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EXPERTS' OPINION

Cardiac function after cardiac arrest: what do we know?

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ABSTRACT

Postcardiac arrest myocardial dysfunction (PCAMD) is a frequent complication faced during post-resuscitation care that adversely impacts survival and neurological outcome. Both mechanical and electrical factors contribute to the occurrence of PCAMD. Prearrest ventricular function, the cause of cardiac arrest, global ischemia, resuscitation factors, ischemia/reperfusion injury and post-resuscitation treatments contribute to the severity of PCMAD. The pathophysiology of PCAMD is complex and include myocytes energy failure, impaired contractility, cardiac edema, mitochondrial damage, activation of inflammatory pathways and the coagulation cascade, persistent ischemic injury and myocardial stiffness. Hypotension and low cardiac output with vasopressor/inotropes need are frequent after resuscitation. However, clinical, hemodynamic and laboratory signs of shock are frequently altered by cardiac arrest pathophysiology and post-resuscitation treatment, potentially being misleading and not fully reflecting the severity of postcardiac arrest syndrome. Even if validated criteria are lacking, an extensive hemodynamic evaluation is useful to define a "benign" and a "malign" form of myocardial dysfunction and circulatory shock, potentially having treatment and prognostic implications. Cardiac output is frequently decreased after cardiac arrest, particularly in patients treated with target temperature management (TTM); however, it is not independently associated with outcome. Sinus bradycardia during TTM seems independently associated with survival and good neurological outcome, representing a promising prognostic indicator. Higher mean arterial pressure (MAP) seems to be associated with improved survival and cerebral function after cardiac arrest; however, two recent randomized clinical trials failed to replicate these results. Recommendations on hemodynamic optimization are relatively poor and are largely based on general principle of intensive care medicine.

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Cardiac arrest (CA) is a leading cause of death in Europe and has an incidence of 84.0-88.6 cases per 100,000 adults every year, with survival rates of only 8-10% and few with good neurological outcomes.[1, 2] Despite significant improvements in resuscitation and post-resuscitation care, CA survival has only slightly increased.[3] About half of the patients admitted alive in hospital die before discharge, and even fewer show good long-term neurological outcomes.[4] Poor prognosis is due to post-CA syndrome (PCAS), a pathophysiological state that includes post-CA myocardial dysfunction (PCAMD) and cerebral injury and is related to the whole-body ischemia-reperfusion (I/R) injury.[4]

PCAMD is a complex condition where prearrest ventricular function, the cause of CA, global ischemia, resuscitation factors, I/R injury and post-CA treatments contribute to the severity of myocardial injury and cardiac dysfunction.[4-7]

Hemodynamic instability requiring pharmacological/mechanical support occurs in two thirds of CA patients with ventricular fibrillation.[8] If not promptly recognized and treated, this clinical condition can deteriorate, causing multiorgan dysfunction and early death.[4, 9, 10] In patients that survive to hospital discharge, poor cerebral perfusion and ischemia during intensive care unit stay exacerbates the neurological injury.[4]

The mechanisms of PCAMD overlap with those observed in other clinical syndromes, such as myocardial infarction, sepsis-induced cardiomyopathy and stress-related cardiomyopathy (*i.e.* Tako-Tsubo Syndrome), and after cardiopulmonary bypass. Nonetheless, PCAMD has a typical time course and features that need to be considered in order to provide comprehensive care.[4, 6, 7]

Pathophysiology of myocardial dysfunction after CA

PCAMD is defined as a reversible deterioration of cardiac performance that occurs after return of spontaneous circulation (ROSC), not fully explained by myocardial ischemia or persistent coronary occlusion. As opposed to the regional distribution of myocardial wall dyskinesis in acute myocardial infarction, PCAMD impacts the heart globally. Both mechanical and electrical factors contribute to the occurrence of PCAMD; typical features include severe impairment in systolic and diastolic function and cardiac dysrhythmias and recurrent CA.[11] PCAMD overlaps with prearrest cardiac performance and myocytes necrosis, due to coronary ischemia and I/R injury, so it is particularly tricky to accurately distinguish between reversible and irreversible myocardial injury.

