Viewpoint

Non-Ischemic Cardiogenic Shock: How to Improve Outcomes – From Early Recognition to Distinctive Management

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Introduction

Cardiogenic shock is a clinical condition with an increasing incidence that presents with tissue hypoperfusion, leading to multiorgan dysfunction with a high mortality rate.[1] Non-ischemic cardiogenic shock has been recognized as an important cause of shock in emergency rooms, with an incidence exceeding that of shock related to acute myocardial infarction (AMI) in some populations.[2] Recent data from the Cardiogenic Shock Working Group (CSWG), an international multicenter registry, reveals that the mortality rate for this condition varies from 22 to 32%, depending on the type of institution.[3]

Unlike cardiogenic shock of ischemic origin, in which an index event marks the beginning of myocardial injury, potentially leading to the state of shock, in cardiogenic shock of non-ischemic origin the presentation represents the continuum of advanced heart failure. For the purposes of this article, we will be focusing exclusively on shock related to advanced heart failure, since it is the most prevalent type and often presents with a wide range of symptoms, which can delay diagnosis and contribute to poorer outcomes. The following topics will be covered: definitions pertinent to diagnosing cardiogenic shock and its various clinical presentations; initial systematic evaluation of these patients, including recent updates on the use of pulmonary artery catheters and individualized risk stratification for morbidity and mortality; and management strategies for non-ischemic cardiogenic shock, including pharmacological treatments, mechanical devices, and the role of "Shock Teams" in coordinated care.

Definitions and clinical presentation

Most societies include the following factors in the definition of shock: systolic blood pressure (SBP) < 90 mmHg for more than 30 min and/or requiring vasopressor drugs to maintain SBP ≥ 90 mmHg, associated with changes suggesting hypoperfusion (cold extremities, altered mental status, slowed capillary refill) and lactate levels ≥ 2 mmol/L.[4] However, there is no clear consensus to define the presence of non-ischemic cardiogenic shock. The clinical presentation of patients with advanced heart failure who progress to a state of shock with classic signs of hypoperfusion and multiorgan dysfunction can be slow and often elusive. Many patients have lower baseline blood pressure levels, and this may not be a major sign of impending shock; hypoperfusion often does not require hypotension.[5] The physical examination may not be exuberant, and concomitant congestion, observed in many cases, may not be evident. Thus, point-of-care ultrasound (POCUS) has become increasingly important in evaluating patients with advanced heart failure,[6] as it allows for objective stratification of the patient's hemodynamic profile and aids in guiding the initial therapeutic approach. Moreover, due to the variability in presentations and pre-existing conditions, it is crucial to emphasize the need for dynamic, serial assessments, as relying solely on single-point evaluations can lead to missed early signs of shock and, consequently, delay necessary treatment measures.

Assessment with exams

Alongside the physical examination and point-of-care ultrasound, performing an electrocardiogram is essential, just as it is important to collect the following tests: coagulation, renal function, and liver function tests to swiftly identify the presence and extent of multiorgan dysfunction; inflammatory markers such as C-reactive protein and leukogram; and markers of tissue perfusion and cardiac output, including lactate, bicarbonate, and central venous saturation. Lactate clearance within the first 24 hours of assessment has been studied as a predictor of mortality in patients with cardiogenic shock, and it may serve as an objective therapeutic target and an important factor in the decision-making process when managing this patient population.[7,8]

Use of pulmonary artery catheter

Although data from the ESCAPE study[9] and other reports question or even contraindicate the use of the Swan-Ganz catheter (pulmonary artery catheter/PAC) in the past, contemporary management of cardiogenic shock unequivocally includes this resource. This shift in perspective may be attributed to improved indications for the method's use, as well as a better understanding and application of the information it provides.[10-12] Currently, the use of the Swan-Ganz catheter is crucial for the diagnosis and management of non-ischemic cardiogenic shock, and its early use should be promoted. Recent studies have associated the use of PAC with greater use of ventricular assist devices and reduced mortality.[12]

Keywords

Cardiogenic Shock; Heart Failure; Intensive Care Unit

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More specifically, a study by Kanwar et al. demonstrated that the use of CAP in the first six hours of hospitalization for non-ischemic cardiogenic shock was associated with reduced in-hospital mortality compared with later use of PAC or no use of this resource (OR 0.37; 95% CI, 017-0.82).[13] To maximize the benefits of the Swan-Ganz catheter in shock management, healthcare teams must be well-trained in its use, measurements should be taken at least 2 to 3 times daily, and the data should be integrated into daily patient discussions and reassessments.

