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Devenir à long terme des patients présentant un choc cardiogénique à la phase aiguë d'une infarctus du myocarde en fonction de la fonction ventriculaire gauche : données issues de FAST-MI

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Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CS, cardiogenic shock; HR, hazard ratio; IABP, intra-aortic balloon pump; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

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KEYWORDS
Acute myocardial infarction;
Cardiogenic shock;
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Summary
Background. — Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) remains a major concern. Failure of the left ventricular (LV) pump is the primary insult in most forms of CS, but other parts of the circulatory system and diastolic function contribute to shock. However, little is known of the clinical presentation, management and outcomes according to LV function in these patients.
Objectives. — To assess the presentation, management and clinical outcomes in patients admitted for AMI with CS according to early LV ejection fraction (LVEF), using long-term data from the French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction (FAST-MI) 2010.
Methods. — We analysed baseline characteristics, management and 3-year mortality in patients with CS, according to LVEF ($\leq$ 40% vs > 40%). The analyses were replicated in the FAST-MI 2005 cohort.
Results. — Among 4169 patients with AMI included in the survey, the incidence of CS was 3.3%. LVEF was > 40% in 43%. Early PCI ($\leq$ 24 hours) was used more often in patients with LV dysfunction (61% vs 42%), as was the use of optimal medical therapy at discharge (66% vs 40%). CS remained associated with a major increase in 3-year mortality, both in patients with LVEF $\leq$ 40% (55%) and in those with LVEF > 40% (44%). Using Cox multivariable analysis, LVEF $\leq$ 40% was associated with higher 3-year mortality (hazard ratio 2.08, 95% confidence interval 1.15—3.78) in patients with AMI with CS. Consistent results were found in the replication cohort.
Conclusions. — Despite the many circulatory system contributors to the physiopathology of CS in patients with AMI, the occurrence of early LV systolic dysfunction is associated with higher long-term mortality.

MOTS CLÉS
Infarctus du myocarde ;
Choc cardiogénique ;
Fonction ventriculaire gauche

Résumé
Contexte. — Le choc cardiogénique (CC) reste une complication redoutable de l'infarctus du myocarde (IDM). Il résulte le plus souvent d'une dysfonction systolique sévère mais la dysfonction diastolique ainsi que la vasodilatation périphérique conséquence du syndrome de réponse inflammatoire systémique peuvent contribuer aux mécanismes du choc. Pourtant peu de données sont disponibles sur l'épidémiologie des patients présentant un IDM compliqué de CC en fonction de la fonction ventriculaire gauche (VG).
Objectifs. — Évaluer la présentation clinique, la prise en charge et la mortalité à trois ans des patients avec CC à la phase aiguë d'un IDM en fonction de la présence ou non d'une dysfonction VG (DVG) à partir des données de FAST-MI2010.
Méthodes. — Les patients avec DVG (fraction d'éjection VG [FEVG] $\leq$ 40 %) étaient comparés aux patients sans DVG. Les analyses étaient répliquées dans la cohorte FAST-MI 2005.

Résultats. — Parmi les 4169 patients ayant présenté un IDM, 3,3 % des patients ont présenté un CC dont 43 % avec FEVG > 40 %. L'angioplastie percutanée précoce (≤ 24 heures) était utilisée plus souvent chez les patients avec DVG (61 % vs 42 %). Le CC restait associé à une mortalité élevée à trois ans dans les deux groupes ; 55 % chez le groupe FEVG ≤ 40 % et 44 % dans le groupe FEVG > 40 %. En analyse multivariée, la DVG < 40 % était associée à une surmortalité à trois ans (HR 2,08, IC95 % 1,15—3,78) chez les patients en CC. L'analyse dans la cohorte 2005 retrouvait des résultats similaires.
Conclusions. — Malgré une physiopathologie complexe du CC compliquant l'IDM, la DVG ≤ 40 % reste associé à une mortalité élevée à trois ans.