Cardiac arrest

Decrease in oxygen delivery shifts cellular metabolism to non-oxidative glycolysis, decreasing ATP production and causing intracellular acidosis and sodium imbalance due to Na^+/K^+ ATPase inhibition; furthermore, accumulated H^+ activates the sarcolemmal sodium-hydrogen exchanger isoform-1, worsening Na^+ overloads.[12] Increase in cytosolic sodium causes cell swelling and promotes intracellular Ca^{2+} influx through Na^+/Ca^{2+} exchangers; ATP deficit impairs the activity of both plasma membrane calcium ATPase and sarco-/endoplasmatic reticulum calcium ATPase, further exacerbating Ca^{2+} overload. Calcium overload promotes apoptosis by caspases activation, activates intracellular proteases/phospholipases and initiates the formation of the mitochondrial permeability transition pore. Global hypoperfusion and ischemia trigger a whole-body inflammatory response, aggravating mitochondrial injury, damaging membrane phospholipids and impairing fatty acid metabolism. Finally, endothelial damage and initiation of the coagulation cascade occur, causing neutrophil and platelet adhesion and microthrombi formation in peripheral microcirculation.

During cardiopulmonary resuscitation

Chest compression efficacy is intrinsically limited, and the resulting heart perfusion is not enough to revert cardiac ischemia. Cardiac stiffening caused by prolonged ischemia (*i.e.* "stone heart") and by progressive dilatation of the ventricles during CPR[13] impairs the blood flow generated during chest compressions. Microthrombosis and leucocyte adhesion will further impede myocardial reperfusion (*i.e.* "no-reflow phenomenon").[14] High levels of circulating adrenaline bind with β-2 receptors, coupled with inhibitory G proteins, and decrease contractility;[15] furthermore, catecholamines cause microvascular coronary vasoconstriction, increase oxygen consumption and exacerbate oxidative stress, intensifying the severity of PCAMD.[16] Cardiac defibrillation contributes to myocardial injury proportional to the energy and the number of shocks delivered.[17, 18]

After return of spontaneous circulation

The detrimental effects initiated during CA continue after ROSC, particularly in the first hours after resuscitation. Indeed, the restoration of tissue perfusion initially paradoxically aggravates the I/R injury due to overproduction of reactive oxygen species (ROS), further impairing beta-adrenergic signaling and ATP production in the heart. Cytokines released have direct negative inotropic effects and intensify cellular energy

failure and ROS production.[19] Glycolysis is persistently uncoupled from oxidative phosphorylation, worsening intracellular acidosis and impairing myocyte contractile function. Persistently high levels of intracellular Ca^{2+} and circulating catecholamines aggravate the potential for cardiac dysrhythmia and recurrent CA. Cell metabolism starts to improve 3-6 hours after ROSC, due to enhanced ATP and antioxidant production. Ion pumps and cellular enzymes increase their functionality, restoring intracellular Na^{+} and Ca^{2+} normal concentrations. The fading of the "no-reflow" phenomenon, the catabolism of circulating catecholamines and a decrease in H^{+} concentration increase the sensitivity of contractile proteins to Ca^{2+} and ameliorate cardiac contractility. Generally, the alterations associated with PCAMD resolve in the next 24-72 hours, even if longer recovery has been reported.[20]

Cardiac and hemodynamic characteristics after CA

After CA, patients frequently exhibit various degrees of hemodynamic instability and hypotension, requiring advanced hemodynamic monitoring, aggressive fluid replacement, vasopressor/inotropic drugs and, in selected cases, mechanical support of the circulation.[7, 11, 21] As in other clinical conditions, hemodynamic optimization has become a cornerstone of post-resuscitation care;[22] however, the level of evidence is scarce, and the impact on the outcome is unclear,[23-25] representing a relevant knowledge gap in resuscitation science.[26]

Soon after resuscitation, the heart rate and arterial pressure are elevated, due to high concentrations of endogenous and exogenous catecholamines. The heart shows signs of both diastolic dysfunction (cardiac edema, ischemic contracture and impaired relaxation) and systolic dysfunction (impaired contractility, inadequate oxygen delivery, intracellular acid-base and ion imbalance); as a result, cardiac output is generally decreased and patients may manifest with hypotension, low cardiac output and poor tissue perfusion (*i.e.* cardiogenic shock).[27] Moreover, distributive shock may overlap with cardiogenic shock, due to superimposed vasodilation secondary to I/R injury and systemic inflammation, requiring volume expansion and prolonged vasopressor support.[4, 9]

