock at the acute stage. Early survivors with CS had a more severe clinical profile, had more frequent concomitant in-hospital complications, and were less often managed invasively (Table 1). Long-term survival (5 years) was

	No shock N = 3315	Shock N = 99	P value
Age (years), mean ± SD	66 ± 14	70 ± 13	< 0.001
Sex (F)	1014 (30.6)	37 (37.4)	
BMI (Kg/m²) mean ± SD	27.2 ± 4.7	26.5 ± 4.9	0.15
Current episode			
Typical chest pain	2538 (79.0) (n = 3213)	58 (65.2) (n = 89)	0.002
Resuscitated cardiac arrest	31 (0.9)	10 (10.1)	< 0.001
ST-elevation MI	1688 (50.9)	54 (54.5)	0.47
Anemia on admission	689 (21.5) (n = 3202)	35 (36.8) (n = 95)	< 0.001
Admission glycemia (mg/dl) mean ± SD	156 ± 77	203 ± 109	< 0.001
LVEF (%) mean ± SD	53 ± 13	42 ± 16	< 0.001
Medications within first 48 hours			
Low molecular weight heparin	2159 (65.1)	45 (45.5)	< 0.001
Clopidogrel	2882 (86.9)	81 (81.8)	0.14
GP IIb-IIIa inhibitors	1236 (37.3)	35 (35.4)	0.69
Procedures during hospital stay			
Coronary angiography	2898 (87.4)	79 (79.8)	0.03
PCI	2186 (65.9)	60 (60.9)	0.27
CABG	140 (4.2)	4 (4.0)	0.93
In-hospital complications			
Reinfarction	51 (1.5)	3 (3.0)	0.24
Stroke	19 (0.6)	4 (4.0)	< 0.001
Major bleeding	54 (1.6)	7 (7.1)	< 0.001
Transfusion	119 (3.6)	13 (13.1)	< 0.001
Ventricular fibrillation	44 (1.3)	12 (12.1)	< 0.001
Atrial fibrillation (new)	150 (4.5)	25 (25.3)	< 0.001
AV block	39 (1.2)	4 (4.0)	0.01

59% in patients with, versus 76% in those without shock (adjusted HR = 1.72 [1.24-2.38], P = 0.001). The excess of death associated with CS, however, was observed only during the first year (one-year survival: 77% vs 93%, adjusted HR: 3.31 [2.12-5.17], P < 0.001), while survival from one year to 5 years was similar (76% vs 82%, adjusted HR: 1.09 [0.67-1.79]). Propensity score-matched analyses yielded similar results.

Conclusion: In patients surviving the early phase of AMI, CS at the initial stage carries an increased risk of death up to one year after the acute event. Beyond one year, however, mortality is similar to that of patients without shock.

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Early and late prognosis factor in cardiogenic shock complicating acute myocardial infarction

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Introduction: Short and long term prognosis factors in patients with cardiogenic shock (CS) complicating acute myocardial infarction (AMI) have previously been established by using only hemodynamic parameters without taking into account classical ICU severity score or organ failure/support. The aim of the study is to describe the ICU resources used by cardiogenic shock patients as well as to assess early predictors of in-hospital mortality and long-term follow-up of a large cohort of patients with ST-elevation myocardial infarction complicated by early CS. We retrospectively studied 85 consecutive patients with CS complicating AMI and TIMI flow 3 after percutaneous coronary revascularization. All patients were managed according to the following algorithm: initial resuscitation by a mobile medical unit or by in-hospital critical care physician unit followed by percutaneous coronary revascularization and CS management in the ICU.

Results: Pre-hospital cardiogenic shock was diagnosed in 69% of cases, initially complicated by an out-of-hospital cardiac arrest (OHCA) in 64% of cases. All patients were treated with vasopressors, 82% were ventilated and 22% underwent extrarenal epuration. During hospitalization in the ICU, several adverse events occurred, namely sepsis in 25 (30%) patients and major bleeding complications in 8 (9%) patients. A subsequent emergency PCI was performed in 4 patients subsequent to stent thrombosis. An ECMO was used in one patient, and a second patient died before ECMO installation.

None of the patients underwent coronary artery bypass graft surgery. The 28 days mortality rate was 39%. Under multivariate analysis, initial cardiac power index (CPI), mean arterial pressure (MAP) < 75 mmHg at hour 6 of ICU management and Simplified Acute Physiology Score (SAPS II) were independent predictive factors of in-hospital mortality. During the six-month follow-up, cardiovascular events occurred in 15% of cases and included cardiac death, myocardial infarction, new myocardial revascularization and stroke. Mean systolic left ejection fraction was 45 ± 10%. Twenty-seven (87%) of the OHCA survivors showed almost complete neurological recovery while 4 (13%) exhibited moderate neurological disability.

