Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure

Thomas d'Humières, Damien Fard, Thibaud Damy, François Roubille, Arnaud Galat, Huy-Long Doan, Leopold Oliver, Jean-Luc Dubois-Randé, Pierre Squara, Pascal Lim, et al.

Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure

Pronostic de l'insuffisance cardiaque aiguë des amyloses cardiaques admis aux soins intensifs

Thomas d'Humières[a,b,c], Damien Fard[a,b,c], Thibaud Damy[a,b,c], Francois Roubille[d], Arnaud Galat[a,b,c], Huy-Long Doan[a,b,c], Leopold Oliver[a,b,c], Jean-Luc Dubois-Randé[a,b,c], Pierre Squara[e], Pascal Lim[a,b,c,*], Julien Ternacle[a,b,c]

[a] *UPEC, Henri-Mondor University Hospital, AP—HP, 94000 Créteil, France*
[b] *Inserm U955, 94000 Créteil, France*
[c] *DHU ATVB, 94000 Créteil, France*
[d] *Cardiology Department, University Hospital of Montpellier, 34090 Montpellier, France*
[e] *Clinique Ambroise-Paré, CERIC, 92200 Neuilly-sur-Seine, France*

KEYWORDS
Amyloidosis;
Acute heart failure;
Cardiogenic shock;
Intensive care unit;
Outcomes

Summary
Background. — The outcome of cardiac amyloidosis (CA) has been reported mainly in stable populations; limited data are available in patients referred for acute heart failure (AHF) to an intensive cardiac care unit (ICCU).

Abbreviations: AHF, Acute heart failure; AL, Light-chain; BP, Blood pressure; CA, Cardiac amyloidosis; ICCU, Intensive cardiac care unit; LV, Left ventricular; LVEF, Left ventricular ejection fraction; M-TTR, Hereditary transthyretin; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; RV, Right ventricular; SOFA, Sequential organ failure assessment; TAPSE, Tricuspid annular plane systolic excursion; WT-TTR, Wild-type transthyretin.

* Corresponding author. Department of Cardiovascular Medicine, Henri—Mondor University Hospital, 51, avenue de Lattre-de-Tassigny, 94100 Créteil, France.
E-mail address: lim.pascal.hmn@gmail.com (P. Lim).

Aims. — To address the characteristics and outcomes of patients with confirmed CA admitted to an ICCU for AHF and then to identify the predictors of evolution to cardiogenic shock.
Methods. — All patients with CA referred to an ICCU for AHF between 2009 and 2015 were included. The clinical endpoint was 3-month death. Data from the population with cardiogenic shock, obtained in a stable haemodynamic state, were matched with data from a control group to determine predictors of evolution to cardiogenic shock.
Results. — Among the 421 patients followed for CA in our expert centre, 46 patients (mean age: 64 ± 14 years; 65% light-chain [AL] CA) were referred to the ICCU for AHF ($n = 26$ with cardiogenic shock). At 3 months, death occurred in 24 (52%) patients, mostly in the cardiogenic shock group ($n = 21/26$, 81%). Most deaths occurred 5 days [interquartile range 3—9 days] after catecholamine infusion and 50% occurred in patients aged < 65 years. The majority of deaths were reported in patients with AL CA ($n = 19/24$, 79%). Independent variables associated with in-hospital mortality were cardiogenic shock and uraemia level. N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration obtained in a stable haemodynamic state was the only predictor of short-term evolution to cardiogenic shock (odds ratio: 8.7, 95% confidence interval: 2.2—34.6), with an optimal cut-off of 4040 pg/mL (sensitivity = 92%; specificity = 81%).
Conclusions. — The study confirms the dramatic mortality associated with CA when presenting as cardiogenic shock and underlines the limited efficiency of conventional treatments. Given the rapid occurrence of death in a young population, an alternative strategy to dobutamine support should be investigated in patients with elevated NT-proBNP concentration.

MOTS CLÉS
Amylose cardiaque ;
Pronostic ;
Insuffisance cardiaque ;
Choc cardiogénique

