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Review Article

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Cardiogenic shock in acute coronary syndrome

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Summary

This is a review of current knowledge on cardiogenic shock (CS), with particular attention to recommended management. The bibliography for the study was compiled through a search of different databases between 1966–2008. The references cited in the selected articles were also reviewed. The selection criteria included all reports published on CS, from case reports and case series to controlled studies. Languages used were Spanish, French, Italian, Portuguese, German, and English. Cardiogenic shock is the most frequent cause of in-hospital death as a complication of acute coronary syndrome. The incidence is about 7% and, despite therapeutic advances, it continues to have an ominous prognosis, with mortality rates of over 50%. Coronary reperfusion is fundamental in the management of cardiogenic shock, particularly with the use of percutaneous coronary intervention. However, if this is not available, systemic thrombolysis may be performed together with balloon counterpulsation or the use of pressor drugs. Despite the historical importance of the Swan-Ganz catheter, this would appear to have limited use, with echocardiography nonetheless having a fundamental role in the management of CS. Although patients with cardiogenic shock often present a left ventricular ejection fraction of around 30%, survivors often have a good functional classification one year after the event. Neurohormonal and inflammatory mechanisms play a fundamental role in the pathophysiology of CS. These mechanisms are currently the target of studies looking into developing new therapeutic strategies.

key words: **cardiogenic shock • percutaneous coronary intervention • mortality • pathophysiology • acute coronary syndrome**

Abbreviations: **IABP** – intra-aortic balloon counterpulsation; **LVEF** – left ventricular ejection fraction; **CI** – cardiac index; **STEMI** – ST-segment elevation myocardial infarction; **AMI** – acute myocardial infarction; **PCI** – percutaneous coronary intervention; **NRMI** – National Registry Myocardial Infarction; **sSBP** – systolic systemic blood pressure; **PCwP** – pulmonary capillary wedge pressure; **CRP** – C-reactive protein; **CS** – cardiogenic shock; **ACS** – acute coronary syndrome; **NSTECS** – non-ST-segment elevation coronary syndrome; **SIRS** – systemic inflammatory response syndrome; **non-STEMI** – non-segment-elevation myocardial infarction

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Background

Cardiogenic shock is a complication of acute coronary syndrome and has high mortality rates. It has usually been attributed to myocardical necrosis size. Nevertheless, other responses are now related to it, such as a neurohormonal or systemic inflammatory response. At the same time, management and prognosis depend largely on culprit artery primary reperfusion. On the other hand, there is some controversy over topics such as the pathophysiology and development of CS and the utility of revascularization in the senile population. Therefore the main aim of this study is to review current knowledge of CS with special attention to its pathophysiology, fibrinolysis, percutaneous coronary intervention, and relationship with age and intra-aortic balloon pump use.

Definition

Cardiogenic shock (CS) is responsible for the high hospital mortality rates due to acute coronary syndrome (ACS) and, particularly, acute myocardial infarction (AMI) [1,2]. The classic definition by Forrester et al. [3,4], used in several subsequent studies, is the most widely used. This considers CS to be systolic systemic blood pressure (sSBP) <90 mmHg for more than 30 minutes, a cardiac index (CI) of <2.2 l/min/m^2, and pulmonary capillary wedge pressure (PCwP) >15 mmHg. In patients with hypertension, CS is defined as a reduction in the usual sSBP of 30 mmHg [5]. Due to a mortality rate of 43% [6], recent studies have looked at the concept of pre-shock (the same signs and symptoms as CS but without hypotension), which may precipitate the onset of CS with the concomitant administration of certain drugs [7]. Even if the diagnosis is defined on the basis of hemodynamic parameters, clinical data are fundamental. In the SHOCK registry, 64% of patients present the signs that are supposedly typical of CS, such as hypotension, evidence of low cardiac output, tachycardia, disturbed mental state, oliguria, peripheral coldness, and pulmonary congestion. Nevertheless, up to 28% of patients present signs of hypoperfusion without pulmonary congestion, although these patients have identical rates of previous AMI (50%) and a PCwP of about 21.5±6.7 mmHg. Interestingly, the mortality rate detected in the patient group without signs of pulmonary edema is higher (70 vs. 60%, p=0.036) [8].