Conclusion: Patients with CS after AMI consume a high level of ICU resources. Parameters directly related to cardiac performance and vascular responses to vasopressors and admission SAPS II are strong predictors of in-hospital mortality. Neurological prognostic appears to be very good in this situation.

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Therapeutic modulation of the TREM-1 pathway during myocardial infarction

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Introduction: The response to injury in myocardial infarction (MI) can be parsed into multiple overlapping phases. The initial phase involves an acute inflammatory response and includes recruitment of inflammatory cells and the clearance of dead tissue. A subsequent phase involves the initial reparative response replacing the lost tissue and includes immune cells that will both terminate the initial inflammatory response and begin repair. The innate immune system has recently been shown to be important in cardiac response to MI.

TREM-1 is an immune-receptor expressed by neutrophils, macrophages, and mature monocytes that acts as an amplifier of the innate immune response triggered by Toll-Like Receptors (TLRs) engagement. We recently showed that blockade of TREM-1 activation by the use of short inhibitory peptide (LR12) modulated the inflammatory response and protected from death in mouse MI experimental. We here aim at investigating the mechanisms by which LR12 confers protection.

Material and methods: We used adult male mice TREM-1$^{-/-}$, Rag1$^{-/-}$ (lacking B and T cells) and mice depleted in neutrophils with anti-Ly6G 1A8. Animals were submitted to a permanent MI obtained through LAD ligation and then randomized to receive LR12 (a synthetic TREM-1 inhibitory peptide), LR12 scramble or anti-TREM-1 mAb (as a TREM-1 agonist) ip beginning 1 hour after MI, then daily for 5 days. Animals were sacrificed at indicated times for investigation of: myocardial TREM-1 expression; infarct size; recruitment and activation of leucocytes in ischemic myocardium and in different remote compartments (blood, spleen, bone marrow) by immunohistology, flow cytometry, western-blot, Elisa, and qRT-PCR; protease activity. Blood and tissue myocardia were sequentially drawn to study production of MCP-1 and MPO. Finally in another set of experiments, survival was monitored.

Results: In different types of mice, we first observed that TREM-1 was expressed (except in TREM-1$^{-/-}$) in myocardial tissue, especially in infarcted areas with an expression peaking at 24h after MI. We next observed that in TREM-1$^{-/-}$ and LR12 treated animals infarct size was reduced. Recruitment of inflammatory cells (neutrophils, Ly6C^{hi} monocytes, B cells) was also reduced, while 'anit-inflammatory' Ly6C^{low} monocytes number was increased. In LR12 treated and TREM-1$^{-/-}$ mice we observed a reduction of leucocytes activation: the expression of many inflammatory cytokines and chemokines (IL-6, -13, -17, TNF-α, JE, ICAM-1, MIP-2...) was decreased. Using both qRT-PCR and zymography we found deletion or modulation of TREM-1 was associated with a decreased protease activity in infarcted areas (MMP9/TIMP1). Finally, while activation of TREM-1 through anti-TREM-1 mAb administration decreased survival, LR12 and deletion of TREM-1 conferred protection. The phenomena obtained in TREM-1$^{-/-}$ and LR12 treated was also observed in Rag1$^{-/-}$ and mice depleted in neutrophils.

Conclusion: TREM-1 plays an important role in mediating inflammatory cells recruitment and activation following myocardial infarction. Its therapeutic modulation achieved through LR12 administration confers protection in mice.

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Prise en charge des patients de réanimation ayant une élévation de la concentration plasmatique de la troponine I cardiaque non liée au syndrome coronarien aigu

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Introduction : L'élévation plasmatique de la troponine Ic (cTnI) chez des patients hospitalisés en réanimation est une situation fréquemment rencontrée (> 50 % des patients hospitalisés). En dehors des syndromes coronaires aigus (SCA), cette augmentation ne fait l'objet d'aucune recommandation précise. Il en résulte des prises en charge hétérogènes qui peuvent varier entre cliniciens et entre les centres d'hospitalisation. Le but de cette étude est de décrire la prise en charge des patients ayant une élévation de la cTnI en réanimation non liée à un SCA et d'évaluer l'impact des thérapeutiques entreprises.

Matériels et méthodes : Étude prospective, bicentrique et observationnelle menée de novembre 2012 à Juillet 2013 dans 2 réanimations de CHU. Tous les patients hospitalisés en réanimation et ayant une élévation de la cTnI > 0,04 µg/l non liée à un SCA ont été inclus consécutivement. Les patients ayant eu une chirurgie cardiaque ou une assistance circulatoire ont été exclus. Les caractéristiques démographiques, le passé médical et un ECG ont été recueillis pour chaque patient. Avis favorable du CEERB Paris Nord (Projet 13-005 IRB 00006477).

