Archives of Cardiovascular Disease (2019) 112, 738—747

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CLINICAL RESEARCH

Predictive factors for long-term mortality in miscellaneous cardiogenic shock: Protective role of beta-blockers at admission

Facteurs prédictifs de mortalité à long terme dans le choc cardiogénique toutes étiologies confondues : rôle protecteur des bêtabloquants à l'admission

Clément Delmas[a,b,*], Elisabeth Orloff[a], Frédéric Bouisset[a], Thomas Moine[a], Barbara Citoni[c], Caroline Biendel[a,b], Jean Porterie[d], Didier Carrié[a,e], Michel Galinier[a,f], Meyer Elbaz[a,f], Olivier Lairez[a,f,g,h]

[a] *Department of cardiology, Rangueil university hospital, 31059 Toulouse, France*
[b] *Intensive cardiac care unit, Rangueil university hospital, 31059 Toulouse, France*
[c] *Sapienza University of Rome, 00185 Rome, Italy*
[d] *Department of cardiovascular surgery, Rangueil university hospital, 31059 Toulouse, France*
[e] *Purpan medical school, university Paul Sabatier, 31300 Toulouse, France*
[f] *Rangueil medical school, university Paul Sabatier, 31059 Toulouse, France*
[g] *Cardiac imaging centre, Toulouse university hospital, 31059 Toulouse, France*
[h] *Department of nuclear medicine, Rangueil university hospital, 31059 Toulouse, France*

Received 19 February 2019; received in revised form 8 April 2019; accepted 15 April 2019
Available online 31 May 2019

KEYWORDS
Cardiogenic shock;
Prognosis;
Mortality

Summary
Background. — Despite advances in intensive care medicine, management of cardiogenic shock (CS) remains difficult and imperfect, with high mortality rates, regardless of aetiology. Predictive data regarding long-term mortality rates in patients presenting CS are sparse.
Aim. — To describe prognostic factors for long-term mortality in CS of different aetiologies.
Methods. — Two hundred and seventy-five patients with CS admitted to our tertiary centre between January 2013 and December 2014 were reviewed retrospectively. Mortality was recorded in December 2016. A Cox proportional-hazards model was used to determine predictors of long-term mortality.

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CS, cardiogenic shock; HR, hazard ratio; ICCU, intensive cardiac care unit; MCS, mechanical circulatory support.

* Corresponding author at: Department of cardiology, Toulouse university hospital, 1, avenue Jean Poulhès, TSA 50032, 31059 Toulouse cedex 9, France.
E-mail addresses: delmas.clement@chu-toulouse.fr, clement23185@hotmail.fr (C. Delmas).

https://doi.org/10.1016/j.acvd.2019.04.004

Results. — Most patients were male (72.7%), with an average age of 64 ± 16 years and a history of cardiomyopathy (63.5%), mainly ischaemic (42.3%). Leading causes of CS were myocardial infarction (35.3%), decompensated heart failure (34.2%) and cardiac arrest (20.7%). Long-term mortality was 62.5%. After multivariable analysis, previous use of beta-blockers (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.41—0.89; $P = 0.02$) and coronary angiography exploration at admission (HR 0.57, 95% CI 0.38—0.86; $P = 0.02$) were associated with a lower risk of long-term mortality. Conversely, age (HR 1.02 per year, 95% CI 1.01—1.04; $P < 0.001$), catecholamine support (HR 1.45 for each additional agent, 95% CI 1.20—1.75; $P < 0.001$) and renal replacement therapy (HR 1.66, 95% CI 1.09—2.55; $P = 0.02$) were associated with an increased risk of long-term mortality.
Conclusions. — Long-term mortality rates in CS remain high, reaching 60% at 1-year follow-up. Previous use of beta-blockers and coronary angiography exploration at admission were associated with better long-term survival, while age, renal replacement therapy and the use of catecholamines appeared to worsen the prognosis, and should lead to intensification of CS management.

MOTS CLÉS
Choc cardiogénique ;
Pronostic ;
Mortalité

Résumé
Contexte. — Malgré les progrès médicaux récents, la mortalité du choc cardiogénique (CC) reste élevée quelle qu'en soit l'étiologie.
But. — Décrire les facteurs prédictifs de mortalité à long terme (LT) du CC toutes causes confondues.
Méthodes. — Au total, 275 patients en CC admis entre 01/2013 et 12/2014 ont été rétrospectivement inclus. La mortalité a été recueillie en décembre 2016. Un modèle de risque proportionnel de Cox a été utilisé pour déterminer les variables indépendamment corrélées à la mortalité à LT.
Résultats. — Cette étude a inclus majoritairement des hommes (72,7 %) d'un âge moyen de 64 ± 16 ans. Les principales causes de CC étaient le syndrome coronaire aigu (35,3 %), la décompensation d'insuffisance cardiaque chronique (34,2 %) et le choc post arrêt cardiaque (20,7 %). La mortalité à LT était de 62,5 %. La prescription antérieure de bêtabloquants (HR 0,62, IC95 % 0,41—0,89 ; $p = 0,01$) et la réalisation initiale d'une angiocoronarographie (HR 0,57, IC95 % 0,38—0,86 ; $p = 0,007$) étaient des facteurs associés à la survie. L'âge (HR 1,02 par an, IC95 % 1,01—1,04 ; $p < 0,001$), le nombre d'amines utilisées (HR 1,45 par unité, IC95 % 1,20—1,75 ; $p < 0,001$) et le recours à l'épuration extra-rénale (hR 1,66, IC95 % 1,09—2,55 ; $p = 0,02$) étaient associés à une surmortalité à LT.
Conclusions. — La mortalité à LT du CC demeure importante et concerne plus de la moitié des patients. La prescription antérieure de bêtabloquants et la réalisation initiale d'une coronarographie sont associées à une meilleure survie à LT alors que l'âge, l'insuffisance rénale et l'utilisation d'amines semblent aggraver le pronostic.