Background

Cardiogenic shock (CS) is the leading cause of hospital mortality associated with acute myocardial infarction (AMI) [1,2]. Although the mortality associated with CS has decreased over the last 20 years, related to the broader use of percutaneous coronary intervention (PCI) and appropriate medications at the acute stage, it remains a major concern, with mortality rates reaching 45% at 1 month [3—7].

Failure of the left ventricular (LV) pump is the primary insult in most forms of CS, but other parts of the circulatory system contribute to shock, with inadequate compensation or additional defects [8]. Indeed, the peripheral vasculature, neurohormonal and cytokine systems play a role in the pathogenesis and persistence of CS. In light of the complex pathophysiology of CS, LV ejection fraction (LVEF) may be only moderately depressed in CS complicating AMI without mechanical complications [8,9]. In the SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK (SHOCK) trial, mean LVEF was ≈30%. In the FAST-MI registries, we reported that 37% of patients with CS had LVEF > 40%, whereas 19% of patients without CS had LV dysfunction (< 40%) [6]. However, among patients with CS complicating AMI, previous studies have reported that LVEF remains a prognostic indicator [10—17]. Overall in patients with CS, little is known about the clinical presentation, management and long-term mortality according to early LV function (i.e. assessed at the acute phase of AMI).

The aim of the present study was to assess presentation, management and clinical outcomes in patients admitted for AMI with CS, according to early LVEF, using long-term data from the French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction (FAST-MI) 2010.

Methods

FAST-MI 2010 registry

FAST-MI 2010 is a national prospective multicentre registry including consecutive adult patients hospitalized for ST-segment elevation and non-ST-segment elevation AMI (STEMI and NSTEMI) (with symptom onset ≤ 48 hours) over a period of 1 month (from October 2010). Patients with AMI after cardiovascular procedures were excluded. Participation in the study was offered to all intensive care units in French institutions (university teaching hospitals, general and regional hospitals and private clinics) with the capacity to receive acute coronary syndrome emergencies. Details of the methodology have been described previously [18,19]. The main objective of this registry was to evaluate strategies for the management of myocardial infarction (MI) in routine practice and to measure their association with outcomes over a 10-year follow-up. The registry was conducted in compliance with Good Clinical Practice guidelines, French law and the French data protection law. The protocol was reviewed and approved by the Committee for the Protection of Human Subjects of Saint-Louis University Hospital, and the FAST-MI data file was declared to the Commission Nationale Informatique et Liberté. The trial is registered at Clinicaltrials.gov: identifier NCT01237418.

Study population

A total of 4169 patients in 213 centres (76% of active centres in France) were included in this registry. Baseline characteristics were collected prospectively. All data were recorded on computerized case record forms by dedicated research technicians sent to each of the centres at least once a week. The research technicians were also asked to ensure that recruitment was consecutive. In the current analysis, we selected all patients with AMI (STEMI and NSTEMI) with CS.

CS was defined as systolic blood pressure < 90 mmHg in the absence of hypovolaemia, and associated with cyanosis, cold extremities, changes in mental status, persistent oliguria or congestive heart failure. Decreased LVEF was defined as LVEF ≤ 40% [20]. The last LVEF assessed during the stay in the intensive care unit was analysed.

Statistical analysis

Statistical analysis was performed using SPSS premium statistics software, version 23.0 (IBM, Armonk, NY, USA). For quantitative variables, means and standard deviations were calculated. In addition, medians with interquartile ranges were calculated when appropriate. Discrete variables are presented as numbers of events and percentages. Comparisons were made with the χ^2 test or Fisher's exact

tests for discrete variables, and by unpaired t tests, Mann-Whitney tests or one-way analyses of variance for continuous variables. Survival curves were estimated using Kaplan-Meier estimators, and were compared using log-rank tests. Correlates of survival were determined using a multivariable backward stepwise Cox analysis. Cumulative hazard functions were computed to assess proportionality. The candidate variables included in the multivariable analyses were selected ad hoc, based upon their physiological relevance and potential to be associated with long-term mortality. To adjust for confounders, in addition to LV function, we adjusted for age, sex, type of AMI, risk factors, non-cardiovascular co-morbidity, medications and revascularization (variables listed in Table 1 and Table 2) in the whole population. For all analyses, a P value < 0.05 was considered significant.