Résultats : Durant la période 190 des 835 (23 %) patients ont une cTnI > 0,04 µg/l à l'admission non liée à un SCA. Le pic de troponine médian [25^{e}-75^{e} percentiles] est de 0,75 µg/l [0,32-1,52]. L'âge moyen est de 59 ± 16 ans et l'IGS2 moyen est de 52 ± 19. Les motifs d'admission les plus fréquents sont le choc septique (28 %) et la défaillance respiratoire (25 %). 63 % ont eu une échographie cardiaque dont 11 % pour explorer l'élévation de la cTnI. 99 % ont eu un ECG et les anomalies les plus fréquemment retrouvées sont une tachycardie sinusale (46 %) des ondes T négatives (16 %) ou un sous décalage du segment ST dans un territoire (9 %). Les traitements les plus souvent mis en place dans les 48h après l'admission sont l'Aspégic (29 %) et/ou une statine (26 %). Il y a une contre-indication à un éventuel traitement par bétabloquant ou IEC dans 59 % des cas. La décision de

traiter les patients par une statine ou par Aspégic est liée à leur terrain : cardiopathie ischémique (P < 0,0001) et artériopathie périphérique (P < 0,0001). La mortalité intra-hospitalière est de 34 %. Le traitement par statine n'est pas associé à une diminution de la mortalité (P = 0,28). Le traitement par Aspégic est associé avec une diminution significative de la mortalité en analyse univariée (mortalité de 23 % dans le groupe Aspégic vs 39 % dans le groupe sans Aspégic, P = 0,039). En analyse multivariée le traitement par Aspégic est également associé à une diminution de la mortalité intrahospitalière (OR = 0,33 ; IC 95 = 0,15-0,76 ; P = 0,01). Les autres facteurs de risque indépendants de mortalité en analyse multivariée sont l'âge élevé (P = 0,002), la diminution du taux de prothrombine (P = 0,01) et l'insuffisance rénale aiguë (P = 0,02).

Conclusion: L'élévation de la cTnI est fréquente en réanimation même si l'admission n'est pas liée à un SCA (23 %). Ces résultats suggèrent que la décision de traitement par statine ou antiagrégants plaquettaires en cas d'élévation de la cTnI dépend essentiellement du terrain du patient (présence de cardiopathie ischémique ou artériopathie périphérique). Le traitement par Aspégic pourrait être associé à une diminution de la mortalité intra-hospitalière.

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Acute stent thrombosis is a frequent adverse event after angioplasty following resuscitated cardiac arrest

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Introduction: The leading cause of sudden cardiac death is myocardial ischemia. As for uncomplicated acute myocardial infarction (AMI), international guidelines plead for early coronary angiography with, in case of culprit lesion, angioplasty and stent implantation. However after cardiac arrest (CA), shock, hypothermia and changes in antiplatelet pharmacokinetic may promote acute stent thrombosis (AST). Incidence of AST in this situation has never been studied. The aim of this study was to investigate incidence and determinants of AST after ischemic CA revascularized.

Patients and methods: We analyzed 208 consecutive patients admitted in our institution for AMI and who underwent PCI with stent implantation. Among these patients, 55 presented a resuscitated CA and were compared to 153 without CA (control group). All the CA group received a 24 h hypothermia following resuscitation and PCI.

Results: In the CA group, we observed a significantly higher incidence of AST than in the control group: 10.9% vs 1.9%, (p = 0.01). There was no difference between the 2 groups for age, gender, cardiovascular risk factors, coronary lesions and type of stent. In the CA group, patients were less frequently pre-treated with heparin (50.9% vs 98.7%, p < 0.001) and aspirin (52.7% vs 99%, p < 0.001). None of them had received a dual antiplatelets therapy (0% Vs 99%). LVEF at admission was lower in the CA group (40.3% vs 48%; p < 0.001), and shock was more frequent (83.6% vs 8.5%; p < 0.001). Survival at 28 days was 50,1% in CA group vs 98.0% (p < 0.001). In multivariate analysis, CA appears to be an independent risk factor for AST (OR = 12.9; 95%CI 1.3-124.6; p = 0.027).

Conclusion: In CA patients treated with cooling, stenting for AMI is associated with a high risk of AST. Shock, insufficient antithrombotic treatment, pharmacokinetic changes related to hypothermia may contribute to this higher risk. A strategy aiming to reduce this complication may improve prognosis of patients who underwent coronary sudden death.

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