Background

Cardiogenic shock (CS) is a state of organ hypoperfusion caused by severe cardiac dysfunction; it progresses rapidly to multisystem failure and death without adequate treatment [1]. Myocardial infarction and related complications account for most cases of CS, but the prevalence of CS among patients with acute coronary syndrome (ACS) has tended to decrease over the past few decades [2]. Other causes are probably underestimated, and correspond to decompensated heart failure, arrhythmia, valvular disease, cardiac arrest and any other condition related to cardiac failure.

The SHOCK trial publication led to radical change in the management of CS after myocardial infarction, with the addition of early myocardial revascularization to the standard therapy [3]. This strategy and the improvement in intensive care management have significantly decreased CS-related mortality rates, as highlighted in recent studies with a reported 30-day mortality rate of around 40% [4,5]. However, data on long-term prognosis are scarce. Mortality heterogeneity seems to depend on the clinical profile

of patients, which suggests that some factors may be associated with a higher risk of mortality (e.g. age, hepatic or renal dysfunction and elevated lactate concentration) [6–8].

Throughout the past decade, the introduction of mechanical circulatory support (MCS) has led to considerable changes in the management and prognosis of patients with advanced heart failure. Large studies are missing, however, and it seems necessary to gather more updated data on patients with CS to better characterize predictive factors that could alter risk stratification and management.

The aim of our study was to investigate the characteristics and management of CS of all aetiologies in a French contemporary cohort, in order to establish predictive risk factors for long-term mortality.

Methods

Between January 2013 and December 2014, consecutive patients admitted to the Intensive Cardiac Care Unit (ICCU) of Rangueil university hospital (Toulouse, France) were included retrospectively. Patients with other causes of shock or who did not meet the subsequent criteria in accordance with the SHOCK study were excluded from the study. Patients hospitalized twice during the inclusion period were censored at the first hospitalization.

Data collection

Demographic data, medical history, treatment at admission and biochemical variables were collected from medical records. Up to three CS aetiologies among the following were considered for each patient: acute myocardial infarction, decompensated heart failure, cardiac arrest, ventricular and supraventricular arrhythmia, iatrogeny, infections, bradycardia, acute valvular disease or other (including intoxication, myocarditis, pulmonary embolism, cardiotomy, non-compliance and tamponade). Transthoracic echocardiograms were extracted from our picture archiving and communication system. Regarding biochemical variables, assay techniques for troponin T and brain natriuretic peptide were modified during the inclusion period, switching to troponin US and N-terminal prohormone of brain natriuretic peptide, respectively, in October 2013.

CS treatment, including organ replacement therapies, continuous or one-time use of catecholamines (i.e. inotropes and/or vasopressors), diuretics, mechanical or non-invasive ventilation, MCS (i.e., intra-aortic balloon pump, extracorporeal membrane oxygenation or Impella® device [Abiomed Inc., Danvers, MA, USA]) and end-stage heart failure treatment (i.e., left ventricular assist device implantation or heart transplantation) were recorded.

Endpoints

Thirty-day and 1-year mortality data were collected from medical records. Long-term survival status (≥ 2 years) was collected in December 2016 by calling patients, or their relatives or medical referents (general practitioners or cardiologists) when patients were not available. Patients unable to be interviewed up to 3 months from the date of follow-up were considered as lost to follow-up.

Ethics

The study complies with the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Ethics Committees of our institution (No. 06-0216).

Statistical analysis

Statistical analysis was performed using Stata® statistical software, release 14.1 (Stata Corporation, College Station, TX, USA).

Continuous variables are summarized as means and standard deviations for normal distributions, and as medians and interquartile ranges for abnormal distributions. Categorical variables are presented as proportions. In the univariate analysis, qualitative variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Student's t test was used to compare the distribution of quantitative normally distributed data according to qualitative variables. The Mann-Whitney test was used to compare ranges of continuous abnormally distributed variables according to qualitative variables. A P value < 0.05 was considered statistically significant.

Cumulative patient survival was determined using the Kaplan-Meier method, and compared using the log-rank test. Univariate and multivariable Cox regression models were used to investigate the correlation between variables and mortality during the follow-up period, and to determine hazard ratios (HRs) for mortality and 95% confidence intervals (CIs). If the log-linearity hypothesis was not complied with, continuous variables were transformed into qualitative data. All variables associated with a P value < 0.20 in the univariate analysis were introduced into a multivariable Cox model. The C-statistic was calculated to evaluate the goodness-of-fit of the multivariable model.