Defining cardiogenic shock in the post-cardiac arrest patient

A clear impediment for the research of cardiac dysfunction after CA is the lack of well validated criteria to define cardiogenic shock. Criteria such as hypotension (*i.e.* systolic blood pressure <90 mmHg, or vasopressors required to achieve a blood pressure ≥90 mmHg), signs of impaired organ perfusion (*e.g.* central nervous system abnormalities including confusion, lack of alertness or loss of consciousness; oliguria; cold, clammy skin and extremities; increased arterial lactate >2 mmol l^{-1}) in the state of normo- or hypervolemia and reduced cardiac index (CI, *i.e.* <1.8 or <2.2 l min^{-1} m^{-2} with cardiac support) or elevated left ventricular filling pressures (*i.e.* pulmonary capillary wedge pressure >15 mmHg) are not useful.[28] Indeed, all CA patients have high blood lactate at admission to the hospital, and patients receive target temperature management (TTM), resulting in cool extremities, skin mottling and hypothermic diuresis. In addition, patients receive sedative and neuromuscular-blocking agents, which makes neurological evaluation impossible. Lactate may also be a poor indicator of tissue oxygenation in post-CA patients, since gut ischemia and seizures may increase serum lactate levels, and hypothermia may reduce lactate clearance by the liver.[29]

General criteria for adequate perfusion include lactate clearance and adequate diuresis.[22] However, normal serum lactate levels do not guarantee optimal brain oxygenation. Therefore, low cardiac output is easily undetected if advanced hemodynamic monitoring is not used.[8]

Cardiac output

Low cardiac output is present in up to two thirds of CA patients,[8, 9] particularly in those with a cardiac cause of the CA.[8, 30] Some studies indicate that it accounts for most of the early death in the ICU in the first three days.[10] Typically, the patients are in cardiogenic shock and suffer from low diastolic pressure, causing coronary

hypoperfusion with a progressive lowering of cardiac output, ultimately resulting in multiple organ failure, refractory shock and death.[5, 9] It has been reported that cardiac output remains depressed for 8 h after ROSC and progressively recovers in the next 24-48 h, demonstrating the reversible nature of PCAMD in patients without large acute myocardial infarction (AMI) as the precipitating cause of CA.[9] These data are consistent with numerous experimental reports.[31-33] Patients with pre-existing cardiac dysfunction have lower postresuscitation echocardiographic left ventricular ejection fraction (LVEF) and cardiac output compared to the healthy population; however, the relative decline in LVEF from baseline values is similar in both patient groups.[34] Adequate measurement of cardiac output by continuous thermodilution may be challenging when intravascular cooling devices are used, and continuous mixed venous oxygen (SvO_2) saturation may better reflect the cellular oxygen balance.[35] Various studies have questioned the impact of cardiac output on resuscitation outcomes. In a subgroup analysis from the TTM Trial, cardiac index during TTM after CA was not associated with mortality or cause of death (cerebral *vs*. non-neurological) regardless of the level of the TTM target temperature (Table I).[36-42] Nonetheless, hemodynamic profiles of patients dying from non-neurological death significantly differed compared to survivors and cerebral deaths, showing that reduced mean arterial pressure and elevated lactate were independent predictors of non-neurological mortality. Even if the cardiac index was not a mortality predictor by itself, the presence of CI <2.5 L min^{-1} m^{-2} and blood lactate >2 mmol L^{-1} identified patients with higher mortality. Similarly, cardiac output failed to predict the incidence of acute kidney failure and the need for renal replacement therapy, whereas heart rate, lactate levels and mean arterial pressure were better predictors (Table I).[42]

Postresuscitation care (including hypothermia, sedation, analgesia, paralysis and mechanical ventilation) may affect cardiac output independently of the extent of myocardial injury and PCAMD. Indeed, patients treated with TTM (deeply sedated and frequently paralyzed) reduce cellular metabolism and oxygen consumption, so even low cardiac output may guarantee adequate oxygen delivery. Moreover, superimposed vasodilation may deceptively increase cardiac output without any improvement in tissue perfusion.[4, 9] In fact, a preserved or augmented CI does not exclude the presence of extensive microcirculatory alterations, resulting in regional hypoperfusion and organ dysfunction.[27]