Résumé
Contexte. — Le pronostic des patients porteurs d'une amylose cardiaque a de nombreuses fois été décrit chez des populations stables, mais peu de données existent concernant les patients admis en soins intensifs cardiologiques (USIC) pour décompensation cardiaque aiguë (DCA).
Objectifs. — Décrire les caractéristiques ainsi que le pronostic des patients porteurs d'une amylose cardiaque admis en USIC pour DCA et identifier les facteurs prédictifs d'évolution vers le choc cardiogénique dans cette population.
Méthodes. — Tous les patients porteurs d'une amylose cardiaque ayant été admis en USIC pour DCA entre 2009 et 2015 ont été inclus. Le critère d'évaluation principal était la mortalité à 3 mois. Concernant la sous-population des patients en choc cardiogénique, leurs données en état stable (quelques mois avant l'hospitalisation) ont été recueillies, puis comparées à un groupe témoin afin de déterminer les facteurs prédictifs d'évolution vers un état de choc cardiogénique.
Résultats. — Parmi les 421 patients suivis pour amylose cardiaque dans notre centre expert, 46 patients (64 ± 14 ans, 65 % de type AL) ont été admis en USIC pour DCA ($n = 26$ chocs cardiogéniques). La mortalité à 3 mois était de 52 %, principalement dans le groupe en choc cardiogénique ($n = 21/26$, 81 %). Le délai moyen entre le décès et l'introduction des catécholamines était de 5 jours [IQR : 3—9] et la moitié des patients en choc étaient âgés de moins de 65 ans. La majorité des décès concernait les patients porteurs d'une amylose AL ($n = 19/24$, 79 %). Les variables indépendamment associées à la mortalité intrahospitalière étaient l'état de choc cardiogénique et l'urémie à l'entrée. De façon intéressante, la valeur du NT-proBNP (*OR* : 8,7, IC 95 % : 2,2—34,6) en situation clinique stable était le seul facteur prédictif d'évolution à court terme vers un état de choc, avec un seuil optimal de 4040 pg/mL (Se = 92 % ; Sp = 81 %).
Conclusions. — Cette étude confirme le caractère catastrophique du pronostic des patients porteurs d'une amylose cardiaque en situation clinique instable et souligne l'efficacité limitée des traitements conventionnels. L'évolution très rapidement défavorable chez des patients jeunes souligne la nécessité de développer des stratégies alternatives, notamment en cas de NT-proBNP élevé.

Background

Amyloidosis is a severe systemic disease that can affect various organs. The three main types of amyloidosis associated with cardiac involvement are wild-type transthyretin (WT-TTR), hereditary transthyretin (M-TTR) and light-chain (AL) [1]. Cardiac amyloidosis (CA) results in extracellular amyloid protein deposition in the entire heart, according to a base-apex gradient [2]. Cardiac events include acute heart failure (AHF), arrhythmia and death, with a median survival of 6 months in symptomatic patients [3,4]. The main prognostic markers in CA include New York Heart Association functional class, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) serum concentration (cut-off: 3000—4000 pg/mL) [5] and reduced longitudinal strain derived from speckle-tracking imaging [2]. Most of these criteria were reported in stable patients with CA [6]. Limited data are available for patients referred to intensive cardiac care units (ICCUs) [7]. The aims of this study were first to address the characteristics and outcomes of patients with confirmed CA admitted to an ICCU for acute heart failure and then to identify predictors of evolution to cardiogenic shock.

Methods

Study population

Of the 421 patients with CA followed by the Henri-Mondor University Hospital Multidisciplinary Amyloidosis Network (132 AL, 173 M-TTR and 94 WT-TTR), 59 were admitted to the ICCU between January 2009 and December 2015. Overall, 20 were hospitalized for AHF, 26 for cardiogenic shock and 13 for various other reasons (syncope [$n = 4$], acute coronary syndrome [$n = 2$], cardiac tamponade [$n = 3$], hypovolaemia or haemorrhage [$n = 3$] and cardiac arrest [$n = 1$]). All clinical baseline characteristics and outcomes were collected prospectively and recorded electronically according to the French Comité national informatique et liberté rules (authorization number #1431858). All patients provided written informed consent to participation in the Amyloidosis Network registry and the study was approved by our local ethics committee.

Diagnosis of CA

The diagnosis of CA was made from the combination of a typical imaging pattern and one of the following criteria: positive red Congo staining with specific antibody labelling on endomyocardial or extracardiac biopsy; evidence of *TTR* gene mutation; presence of monoclonal gammopathy on blood sample electrophoresis; or strong cardiac uptake on technetium 99 biphosphonate scintigraphy [8].

Echocardiography data

Standard transthoracic echocardiography data (Vivid 7; GE Healthcare, Horton, Norway) were acquired systematically at ICCU admission. Left ventricular (LV) ejection fraction (LVEF) was calculated using Simpson's biplane method. E-wave velocity and E-wave deceleration time were used to assess diastolic function. Right ventricular (RV) function was assessed using tricuspid annular plane systolic excursion (TAPSE). Cardiac output was derived from the conventional pulsed Doppler method positioned at the LV outflow tract. Systolic pulmonary arterial pressure was calculated from tricuspid regurgitation flow using the Doppler method. LV and RV systolic dysfunction were defined as LVEF < 50% and TAPSE < 16 mm, respectively.