Risk stratification

In recent years, more than 30 scores for predicting the risk and severity of cardiogenic shock have been created.[14] The SCAI (Society for Cardiovascular Angiography and Interventions) indicator of cardiogenic shock, developed in 2019,[15] has been widely used to stratify severity and serve as a basis for implementing therapies and defining prognosis. This ranges from "A" (at risk) to "E" (extremis) on a scale that covers clinical, hemodynamic, and laboratory parameters.[16] Since its inception, this indicator has gained significant importance in non-ischemic cardiogenic shock due to its practical application, reproducibility, and widespread acceptance in academic circles. The SCAI classification was recently refined by the CSWG, including progression of shock and worsening of hemodynamic parameters, as well as clinical recovery. The dynamic profile of this classification thus became clearer, with a progressively increased risk of mortality between phases "B" and "E".[17]

Management

The initial stage of managing non-ischemic cardiogenic shock involves accurately identifying and understanding the patient's hemodynamic profile to enable effective hemodynamic resuscitation and clinical stabilization.[4] Simultaneously, medications aimed at optimizing cardiac function, such as vasopressors and inotropes, should be considered as established practices. These represent the main tools in the initial management of non-ischemic cardiogenic shock.[18]

The use of oxygen support is indicated for hypoxemic patients with peripheral O_2 saturation < 90% or PaO_2 < 60 mmHg in order to correct hypoxemia. Its routine use is not recommended since it causes vasoconstriction and a reduction in cardiac output.[19] The use of non-invasive positive pressure ventilation (NIV) is also indicated for certain patients with ventilatory dysfunction, which potentially reduces the need for orotracheal intubation.[20] Blood pressure (BP) should be monitored during NIV therapy, as the increase in intrathoracic pressure reduces venous return and ventricular preload. There may also be impairment of right ventricular (RV) function due to the increased pulmonary vascular resistance and RV afterload. In patients with progressive ventilatory dysfunction, orotracheal intubation is recommended. For patients who do not respond to initial treatment, the use of temporary mechanical circulatory support (MCS) devices should be assessed, with increasing benefits observed when care is guided by decisions from a dedicated "Shock Team." These topics will be discussed in greater detail below.

Pharmacological therapies

In our routine, the initial management of non-ischemic cardiogenic shock essentially comprises the use of vasoactive and inotropic drugs, considering the state of systemic hypoperfusion and insufficient cardiac output for metabolic demand. The main representatives of these pharmacological classes and their main characteristics are presented in Table 1. The main objective of treating this condition is restoring cardiac output, followed by relieving congestion, if present. In addition to drugs that act to regulate cardiovascular hemodynamics, loop diuretics are also key to the management of patients with acutely decompensated advanced heart failure by improving volume overload and systemic and pulmonary congestion resulting from increased renal excretion of water and sodium.[5] Therefore, it is indicated when there is evidence of congestion, as determined by Swan-Ganz catheter measurements and POCUS assessment.

The initial pharmacological therapy for non-ischemic cardiogenic shock depends on the patient's pressure threshold. In patients with permissive BP (usually systolic blood pressure [SBP] of at least 90 mmHg or mean arterial pressure [MAP] of 65 mmHg), we opt for an initial strategy of intravenous vasodilators, with sodium nitroprusside (SNP) being the preferred drug. This should be administered as a slow infusion, with a low initial dose and strict observation of BP behavior immediately after the start of administration. The usual expected response is a slight increase in BP,

Table 1 – Main medications used in cardiogenic shock and characteristics

Medication	Mechanism of action	Dose	SVR	BP	CO	HR
Norepinephrine	α1 >> β1 >β2	0,05-1 µg/kg/min	↑↑	↑↑	↑	↓↔
Vasopressin	V1	0,01 - 0,06 U/min	↑↑	↑↑	-	-
Sodium nitroprusside	NO	0,1 - 3 µg/kg/min	↓↓	↓↔	↔↑	↔
Dobutamine	β1 >> β2 > α1	2-20 µg/kg/min	↓↔	↓↔	↑↑	↑
Milrinone	PDE3 - Inhibitor	0,125-0,75 µg/kg/min	↓↓	↓↓	↑↑	↔