For assessing the robustness of the results, we repeated the analysis in patients with CS in the FAST-MI 2005 registry, which had been carried out five years earlier, using similar methodology (Clinicaltrials.gov identifier: NCT00673036) [18]. The set of variables collected in 2005 was essentially similar to that collected in 2010.

Results

Main analysis: FAST-MI 2010

Characteristics and clinical presentation

Of the 4169 patients included in the FAST-MI 2010 registry, 138 (3.3%) patients with AMI developed CS during hospitalization, and 112 had LVEF data available (Table 1). Fifty-seven percent of patients with CS had LV systolic dysfunction. The two groups (LVEF $\leq$ 40% and LVEF > 40%) did not differ in many respects, particularly regarding past medical history. However, patients with decreased LVEF were significantly younger (70.1 $\pm$ 12.9 vs 75.5 $\pm$ 12.3 years). The GRACE (Global Registry of Acute Coronary Events) score was similar in both groups (201 $\pm$ 42 vs 204 $\pm$ 37). Clinical presentation at admission was slightly different according to LV function, with numerically higher proportions of STEMI, cardiac arrest and typical chest pain in patients with LV systolic dysfunction. The left anterior descending artery was the most frequent culprit lesion in patients with LVEF $\leq$ 40%, while the right coronary artery was the most frequent culprit lesion in patients with LVEF > 40%. Finally, multivessel

Table 1 Baseline characteristics and clinical presentation in patients with cardiogenic shock, according to left ventricular function (FAST-MI 2010 cohort).

	LV function $\leq$ 40% (n = 64)	LV function > 40% (n = 48)	P
Age (years)	70.1 $\pm$ 12.9	75.5 $\pm$ 12.3	0.03
Age > 75 years	27 (42)	30 (62.5)	0.03
Body mass index (kg/m^2)	26.7 $\pm$ 4.7	27.3 $\pm$ 5.8	0.56
Women	17 (27)	31 (65)	0.19
Risk factors			
Hypertension	44 (69)	35 (73)	0.63
Diabetes	42 (34)	15 (31)	0.73
Dyslipidaemia	30 (47)	26 (54)	0.45
Current smoker	12 (19)	41 (15)	0.56
Cardiovascular history and co-morbidities			
History of MI	12 (19)	8 (17)	0.78
Previous PCI	10 (16)	6 (12.5)	0.64
Previous CABG	5 (8)	1 (2)	0.18
History of heart failure	6 (9)	6 (12.5)	0.60
History of stroke	2 (3)	0 (0)	0.22
Peripheral artery disease	8 (12.5)	6 (12.5)	1.0
Chronic renal failure	6 (9)	3 (6)	0.55
Medication history			
Aspirin	15 (23)	14 (29)	0.67
Clopidogrel	9 (14)	4 (31)	0.35
Beta-blocker	19 (30)	21 (44)	0.12
Statin	19 (30)	21 (44)	0.12
ACE inhibitor or ARB	20 (31)	28 (58)	0.004
Clinical presentation			
STEMI	19 (70)	28 (58)	0.19
Typical chest pain	52 (81)	26 (54)	0.002
Cardiac arrest	5 (8)	2 (4)	0.43
GRACE score	201 $\pm$ 42	204 $\pm$ 37	0.78

Data are expressed as mean $\pm$ standard deviation or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; GRACE: Global Registry of Acute Coronary Events; LV: left ventricular; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Table 2 In-hospital management of patients with cardiogenic shock, according to left ventricular function (FAST-MI 2010 cohort).