Heart failure and cardiogenic shock management

Patients admitted for AHF received standard care according to our local protocol, based on the current European Society of Cardiology heart failure guidelines [9]. Intravenous loop diuretics and vasodilator drugs were delivered before inotropic support when the mean blood pressure (BP) was > 65 mmHg. The initial dose was defined as 50% higher than the daily oral dose. The diuretic dose was reduced by half when the inferior vena cava became compliant on echocardiography (sniff test diameter changes > 50%). Cardiogenic shock was defined as mean BP < 65 mmHg or systolic BP < 90 mmHg and clinical signs of low organ perfusion or with persistent oligoanuria. For all patients in cardiogenic shock, a radial arterial catheter was placed for BP monitoring and a right jugular catheter for central venous pressure and oxygen saturation measurements. Dobutamine infusion was started at the rate of 5 μg/kg/min and increased progressively (+2.5 μg/kg/min to a maximum of 20 μg/kg/min) to maintain mean BP > 65 mmHg and central venous oxygen saturation > 60%. If mean BP remained < 65 mmHg, norepinephrine was added at an initial rate of 0.5 mg/h. In patients previously treated with beta-blockers, with no response to dobutamine, levosimendan was used as an alternative to dobutamine at the rate of 0.2 μg/kg/min over 24 hours (without loading dose). Intravenous loop diuretics were systematically combined with catecholamine support. The furosemide rate was divided by half if the urine output was > 4 L and was stopped if the central venous pressure was < 15 mmHg. Dobutamine infusion was withdrawn progressively (0.1 g/kg/min/h) when euvolaemia was reached (central venous pressure < 15 mmHg and central venous oxygen saturation > 60%). All patients aged < 65 years were referred to the heart team for potential circulatory support or heart transplantation. When severe co-morbidities existed, a palliative care strategy was considered systematically with the patient and relatives before initiating inotropic support.

Clinical endpoints

The primary endpoint was 3-month mortality.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median ± interquartile range if not normally distributed and nominal variables are expressed as percentages. Continuous variables between groups were compared using variance analysis and nominal variables using the χ^2 test. Time series analysis was used to assess changes in clinical and biological variables under catecholamine. Variables with

P values < 0.1, the in univariate analysis were then entered into the multivariable logistic regression, using a stepwise approach with a forward method for variable selection. To determine predictors of cardiogenic shock, we compared the clinical characteristics of the cardiogenic shock group in a clinical stable state (3—12 months before hospitalization, $n = 12$) with an individually matched control group of patients with CA without 1-year cardiac events ($n = 36$). Matching variables included age, sex, amyloidosis type and history of previous chemotherapy. The control group was selected randomly and the case—control ratio was determined to detect predictors of cardiogenic shock with a minimal odds ratio of 7. The sensitivity and specificity of continuous variables associated with outcome were obtained from receiver operating characteristic curves. Two-tailed P values < 0.05 were considered statistically significant. Statistical analyses were performed using StatView, version 5.0 (SAS Institute, Inc., Cary, NC, USA) and SPSS for Windows (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Of the 46 patients (59% men; mean age 64 ± 14 years) admitted for AHF (26 with cardiogenic shock), 65% had AL CA and 35% had TTR CA. CA was confirmed from endomyocardial biopsy for 13 patients and from extracardiac biopsy associated with a typical imaging pattern for 21 patients (Table 1). Only one patient with TTR CA benefited from a liver transplant and none had a kidney or stem cell transplant. In the AL CA group ($n = 30$), 60% had been treated by chemotherapy (cyclophosphamide, $n = 13$; lenalidomide, $n = 3$; melphalan, $n = 2$). Heart failure hospitalization was more frequent for patients with AL CA ($P < 0.001$). At admission, 52% of patients had atrial fibrillation, mean LVEF was 37 ± 14% and 63% ($n = 27$) of patients had RV systolic dysfunction (TAPSE < 16 mm). All patients had an elevated NT-proBNP concentration (> 332 pg/mL) and a positive troponin concentration. Baseline characteristics according to amyloidosis type are detailed in Table 2. Patients admitted for cardiogenic shock ($n = 26$) had a lower LVEF (42 ± 14% vs 37 ± 14%; $P = 0.04$) and more frequent RV dysfunction (37% vs 83%; $P = 0.004$).

Global outcome

Death occurred in 24 patients (52%): 20 (83%) during the hospitalization period and four at 3 months after discharge. Of the 24 patients who died, 50% were aged < 65 years (Table 3).