Epidemiology

The incidence of CS has remained unchanged at about 7% throughout the past few decades (oscillating between 4 and 11%) [1,2,9–11]. It is reduced with thrombolysis [12], even if this is administered outside of the hospital setting (incidence of CAPTIM is 1.3) [13], and with percutaneous coronary interventions (PCI) [14]. Patients with CS tend to be older and are predominantly female, with a history of arterial hypertension and, especially, diabetes [15]. The most frequent type of AMI responsible for the CS is anterior. Hochman et al. [16] found that 55% of AMI were anterior, 46% inferior, 21% posterior, and the other 50% were multiple; these rates are similar in other studies [17]. CS patients have generally required previous coronary surgery, often have lower initial sSBP, more delayed treatment, more previous infarcts, more peripheral vascular and cerebrovascular disease or cardiovascular events [18,19], lower left ventricular ejection fraction (LVEF), and greater enzymatic peak height [18]. A predictor scale for CS was developed from the results of GUSTO I [20], which was then validated in the GUSTO III trial (patients treated with thrombolysis), observing that the predictor variables for the development of CS are age, sSBP, heart rate, Killip on arrival, anterior location of AMI, previous AMI, previous cardiovascular surgery, weight, sex, previous PCI, and diastolic SBP [20,21]. Age is one of the most important independent variables associated with CS. Hasdai et al. found that for each increase of 10 years there is a 47.5% increased risk of developing CS. Elderly patients who suffer from CS are more prone to hypertension (49% vs. 21%), include fewer smokers (13% vs. 46%), and fewer have ST elevation (79% vs. 49%) [21,24]. In addition, they are more likely to present previous infarcts, congestive heart failure, renal impairment, other comorbidities, and more severe coronary disease [24]. However, primary reperfusion is conducted less often than in younger patients (40% vs. 82%), this difference being due primarily to the lower number of PCIs (31% vs. 68%). Elderly patients also present more arrhythmic and mechanical complications [22,23].

The predictive factors for the development of CS may have changed over the years. Menon et al. [25] examined the differences between GUSTO I (n=2814, 1990-1993) [6] and GUSTO III (n=695, 1995–1997) [26]. In GUSTO III the patients were older and more had diabetes and hypertension. In GUSTO I the patients had higher Killip scores and a higher incidence of previous infarcts.

Pathophysiology

The time of onset of CS varies considerably, the majority starting within the first 48 hours of admission. In the TRACE registry, 59% occurred within this time period and 30% suffered CS between days 2 and 5 [9,27]. Overall, only 10% of patients arrive at the hospital in CS [11]. In the GUSTO trial, 11% of patients arrived at hospital in CS [6]. Of the 296,633 patients with acute ST-segment elevation myocardial infarction (STEMI) in the NRMI, 8.6% were admitted in CS [28]. The onset of CS often occurs in the first 5 to 8 hours of the ischemic event, appearing much later in non-ST-segment elevation myocardial infarction (non-STEMI) [29]. The onset of CS also varies depending on the culprit artery [7,30], with a shorter delay in right ventricular AMI [31].

The primary cause of CS is left ventricular failure, the SHOCK trial registry finding that this cause is followed by mitral impairment (8.3%), septal rupture (4.6%), isolated right ventricular dysfunction (3.4%), cardiac rupture and tamponade (1.7%), and other causes (7.5%) [32]. Classically, and supported primarily by anatomopathologic studies, it is considered that CS as a complication of AMI is caused by left ventricular necrosis, which affects 40% of the left ventricular mass [17–19,27]. Nevertheless, there are other considerations that may cast doubt over this assertion [1]: a) survival is around 40–50% in revascularized patients [14,20,32], b) improved temporal LVEF in survivors [33], and c) in the SHOCK trial, 58% of survivors at one year were in NYHA functional class 1 (83% of patients were in NYHA 1 or 2, 85% for the revascularized patients, 80% in the medication group) [29].

Episodes of infarction extension occur in CS, with re-occlusion, micro-infarcts, and embolization [18,19]. The myocytes

in the border area are more likely to present ischemia. The ischemia remote from the infarcted area is also important, especially in the case of multi-vessel disease, as it may contribute to the dysfunction, with the vasodilatory reserve being limited and the auto-regulation altered; myocardial depression or cardiotoxicity phenomena may occur, and all of this may limit the hyperkinetic response of healthy segments. A fundamental fact is that in addition to the irreversible myocardial damage, there are also non-necrotic areas, viable but not functional, which may also contribute to the development of CS [35]. Significantly, it was deduced from the SHOCK trial that CS is not only induced or explained by left ventricular failure, but that other possible explanations should also be considered. In this clinical trial it was observed that the LVEF found in CS was around 30% [33], identical to that found in other studies [36,37]. Nevertheless, in patients with dilated myocardiopathy and patients with moderate to severe cardiac failure, there is often a higher level of left ventricular dysfunction. These observations may indicate the value of ventricular dilation and neurohormonal adaptation to maintain cardiac output [38,39]. After myocardial ischemia, there is an activation of the neuroendocrine response which tries to maintain cardiac output by increasing peripheral resistance and inducing a hyperkinetic response [40]. It is traditionally recognized that the variability of the type of neuroendocrine response is partly responsible for CS [1,41]. However, the systemic vascular resistance observed in CS is not always raised on average, there being a wide range of measurements. From the SHOCK trial registry data, resistance of 1350–1400 dynes×s/cm^5 was observed [42]. A small subgroup of patients in the SHOCK trial registry had normal sSBP, despite presenting hypoperfusion, low cardiac output, and elevated filling pressures. Mortality in this subgroup was 43% vs. 66% of patients with classical CS criteria, despite both groups having LVEF of 34%, a cardiac index of 1.9 l/min/m^2 and a PCwP of 25 mmHg [42]. This ability to maintain the sSBP probably explains the better prognosis.

