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Cardiogenic shock management: Still a challenge and a need for large-registry data

Prise en charge du choc cardiogénique : encore un défi nécessitant la réalisation de larges registres

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Cardiogenic shock (CS) is defined as organ hypoperfusion secondary to impaired cardiac output. CS criteria have been well codified since the SHOCK study [1], combining systolic blood pressure < 90 mmHg for > 30 minutes or the need for vasopressors to maintain systolic blood pressure > 90 mmHg; pulmonary congestion or increased left ventricular pressures; and organ malperfusion signs (impaired consciousness or confusion, cold extremities or marbling, oliguria and increased serum lactate). Beyond the clinical signs, assessment of cardiac output and left ventricular filling pressures with transthoracic echocardiography or right catheterization is needed [2,3].

Lack of clinical applicability of the CS definition

In clinical practice, CS presentations include a large span of different clinical conditions, from the state of ''pre-shock'' to severe shock refractory to treatment. Even if used widely

Abbreviations: ACS, acute coronary syndrome; CS, cardiogenic shock; IABP, intra-aortic balloon pump.

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in clinical practice, defining these different shock states is difficult. In clinical practice ''pre-shock'' is a term often used to define patients who do not fulfil shock criteria at admission, but who are at high-risk of developing shock or present with clinical signs of haemodynamic instability, such as tachycardia with normal blood pressure. Yet, this definition is subjective, and is difficult to apply on a daily basis. Similarly, the definition of refractory CS is unclear: it is classically defined as the absence of response to conventional medical treatment, and its management is controversial. Classifications, such as the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), are based on several clinical stages of CS. However, they are difficult to apply to an individual situation, as most patients go through the different stages with treatment.

CS is not uncommon and is not always caused by myocardial ischaemia

CS occurs in 5—15% of acute coronary syndromes (ACS) [4], involving approximately 40—50,000 patients/year in the USA and about 60—70,000 patients/year in Europe [5].

ACS and their complications are the cause of >60% of CS cases. However, the rate of non-ischaemic causes (acute myocarditis, acute intoxications, acute onset of cardiomyopathies or the late evolution of the underlying heart disease) has probably been underestimated [6,7].

Data from registries including patients with CS caused by ACS are important, and may help to change clinical practice by highlighting the importance of a network organization. There are few data on CS resulting from non-ACS causes; small series have been published on CS caused by dilated cardiomyopathies, post-cardiac arrest shock and terminal heart failure [8]. Extrapolating results obtained in patients with CS caused by an ACS to CS resulting from other causes is hazardous.

Hence, there is an obvious need for contemporary epidemiological data from large cohorts, long-term follow-up and evidence-based strategies reducing short- and long-term mortality rates.

Therapeutic uncertainties and poor prognosis

Aissaoui et al. reported a reduction in short- and long-term mortality rates as a result of CS caused by ST-segment elevation myocardial infarction (STEMI) in the FAST-MI registries [6]; this was probably the result of an increase in the rate of early revascularization and improvements in antithrombotic therapies [6,9].

Despite a strong and continuous interest in CS physiopathology and treatment, its management remains a matter of debate and is generally disappointing. To date, revascularization is the only treatment that has demonstrated its effectiveness in the management of CS caused by an ACS. Early revascularization also decreases the occurrence of CS during an ACS [1,10—12]; however, its benefit is not always immediate. The SHOCK trial failed to demonstrate a superior effect of revascularization on mortality rates compared with medical treatment at 30 days. However, a significant difference in favour of revascularization was found at 6-month and 5-year follow-up.

Treatments such as inotropes, vasopressors, diuretics, invasive mechanical ventilation and cardiocirculatory support have largely failed to improve survival or quality of life convincingly [5,13—15].

As for patients with chronic heart failure, who are better managed by specialized heart teams, patients with CS are at the crossroads of several specialties; they should be managed as soon as possible by a team that includes cardiologists, intensive care specialists and cardiac surgeons. The CS team will make the best use of specialized clinical and technical expertise, combining coronary angiography and coronary revascularization, electrophysiology, cardiocirculatory support, cardiac surgery and intensive cardiac care units. The aim is to optimize management by tailoring it to patient characteristics (age, co-morbidities, etc.). Knowledge is the key to improve organization and collaboration between different specialties with the patient at the centre [16,17].