Outcome of patients admitted for AHF (without cardiogenic shock)

Three of 20 (15%) patients died during hospitalization and none after discharge. The causes of death were refractory cardiac arrest ($n = 1$), septic shock ($n = 1$) and refractory acute pulmonary oedema ($n = 1$).

Outcome of population with cardiogenic shock

A palliative care decision was made for five patients because of severe co-morbidities. The remaining 21 patients were treated with dobutamine, with noradrenaline added in 10 patients. The initial catecholamine dose was increased progressively over the first 48 hours (Fig. 1); this resulted in an increase in the sequential organ failure assessment (SOFA) score and a decrease in lactate concentration (Fig. 1). However, no change was observed for heart rate, mean BP and

Table 1 Methods of diagnosis of light-chain and transthyretin amyloidosis.

	AL CA	M-TTR CA	WT-TTR CA
	($n = 30$)	($n = 8$)	($n = 8$)
Method of diagnosis			
Endomyocardial biopsy	9 (30)	1 (13)	3 (38)
Extracardiac biopsy and typical imaging pattern	17 (57)	2 (18)	2 (18)
Accessory salivary gland	10	2	1
Adenopathy	1		
Abdominal fat	1		
Muscular	1		
Synovial			1
Renal	2		
Osteomedullary	2		
Monoclonal gammopathy and typical imaging pattern	4 (13)		
Genetic *TTR* mutation		8	
Val122Ile		6	
Al19Asp		1	
Ser50Arg		1	
Positive ^{99m}Tc-HMDP scintigraphy and typical imaging pattern			3 (45)

Data are expressed as number or number (%). AL: light-chain; CA: cardiac amyloidosis; HMDP: hydroxymethylene diphosphonate; M-TTR: hereditary transthyretin; Tc: technetium; WT-TTR: wild-type transthyretin.

Table 2 Characteristics of patients with cardiac amyloidosis admitted to an intensive cardiac care unit, according to amyloidosis type.

	AL CA	M-TTR CA	WT-TTR CA	*P*
	(*n* = 30)	(*n* = 8)	(*n* = 8)	
Medical history				
Age (years)	64 ± 14	70 ± 8	80 ± 4	< 0.01
Age < 65 years	15 (50)	2 (25)	0 (0)	0.02
Baseline creatinine clearance (mL/min)	57 ± 22	51 ± 28	72 ± 19	0.2
History of organ transplantation	0	1 (13)	0	—
History of heart failure	28 (93)	7 (88)	7 (88)	0.8
Time interval from CA diagnosis (days)	224 ± 557	350 ± 535	438 ± 856	0.55
LVEF (%)	41 ± 13	26 ± 9	34 ± 14	0.01
Ischaemic cardiomyopathy	5 (17)	1 (13)	1 (13)	0.9
Atrial fibrillation	4 (14)	3 (37)	2 (25)	0.3
Pacemaker or ICD	6 (20)	5 (63)	6 (75)	0.003
Chemotherapy	18 (60)	—	—	
Clinical data				
Systolic BP (mmHg)	108 ± 30	109 ± 27	122 ± 33	0.5
Diastolic BP (mmHg)	78 ± 17	85 ± 20	91 ± 20	0.2
Heart rate (beats/min)	91 ± 19	74 ± 15	86 ± 39	0.16
Biological data				
Admission plasma creatinine (μmol/L)	176 ± 95	165 ± 98	121 ± 36	0.3
Uraemia level (mmol/L)	17 ± 10	12 ± 7	14 ± 13	0.5
US troponin-T (pg/mL)	200 [77]	118 [88]	195 [206]	0.7
NT-proBNP (ng/mL)	28,8851 [22,054]	19,231 [29,083]	8592 [7985]	0.09
Lactataemia level (mmol/L) (*n* = 40)	2.3 ± 1.7	2.0 ± 0.9	2.5 ± 1.2	0.8

Data are expressed as mean ± standard deviation, number (%) or median [interquartile range]. AL: light-chain; BP: blood pressure; CA: cardiac amyloidosis; ICD: intracardiac defibrillator; LVEF: left ventricular ejection fraction; M-TTR: hereditary transthyretin; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; US: ultrasensitivity; WT-TTR: wild-type transthyretin.

bilirubin and creatinine concentrations (Fig. 1). Echocardiography data showed no significant improvement in stroke volume and congestion echocardiography markers. Finally, two patients required levosimendan to facilitate dobutamine withdrawal, two were referred for cardiac assistance (one received biventricular assistance and one received an LV device) and one was referred for cardiac transplant.