	LV function ≤ 40% ($n = 64$)	LV function > 40% ($n = 48$)	*P*
Aspirin	57 (89)	46 (96)	0.19
Clopidogrel	44 (69)	41 (85)	0.04
Prasugrel	10 (16)	6 (12.5)	0.64
GP IIb/IIIa	25 (39)	12 (25)	0.18
UFH	42 (66)	27 (56)	0.31
LMWH	23 (36)	21 (44)	0.40
Bivalirudine	5 (8)	2 (4)	0.43
Fondaparinux	6 (9)	6 (12.5)	0.60
Proton pump inhibitor	35 (55)	30 (62.5)	0.41
Statin	46 (72)	35 (73)	0.90
Beta-blocker	23 (36)	21 (44)	0.40
ACE inhibitor	26 (41)	16 (33)	0.43
Inotrope	30 (47)	10 (19)	0.002
Diuretic	40 (62.5)	28 (58)	0.66
Femoral access	24 (56)	20 (44)	0.24
Drug-eluting stent	13 (27)	8 (23)	0.67
IABP	25 (39)	8 (17)	0.01
Other short-term assist devices	6 (9.5)	2 (4)	0.29
Management in patients with STEMI			
ECG to primary PCI (minutes)	127 [95; 258] ($n = 31$)	116 [78; 191] ($n = 16$)	< 0.001
Primary PCI	33 (77)	16 (59)	0.12
Thromboaspiration	14 (37)	10 (48)	0.72
Fibrinolysis	3 (7)	3 (11)	0.54
Management in patients with NSTEMI			
PCI ≤ 24 hours	6 (32)	4 (20)	0.11
PCI during hospitalization	10 (53)	14 (70)	0.27
CAG during hospitalization	15 (79)	16 (80)	0.94
Culprit lesion			
Left main coronary artery	4 (6)	2 (4)	0.26
Left anterior descending artery	26 (41)	9 (19)	
Circumflex artery	8 (12.5)	8 (17)	
Right coronary artery	15 (23)	20 (42)	

Data are expressed as number (%) or median [interquartile range]. ACE: angiotensin-converting enzyme; CAG: coronary angiography; ECG: electrocardiogram; GP: glycoprotein; IABP: intra-aortic balloon pump; LMWH: low-molecular-weight heparin; LV: left ventricular; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UFH: unfractionated heparin.

coronary artery disease was slightly more frequent in patients with LVEF ≤ 40% (Table 2).

Initial management

Initial management is presented in Table 2. Numerically more patients with decreased LVEF received prasugrel, glycoprotein IIb/IIIa inhibitors and unfractionated heparin. The use of life-support therapies (inotropes and intra-aortic balloon pump [IABP]) were significantly higher in patients with LV systolic dysfunction, but < 50% of the patients with CS received inotropes in the first 48 hours after admission.

In patients with STEMI, the rate of primary PCI was numerically higher in patients with LVEF ≤ 40%, and the time from electrocardiogram to primary PCI was significantly higher in these patients (median [IQR]: 127 [95; 258] vs 116 [78; 191] minutes). In patients with NSTEMI, the rate of early PCI (i.e. performed during the first 24 hours) was numerically higher in patients with decreased LVEF.

In-hospital complications and clinical outcomes

In-hospital complications (recurrent MI, intrastent thrombosis, atrial fibrillation, stroke and bleeding) were similar regardless of LVEF. The use of blood transfusion was also similar in both groups. In-hospital death was numerically higher in patients with LVEF ≤ 40% (36% vs 29%), as was mortality at 1 year (47% vs 35%) and 3 years (55% vs 44%) (Table 3).

Using multivariable analysis, early LV systolic dysfunction was associated with a higher 3-year mortality risk (hazard ratio [HR] 2.08; 95% confidence interval [CI] 1.15—3.78) (Fig. 1 and Table A.1]. In patients with NSTEMI, LVEF ≤ 40% was associated with a high risk of mortality at 3 years after adjustment (HR 5.29, 95% CI 1.71—16.44), while only

Table 3 In-hospital complications and clinical outcomes in patients with cardiogenic shock, according to left ventricular function (FAST-MI 2010 cohort).

