Cardiogenic shock in women: From risk factors to therapy

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ABSTRACT

Cardiogenic shock (CS) in women is a serious cardiovascular (CV) event associated with a high mortality rate. Non-ischemic etiologies are the most common etiologies in women, such as CS in the setting of stress-induced cardiomyopathy or peripartum/postpartum cardiomyopathy, heart failure-related CS, or CS due to myocarditis or valvular heart disease. Although not being the most common etiology in women, acute myocardial infarction is still an important one. Guidelines recommend similar treatment of CS in both sexes, but women have consistently been underrepresented in randomized trials regarding treatment of CS, and more robust data on the optimal management of CS in women is needed. Particularly, the role of mechanical circulatory support in women with CS is still unsettled. Several registries have shown that women with CS are less likely to receive evidence-based therapy compared to men. There is therefore a need for increased awareness about CS in women, in order to increase timely diagnosis and management. In this paper we give a short overview over the etiology, risk factors, diagnosis and treatment of CS in women.

Key words: cardiogenic shock, women, acute myocardial infarction, mechanical circulatory support

INTRODUCTION

Cardiogenic shock (CS) in women is a serious cardiovascular (CV) event associated with a high 30-day mortality rate varying from 30 % to 60% depending on the population studied [1, 2].

In registries of patients with CS related to acute myocardial infarction (AMI), as well as in CS related to non-ischemic etiologies, women represents 20%–30% of patients [3–6]. While the overall incidence of CS appears to be lower in women, they often present with higher acuity and a greater burden of comorbidities [3, 7]. This underscores the need for heightened awareness and timely intervention for women experiencing CS.

ETIOLOGY AND RISK FACTORS

Acute myocardial infarction (AMI) has previously been the dominating cause of CS. However, CS in the setting of AMI (AMI-CS) is a decreasing percentage of all CS cases represented in the cardiac intensive care units [8]. This is particularly the case for CS in women. Non-ischemic etiologies of CS are now more prevalent, such as CS in the setting of stress-induced cardiomyopathy or peripartum/postpartum cardiomyopathy (PPCM), heart failure-related CS, or CS due to myocarditis or valvular heart disease. In takotsubo syndrome, which affects predominantly women, CS is reported in 5%–10%, and in peripartum cardiomyopathy, CS occurs in approximately 4% of cases [1]. Particularly for younger women, spontaneous coronary artery dissection resulting in CS (SCAD-CS) is an important consideration [9, 10].

Among 978 patients presenting with CS to a tertiary care hospital in Germany between October 2009 and October 2017, female patients with CS represented 30% (n = 293) [6]. Compared to men with CS, they were older (73.0 years vs. 69.0 years; P <0.001), presented less frequently with AMI (18.4% vs. 27%; P = 0.006), and more frequently with acute heart failure (32.2% vs. 25.5%; P = 0.037). They

were also less likely to have had a previous MI (18% vs. 27%) and less likely to be smokers (20.1% vs. 34.8%; *P* <0.001) [6].

Cardiogenic shock in the setting of AMI

Despite the fact that AMI is not the dominating cause of CS in women, several studies have suggested that women with AMI are more likely to develop CS compared to men [7, 11]. As an example, data from the FAST-MI programme in France for the time period 1995 to 2010 showed that the rate of CS among AMI patients was significantly higher among women compared with men (8.2% vs 4.8%; *P* <0.001) [12]. After adjusting for age, type of AMI, and other baseline characteristics, female sex was still associated with an increased risk of developing cardiogenic shock compared to men (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.00–1.45) [12].

Women with infarct-related CS tend to present with an overall higher risk profile than men; they are more likely to be older and to have more co-morbidities (e.g. hypertension, diabetes, prior heart failure, renal disease) [1, 7, 13]. In a large nationwide analysis of patients with AMI-CS (n = 17 195; 37% women), women with CS were older, had a higher prevalence of comorbidities, and worse renal function at admittance [13]. They also had more hemodynamic derangement during admission, and were less likely to receive evidence-directed therapy [13]. In the randomized Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT SHOCK) trial including 686 AMI patients, 24% of patients were women. Women were older than men and more likely to have diabetes mellitus and renal insufficiency, but less likely to have a history of previous AMI or smoking compared to men [4].

DIAGNOSIS

Both the diagnosis of AMI and of CS are more often delayed in women compared to men, possibly due to more atypical symptoms, later recognition, and lower awareness of CS in women [7, 11]. Repeated clinical evaluation, ECG, echocardiography and invasive monitoring are useful tools for identification of CS and evaluation in both men and women with suspected CS. Early and frequent assessment of end-organ function, including lactate measurements, are useful to improve CS diagnosis and risk stratification aiming to reduce current sex-based disparities in care. Based on data from observational studies, recent guidelines and position papers suggest that early placement of a pulmonary artery catheter may be considered to assist in diagnosis and early management [14, 15].