The majority of patients (21/26, 81%) died and most deaths occurred during the hospitalization period (17/21, 81%). All patients under palliative care died (four in hospital and one after discharge). In the catecholamine group, 16/21 (76%) patients died (13 in hospital and three after discharge). In patients treated with catecholamines, the median time interval between death and catecholamine initiation was 5 days [interquartile range: 3—9]. The cause of death was mainly refractory cardiogenic shock with multiorgan failure (*n* = 13). The two patients referred for cardiac assistance died from septic and haemorrhagic complications, while the only patient referred for cardiac transplantation survived.

Variables associated with patient outcome

Variables associated with death are reported in Table 3. Most patients who died had AL CA (19/24, 79%) and the mean time interval between amyloidosis diagnosis and heart failure hospitalization was < 3 months (74 ± 151 days). Cardiogenic shock was strongly associated with death. The mean admission SOFA score (5.5 ± 2.1 vs 2.7 ± 1.9; *P* < 0.001), frequency of RV dysfunction (77% vs 48%; *P* = 0.04), NT-pro-BNP concentration and uraemia level were greater in the death group than the survival group. Troponin serum concentration did not differ between the death and survival groups (237 [89] vs 118 [99]; *P* = 0.2). Multivariable analysis (including age, cardiogenic shock, RV dysfunction, NT-proBNP concentration and uraemia level) showed that cardiogenic shock (odds ratio: 10, 95% CI: 1.7—60) and uraemia (odds ratio: 1.2, 95% CI: 1.0—1.5) were independently associated with in-hospital and 3-month death (Table A.1).

Variables associated with a risk of cardiogenic shock occurrence

Patients who developed cardiogenic shock had a lower natraemia level, a higher uraemia level and a higher NT-proBNP concentration (Table 4). Moreover, the troponin serum concentration was slightly higher in the cardiogenic shock group (92 [111] vs 62 [37]; *P* = 0.09). LV mass (g/m^2) and functional myocardial characteristics (strain, stroke volume, LVEF and diastolic function) were not associated with the occurrence of cardiogenic shock. Multivariable analysis (including NT-proBNP concentration,

Table 3 Baseline and in-hospital characteristics of patients with cardiac amyloidosis, according to death or survival at 3 months.

	Survival ($n=22$)	Death ($n=24$)	*P*
Medical history			
Age (years)	72 ± 12	63 ± 13	0.02
AL CA	11 (50)	19 (79)	0.04
History of heart failure	18 (82)	24 (100)	0.04
Time delay from diagnosis to hospitalization (days)			
TTR CA ($n=16$)	464 ± 815	303 ± 262	0.7
AL CA ($n=30$)	484 ± 861	74 ± 151	0.05
Chemotherapy for AL CA ($n=30$)	8 (73)	10 (53)	0.3
Recent chemotherapy < 7 days for AL CA	4 (36)	8 (42)	0.2
Clinical data			
Systolic BP (mmHg)	121 ± 33	102 ± 24	0.03
Diastolic BP (mmHg)	73 ± 17	62 ± 8	0.006
Mean BP (mmHg)	89 ± 21	75 ± 12	0.01
Heart rate (beats/min)	90 ± 28	85 ± 18	0.5
Sinusal rhythm	10 (45)	12 (55)	0.5
Biological data			
Creatinine (μmol/L)	146 ± 89	182 ± 87	0.2
Uraemia level (mmol/L)	10 ± 5	20 ± 11	< 0.001
Natraemia level (mmol/L)	134 ± 7	130 ± 8	0.1
US troponin-T (pg/mL)	118 [99]	237 [89]	0.2
NT-proBNP (pg/mL)	11,408 [10,714]	34,882 [20,098]	0.02
Lactataemia level (mmol/L) ($n=40$)	2.0 ± 1.0	2.5 ± 1.7	0.3
Echocardiography data			
LVEF (%)	37 ± 15	38 ± 13	0.8
Cardiac output (L/min)	3.5 ± 1.5	3.4 ± 1.7	0.7
RV dysfunction ($n=43$)	10 (48)	17 (77)	0.04
LV mass index (g/m^2)	303 ± 112	260 ± 54	0.2
Tricuspid regurgitation grade > 2 ($n=42$)	4 (18)	5 (21)	0.9
Inferior vena cava diameter (mm)	21 ± 7	20 ± 6	0.6
Treatment and evolution			
Cumulative 48-hour furosemide dose (mg)	765 ± 701	1452 ± 627	0.001
Urine output at 24 hours (L)	3.0 ± 1.6	1.7 ± 1.0	0.02
Cardiogenic shock	6 (27)	20 (91)	< 0.001
Dobutamine maximum rate (μg/kg/min)	8.0 ± 4.5	7.7 ± 3.1	0.9
Norepinephrine	1 (5)	10 (42)	0.003
Mortality score			
Admission SOFA score	2.7 ± 1.9	5.5 ± 2.1	< 0.001