	LV function ≤ 40% ($n = 64$)	LV function > 40% ($n = 48$)	*P*
Recurrent MI	2 (3)	1 (2)	0.74
Intrastent thrombosis	2 (3)	1 (2)	0.74
Atrial fibrillation	14 (22)	7 (15)	0.33
New AV block	10 (16)	6 (12.5)	0.59
Ventricular fibrillation	9 (14)	3 (6)	0.19
Ventricular tachycardia	9 (14)	3 (6)	0.19
Stroke	1 (2)	0 (0)	0.38
Major bleeding	3 (5)	3 (6)	0.71
Minor bleeding	3 (5)	3 (6)	0.71
Red cell transfusions	9 (14)	5 (10)	0.56
In-hospital death	23 (36)	14 (29)	0.29
Death at 1 year	30 (47)	17 (35)	0.29
Death at 3 years	35 (55)	21 (44)	0.13

Data are expressed as number (%). AV: atrioventricular; LV: left ventricular; MI: myocardial infarction.

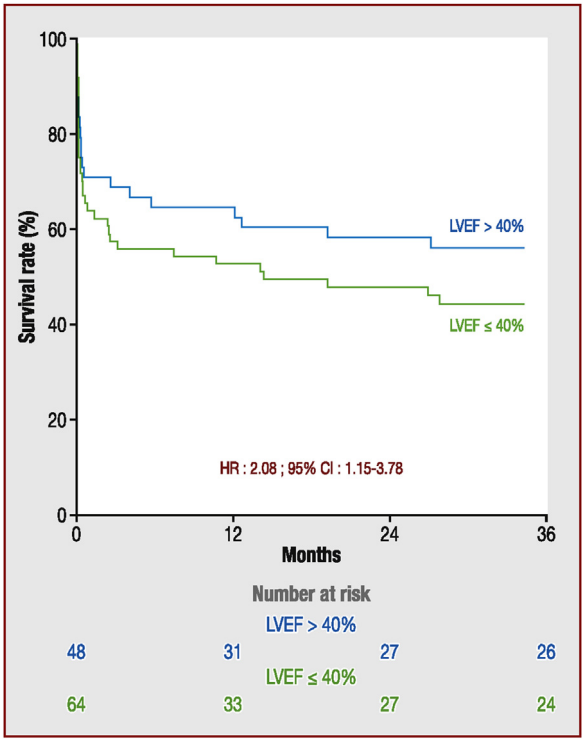

Figure 1. Long-term survival in patients with cardiogenic shock, according to left ventricular function (FAST-MI 2010 cohort).

a trend was observed in patients with STEMI (HR 1.68, 95% CI 0.80—3.54).

Replication cohort: FAST-MI 2005

Among the 3670 patients included in the FAST-MI 2005 registry, 224 (6.1%) patients with AMI developed CS during hospitalization (164 patients with LVEF data available). Baseline characteristics did not differ between patients with CS with or without LV systolic dysfunction (Table A.2 and Table A.3). In-hospital complications (recurrent MI, intrastent thrombosis, atrial fibrillation, stroke and bleeding) were also similar regardless of the LVEF (Table A.4). In-hospital death was numerically higher in patients with LVEF ≤ 40% (50% vs 41%), as was mortality at 1 year (67% vs 49%) and three years (75% vs 52%). Using multivariable analysis, LV systolic dysfunction was associated with higher 3-year mortality in the overall population (HR 1.96, 95% CI 1.29—3.00), as well as in patients with STEMI (HR 1.94, 95% CI 1.11—3.38) and patients with NSTEMI (HR 2.68, 95% CI 1.30—5.12) (Table A.5).