Lack of homogeneous and robust recommendations

Many expert consensus statements have been published on CS management [2,17—20], but European [21] and American [22] societies have presented only low-level of evidence recommendations based on just a few randomized and small-sized studies. Clinicians therefore refer to expert proposals and consensuses based on CS registries of varying sizes, but almost exclusively of ischaemic origin.

An example illustrating the limitations of the expert consensus is the intra-aortic balloon pump (IABP). This device has been used since the 1960s, based on an appealing pathophysiological concept. The European guidelines in 2008 strongly recommended the use of the IABP (class I, level C), but this recommendation was revised downwards to class IIb, level C in 2012 [23], and finally to class III, level B in 2014, based on reanalysis of the available data [24]. This last statement was confirmed recently in 2016 [21], following the publication of the landmark IABP-SHOCK2 study [25,26].

Need for more clinical data

To date, the gap in knowledge is significant. There is an acute need to validate common therapeutics, and to assess new drugs and cardiocirculatory support. Ideally, this should be done through large prospective randomized studies, but they are exceedingly difficult to conduct in this setting. Most studies (Table 1) are small, and encounter difficulties with recruitment. Moreover, with such high mortality rates related to multiple factors [27], demonstrating a survival benefit is a huge challenge.

Challenges for clinical studies are high: heterogeneity of the studied populations and the mechanisms or stages of the CS; undersized populations; and uncertainties and difficulties in defining the severity of the enrolled patients [5].

Table 1 Ongoing or scheduled studies on cardiogenic shock; adapted and updated with permission from Akodad et al. [31].

Country	Intervention	Primary endpoint	Main objective	Number of patients	Results available	Registry number
Epidemiology, prognostic stratification						
France	Registry	Observatory	Current practice in a nationwide register	500	2017	NCT02703038
Spain	Observatory	Mortality	Prognostic value of circulating microRNAs in patients with STEMI complicated by CS	142	2017	NCT02691286
USA	Registry	Mortality at 1 year	Information on patients eligible for mechanical support or heart transplant	200.000	2019	NCT02790242
Korea	Registry	In-hospital mortality	Description of management, comparing IABP, ECMO, medical strategies	1000	2019	NCT02985008
Mechanical treatments						
Czech Republic	ECLS	30-day composite of death from any cause, resuscitated circulatory arrest and implantation of another MCSD	Immediate venoarterial ECMO versus early conservative therapy according to standard practice	120	2019	NCT02301819
Europe	Heartmate®[a]	Safety and efficiency: clinical stabilization at 72 hours, defined as improvement in cardiac index to > 2.2 L/min/m^2	HeartMate PHP®[a] to provide haemodynamic support for up to 72 hours in patients with CS requiring stabilization	25	2017	NCT02279979
Denmark	Impella® cVAD[b]	Death from all causes at > 6 months	Impella® device versus standard therapy	360	2018	NCT01633502
France	ECLS ± hypothermia	30-day all-cause mortality	Randomization for hypothermia	334	2020	NCT02754193
Germany	ECLS	LVEF on day 30	ECLS versus standard therapy in patients with CS complicating AMI	42	2019	NCT02544594
China	ECMO ± RRT	All-cause mortality on day 30	ECMO for both arms: one arm ''standard care''; the other with simultaneous RRT	262	2019	NCT02870946

Table 1 (*Continued*)

Country	Intervention	Primary endpoint	Main objective	Number of patients	Results available	Registry number
New management avenues						
Italy	Adrenaline	Day 60 mortality	IV adrenaline infusion as early and fast haemodynamic stabilizer	24	2017	NCT02591771
France	Epinephrine or norepinephrine	Cardiac index until release from ICU	IV epinephrine or norepinephrine prepared in syringes to obtain a MAP of 65—70 mmHg	80	2017	NCT01367743
Germany	Hypothermia	Cardiac power index after 24 hours	Mild hypothermia for 24 hours with invasive cooling plus PCI and OMT versus PCI and OMT	40	2016	NCT01890317
China	Hypothermia	Anti-inflammatory impact (TNF-α, IL-1β, IL-6, IL-10)	Therapeutic hypothermia (33—34 °C)	50	2017	NCT02633358
Germany	PCI	30-day mortality and/or severe renal failure requiring RRT	Immediate multivessel versus culprit vessel-only angioplasty	706	2017	NCT01927549