Data are expressed as mean ± standard deviation, number (%) or median [interquartile range]. AL: light-chain; BP: blood pressure; CA: cardiac amyloidosis; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; SOFA: sequential organ failure assessment; TTR: transthyretin; US: ultrasensitivity.

uraemia level, troponin concentration and cardiac output) showed that NT-proBNP concentration (odds ratio: 8.7, 95% CI: 2.2–34.6) was the only independent predictor of cardiogenic shock (Table A.2), with an optimal cut-off value of 4040 pg/mL (sensitivity = 92%; specificity = 81%; area under the curve = 0.9 [0.87–0.95]).

Discussion

The outcome of CA has mostly been reported in stable patients, and limited data have been published on patients admitted to an ICCU for AHF [7]. The present study shows that the mortality rate is very high in patients with CA admitted for cardiogenic shock (approximately 80%), despite an aggressive strategy, including catecholamine support and cardiac assistance. Importantly, death occurs quickly after catecholamine support (median time, 5 days) and mostly in young patients (aged < 65 years) with a recent diagnosis of AL CA. This underlines the limited efficiency of current cardiogenic shock treatment and highlights the need to develop alternative strategies in this population, especially when the NT-pro-BNP concentration is elevated.

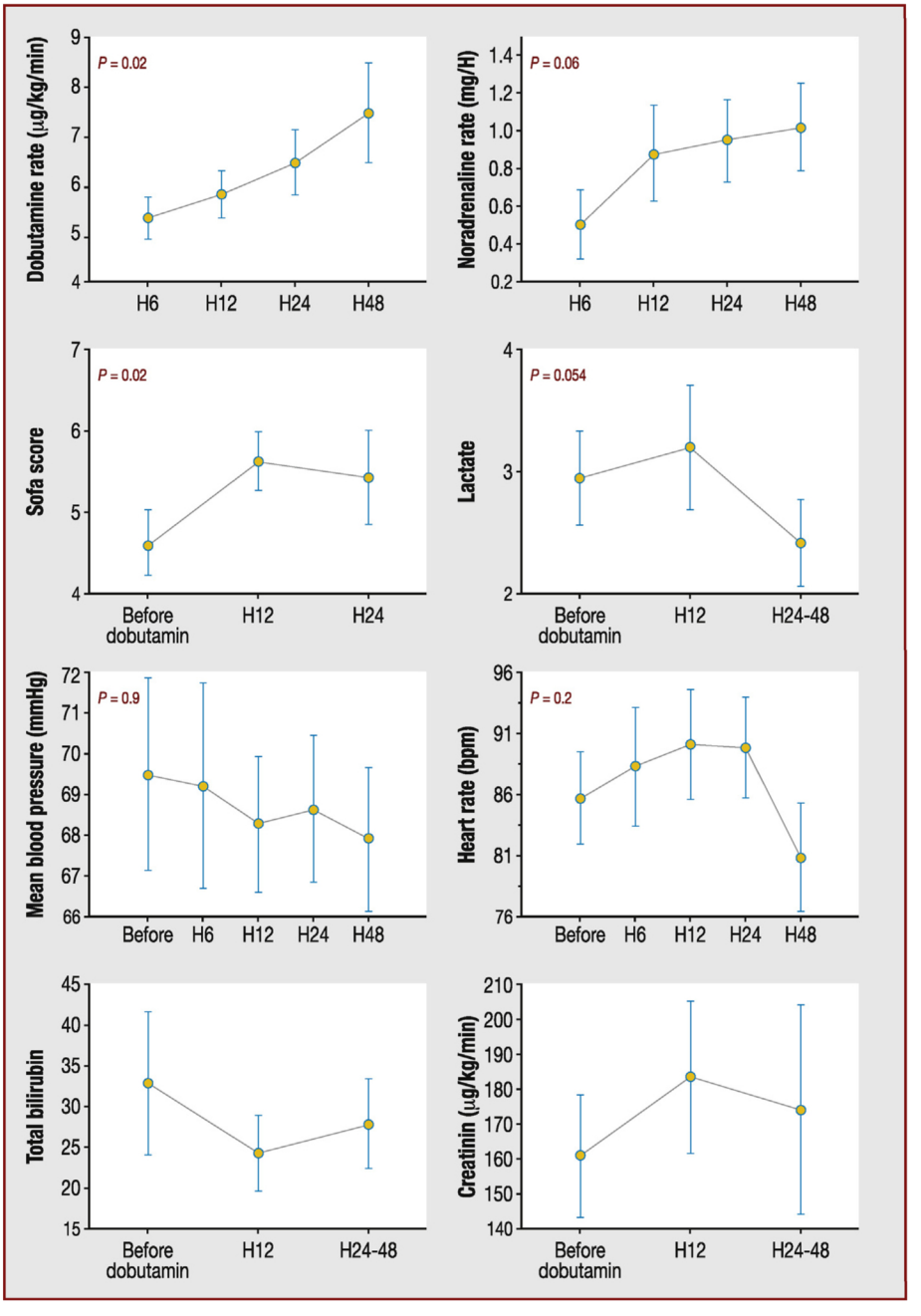

Figure 1. Evolution of clinical and biological variables during the first 48 hours of catecholamine treatment. SOFA: sequential organ failure assessment.

Management of heart failure and cardiogenic shock in CA

No specific guideline is available for the medical management of acute heart failure in CA. Diuretics are the first-line treatment and should be carefully titrated to reduce congestion and avoid hypovolaemia, particularly as these patients often present relaxation impairment. Catecholamine support is added in patients who are refractory to diuretics or in those with clinical signs of cardiogenic shock. In the present study, we observed a limited clinical benefit of catecholamine, despite lactate improvement. A non-significant increase in stroke volume, despite an incremental dose of catecholamine, indicates either end-stage heart failure or a limited efficiency of dobutamine. Indeed, tachycardia (Fig. 1) probably limits dobutamine efficiency because of severe relaxation