Discussion

The present data from a nationwide registry indicate that approximately 40% of patients who develop CS during AMI have no severe LV systolic dysfunction. Among patients with CS, there was only little difference between those with or without LV systolic dysfunction; from an anatomical standpoint, CS was more often related to left anterior descending artery involvement in those with low LVEF, while the right coronary artery was the predominant culprit artery in those without severe LV systolic dysfunction. The management of the two LVEF groups did not differ essentially, except for more frequent use of life-support therapies (inotropes and IABP) in those with low LVEF. LVEF ≤ 40%, however, was associated with higher long-term mortality after full adjustment for clinical presentation and management.

LV dysfunction is an established correlate of increased short- and long-term mortality after AMI [10—14,16,17]. Several studies have demonstrated that patients with STEMI with LV dysfunction have increased rates of mortality, major adverse cardiovascular events (MACE) and major bleeding [21,22]. However, in most reports examining the significance of LVEF after MI, LVEF assessment occurred later during the healing process, and very few data are available related to LVEF and dysfunction in patients with AMI with CS. Our data show that early LV systolic dysfunction affects 57% of patients with AMI with CS. Since the SHOCK study, the complex pathophysiology of CS has been highlighted, and it is

now recognized that LVEF may be only moderately depressed in CS complicating AMI without mechanical complications [8,9]. However, a rate of 40% of patients with CS having an LVEF > 40% may appear high. The assessment of cardiac function is difficult, and LVEF has many determinants: not only cardiac performance, but also preload, afterload, heart rate and synchronization [23]. Of note, patients with LVEF > 40% were older compared with those with decreased LVEF. Subanalyses according to type of MI suggest that the proportion of patients with CS with LVEF > 40% was increased in NSTEMI compared with STEMI, which can be explained by the clinical characteristics of both populations. Typically, patients with NSTEMI are older and have more frequent risk factors (especially hypertension), co-morbidities and a higher burden of coronary artery disease [24—26]. These characteristics could contribute to LV diastolic dysfunction. Indeed, it is likely that abnormalities of ventricular relaxation and compliance contribute to CS in some cases [8].

Interestingly, the use of inotrope therapy during the first 48 hours after admission was increased in patients with LV dysfunction, but remained < 50% in both groups. This finding may arise from the fact that CS might have developed at a later stage after admission, from a lack of evidence for clinical benefits of inotropes and from the fear of potential harm with inotropes in CS, resulting in disparities in clinical practice [20,27]. Finally, increased use of circulatory assist devices may explain the reduced catecholamine requirements [20,27]. In our population, the use of assist devices and IABP was also increased in patients with LVEF < 40%. IABP has been used widely as mechanical support in CS [28]. However, the IABP-SHOCK II trial, including 600 patients with AMI with CS, did not show any beneficial effect on 30-day mortality with the use of IABP [29,30]. Thus, the use of IABP for this indication is not routinely recommended [20,29,31]. The LVEF assessments were not performed at the same time of hospital stay, and could be done with or without inotropic and IABP support. However, the in SHOCK trial, LVEF was usually measured while patients were on inotropic and/or balloon support, and the authors reported that LVEF was similar in the acute phase of CS and two weeks later, when functional status was quite different [8,15].

Finally, LVEF $\leq$ 40% at the acute phase of AMI with CS was associated with higher long-term mortality after full adjustment for clinical presentation and management. These findings were consistent with previous studies [10—17], and may support a strategy of aggressive manoeuvres to enhance forward LV stroke volume and improve regional and global LV systolic function in patients with CS caused by extensive LV dysfunction [8].

Study limitations

The study suffers from the same limitation as all observational studies, i.e. no causality can be asserted between variables that are correlated. Comparisons between patients according to LV systolic function were not randomized and, despite careful adjustments for a large number of potentially confounding variables, and the use of statistical adjustment with the inverse probability weighting, the results can only be considered indicative. Only medications administered during the first 48 hours and/or at discharge were recorded. Finally, LVEF was not available in a number of patients.

Conclusions

In conclusion, CS carries a very high short-term and long-term mortality risk, irrespective of initial LV systolic dysfunction. Low LVEF in patients with CS, however, has an independent prognostic significance regarding long-term mortality.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2017.11.002.

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