Results

Study population

The study flow chart is shown in Fig. 1. Two hundred and seventy-five patients were included in the study. Baseline characteristics are presented in Table 1. Patients were mainly middle-aged (64 ± 16 years) and men ($n = 200$; 72.7%), with standard risk factors in more than one-third of cases (e.g. smoking habits, hypertension, dyslipidaemia and diabetes). Most of the patients had a history of cardiovascular disease, mainly ischaemic cardiomyopathy. Treatment at admission frequently included beta-blockers and aspirin. Acute myocardial infarction, decompensation of chronic heart failure and cardiac arrest were the most common CS aetiologies.

Clinical, biological and echocardiographical data are presented in Table 1. Patient management data are shown in Table 2. As expected, most patients required catecholamine support, mainly dobutamine infusion. More than one-third of patients received MCS, mainly venoarterial extracorporeal membrane oxygenation ($n = 90$; 52.9%).

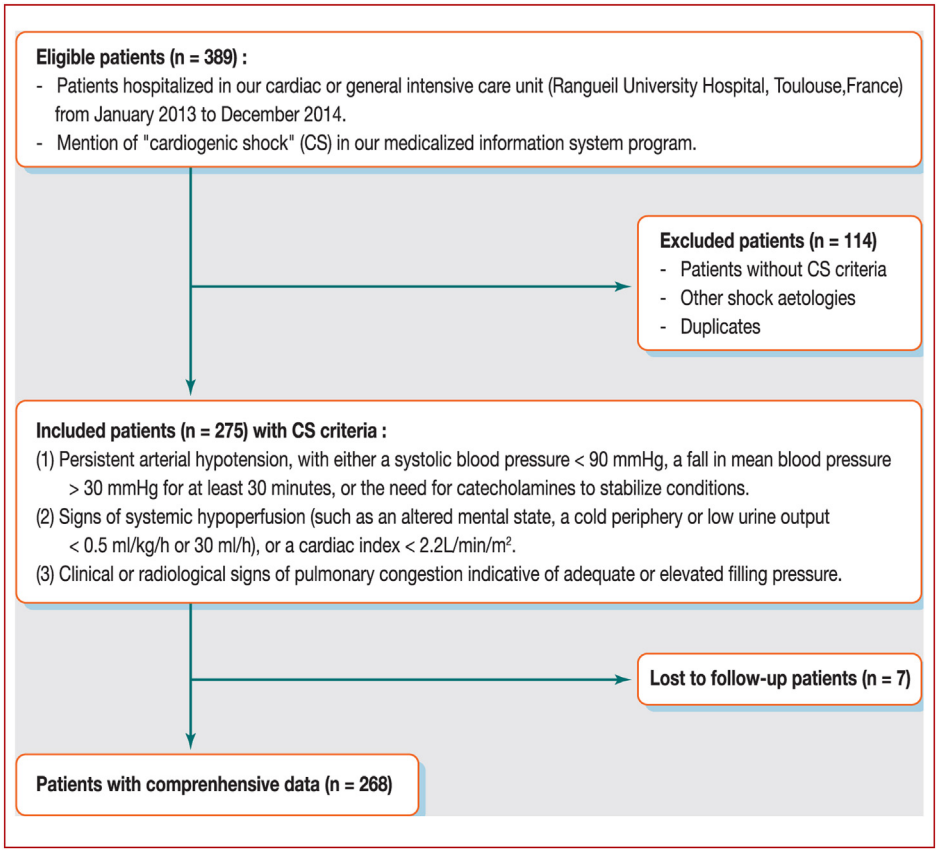

Figure 1. Study flow chart. CS: cardiogenic shock.

Prognosis

Seven (2.5%) patients were lost to follow-up, and were excluded from the analysis. The median duration of follow-up was 31 days (interquartile range 5—885 days), with the longest follow-up being 1446 days. Thirty-day and 1-year mortality rates were 49.4% and 60.4%, respectively. Twenty-four (8.7%) patients were referred for an emergency heart transplant, which was achieved in 11 (4.0%) cases, whereas nine (3.3%) were implanted with a left ventricular assist device. At the end of (long-term) follow-up, the mortality rate was 62.5% (Fig. 2).

Long-term mortality risk factors

Predictive factors for 1-year mortality are described in Table A.1. At the end of follow-up, the univariate analysis identified age, diabetes mellitus, severe aortic stenosis, blood glucose > 12 mmol/L, arterial lactate > 10 mmol/L, catecholamine support and the implementation of renal replacement therapy as predictive factors for long-term mortality. On the other hand, CS associated with supraventricular arrhythmia and coronary angiography exploration at admission were identified as being protective factors (Table 3).

Significant variables, and those with a P value < 0.2 by univariate analysis (i.e. male sex, hypertension, beta-blocker treatment at admission, previous use of an anticoagulant, such as a vitamin K antagonist, C-reactive protein > 100 mg/L and non-invasive ventilation) were included in the multivariable Cox proportional hazard model.