impairment related to amyloid protein infiltration [10,11]. In our study, the two patients referred for extracorporeal membrane oxygenation died from bleeding or sepsis and the one patient referred for cardiac transplantation survived. Chemotherapy should first be attempted in AL CA, but the short time interval between amyloidosis diagnosis and cardiogenic shock limits this strategy. Given the high chance of haematological remission, heart transplantation may be considered in young patients admitted for cardiogenic shock [12,13].

Table 4 Previous characteristics of patients with cardiac amyloidosis who evolved to cardiogenic shock within a year, compared with control group.

	Evolution to cardiogenic shock ($n = 12$)	Control ($n = 36$)	*P*
Clinical data			
Age (years)	68.3 ± 15	68.1 ± 10	0.6
Male sex	8 (67)	25 (69)	0.9
BMI (kg/m^2)	25 ± 3.6	23 ± 3.4	0.1
NYHA class	2.7 ± 0.7	2.5 ± 0.8	0.5
Atrial fibrillation	5 (42)	13 (36)	0.4
CA type			
AL	6 (50)	18 (50)	> 0.9
WT-TTR	4 (33)	12 (33)	> 0.9
M-TTR	2 (17)	6 (17)	> 0.9
Medical history			
Diabetes	2 (17)	2 (6)	0.3
Hypertension	4 (33)	12 (33)	> 0.9
Ischaemic cardiopathy	3 (25)	6 (17)	0.5
Pacemaker	6 (50)	8 (22)	0.1
Previous chemotherapy for AL CA	4 (67)	13 (72)	> 0.9
Biological data			
Creatinine (μmol/L)	136 ± 88	107 ± 54	0.1
Uraemia level (mmol/L)	12.3 ± 6.7	9.1 ± 4.2	0.05
Natraemia level (mmol/L)	136.1 ± 5.6	139.4 ± 2.9	0.01
US troponin-T (pg/mL)	92 [111]	62 [37]	0.09
NT-proBNP (pg/mL)	11,083 [5234]	3825 [1917]	< 0.0001
Bilirubin (μmol/L)	13.7 ± 11.6	10.5 ± 5.7	0.2
Echocardiography data			
LVEF (%)	40 ± 15	47 ± 13	0.1
Global longitudinal strain (%)	−8 ± 3.8	−10 ± 4.2	0.1
Cardiac output (L/min)	3.0 ± 1.1	3.8 ± 1.5	0.07
Septum thickness (mm)	18 ± 4	17 ± 4	0.8
LV mass index (g/m^2)	193 ± 94	181 ± 62	0.6
E-wave velocity (m/s)	7.4 ± 2.2	9.2 ± 2.5	0.07
E-wave deceleration time (ms)	145 ± 56	162 ± 74	0.5
RV dysfunction	7 (58)	22 (61)	> 0.9
Tricuspid regurgitation grade > 2	2 (17)	6 (17)	> 0.9
Inferior vena cava (mm)	20.3 ± 5.9	21 ± 6.7	0.8

Data are expressed as mean ± standard deviation, number (%) or median [interquartile range]. AL: light-chain; BMI: body mass index; CA: cardiac amyloidosis; LV: left ventricular; LVEF: left ventricular ejection fraction; M-TTR: hereditary transthyretin; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association; RV: right ventricular; US: ultrasensitivity; WT-TTR: wild-type transthyretin.