α1: alpha-1 adrenergic receptor; α2: alpha-2 adrenergic receptor; β1: beta-1 adrenergic receptor; β2: beta-2 adrenergic receptor; CO: cardiac output; HR: heart rate; NO: nitric oxide; BP: blood pressure; PDE3: phosphodiesterase 3; SVR: systemic vascular resistance; VR1: vasopressin V1 receptor.

improvement in peripheral perfusion, increased diuresis and clinical improvement.[21] In case of a hypotensive response, excessive NPS dose or hypovolemia should be considered. As an alternative to NPS, nitroglycerin (NTG) can be used, but with a lower arterial vasodilatory effect and less robust evidence supporting its use.

In patients with hypotension at initial presentation, a vasopressor can be started, especially norepinephrine, considered a first-line agent in this clinical context. Previous studies have demonstrated that this catecholamine is more effective than both dopamine and epinephrine. A recommendation IIb/B supports its use for maintaining organic perfusion pressure in recent guidelines.[20] The effect of norepinephrine on vital organ perfusion is accompanied by an increased left ventricular (LV) afterload, with a potential reduction in cardiac output. Therefore, the combination of norepinephrine with inotropes should be considered, especially in the population of patients with non-ischemic cardiogenic shock.[20]

Vasopressin, a non-sympathomimetic vasoconstrictor, increases systemic vascular resistance through a mechanism similar to the vasodilation effect of milrinone, and it is used alongside this inotropic agent to counterbalance hypotension, which allows for reduced use of norepinephrine.[22]

Inotropic therapy is commonly used in cardiogenic shock due to its effectiveness in increasing cardiac output. However, its application is not strongly supported by large-scale studies, with only a class IIb/C recommendation for use in this setting. Therefore, inotropic agents such as dobutamine or milrinone should be considered for patients with shock who do not respond to initial management.[20] These agents should be used for a short period, with ongoing hemodynamic reassessment and transition to vasodilator therapy as soon as feasible.

The DOREMI randomized clinical trial (RCT) compared the treatment of patients in cardiogenic shock with dobutamine versus milrinone.[23] This study included mostly ischemic patients and revealed a neutral result in the primary composite outcome involving in-hospital death, aborted cardiopulmonary arrest, heart transplantation, use of mechanical circulatory support devices, or cardiac or cerebral ischemic event. However, an observational study suggests that there may be a benefit in using milrinone as the inotropic therapy of choice in non-ischemic cardiogenic shock,[24] requiring an RCT involving this specific population.

Temporary mechanical circulatory support devices

For patients with persistent organ dysfunction despite initial treatment, the use of MCS devices should be evaluated. The choice of device depends on equipment availability, the care team's familiarity, and the specific needs of the patient. In Brazil, we can use the intra-aortic balloon pump (IABP), an extracorporeal membrane oxygenation (ECMO) device, and, more rarely, a microaxial flow pump (Impella).

The decision to escalate treatment to temporary circulatory support devices is critical and sensitive when managing patients at SCAI stage B or higher. Just as the early use of these devices can expose the patient to the risk of complications, a delayed indication may provide results below expectations. The concept of "door-to-support time" in the management of shock has gained strength, as was the case in the past with the "door-to-balloon" parameter in primary angioplasty for infarction.[25] Therefore, the ideal indication for MCS should occur according to the use of vasoactive drugs while considering, for example, the vasoactive drug score.[26] Before installing these devices, it is essential to define their objectives, such as achieving hemodynamic stabilization and improving perfusion parameters.[27] The main potential complications of MCS devices include vascular injury leading to limb ischemia, infection at the vascular access site, damage to heart valves, thromboembolic events, and bleeding.[28]