After multivariable analysis, independent predictive factors of long-term mortality were age (HR 1.02 per year, 95% CI 1.01—1.04; $P < 0.001$), catecholamine support (HR 1.45 per drug, 95% CI 1.20—1.75; $P < 0.001$) and use of renal replacement therapy (HR 1.66, 95% CI 1.09—2.55; $P = 0.02$). Previous use of beta-blockers (HR 0.61, 95% CI 0.41—0.89; $P = 0.01$) and coronary angiography exploration at admission (HR 0.57, 95% CI 0.38—0.86; $P = 0.007$) were protective factors. The discrimination performance of our model was acceptable, with an area under the curve of 0.79 (95% CI 0.77—0.81; $P = 0.03$).

Link between beta-blocker use and prognosis

Patients with beta-blockers at admission ($n = 109$) had more frequent history of cardiomyopathy (61.7% vs. 38.3%; $P < 0.001$), notably of ischaemic aetiology (61.6%). There was no link between beta-blockers at admission and beta-blockers at hospital discharge (54.6% of patients without beta-blockers at admission had beta-blockers at discharge versus 66.1% for patients with beta-blockers at admission; $P = 0.2$). Patients with beta-blockers at discharge tended to have a lower long-term mortality rate (46.7% vs. 53.3%; $P = 0.09$).

Table 1 Baseline characteristics and univariate association with long-term mortality.

Variables	All ($n=275$)	Long-term mortality		
		Survivors ($n=103$)	Non-survivors ($n=172$)	P
Cardiovascular risk factors				
Age (years)	64.1 ± 15.5	61 ± 15.9	66 ± 15.0	0.01
Male	200 (72.7)	80 (77.7)	120 (69.8)	0.15
BMI (kg/m^2)	26.6 ± 6.1	26.1 ± 6.4	27 ± 6.0	0.25
Smoking	123 (47.1)	53 (51.5)	70 (44.3)	0.25
Hypertension	116 (44.4)	40 (38.8)	76 (48.1)	0.14
Dyslipidaemia	105 (40.7)	41 (40.2)	64 (41.0)	0.89
Diabetes mellitus	82 (31.5)	24 (23.3)	58 (36.9)	0.02
History of cardiopathy	174 (63.5)	61 (59.2)	113 (66.1)	0.25
Ischaemic	116 (42.3)	41 (39.8)	75 (43.9)	0.51
Treatment at admission				
Aspirin	99 (42.7)	37 (41.1)	62 (43.7)	0.7
Other antiaggregating agent	42 (18.1)	17 (18.9)	25 (17.6)	0.8
VKA	56 (24.4)	14 (15.6)	42 (30.0)	0.01
NOAC	4 (1.74)	2 (2.2)	2 (1.4)	0.51
Beta-blocker	109 (47)	46 (51.1)	63 (44.4)	0.31
ACEI-ARB	95 (40.1)	33 (36.7)	62 (43.7)	0.29
Statin	90 (39.0)	46 (51.1)	63 (44.4)	0.26
Aetiology				
ACS	97 (35.3)	34 (33.0)	63 (36.6)	0.54
Decompensated heart failure	94 (34.2)	34 (33.0)	60 (34.9)	0.75
Cardiac arrest	57 (20.7)	21 (20.4)	36 (20.9)	0.1
Ventricular arrhythmia	43 (15.6)	19 (18.5)	24 (14.0)	0,32
Supraventricular arrhythmia	28 (10.2)	18 (17.5)	10 (5.8)	0.002
Iatrogeny	25 (9.1)	8 (7.8)	17 (9.9)	0.23
Infection	17 (6.2)	6 (5.8)	11 (6.4)	0.84
Bradycardia	16 (5.8)	4 (3.8)	12 (7.0)	0.84
Acute valvular disease	10 (3.6)	3 (2.9)	7 (4.1)	0.44
Other	40 (14.6)	20 (19.4)	20 (11.6)	0.08
Echocardiography				
LVEF (%)	28 ± 16	27 ± 15	28 ± 17	0.84
Severe aortic stenosis	21 (7.6)	4 (3.9)	17 (9.9)	0.07
Severe mitral insufficiency	23 (10.7)	12 (13.8)	11 (8.6)	0.22
Severe aortic insufficiency	7 (3.3)	3 (3.5)	4 (3.2)	0.59
Severe mitral stenosis	3 (1.4)	2 (2.4)	1 (0.8)	0.35
Biology				
eGFR (mL/min)	50 (32—67)	54 (36—73)	45 (30—66)	0.02
AST (mmol/L)	102 (44—338)	97 (44—215)	111 (45—432)	0.36
ALT (mmol/L)	70 (32—204)	77 (31—216)	69 (33—202)	0.93
Arterial pH	7.31 ± 0.16	7.33 ± 0.14	7.30 ± 0.18	0.18
Arterial lactate (mmol/L)	3.8 (2—7.8)	3.5 (2.0—5.6)	4.0 (2.2—9.8)	0.07
Blood glucose (mmol/L)	9.6 (7.2—15)	9 (6.6—13.4)	10.2 (7.8—16.3)	0.01
PTT (%)	58 ± 22	62 ± 23	56 ± 22	0.04
CRP (mg/L)	29 (8—84)	19 (5—61)	42 (9—104)	0.02
BNP (pg/mL) ($n=64$)	1028 (491—1578)	769 (459—1413)	1122 (496—1813)	0.36
NTproBNP (pg/mL) ($n=78$)	7788 (2639—17206)	5082 (2226—10412)	10486 (3032—31150)	0.03
Troponin T (ng/mL) ($n=92$)	2.7 (0.1—17.9)	3.5 (0.1—10.8)	2.1 (0.2—19)	0.58
Troponin US (ng/mL) ($n=139$)	1135 (121—7319)	493 (76—2581)	2076 (251—8986)	0.006