There is evidence of a systemic inflammatory response syndrome (SIRS) in CS manifested by an increase in leukocytes, fever, and reduction in systemic resistance. These findings, classically considered as a new complication, i.e. sepsis, are now thought to be due to SIRS. And it is here that a new hypothesis arises; that the high levels of nitric oxide and its derivatives, such as peroxynitrites, induce SIRS. There is a marked variability in the systemic inflammatory response which occurs after CS, with this also playing a very different role from one patient to another. A very variable inflammatory response has been found in unstable angina, with levels of IL-6 and C-reactive protein (CRP) being detected moments prior to the PCI [43]. There is also a marked relationship between the increase in leukocytes and the severity of the AMI [43,44]. In addition, lymphocytes are detected which express HLA-DR, an accepted indicator of the activation of T lymphocytes in myocardial regions remote from the ischemia [45]. Activation of neutrophils after 15 minutes of myocardial ischemia was observed in experimental animal models [45]. In the animal model studies, the inhibition of nitric oxide synthase appears to have a beneficial effect at a metabolic level, on anti-stunning, and on coronary flow [46]. There are few studies conducted on human models, survival at 30 days being 72% with the inhibition of nitric oxide synthase [47]. Theoretically, inhibition of the complement cascade, especially at C5, may inhibit the onset of shock. The preliminary results of the COMMA study show that the inhibition at C5 is associated with a lower rate of shock and death in primary PCI [48]. Patients with CS may have similar IL-6 concentrations to those with septic shock, and when this occurs, as with septic shock, patients often have multi-organ failure, with IL-6 being an independent variable of mortality in CS [49]. An interesting fact is the cut-off point for a poor diagnosis in intensive care patients, as it has been observed that this may be 3–10 mg/l for CRP and 5-10 ng/l for IL-6. The FRISC II results showed that an IL-6 level >0.5 ng/l is an independent factor of poor prognosis, it also being observed that PCI reduced mortality in the subgroup of patients who had reduced IL-6, but not when IL-6 was not modified [50]. Another interesting aspect is the interrelation between inflammation and coagulation, as demonstrated by the reduction in the existing inflammatory response with dalteparin, activated C-protein, or glycoprotein IIb/IIIa inhibitors [51]. Paradoxically, coronary reperfusion induces an inflammatory response which reduces the proportion of viable myocardium in the first two hours of reperfusion, with the cell apoptosis mechanisms being prominent here [52].

The pathogenesis of CS may be related to the extent of the occluded epicardial coronary lesion, the severity of the ischemia and necrosis produced, the microvascular cellular damage, a poorly adapted neuroendocrine response and the damage caused by the myocardial reperfusion, which may lead to the production of toxic and myocardial depression-inducing agents [11]. The restrictive filling pattern is common in patients with CS, which may suggest that diastolic dysfunction contributes to CS pathogenesis [53].

Right ventricular AMI occurs in 30-50% of patients with inferoposterior AMI (clinically significant in 10%) [54] and in ⩽10% of patients with anterior AMI [55]. It may have a better prognosis than that of CS due to left AMI, although these patients may require longer support [54]. Nevertheless, the data are conflicting. Jacobs et al. [31] find no differences in mortality rates. The cardiac index was similar in the two groups, although the right pressures were greater in the right infarct and the left pressures were greater in the left infarct. The LVEF was greater in the right ventricular AMI (42% vs. 30%, $p<0.002$), with these patients presenting a lower heart rate (85 vs. 95 bpm, $p<0.05$) [31]. A subgroup of patients presented an elevated PCwP (23 mmHg), similar to that of left AMI, but without primary left disturbance, probably due to left interrelation, pericardium, or excessive preload [31]. Coronary reperfusion is crucial with right-sided affectation [56]. An interesting fact is the right ventricular disturbance in cases of left ventricular dysfunction. Of 99 patients in the SHOCK trial with left dysfunction, the added dysfunction of the right ventricle was not associated with lower survival at one year [57].