In order to reduce overall mortality, early identification of patients *at risk* of CS is adviced, making it possible to apply therapeutic strategies early in those at high risk. Several scores have been developed for prediction of in-hospital CS. While the widely used ORBI score is less accurate in predicting CS in women compared to men, the recently developed SEX-SHOCK score for early detection of AMI-CS has demonstrated better discriminatory performance for the prediction of in-hospital CS in both females and males [16]. The SEX-SHOCK score facilitates early identification of ACS patients of both sexes at high risk of CS and may guide contemporary clinical decision-making.

TREATMENT

The goals of treatment in CS is restoration of sufficient perfusion of myocardium and other vital organs in order to prevent multiorgan failure. Identifying and treating the cause of CS is crucial for success. The main types of treatment are pharmacotherapy, early culprit revascularization in case of AMI, mechanical assist devices, respiratory support and renal replacement therapy [17, 18]. The two latter types are not discussed in this article.

Women have consistently been underrepresented in randomized trials on management of CS [19], and there is limited sex-specific data to guide management of CS in women, limiting the generalizability of observed results for women. Little information is therefor available on sex-specific therapy, and the current guidelines do not give any sex-specific recommendations.

Pharmacotherapy

Vasopressors and inotropes titrated to restore arterial pressure and perfusion are the cornerstone of initial medical therapy for CS. Noradrenaline is the recommended first-line vasopressor drug due to its lower risk of arrhythmia compared to dopamine and epinephrine [20, 21]. Among intravenous inotropes, dobutamine is the recommended choice to improve myocardial contractility and cardiac output. In the Dobutamin compared with Milrinone (DOREMI) trial (n = 192; 36% women), milrinone was compared to dobutamine in patients with CS, but no significant differences were found [22]. Subgroup analyses of female patients showed similar results as for men. Levosimendan improves myocardial contractility by increasing myofilament calcium sensitivity, without raising intracellular calcium and AMP concentrations. However few data support its use in CS, except for in patients on chronic beta-blocker treatment [20]. Furthermore, in takotsubo syndrome and PPCM, levosimendan might be the preferred inotropic choice [1, 19].

Early revascularization

In infarct-related CS, early revascularization of the culprit artery is the recommended treatment based on results from the well-known SHOCK trial [23]. Further information was obtained from the Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial [24]. The CULPRIT-SHOCK trial included 686 patients (24% women) with multivessel disease and infarct-related CS who were randomly assigned to culprit-lesion-only PCI *versus* multivessel PCI. The primary outcome was a composite of death from any cause or renal failure leading to renal replacement therapy within 30 days. The results showed that revascularization of the culprit lesion only reduced

Table 1. Female representation and outcomes in landmark RCTs on management of infarct-related cardiogenic shock

Study name	Year	Intervention	Indication	N	Women (%)	Main outcomes
IABP-SHOCK II [25]	2012	IABP vs. no IABP	AMI-CS	600	31	No reduction in 30-day mortality with IABP. Consistent results in men and women
CULPRIT-SHOCK [4, 24]	2017	Culprit-lesion-only vs. multivessel PCI	AMI-CS in patients with multivessel coronary artery disease	686	24	Revascularization of culprit lesion only was superior to complete revascularization with respect to the primary outcome mortality or severe renal failure within 30 days. No interaction between sex and coronary revascularization strategy regarding the primary outcome (interaction $P = 0.11$)
ECLS-SHOCK [26]	2023	ECLS vs. no ECLS	AMI-CS	420	19	No reduction in mortality at 30 days with ECLS compared to medical therapy. Consistent results in men and women
DanGer Shock [27]	2024	Impella CP + standard care vs. standard care alone	AMI-CS	355	21	Treatment with Impella CP reduced the risk of death at 180 days by 26% compared to standard care. In the subgroup of women, the mortality benefit seemed to be attenuated

Abbreviations: AMI-CS, acute myocardial infarction-cardiogenic shock; ECLS, extracorporeal life support; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial

the risk by 17% compared to complete revascularization. In a prespecified subgroup analysis, the effect of sex on outcome was assessed [4]. Sex did not influence mortality or renal failure according to revascularization strategies (interaction $P = 0.11$) (Table 1). Hence, acute revascularization of the culprit lesion only should be the preferred strategy equally among women and men.

Mechanical circulatory support (MCS)

In the Intraaortic Balloon Pump in Cardiogenic Shock (IABP-SHOCK) II trial, assessing the effect of IABP in patients with infarct-related CS, the results were neutral and similar in men and women [25]. The effect of venoarterial extracorporeal membrane oxygenation, also called extracorporeal life support (ECLS), in infarct-related CS was studied in the ECLS-SHOCK study [26]. The results showed no benefit of ECLS compared to usual medical therapy on mortality. Despite the low number of women included (n = 78; 19%), the results for women were consistent with the overall results (Table 1) [26].