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ACEI: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ALT: alanine transaminase; ARB: angiotensin receptor blocker; AST: aspartate transaminase; BMI: body mass index; BNP: brain natriuretic peptide; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate with Cockcroft and Gault formula; LVEF: left ventricular ejection fraction; NOAC: non-vitamin K antagonist oral anticoagulant; NTproBNP: N-terminal prohormone of BNP; PTT: prothrombin time; VKA: vitamin K antagonist.

Table 2 Management and univariate association with long-term mortality.

Variables	All ($n=275$)	Long-term mortality		
		Survivors ($n=103$)	Non-survivors ($n=172$)	P
Non-invasive management				
Diuretics	119 (43.3)	48 (46.6)	71 (41.3)	0.38
Catecholamine	231 (84.0)	80 (77.7)	151 (87.8)	0.03
Dobutamine	163 (59.3)	59 (57.3)	104 (60.5)	0.6
Norepinephrine	158 (57.5)	51 (49.5)	107 (62.2)	0.04
Epinephrine	123 (44.7)	32 (31.1)	91 (52.9)	< 0.001
Catecholamine support	1.6 ± 1	1.4 ± 1	1.8 ± 1	0.003
Invasive management				
Pulmonary artery catheterization	26 (9.5)	14 (13.6)	12 (7.0)	0.07
Coronary angiography	141 (51.3)	65 (63.1)	76 (44.2)	0.002
PCI	97 (35.3)	35 (34.0)	62 (36.1)	0.72
CABG	7 (2.6)	4 (3.9)	3 (1.7)	0.24
Valvular surgery	12 (4.4)	6 (5.8)	6 (3.5)	0.35
Circulatory support	117 (42.6)	40 (38.8)	77 (44.8)	0.33
ECMO	90 (32.7)	30 (29.1)	60 (34.9)	0.35
IABP	50 (18.2)	16 (15.5)	34 (19.8)	0.37
Impella® (2.5 or 5.0)	3 (1.1)	1 (1.0)	2 (1.2)	0.43
Ventilation support				
Non-invasive ($n=250$)	46 (18.4)	22 (23.7)	24 (15.3)	0.09
Mechanical	157 (57.1)	57 (55.3)	100 (58.1)	0.65
Renal replacement therapy				
CVVHDF	53 (19.3)	14 (13.6)	39 (22.7)	0.06
IHD	19 (6.9)	2 (1.9)	17 (9.9)	0.01

Data are expressed as number (%) or mean ± standard deviation. CABG: coronary artery bypass grafting; CVVHDF: continuous venovenous haemodiafiltration; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IHD: intermittent haemodialysis; PCI: percutaneous coronary intervention.

Discussion

Thanks to a large single-centre cohort of patients with CS, we have shown that, even if acute myocardial infarction was the main aetiology, non-ischaemic CS occurred in two-thirds of our population. Despite significant medical breakthroughs made over the past few years, the CS mortality rate remains high in our experience: 49.4% at 30 days; 60.4% at 1 year; and 62.5% long term (≥ 2 years) [5].

Age, catecholamine support and the implementation of renal replacement therapy were identified as independent predictive factors for long-term mortality, and are likely markers of the initial severity of the shock. Conversely, previous use of beta-blockers and coronary angiography exploration at admission were found to be independent factors associated with lower long-term mortality.

Age is known to be associated with short-term mortality in ischaemic CS [9]. In our study, age appeared to be a significant and robust risk factor for 1-year (Table A.1) and long-term mortality in CS patients with multiple aetiologies. In daily practice, advanced age often constitutes an exclusion criterion for advanced therapies, such as prolonged intensive care, cardiac transplantation or the use of MCS. However, age should be considered cautiously, as some studies have demonstrated that early revascularization in ischaemic CS lowers the mortality rate in elderly patients. This explains why guidelines recommend emergency percutaneous coronary intervention for all patients presenting CS complicating ACS (class I, level of evidence B), regardless of their age [2]. But, to date, no specific consideration has been given to non-ischaemic CS management.

In this study, we report for the first time a protective association between beta-blockers at admission and long-term prognosis in patients with CS. The multivariable analysis showed a protective association between beta-blockers at admission and long-term mortality, and a trend towards an association with 1-year mortality ($P=0.08$; Table A.1). Moreover, we also showed a link between beta-blockers at discharge and long-term prognosis, although no link existed between beta-blockers at admission and at discharge. This link between beta-blockers and prognosis has been shown during acute heart failure, and explains why guidelines recommend continuing chronic beta-blocker use to improve survival in the absence of CS [10–13]. The possible protective effect of beta-blockers may be explained by several factors: first, they bring additional long-term clinical benefits; then, they may ''precondition'' for the reduction of myocardial contractility or cardiac output observed during CS.