CS may occur as a result of a lesion of any of the coronary arteries, the most frequent being multi-vessel lesion with a TIMI grade 0 flow or proximal anterior descending (AD) artery lesion. It may also be due to lesion of the dominant circumflex (CX) artery, or RCA, especially when the RV is involved. In one third of patients it may not be possible to identify the culprit lesion [29]. From the data obtained in the SHOCK trial registry, it was observed that the majority

of patients in CS (78%) had multi-vessel disease. The AD was the most frequently affected vessel in both groups, delayed CS was more frequent with the AD, and the RC the most commonly affected in early CS. Two thirds of patients presented a TIMI grade 0/I flow [29]. Furthermore, it was observed that three-vessel disease and disease of the AD is particularly more frequent in elderly patients. Reestablishing of flow (TIMI II or III) was similar in both groups (81.8% in the elderly and 80.6% in the young) [24]. In the SHOCK trial, coronary angiography was performed in 52.6% of patients with non-STEMI and in 64.1% of patients with STEMI (p=0.010). Non-STEMI patients had a lesion of one or no vessel less frequently than STEMI patients (6.9% vs. 24.8%); however, they had more multi-vessel disease (76.7% vs. 53.5%). Patients with STEMI were more often treated with PCI than non-STEMI patients, while the latter required more cardiovascular surgery [36]. Data from the SHOCK trial, evaluated after one year, revealed that the number of vessels affected is associated with survival. Coronary angiography revealed severe lesions of the coronary arteries in both groups, with at least 2/3 of patients having three-vessel disease and 21% having DA lesion. The majority did not have collaterals; the collateral score did not correlate with one-year survival [58]. After PCI, the majority presented a TIMI flow >II [59], and at one year, 32% of patients had TIMI flow III in the culprit artery [58]. The non-STEMI patients presented more three-vessel disease, but lower TIMI 0 flow. The majority of STEMI patients had TIMI 0 flow [29]. In-hospital mortality was correlated with severity of TIMI flow [8,58–61].

CS in Non-STEMI

About 30% of cases of CS occur in NSTECS [36], these patients presenting more adverse factors; they are older and have a higher incidence of previous infarcts and diabetes [6]. The CS predictors in the PURSUIT trial were age, sSBP, ST-segment depression, heart rate, weight, and AMI [62]. Of the 12,084 patients in GUSTO IIb, CS occurred in 4.2% of STEMI patients and 2.5% (p<0.0001) of NSTECS patients. In NSTECS, CS occurs in older patients (70 years vs. 63 years for STEMI), predominantly diabetic females, with a greater incidence of previous AMI and cardiac failure and higher CK. The onset of shock is slower in NSTECS (76.2 hours vs. 9.6 hours for STEMI), recurrent ischemia and re-infarct being much more frequent. Mitral insufficiency occurred in 4.6% (STEMI) and 6.5% (non-STEMI) and septal defect in 2.3% (STEMI) and 1% (non-STEMI) [29]. Patients with NSTECS and left dysfunction CS in the SHOCK trial registry were significantly older and had a higher incidence of previous AMI, cardiac failure, azothemia, coronary surgery, and peripheral vascular disease than patients with STEMI. Both groups had the same LVEF (30%). Among the patients selected to undergo angiography, the CX was the culprit vessel in 34.6% of NSTECS vs. 13.4% of STEMI (p<0.0001). Although the NSTECS patients presented a higher incidence of recurrent ischemia than those with STEMI (25.7% vs. 17.4%, p=0.058), they were less likely to undergo angiography (52.6% vs. 64.1%, p=0.010) [36]. Of the 426,253 patients in the NRMI-2 [28,88] there was CS in non-STEMI patients in 4.9%. In the SHOCK trial registry, the hemodynamic parameters were similar in the two groups [35]. In short, patients with CS and NSTECS have greater risk factors but similar hospital mortality rates. They have more recurrent ischemia and are less likely to undergo angiography [63].