In cases of non-ischemic cardiogenic shock, the IABP is the most commonly used temporary circulatory support device. It serves as a bridge to definitive treatment, which typically involves transitioning to a ventricular assist device or heart transplantation.[29] The IABP works through a counterpulsation mechanism that reduces afterload, increases MAP, and optimizes coronary perfusion pressure, resulting in an average improvement of approximately 1 L/min in cardiac output, along with reductions in left ventricular end-diastolic pressure and myocardial oxygen consumption.[29] Currently, the multicenter RCT "Altshock 2 trial" is underway to evaluate early IABP implantation vs. standard optimized medical therapy in patients with non-ischemic cardiogenic shock. The primary outcome will be 60-day survival or successful bridge to heart transplantation.[30]

In the context of ischemic cardiogenic shock, on the other hand, the use of IABP should be considered only for exceptional cases since the – IABP - SHOCK - II – study showed no difference in mortality rates between the use of this device vs. optimized medical therapy.[31] It is important to recognize the limitations of this RCT, including the inclusion of patients with mild to moderate cardiogenic shock, a low rate of device insertion before primary coronary intervention, and a high crossover rate in the IABP group.

In the context of ischemic cardiogenic shock, the "DanGer Shock" study was recently published. This study compared the use of Impella CP combined with optimized clinical treatment against optimized clinical treatment alone in patients with AMI and cardiogenic shock.[32] A total of 360 patients were randomized, and 45.8% from any cause were recorded in the Impella CP group vs. 58.5% in the clinical treatment group, with a hazard ratio of 0.74 (95% CI, 0.55-0.99, p = 0.04). The Impella is implanted percutaneously through the femoral artery and continuously transfers blood from the LV to the aorta, thus ensuring improvement in cardiac output and reduction in LV wall tension, with a positive effect on myocardial O_2 consumption. Depending on the device, it can provide up to 2.5 - 5 L/min of blood flow.[29]

Venoarterial ECMO consists of a percutaneous ventricular assist device comprised of a circuit between the venous and arterial systems, interposed by a centrifugal propulsion pump and an external membrane blood oxygenation system. Its effect is the result of a reduction in RV preload, pulmonary flow, LV end-diastolic pressure, and LV end-diastolic volume.[29] The use of ECMO in cardiogenic shock is based mainly on observational studies. The 2023 ECLS VA-ECMO study, which included patients with cardiogenic shock regardless of

etiology, found no benefit from the technology.[33] In a recent meta-analysis that included four RCTs addressing the use of venoarterial ECMO in patients with AMI-related cardiogenic shock, the result was also negative, without benefit in 30-day mortality and with an increased risk of major bleeding or vascular complications.[34]

Despite unfavorable results in RCTs, the use of MCS devices continues to be popular as rescue therapy in patients with cardiogenic shock refractory to clinical management.[35] It is noteworthy that the studies evaluating these devices have not accurately reflected real-world clinical scenarios, and there are currently no studies specifically focused on non-ischemic cardiogenic shock. Many RCTs compared the use of MCS devices as part of a protocol with optimized medical therapy combined with the device if deemed necessary by the attending physician, with a rescue ECMO use rate of up to 39% in the control group.[36] Additionally, the clinical study protocols for MCS device use may be less flexible, potentially leading to less optimal device selection for individual patients.

In a prospective cohort study of 49 patients with cardiogenic shock treated with venoarterial ECMO or Impella CP in Brazil, the average mortality rate was 61%, with no significant difference between the devices used.[39] In these patients, the etiology of shock in 45% of cases was acute myocardial infarction (AMI) and, in 20%, advanced HF. In patients with non-ischemic cardiogenic shock, the mortality rate was 70%. In patients with AMI as the etiology for shock, the mortality rate was 59%.

Shock team

For the best results in the management of patients with cardiogenic shock, including the appropriate indication of circulatory support devices, it is essential to apply a concept that has been gaining international traction, although little discussed in national literature: the "shock team" (Figure 1). This involves a team with interventional cardiologists, cardiologists specialized in advanced heart failure, cardiac surgeons, and intensive care specialists, and it seeks early recognition and diagnosis of cardiogenic shock, in addition to rapid coordination between the professionals involved for streamlined decision-making.[38] Several studies have demonstrated better outcomes when shock management is performed with a shock team approach,[39] with increased survival rates in 30 and up to 240 days.