Initial blood glucose concentration and diabetes mellitus were associated with long-term mortality in our study, in line with some previous studies in ischaemic CS [14]. So far, their association with CS of different aetiologies has not been demonstrated. In CS, low cardiac output and

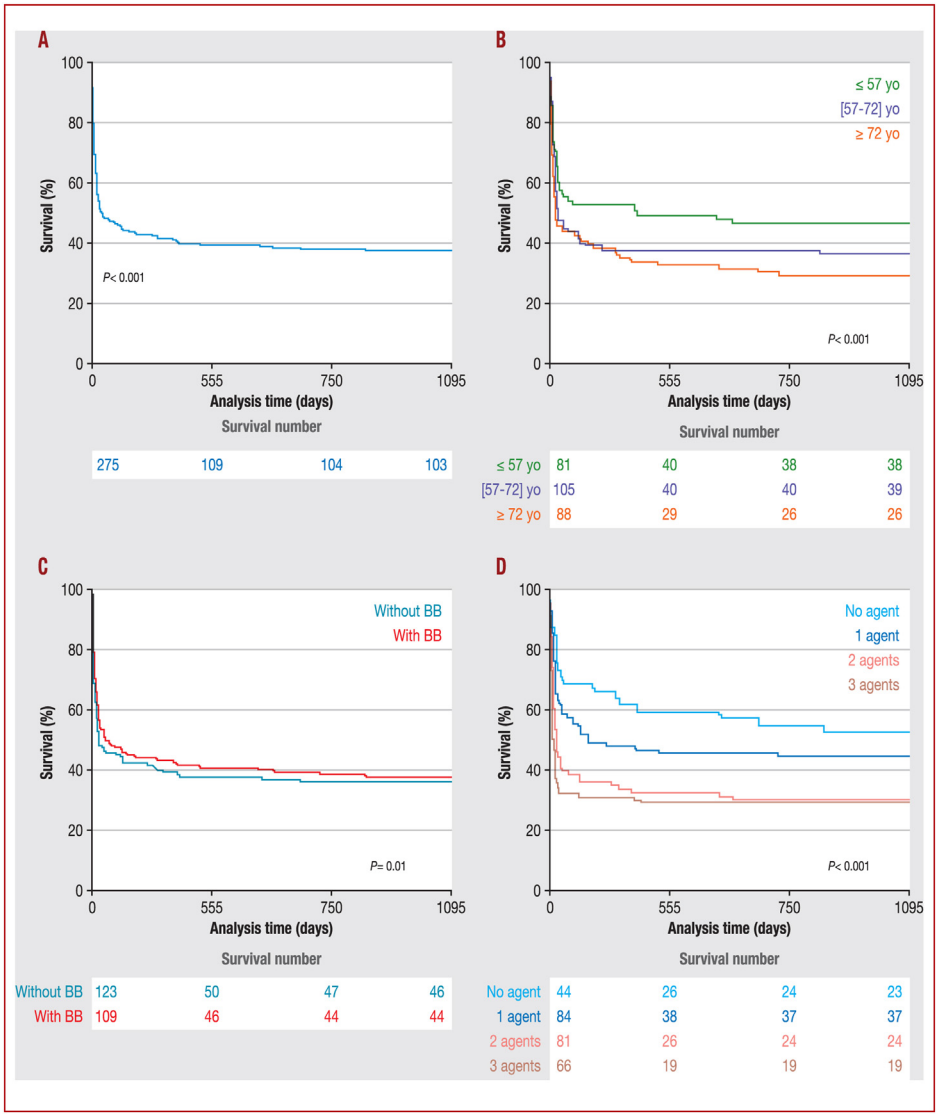

Figure 2. Kaplan-Meier long-term survival curves. A. Overall. B. Depending on patient age. C. Depending on previous use of beta-blockers (BB). D. Depending on catecholamine support. yo: years old.

hypotension both cause hyperglycaemia as a result of stress response, with a subsequent rise in catecholamine and cortisol concentrations, coupled with hyperlactataemia caused by insufficient tissue perfusion [15]. An elevated blood lactate concentration has been also linked to long-term mortality, signalling depth of shock and tissue hypoperfusion, as described previously [16].

In our ''real-life'' non-selected cohort of patients with CS, non-ischaemic CS was frequent, especially after cardiac arrest and decompensated heart failure, which justifies a larger registry in order to confirm these findings [17]. Interestingly, supraventricular tachycardia tended to be associated with better long-term survival, probably because of the easiness of reversibility (i.e. electric or therapeutic cardioversion, radiofrequency ablation). Our multivariable analysis did not show a link between percutaneous coronary intervention and long-term survival rate, probably because of the low prevalence (one-third) of patients with ACS in our population. Nonetheless, coronary angiography exploration was associated with lower 1-year (Table A.1) and long-term mortality, supporting the European Society of Cardiology guidelines and previous report [18].