Anticipation of cardiogenic shock in stable CA

Our data show that heart failure and death occurs more often in an AL CA population with recently diagnosed amyloidosis disease. NT-pro-BNP concentration has been used widely since 2004 to identify cardiac injury in systemic amyloidosis [14] and to assess the severity and prognosis of the three types of CA [5,15]. Similarly to a previous study [5], we consistently found that NT-pro-BNP concentration was a strong independent predictor of outcome (cut-off: 4040 pg/mL). An increase in the NT-pro-BNP concentration to > 4000 pg/mL appears to be a strong predictor of short-term evolution to cardiogenic shock and should be used to stratify newly diagnosed AL CA. This new approach could help with the early proposal of more invasive management and could urge consideration of alternatives, such as heart transplantation.

Clinical perspective

Cardiogenic shock in CA has dramatic outcomes, despite catecholamine support. The mortality observed in the present study is twice that reported elsewhere (35—40%) [16]. In young patients with CA and limited co-morbidities, an alternative strategy to conventional treatments should

be investigated before the stage of cardiogenic shock is reached.

Study limitations

The major limitation of this study is the small size of the population that is underpowered to detect predictors of cardiogenic shock with an odds ratio < 7. Our results and hypothesis need to be validated in a large multicentre cohort of patients.

Conclusions

Dramatic and rapid in-hospital mortality in patients with CA admitted for cardiogenic shock underlines the need to anticipate cardiac support in high-risk patients before heart failure decompensation. High-risk patients can be identified from their NT-pro-BNP concentration.

Sources of funding

None.

Acknowledgements

The authors wish to thank the Fédération française de cardiologie.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Mohty D, Damy T, Cosnay P, et al. Cardiac amyloidosis: updates in diagnosis and management. Arch Cardiovasc Dis 2013;106:528—40.

[2] Ternacle J, Bodez D, Guellich A, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. JACC Cardiovasc Imaging 2016;9:126—38.

[3] Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998;91:141—57.

[4] Gertz MA, Kyle RA, Greipp PR. Response rates and survival in primary systemic amyloidosis. Blood 1991;77:257—62.

[5] Damy T, Jaccard A, Guellich A, et al. Comparison and identification of early clinical, biological and echocardiographic prognostic markers in cardiac amyloidosis. Orphanet J Rare Dis 2015;10:1.

[6] Kristen AV, Perz JB, Schonland SO, et al. Non-invasive predictors of survival in cardiac amyloidosis. Eur J Heart Fail 2007;9:617—24.

[7] Guinault D, Canet E, Huart A, et al. Short- and long-term outcomes of AL amyloidosis patients admitted into intensive care units. Br J Haematol 2016;174:868—75, http://dx.doi.org/10.1111/bjh.14135.

[8] Galat A, Rosso J, Guellich A, et al. Usefulness of (99m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. Amyloid 2015;22:210—20.

[9] Ponikowski P, Voors AA, Anker SD, et al. 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 Heart J 2016;37:2129—200 [10.1093].

[10] Du J, Liu J, Feng HZ, et al. Impaired relaxation is the main manifestation in transgenic mice expressing a restrictive cardiomyopathy mutation, R193H, in cardiac TnI. Am J Physiol Heart Circ Physiol 2008;294:H2604—13.

[11] Davis J, Wen H, Edwards T, Metzger JM. Thin filament disinhibition by restrictive cardiomyopathy mutant R193H troponin I induces Ca2+-independent mechanical tone and acute myocyte remodeling. Circ Res 2007;100:1494—502.

[12] Dey BR, Chung SS, Spitzer TR, et al. Cardiac transplantation followed by dose-intensive melphalan and autologous stem-cell transplantation for light chain amyloidosis and heart failure. Transplantation 2010;90:905—11.

[13] Mahmood S, Palladini G, Sanchorawala V, Wechalekar A. Update on treatment of light chain amyloidosis. Haematologica 2014;99:209—21.

[14] Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation 2003;107:2440—5.

[15] Lehrke S, Steen H, Kristen AV, et al. Serum levels of NT-proBNP as surrogate for cardiac amyloid burden: new evidence from gadolinium-enhanced cardiac magnetic resonance imaging in patients with amyloidosis. Amyloid 2009;16:187—95.

[16] Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc 2014;3:e000590.