The DanGer Shock study was the first study to show improved survival with MCS in infarct-related CS [27]. The study compared the routine use of a microaxial flow pump (Impella CP) on top of standard care with standard care alone in the treatment of STEMI-related CS. A total of 355 patients were included (21% women). The study showed a significant reduction in mortality after 6 months in the Impella CP group compared to standard care alone. In the prespecified subgroups analyses, however, this mortality benefit seemed to be attenuated in women compared to men. Women in the DanGer Shock study were older, and had a longer time from symptom onset to balloon inflation compared to men (8.3 h [2.9–26.3 h] vs. 3.7 h [2.2–8.5 h]; $P < 0.001$) [28]. The apparent reduced benefit of the microaxial flow pump in women might be related to these findings [28]. Further details on the group of female patients in the DanGer Shock study will be published at a later stage.

In a recently published meta-analysis, patient-level data from nine RCTs of MCS used for patients with infarct-related CS were pooled, including studies on venoarterial extracorporeal membrane oxygenation as well as left ventricular assist devices. The meta-analysis showed that the addition of MCS to standard of care in unselected patients with myocardial infarction complicated by CS did not improve survival at 6 months [29]. In the prespecified subgroup analysis of 6-month mortality in men and women, no sex-related differences were found [29]. Furthermore, MCS increased the risk of major bleeding and vascular complications. There was, however, a significant improvement of survival in STEMI patients without longer resuscitation times [29].

There are also data on MCS from registries. The Impella Mechanical Circulatory Support Device in Italy (IMP-IT) registry is an investigator-initiated, multicenter registry, evaluating the trends in use and clinical outcomes of the Impella (Abiomed) percutaneous ventricular assist device in the setting of CS across 17 Italian centers from 2004 to 2018.[30] In a sex-specific analysis, no gender differences were found with respect to inhospital mortality or device-related complications [30]. Apparently, the data regarding the effectiveness and risks of MCS in women is conflicting, and more research is needed.

For patients with non-ischemic CS, no randomized trials exist on the use of MCS [31]. However, in CS in the setting of PPCM, MCS is often used as a bridge to recovery or transplantation, and smaller registries have reported better outcomes with MCS [32].

Although no convincing evidence exists in general, acute MCS is used in quite a few patients with CS. Published data suggest however that women seem to be less likely to be treated with MCS [6, 33]. In a recent cohort study from Germany, female patients with CS were less likely to be treated with percutaneous ventricular assist device and more likely to be treated with catecholamines or vasopressors compared to men [6]. The reasons for this sex disparity remain poorly understood. Data regarding complication rates are conflicting, with some studies reporting MCS use in women is associated with increased complication rates (bleeding, vascular, readmission) and suggesting

Table 2. Summary of etiologies, risk factors, diagnosis and treatment of cardiogenic shock in women

Etiology and risk factors	Diagnosis	Treatment	Areas with lack of data
• Women with CS are more likely to be older and have more co-morbidities compared to men, except for previous AMI and smoking which are more common in men • HF-related CS is more common in women than AMI-related CS • Takotsubo syndrome and peripartum cardiomyopathy are important etiologies to be considered in women	• Increased awareness is needed • Repeated clinical evaluation including lactate measurements is adviced • Placement of pulmonary artery catheter should be considered	• Vasopressors and inotropes titrated to restore sufficient organ perfusion can be used in the same way as in men • Revascularization is recommended in case of AMI-CS • The role of MCS in AMI-CS in women is still unsettled	• There is a need for more knowledge about risk factors and clinical presentation of CS in women • Women have been underrepresented in most RCTs on management of CS, and more research on management of CS in women is urgently needed

Abbreviations: MCS, mechanical circulatory support; other — see Table 1

this might impact decision-making to implement MCS [19, 34]. Furthermore, practical differences due to patient size (e.g. cannulae/vessel dimensions) might present physical limitations regarding the opportunities for safe peripheral MCS in women [19].

Undertreatment

Despite that the guidelines do not give sex-specific recommendations for treatment of CS, several registries have shown that women with CS are less likely to receive evidence-based therapy in general compared to men, including less coronary angiography and revascularization in case of AMI-CS [6, 13, 35]. The reasons for this undertreatment is not clear, but delay in diagnosis, fear of complications and lack of evidence in women might contribute.

OUTCOME

Most previous studies have reported worse outcomes for women with CS compared to men [5, 7, 13]. However, recent studies suggest similar mortality rates after adjusting for baseline differences [6]. In a large international HF-CS registry including patients between 2010 and 2021 (n = 1030; 28% women), sex disparities in risk factors and clinical presentation were observed. Despite these differences, the use of treatments was comparable, and both sexes exhibited similarly high mortality rates [3]. Other studies report comparable outcomes between men and women when patients were treated according to best evidence within a standardized team-based approach, suggesting that standardizing protocols for diagnosis and treatment of CS may improve outcome and narrow the gender gap [36, 37].

CONCLUSION

Cardiogenic shock in women remains a major clinical challenge with high morbidity and mortality. Understanding and addressing sex differences in presentation, treatment and outcome are essential for improving care and reducing disparities. A summary of the most important aspects of etiology, diagnosis and treatment of CS in women is given in Table 2. While significant progress has been made, more research is urgently needed in this field. We also need studies evaluating if sex-tailored treatment, accounting for the differences in cardiovascular risk factors and clinical presentation, might improve outcomes.

Article information

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