Contrary to previous reports in patients with ischaemic CS [19], left ventricular ejection fraction was not predictive of long-term mortality. In our cohort, nearly 25% of patients had an ejection fraction > 40%, and only one-third had CS with an acute ischaemic aetiology. This is probably because CS pathogenesis also involves systemic inflammation with inappropriate vasodilatation and diastolic myocardial dysfunction that were not defined by left ventricular ejection fraction evaluation, especially in CS of different aetiologies [20].

Not surprisingly, acute and chronic renal replacement therapy are major predictive factors for 1-year (Table A.1) and long-term mortality in CS. Patients on chronic dialysis have a higher ICCU admission incidence every year than the general population, and have a high risk of short- and long-term mortality in this context [21,22]. Moreover,

Table 3 Predictors of long-term mortality by Cox model.

Variable	Univariate analysis		Multivariable analysis ($n = 206$)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Baseline characteristics				
Age (for an additional year more)	1.01 (1.00—1.02)	0.02	1.02 (1.01—1.04)	< 0.001
Male	0.80 (0.58—1.11)	0.19	—	NS
Diabetes mellitus	1.46 (1.06—2.03)	0.02	—	NS
Hypertension	1.33 (0.98—1.83)	0.07	—	NS
Beta-blocker at admission	0.77 (0.55—1.08)	0.12	0.61 (0.41—0.89)	0.02
VKA at admission	1.36 (0.95—1.96)	0.09	—	NS
Supraventricular arrhythmia cause of CS	0.40 (0.21—0.76)	0.005	—	NS
Admission data				
Severe aortic stenosis	1.71 (1.04—2.83)	0.03	1.43 (0.74—2.79)	0.28
eGFR < 30 mL/min	1.17 (0.80—1.72)	0.41	—	NS
Blood glucose > 12 mmol/L	1.37 (1.01—1.86)	0.04	—	NS
Arterial lactate > 10 mmol/L	1.69 (1.21—2.34)	0.002	—	NS
PTT < 30%	1.18 (0.77—1.83)	0.43	—	NS
CRP > 100 mg/L	1.27 (0.93—1.72)	0.12	—	NS
Management				
Catecholamine support (for an additional agent more)	1.36 (1.17—1.58)	< 0.001	1.45 (1.20—1.75)	< 0.001
Coronary angiography	0.71 (0.52—0.96)	0.03	0.57 (0.38—0.86)	0.02
Non-invasive ventilation	0.70 (0.45—1.09)	0.12	—	NS
Renal replacement therapy	1.82 (1.32—2.51)	< 0.001	1.66 (1.09—2.55)	0.02

CI: confidence interval; CS: cardiogenic shock; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate with Cockcroft and Gault formula; HR: hazard ratio; NS: not significant; PTT: prothrombin time; VKA: vitamin K antagonist.

Lauridsen et al. demonstrated that in cases of acute myocardial infarction-related CS, implementation of acute renal replacement therapy is significantly associated with chronic dialysis and long-term mortality [23]. Mechanisms underlying these findings, known as heart-kidney type 1 syndrome, may be induced by a low cardiac output, neurohormonal activation and the release of vasoactive substances, resulting in low renal perfusion with possible renal ischaemia and necrosis.

Finally, catecholamine support implementation was associated with early and long-term mortality, with a threshold effect, as mortality was not modified between the use of two or three drugs, signifying the severity of the shock and the need to consider MCS. For many years, catecholamines have been employed to stabilize patients with CS, and current guidelines recommend dobutamine as first-line treatment for low cardiac output, in combination with norepinephrine in case of low blood pressure to correct organ malperfusion (class IIb, level of evidence C). The combination of these drugs appears to be safe [24], and is preferred to epinephrine use, which is associated with higher mortality in CS [25]. But catecholamines do not allow for continued stabilization of patients with severe CS, because of increasing myocardial oxygen consumption, heart rate, arrhythmogenicity and inflammation in the already diseased heart [26], leading to impaired microcirculation and multiorgan failure. For these reasons, some use levosimendan because of its specific mode of action (not passing by the adrenergic receptors) and its prolonged duration of action, even if the level of evidence is low to date in CS. This explains why expert consensus frequently focuses on earlier initiation of MCS to improve the prognosis of patients with severe CS [27]. We did not find that MCS (concerning one-third of patients in our study) improved survival rate. One possible explanation is that patients with less severe forms of CS are more frequently managed in smaller cardiac or general ICCUs, and that tertiary centres treat the most severe forms. Another explanation is that MCS was started too late or with inappropriate support (intra-aortic balloon pump in 42.7% of supported patients [16]). However, in case of refractory CS, short-term MCS is recommended, with a moderately high level of evidence (class IIa, level of evidence C) [2,28], except for intra-aortic balloon pump, which is actually not recommended (class II, level of evidence B). In a recent study, patients who received MCS devices earlier were more likely to survive than those who received them later, with increased doses and inotropes illustrating the importance of shorter ''shock to support'' time [28,29].