Heart rate

Heart rate has been associated with outcome in CA patients; somewhat surprisingly, sinus bradycardia during TTM has been shown to be associated with lower mortality and less severe organ dysfunction (Table I).[40, 43] Moreover, lower time-weighted mean heart rates at 48- and 72-hours postresuscitation were associated with improved one-year neurological outcomes, even if the relationship was less marked in TTM patients.[39] Hypothermia can modify the heart rate through various mechanisms; after an initial phase of tachycardia, the heart rate progressively decreases, due to alterations in the spontaneous depolarization of cardiac pacemaker cells, in the conduction of myocardial impulses, in the duration of action potentials and in autonomic nervous system function during the maintenance phase of TTM. Moreover, by reducing oxygen consumption, a decrease in oxygen delivery is relatively well tolerated. Sinus bradycardia probably represents a marker of preserved autonomic response, and the lack of this reflex could identify patients with more severe PCAS and greater neurological injury.[39, 40] The crosstalk between heart rate and autonomic function (*e.g.* the heart rate variability[44] and the hemodynamic response during different phases of hypothermia[45]) is a topic of growing interest. No prospective trial has evaluated potential strategies to reduce heart rate during postresuscitation care, so it is unclear if lower heart rate represents a prognostic marker or could be a future treatment target. Interestingly, a right bundle branch block recording in the first ECG at hospital admission was directly associated with higher mortality and was independently associated with an unfavourable prognosis;[46] however, further investigations are needed to confirm these results.

TABLE I.—*Relevant recent literature on postresuscitation cardiac function.*

Intervention studies				
Study	Design and patients included	Inclusion criteria	Intervention groups	Main results
COMACARE Trial Jakkula *et al.*[36]	Randomized clinical trial, N.=123	Comatose, ventilated, adult patients resuscitated from VF/pVT OHCA Confirmed or suspected cardiac cause ROSC within 10-45 min from OHCA	Low-normal (65-75 mmHg) *vs*. high-normal (80-100 mmHg) MAP	Targeting a specific range of MAP is feasible. These MAP range are safe. No improvements in NSE after 48 hours from OHCA were observed
NEUROPROTECT post-CA Trial Ameloot *et al.*[37]	Randomized clinical trial, N.=112	Comatose, adult patients resuscitated from OHCA of resumed cardiac cause Sustained ROSC for >20 min	EGDHO (MAP 85-100 mmHg, SvO2 65-75%) *vs*. MAP 65 mmHg	EGDHO was safe, improved cerebral oxygenation measured by NIRS, but did not result in an improvement in neurological outcome
Observational studies				
Study	Design and patients included	Inclusion criteria	Main results	
Kilgannon *et al.*[38]	Prospective observational study, N.=151	Comatose, adult patients resuscitated from IHCA and OHCA	Time-weighted average MAP pressure was associated with good neurologic outcome at a MAP threshold greater than 70 mmHg	
Oksanen *et al.*[39]	Preplanned sub-study of the FINNRESUSCI study, N.=504	Adults patients resuscitated from OHCA	Lower heart rate was independently associated with one-year good neurological outcome	
Thomsen *et al.*[40]	Retrospective study, N.=234	Comatose, adult patients resuscitated from OHCA of presumed cardiac cause Sustained ROSC for >20 min	Synus bradycardia (HR<50 bpm) during TTM at 33°C was independently associated with lower 180-day mortality rate	
Grand *et al.*[41]	*Post-hoc* analysis of the TTM Trial, N.=151	Comatose, adult patients resuscitated from OHCA of presumed cardiac cause Sustained ROSC for >20 min	Cardiac output was not an associated with mortality, independently from the presumed cause of death. If lactate is normal, low cardiac index during TTM seems benign and not associated with mortality	
Grand *et al.*[42]	*Post-hoc* analysis of the TTM Trial, N.=152	Comatose, adult patients resuscitated from OHCA of presumed cardiac cause Sustained ROSC for >20 min	Cardiac output is not an independent predictor of AKI Heart rate, MAP and lactate were independently associated with AKI	

AKI: acute kidney injury; CA: cardiac arrest; EGDHO: early good-directed hemodynamic optimization; IHCA: in-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; MAP: mean arterial pressure; NIRS: near infra-red spectroscopy; NSE: neural serum enolase; pVT: pulseless ventricular tachycardia; ROSC: return of spontaneous circulation; TTM: target temperature management; VF: ventricular fibrillation.