Clinical Assessment and Initial Management

Monitoring

In the GUSTO trial, the Swan-Ganz catheter was used in 42.2% of patients, 96.9% of whom died. Among the patients with CS in whom this catheter was used, hemodynamic values were not independent variables associated with mortality. The PCwP cutoff point which increased or reduced mortality was 20 mmHg [64]. Additionally, its use in critically ill patients is at least questionable. The echocardiograph, however, is an indispensable tool in CS [65,66]. Nowadays, the Swan-Ganz catheter has lost its value, Cohen et al. [67] observing that it was only implanted in 2.8% of 26,437 patients with ACS studied retrospectively, these implants being carried out within 24 hours of admission. Its use is associated with older and diabetic patients, Killip III or IV, PCI, coronary by-pass, or orotracheal intubation. Mortality at 30 days showed an adjusted *OR* of 6.4 [67]. One monitoring method used was "cardiac power", this being a powerful prognostic predictor of cardiac failure [68]. Measuring cardiac output by bioimpedance may also be useful [69]. Another method, in addition to the diagnosis, which may also be useful for the hemodynamic evaluation of CS is echocardiography. Thanks to a sub-study of the SHOCK trial, where 274 echocardiographs were performed (175 carried out randomly within a few hours), it was observed that the mean LVEF was 31%; 39.1% of patients had moderate to severe mitral insufficiency. In the multivariate analysis the only independent variable for survival prediction was the severity of the mitral failure. The right ventricular ejection fraction was reduced in both groups. The segmental contractility score reflected significant regional dysfunction in both groups and hyperkinesia in remote areas (36.6%). After 30 days and one year, the echocardiograph survival predictors were severity of mitral regurgitation (≥2 vs. <2, *OR* for mortality: 6.64, p=0.0003) and LVEF less than 28% (*OR* for mortality at one year: 4.04, p=0.005). LVEF prior to PCI was 29±12% vs. 39±13% after revascularization [33].

Medical Treatments

As regards medical treatments, fibrinolysis and the application of catecholamines are of special interest. Although dopamine and dobutamine improved the hemodynamics of these patients [66], interestingly no increase in survival was demonstrated. Furthermore, it has been suggested that administration of these drugs may accelerate myocardial dysfunction [70]. Therefore, the use of new inotropic drugs, such as levosimendan, is being tested in CS [71,72]. Although it has been convincingly demonstrated that administration of thrombolysis reduces mortality in AMI [73], whether or not its administration in CS reduces mortality has been questioned. The majority of the clinical trials that evaluate the benefits of thrombolysis in AMI exclude patients in CS. In the GISSI trial [74], mortality at 30 days post-CS was 69.9% in patients treated with streptokinase vs. 70.1% in the placebo group. The International Study Group [75] found a mortality rate of 65% in the 93 patients treated with streptokinase and 78% in the 80 patients treated with alteplase. In the GUSTO trial [5], the mortality rate was 56% in patients

treated with streptokinase and 59% in those treated with alteplase [5]. The FTT meta analysis [73] detected that the greatest absolute benefit of thrombolysis occurs with sSBP >100 mmHg (36.1% vs. 29.7%, 66 lives saved per 1000 patients) or with heart rate >100 beats per minute (23.8% vs. 18.9%, 33 lives saved per 1000 treated). This meta-analysis demonstrates the poor efficacy of thrombolytic therapy in cases of CS, although it does have benefits. There is no evidence of superiority of one thrombolytic therapy over another in terms of effectiveness in the case of CS. Although the GUSTO I trial suggests that alteplase is more effective than streptokinase in preventing CS, streptokinase may in fact be slightly superior in its effectiveness [5,76] and alteplase appears to be similar to reteplase [76].

The grade of coronary reperfusion is correlated with survival [76] and reperfusion is lower in patients with CS. The explanation of why thrombolysis may be less effective when there is CS is not clear. It may be due to poorer penetration of the thrombolytic agent [77] as a result of passive collapse of the artery relating to the AMI, or to acidosis, which may inhibit the conversion of plasminogen to plasmin [77]. In animal models, resistance to thrombolysis in CS was observed which may be avoided with the use of intra-aortic balloon pump (IABP) [78]. This effect is not mediated by a significant increase in coronary flow; rather it has been suggested that the benefit is due to an increase in diastolic pressure or doubling of the number of pressure waves in each diastolic period. Nevertheless, the combination of IABP and thrombolysis leads to an increase in hemorrhagic complications, such that in both TAMI-1 [79] and GUSTO I [80], IABP was an independent factor for the development of major [81] or moderate [82] hemorrhagic complications. In human studies, the benefit of the combination of thrombolysis and IABP has been confirmed; it was observed in 64 patients that the mortality rate was similar in patients where IABP or thrombolysis were used in isolation (70%), but this mortality rate reduced to 32% when they were combined (IABP + thrombolysis) [81]. Kovack et al. [82] reported similar findings, with a reduction in mortality that was maintained at one year (initial survival 93% vs. 37% and at one year 67% vs. 32%). Of the 21,178 patients enrolled in the NRMI-2 who developed CS, the mortality rates was lower in patients who were administered thrombolysis plus IABP than in patients to whom only thrombolysis was administered (49% vs. 69%) [83]. From the initial analysis of patients from the SHOCK trial registry, the combination of IABP + thrombolysis was associated with 46% mortality compared with 76% of patients who received neither [84]. Subsequently, of the 884 patients with ventricular dysfunction, the mortality rates due to CS were as follows: patients treated with thrombolysis + IABP 47%, IABP alone 52%, thrombolysis alone 63%, and neither thrombolysis nor IABP 77% ($p<0.0001$) [84]. The TACTIS study [85] was terminated prematurely on demonstration that the mortality rate at 6 months with thrombolysis alone was 80% vs. 39% for thrombolysis + IABP ($p=0.05$). More recent data from the TACTIS trial reveal that IABP was implanted in 27 patients after 30 minutes of the thrombolysis administration and was maintained for 34 hours. Patients with Killip III or IV have a lower mortality rate at 6 months (39% in combined therapy vs. 80% receiving thrombolysis alone, $p=0.05$) [86]. From NRMI-2, a mortality rate of 49% in thrombolysis plus IABP is observed and 70% with thrombolysis alone [87]. In the SHOCK trial, among the 302 patients randomized to medical treatment, patients who received thrombolysis presented a lower mortality rate, which was maintained at twelve-month follow-up [88]. IABP was implanted in 86%, 49% received IABP + thrombolysis, 7% thrombolysis without IABP, 37% IABP without thrombolysis, and 6% nothing. Thrombolysis was administered at a median of 1.3 hours before diagnosis of CS, 66% of patients receiving thrombolysis prior to being diagnosed with CS. Compared with the patients not receiving thrombolysis, those who did tended to be younger and have fewer comorbidities and less severe stenosis (due to reperfusion as a result of the thrombolysis), although the incidence of multi-vessel disease was identical in both groups. With thrombolysis, 58% showed TIMI grade 2-3 flow, while without thrombolysis, 43% showed TIMI flow of 2 or 3 ($p=0.003$). At twelve months, Cox regression demonstrated that there was a clear reduction in the mortality rate (0.59 [0.39–0.88]) in patients treated exclusively with thrombolysis [89]. Another possibility would be to increase the perfusion pressure with inotropes [90]; this has been studied in a small series of eight patients with good results [91].