In cardiology, there are other examples of an interdisciplinary approach to the treatment of specific diseases. The concept of a "Heart Team" is consolidated in the literature for decision-making in structural heart disease and advanced coronary disease. This team approach in cardiogenic shock is especially relevant considering the high morbidity and mortality rates associated with this condition and the complex set of interventions involved in its treatment, including percutaneous, surgical and clinical procedures.[40] Thus, the management of these patients involves good communication and interdisciplinary coordination.

It is becoming increasingly evident that early use of MCS devices is proving to be a strategy that leads to better outcomes for patients with cardiogenic shock. However, to determine these interventions precisely and swiftly, a specialized and cohesive team is essential, as it requires careful consideration of the risk of complications versus potential benefits. The greater the personal and institutional experience with this profile of patients and interventions, the better the outcomes. A learning curve effect has been reported, with improvement in clinical outcomes after the implantation of 40 MCS devices by the care team. The average mortality rate in the first period of this study was 83%, compared to a mortality rate of 40% in the final period of the study (p = 0.002).[37]

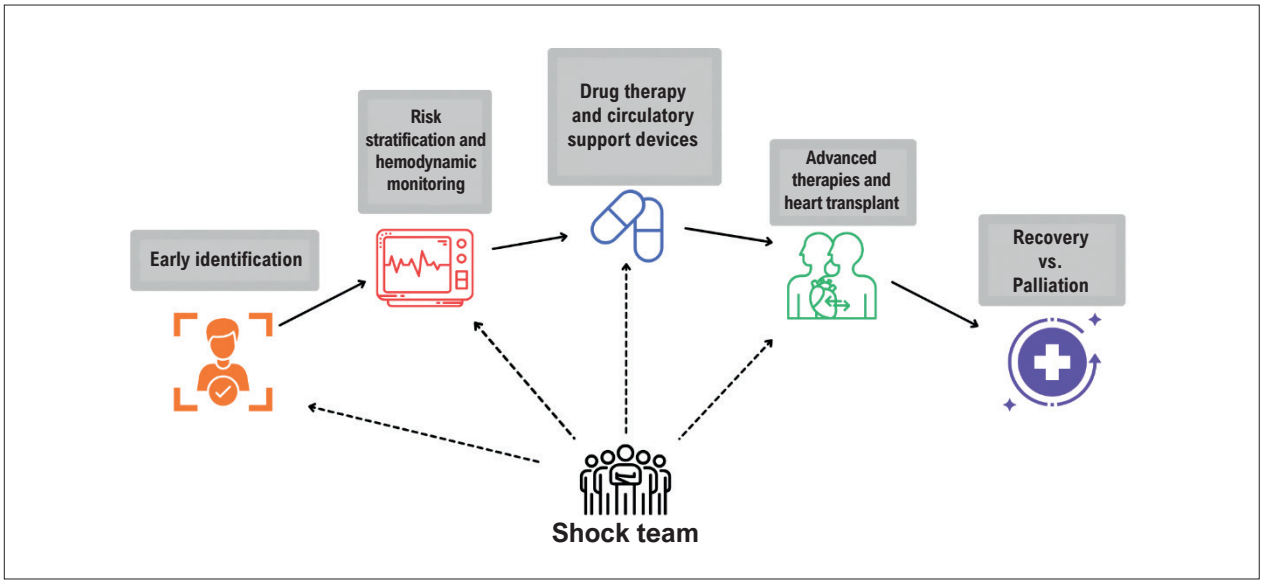

Figure 1 – *General approach to the patient with non-ischemic cardiogenic shock.*

Conclusion

The increased focus on non-ischemic cardiogenic shock has led to a rise in scientific research, gradually establishing key principles that guide modern management. Notable practices include adopting a team-based approach for rapid and integrated decision-making; utilizing a combination of clinical, hemodynamic, and radiological assessments efficiently and sequentially to determine the optimal timing for escalating to mechanical support; employing risk scores to guide the escalation or de-escalation of mechanical support; and aligning the management strategy, which should be patient-centered, with institutional capabilities, including expertise in mechanical support, to maximize benefits and minimize complications.

Author Contributions

Conception and design of the research and Acquisition of data: Amantéa RP, Clausell N; Writing of the manuscript: Amantéa RP, Hastenteufel L, Scolari FL, Goldraich LA, Clausell N; Critical revision of the manuscript for content: Hastenteufel L, Scolari FL, Goldraich LA.

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