Ninety-seven studies were registered on clinicaltrials.gov in January 2017, using the keyword ''cardiogenic shock''; studies were deleted if they were terminated or completed ($n = 41$), withdrawn ($n = 2$) or if status was unknown ($n = 10$); only trials including patients exclusively with CS requiring medical management are presented (e.g. patients benefiting from PCI at high-risk or in a surgical context are not presented). AMI: acute myocardial infarction; CS: cardiogenic shock; cVAD: central venous access device; ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICI: intensive care unit; IL: interleukin; IV: intravenous; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; MCSD: mechanical circulatory support device; OMT: optimal medical therapy; PCI: percutaneous coronary intervention; PHP: percutaneous heart pump; RNA: ribonucleic acid; RRT: renal replacement therapy; STEMI: ST-segment elevation myocardial infarction; TNF: tumour necrosis factor.

[a] Thoratec Corp., Pleasanton, CA, USA.

[b] Abiomed Inc., Danvers, MA, USA.

Table 2 Trials performed using the Impella® [a] device; most were stopped because of poor inclusion rate.

Study	Registry number	Condition	Patients required (*n*)	Patients enrolled (*n*)	Duration (months)	Status	Reason for discontinuation
FRENCH TRIAL (2006)	NCT00314847	AMI CS	200	19	52	Discontinued	Low enrolment
ISAR-SHOCK (2006)	NCT00417378	AMI CS	26	26	19	Completed	N/A
IMPRESS in STEMI trial (2007)	NTR1079[b]	STEMI pre-CS	130	21	22	Discontinued	Low enrolment
RECOVER I FDA (2008)	NCT00596726	PCCS	Up to 20	17	28	Completed	N/A
RECOVER II FDA (2009)	NCT00972270	AMI CS	384	1	18	Discontinued	Low enrolment
RELIEF I (2010)	NCT01185691	ADHF	20	1	33	Discontinued	Low enrolment
DANSHOCK (2012)	NCT01633502	AMI CS	360	~50	40	Enrolling	N/A

AMI: acute myocardial infarction; ADHF: acute decompensated heart failure; CS: cardiogenic shock; N/A: not adapted; PCCS: post-cardiotomy cardiogenic shock; STEMI: ST-segment elevation myocardial infarction.
[a] Abiomed Inc., Danvers, MA, USA.
[b] Trialregister.nl.

For instance, the Impella® cardiocirculatory system (Abiomed Inc., Danvers, MA, USA), which has been available for almost 10 years, is appealing, especially because of the effective left ventricular discharge and cardiac output obtained (up to 5 L/min). However, this device has not demonstrated its effectiveness, probably because of difficult recruitment in randomized studies (Table 2). The Impella CP® (Abiomed Inc., Danvers, MA, USA) has recently been introduced, and is an interesting device, because it delivers up to 4 L/min of flow and can be placed percutaneously. Nonetheless, this device failed to demonstrate better survival compared with the IABP in post-cardiac arrest CS patients with an ACS [28]. New cardiocirculatory support devices are regularly proposed, including the iVAC 2.0® (Terumo, Shibuya, Tokyo, Japan) and the HeartMate PHP® (Thoratec Corp., Pleasanton, CA, USA). These devices are costly, and their benefit has still to be proved.

Pending the results of these studies, it is of the utmost importance to update and improve our knowledge of CS in real life through large contemporary registries. The FRENSHOCK registry (NCT02703038) is a French prospective multicentre register on CS regardless of initial aetiology. The aim of this large observational study is to assess the epidemiology and management of CS in France; it will describe the population, aetiologies, strategies and modalities of management, early (1 month) outcomes and late (1 year) outcomes. This registry may provide an important basis for organization, better management and clinical study design [29,30].

The scientific community has to combine its forces through its human and financial resources in CS research, as it does in clinical practice, to improve knowledge and outcomes. The FRENSHOCK registry paves the way for further collaborative works in the field.

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The authors declare that they have no competing interest.

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