IABP reduces systolic overload, increases diastolic pressure and, therefore, coronary perfusion, improving cardiac output. Although it is effective in the stabilization of initial CS, weaning is difficult [22,56,92]. Nevertheless, small randomized studies from the thrombolytic era do not provide any evidence that IABP increases survival [93]. IABP, be it with thrombolysis or with PCI, is recommended as the first-choice intervention [66,94]. The SHOCK trial registry shows a clear reduction in mortality with cardiac counterpulsation (63 vs. 47%) [84]. Moreover, not only did the coronary flow distal to the critical coronary stenosis improve [95], but also right and left ventricular failure [30]. Although it is not a method that independently improves mortality in CS, it may be beneficial in combination with other methods. In the GUSTO trial, patients treated with IABP presented lower mortality rates [95], even when excluding patients in whom early revascularization was performed. Similar findings were reported in the SHOCK trial registry, although this difference in the mortality rate was not sustained when adjusted for age and for PCI. A decrease in re-occlusions and cardiac events after emergency PCI for AMI with IABP has been described [57]. In the NRMI-2, IABP was used in 31% of CS, being associated with a drop in mortality rates in patients who were treated with thrombolysis (67% vs. 49%), but the benefit was not detected in patients treated with PCI (45% vs. 47%). IABP is generally used for an average of 43.5 hrs (range: 3–144 hrs) and presents a complications rate of around 3% [96]. In the SHOCK trial, IABP was used in 86% of both groups, although its use was lower in other registries and in other countries. Early implanting of the IABP occurred in 20% (60 patients) and later in 80% (248 patients). The majority of implants were in the USA. Although with early IABP implanting there are more episodes of bleeding, there is a tendency towards lower mortality at 30 days and 1 year [95]. Another possible benefit of IABP is in the case of hospital transfer, patients in regional hospitals treated with IABP having a better cardiac index (2 vs. 1.5 l/min/m^2, $p=0.04$), better survival, and a higher rate of transfers (85% vs. 37%). Of the transfer patients, survival was 74%. Overall, patients treated with IABP presented a one-year survival rate of 67% vs. 32% in patients not treated with IABP [82].

In recent years, the use of "Impella", a percutaneous ventricular assist device, is becoming more generalized. Its utility has been clearly demonstrated. In addition to its efficacy in both pre-transplant and in CS, it is also easy to use; it may be implanted under the direction of the echocardiograph and without the need for fluoroscopy [97–99]. Furthermore, different ventricular assist mechanisms are still been designed [100–103] and may prove effective as a bridge to heart transplantation to be performed in the acute AMI phase (in the first eight days post-AMI) [102], which may provide an acute-phase survival rate of up to 70% [103].