Study limitations

Our study has all the limitations associated with retrospective and single-site studies. Selection and confounding biases may be present as a result of the observational and retrospective design, including patients lost to follow-up and lack of data (biological data, for example). However, in contrast to most of the previous studies, which often included only ACS as a cause of CS, we included patients with

CS arising from a broad aetiological spectrum, providing a greater overview of ''real-life practice''.

Moreover, the choice of several CS aetiologies for each patient constitutes a confounding factor and limits its subgroup analysis, although it corresponds to clinical practice.

Our model discrimination performance was acceptable, with an area under the curve of 0.79, but given that our model was derived from and only tested in the same dataset, results should be interpreted carefully.

Conclusions

In ICCUs, patients with CS are not uncommon, and mortality among these patients remains high. Although ACS is the most common aetiology, decompensated heart failure and arrhythmias are also frequent. Age, catecholamine use and renal replacement therapy are significantly associated with long-term mortality, while previous use of beta-blockers and coronary angiography are associated with better survival. All these findings may help to inform clinical decision-making and clarify resource requirements for this population.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgements

The authors would like to thank O. Bouisset for her help in the revision of the manuscript.

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.2019.04.004.

References

[1] Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation 2008;117:686—97.

[2] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891—975.

[3] Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341:625—34.

[4] De Luca L, Olivari Z, Farina A, et al. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. Eur J Heart Fail 2015;17:1124—32.

[5] Puymirat E, Fagon JY, Aegerter P, et al. Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997—2012. Eur J Heart Fail 2017;19:192—200.

[6] Harjola VP, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015;17:501—9.

[7] Katz JN, Stebbins AL, Alexander JH, et al. Predictors of 30-day mortality in patients with refractory cardiogenic shock following acute myocardial infarction despite a patent infarct artery. Am Heart J 2009;158:680—7.

[8] Sleeper LA, Reynolds HR, White HD, Webb JG, Dzavik V, Hochman JS. A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK Trial and Registry. Am Heart J 2010;160:443—50.

[9] Aissaoui N, Puymirat E, Juilliere Y, et al. Fifteen-year trends in the management of cardiogenic shock and associated 1-year mortality in elderly patients with acute myocardial infarction: the FAST-MI programme. Eur J Heart Fail 2016;18:1144—52.

[10] Farmakis D, Parissis J, Karavidas A, et al. In-hospital management of acute heart failure: practical recommendations and future perspectives. Int J Cardiol 2015;201:231—6.

[11] Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol 2008;52:190—9.

[12] Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. Eur Heart J 2009;30:2186—92.

[13] Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015;17:544—58.

[14] Pres D, Gasior M, Strojek K, et al. Blood glucose level on admission determines in-hospital and long-term mortality in patients with ST-segment elevation myocardial infarction complicated by cardiogenic shock treated with percutaneous coronary intervention. Kardiol Pol 2010;68:743—51.

[15] Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol 2014;2:339—47.

[16] Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382:1638—45.

[17] Delmas C, Leurent G, Lamblin N, Bonnefoy E, Roubille F. Cardiogenic shock management: still a challenge and a need for large-registry data. Arch Cardiovasc Dis 2017;110:433—8.

[18] Bangalore S, Gupta N, Guo Y, et al. Outcomes with invasive vs conservative management of cardiogenic shock complicating acute myocardial infarction. Am J Med 2015;128:601—8.

[19] Aissaoui N, Riant E, Lefevre G, et al. Long-term clinical outcomes in patients with cardiogenic shock according to left ventricular function: The French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) programme. Arch Cardiovasc Dis 2018;111:678—85.

[20] van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017;136:e232—68.

[21] Hutchison CA, Crowe AV, Stevens PE, Harrison DA, Lipkin GW. Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC Case Mix Programme Database. Crit Care 2007;11:R50.
[22] Manhes G, Heng AE, Aublet-Cuvelier B, Gazuy N, Deteix P, Souweine B. Clinical features and outcome of chronic dialysis patients admitted to an intensive care unit. Nephrol Dial Transplant 2005;20:1127—33.
[23] Lauridsen MD, Gammelager H, Schmidt M, et al. Acute kidney injury treated with renal replacement therapy and 5-year mortality after myocardial infarction-related cardiogenic shock: a nationwide population-based cohort study. Crit Care 2015;19:452.
[24] Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med 2011;39:450—5.
[25] Tarvasmaki T, Lassus J, Varpula M, et al. Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality. Crit Care 2016;20:208.
[26] Liaudet L, Calderari B, Pacher P. Pathophysiological mechanisms of catecholamine and cocaine-mediated cardiotoxicity. Heart Fail Rev 2014;19:815—24.
[27] Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care (Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie D'intervention). Catheter Cardiovasc Interv 2015;85:E175—96.
[28] Bonello L, Delmas C, Schurtz G, et al. Mechanical circulatory support in patients with cardiogenic shock in intensive care units: a position paper of the ''Unite de Soins Intensifs de Cardiologie'' group of the French Society of Cardiology, endorsed by the ''Groupe Atherome et Cardiologie Interventionnelle'' of the French Society of Cardiology. Arch Cardiovasc Dis 2018;111:601—12.
[29] Basir MB, Schreiber TL, Grines CL, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. Am J Cardiol 2017;119:845—51.