PCI

Until the 1980s, PCI was only used in isolation. Since 1985, several series of cases have been published with spectacular results. Of 2972 patients in CS from the GUSTO I trial [5], a difference in mortality rates was detected at 30 days; 43% vs. 61% (PCI vs. thrombolysis). Furthermore, PCI was detected as an independent variable associated with survival in different studies, such as the Worcester Heart Attack study [104], the California State Database [105], and the GUSTO I [5,20,25,64,76] and GUSTO III trials [26]. Nevertheless, the majority of these studies have various biases, with the patients recruited usually being younger and with less severe conditions. The SMASH study was designed to evaluate the possible benefit of the invasive strategy versus the conservative strategy in CS, but this was suspended with no differences being found; only 55 patients were included in 4 years [23]. Antoniucci et al. reported the benefit of PCI in CS in a prospective study with 66 patients [106]. The SHOCK trial evaluated treatment of AMI complicated by CS with early revascularization [107]. The inclusion criteria were STEMI or a new left bundle branch block, sSBP<90 mmHg for at least 30 minutes, onset of CS within 36 hours of STEMI, and at least 18 hours in CS. Patients were randomly distributed to emergency revascularization (n=152), via surgery or angioplasty, or to initial medical stabilization (n=150). At 30 days, the overall mortality rate was 46.7% in the group managed invasively (p=0.11). However, mortality at six months was significantly lower in the revascularized group compared with the group receiving medical therapy (50.3% vs. 63.1%, respectively, p=0.027). Patients assigned to revascularization had a greater risk of death on days 1 and 2, while in those assigned to the medical treatment group the risk of death remained constant for the first week. The subgroups of the SHOCK trial to particularly benefit from the early revascularization strategy, i.e. reduced mortality at 6 months, were patients under 75 years (81% of patients included were less than 75 years) with prior AMI and those who underwent the intervention within 6 hrs of onset of the infarction. A total of 132 lives were saved per year and per 1000 patients treated compared with non-revascularized patients. In the group assigned to revascularization, when the angioplasty was successful, the mortality rate at 1 month was 38% vs. 79% for those in whom the angioplasty was not successful. After one year, these patients presented survival rates of 46.7% and 33.6%, with an absolute difference in survival of 13.2% (132 lives saved per 1000 patients treated with PCI); only age correlated with mortality, being significant for patients under 75 years (51.6% vs. 3.3%) [34]. This benefit of PCI has been corroborated in clinical registers [108].

Despite the lack of benefit detected in the results from the SHOCK trial in elderly patients, in which the population of elderly patients possibly does not represent the real population [109–111], there are other studies where the efficacy of PCI has been detected in an elderly population. It was observed in the Shock registry that after adjusting the multivariate study, the performing of PCI in elderly patients leads to lower mortality rates than in patients who did not have PCI or who received it after a certain delay [24]. Buller found that the mortality rate in patients aged 75 years or over in CS and treated with PCI was 46% [111]. Early PCI may reduce mortality even in patients over 80. In a study with 61 patients in CS with a mean age of about 80 years treated with PCI within 8 hours of onset of AMI, Prasad reported a survival rate of around 47%, and of these, 75% survived to one year [37]. In addition, in Gusto I [5], the SHOCK registry [111], and the Californian registry [105], patients in CS who underwent surgery appeared to maintain better survival rates than patients treated with PCI. Obviously there are several possible biases that make it difficult to interpret these results adequately. Of the 583 patients in the GRACE study in CS, 40% were ⩾75 years. Revascularization was performed in only 33% of patients aged 75 or over compared with 50% of the younger patients. The mortality rate was 35% in patients with PCI and 74% in the group without PCI. PCI-stent was the most powerful survival predictor [112]. The benefit of PCI in CS remains clear. However, it has been repeatedly demonstrated that this benefit is still not being achieved [20,113], even though the benefits of PCI continue for at least six years [114].

Prognosis

The mean hospital stay in CS is currently around 12–16 days [42,92]. This has decreased (both in surviving and non-surviving patients) over the years [92]. Between 1992 and 1997, the overall mean fell from 11.5±16.0 (median: 5.5 days) to 8.6±9.3 (median: 5.9 days, p=0.039). For survivors, it went down from 23.4±19.5 (median: 18 days) to 15.4±9.4 (median: 12.6 days, p=0.019). In the non-survivors the mean fell from 6.2±10.5 days (median: 3.0 days) to 4.1±6.0 (median: 1.6 days, p<0.0001) [92]. Fifty-five percent of patients came from primary hospitals [107]. Of the >300,000 patients in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR), 483 required PCI for CS, with these patients remaining in hospital after PCI for 7.2±8.0 days [115].

Despite the passage of time and the changes in therapy throughout the 20th century, the prognosis of CS continues to be poor. Short-term mortality fell from 80% to 70% in the 1970s and from 60% to 50% in the 1990s. It has recently been observed that among initial survivors of CS, survival at six years is 62.4% for those treated with early PCI and 44.4% for those managed medically [114]. CS is the cause of death in 60% of patients who die after fibrinolysis, it continues to be the first cause of death in patients hospitalized with AMI, and continues to have a high mortality rate (>50%) [11,63]. The majority of deaths occur within 48 hours of the event. For patients treated conservatively, the mortality rate is around 70–80% [63,92]. Nonetheless, there are studies which, in isolated cases, have detected a very low rate of mortality (26%) with the performing of early PCI [106,115]. However, most of these clinical trials

have various biases, with the recruited patients generally being young and their condition less serious; evidence in large clinical registries showing that mortality when PCI is performed is about 60% [115]. In a study by Tudesco et al. [22] on 1263 patients with AMI, 6% developed CS. For elderly patients with CS, estimated survival at one year and five years was 38% and 24%, respectively, and in younger patients 57% and 52%.

One of the obvious complications of CS is the development of renal failure, which, even when occurring within 24 hours, is an independent predictor of in-hospital mortality (87% vs. 53% without early renal failure, *OR*=6.0) [116]. Other significant mortality predictors include the peak lactic levels, dose of catecholamines, peak of CK, age, parietal motility index, re-infarction, lack of thrombolysis [117], and multiorgan failure [118]. As enzymatic markers, it has been observed that the level of interleukin 10 [119,120] and proB-NP may modify prognosis [121]. Clinical findings such as sensory disturbances, coldness, clammy skin, and oliguria, which were independent and prognostic predictors, were also independent variables of mortality. Patients who were admitted in CS had a better prognosis than patients in whom CS developed later. The prognosis was also worse in patients with Killip II or III [64]. From the results obtained in the SHOCK trial, it was observed that survival at 1 year was correlated with the vessels affected and with LVEF (an *OR* for death of 0.68 per 5 unit increase in LVEF, *OR*=0.68 [0.54–0.86]) as opposed to the treatment group. Mitral regurgitation was inversely associated with one-year survival in the medical treatment group, this not being observed in the invasive group [58]. In CS, 28% of patients do not have pulmonary congestion (only hypoperfusion); patients with pulmonary congestion were more likely to have had previous infarcts, anterior AMI, and cardiac failure. LVEF and cardiac output were similar, but PCWP was different in patients with no pulmonary congestion, being 22 mmHg vs. 24 mmHg in those with congestion (p=0.012). Mortality in patients without pulmonary congestion was 70% and 60% in the remaining patients [59]. In the SHOCK trial registry, mortality in patients with sSBP <90 mmHg, without signs of hypoperfusion, was 26% [42]. The prognosis may depend on the country. The GUSTO data reveal a lower mortality rate in the USA. Forty-five percent were transferred from other hospitals. The drop in mortality was lower in patients transferred from other hospitals [122].

Using a regression logistic, the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) [115] found that the variables associated with mortality in CS were female gender, creatinine over 2 mg/dl, occlusion of AD artery, not using glycoprotein IIb/IIIa inhibitors during PCI, and not using a stent.

PCI obviously reduces mortality. However, despite its use, mortality rates are still significant. The mortality predictor factors in patients treated with PCI have been examined, highlighting the following factors: lack of response to previous inotropes with PCI [123], female gender [115], age [115,123], multi-vessel disease [124], AD artery lesion [115], failure of thrombolysis, delay in PCI or its result, evaluated by residual TIMI flow [125] or level of blush [123], not using a stent or glycoprotein inhibitors during PCI [115,125], or not using the double anti-aggregation together with glycoprotein IIb/IIIa inhibitors [126]. In patients managed without PCI, glycoprotein IIb/IIIa inhibitors may reduce mortality in CS [62], a benefit which may persist up to one year [127]. Other mortality predictor variables in patients managed with PCI are LVEF<0.30 [125], creatinine over 2 mg/dl [115], or the existence of inflammatory markers [128].

Conclusions

Cardiogenic shock is the most frequent cause of in-hospital death as a complication of acute coronary syndrome. The incidence is about 7% and, despite therapeutic advances, it continues to have an ominous prognosis, with mortality rates of over 50%. Coronary reperfusion is fundamental in the management of cardiogenic shock, particularly with the use of percutaneous coronary intervention. However, if this is not available, systemic thrombolysis may be performed together with the implantation of balloon counterpulsation or the use of pressor drugs. Percutaneous coronary intervention must be used early, probably at any age. Despite the historical importance of the Swan-Ganz catheter, this would appear to have limited use, with echocardiography nonetheless having a fundamental role in the management of CS. Although patients with cardiogenic shock often present a left ventricular ejection fraction of around 30%, survivors often have a good functional classification one year on from the event. Neurohormonal and inflammatory mechanisms play a fundamental role in the pathophysiology of CS. These mechanisms are currently the target of studies looking into developing new therapeutic strategies.

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