Arterial pressure

Mean arterial pressure (MAP) has been widely investigated as a potential hemodynamic goal in postresuscitation care, and various studies reported a positive association between MAP and outcome (Table I).[38, 47, 48] Furthermore, MAP<65-70 mmHg and higher doses of vasopressor were associated with increased incidence of organ dysfunction (*e.g.* acute kidney injury), mortality and a poor neurological outcome.[38, 49-52] Two prospective randomized clinical trials (COMACARE[36] and Neuroprotect post-CA[37] trials; Table I) compared the impact of higher MAP (80-100 mmHg and 85-100 mmHg with SvO_2 65-75%) with low-normal MAP values (65-75 mmHg and 65 mmHg, respectively); in both studies, a hemodynamic strategy with higher MAP was feasible and safe; however, no improvements in neurological outcome were observed at 180 days.[36, 37] However, higher MAP was associated with lower plasma cardiac troponin T levels when data from

both studies were merged, suggesting that a balanced use of α-1 vasoconstrictor could increase coronary perfusion pressure and ameliorate myocardial ischemia without significant side effects (personal communication from Pekka Jakkula).

Targeting higher MAP values has a pathophysiological rationale, particularly in the immediate hours after resuscitation. Cerebral perfusion is severely impaired, due to intracerebral vasoconstriction, high circulating catecholamines, persistent vascular occlusion, a right-shift of cerebral autoregulation limits and a heterogeneous distribution of blood flow;[14, 53, 54] concordantly, a higher MAP should better preserve cerebral blood flow. However, the evidence is limited regarding this hypothesis. Even if no target arterial pressure can be recommended, a MAP>65-70 mmHg seems reasonably safe and consistent with similar recommendations in critical care. Possibly, a fixed MAP value simply does not fit every patient need, and a personalized approach based on individual comorbidities and physiological response should be encouraged.[36, 37, 52]

Practical considerations

Cardiac output by itself may not be the best indicator to identify patients with increased risk of mortality and poor long-term neurological function. However, when cardiac function is contextualized with other clinical, hemodynamic and laboratory variables, two distinct hemodynamic phenotypes could be observed in patients with low cardiac output at admission: a "benign" and a "malign" form of myocardial dysfunction and cardiogenic shock (Table II). It is important to recognize these two different patterns, because they potentially have treatment and prognostic implications (Figure 1).

Recommendations on hemodynamic optimization are relatively poor and are largely based on general principle.[22] An echocardiogram should be obtained as early as possible, ideally on admission; serial echocardiographic evaluation allows continuous monitoring and treatment titration. Cerebral tissue oxygen saturation as measured with near infrared spectroscopy did not show a good correlation with prognosis. In the absence of good indicators of adequate cerebral and vital organ oxygenation, treatment should be guided by hemodynamic variables (*e.g.* blood pressure, heart rate, urine output, rate of lactate clearance and central venous oxygen saturation), taking into consideration their specific limitations, as previously discussed. In intensive care, an arterial line for continuous blood pressure monitoring is essential, and a central venous access is also indispensable for blood

TABLE II.—*Proposed phenotypes of cardiogenic shock in patients resuscitated from cardiac arrest.*

	Benign	Malign
Arterial pressure	MAP>65-70 mmHg No/moderate vasopressor support	MAP<60-65 mmHg High dosage of vasopressor for prolonged time
Heart rate and cardiac rhythm	Sinus bradycardia during TTM Increase after rewarming within physiological limits	Constantly elevated No significant changes during the various phases of TTM Various degree of dysrhythmia (*e.g.* rapid atrial fibrillation, sustained ventricular ectopy, ventricular tachycardia, recurrent CA)
Cardiac output	Recovery in the first 3 days after admission	Progressive decrease Need for mechanical circulatory support
Diuresis	>0.5 mL kg-1 h-1	<0.5 mL kg-1 h-1 Need for renal replacement therapy
Lactate	Constant clearance Decrease to low/normal value within 6-12 hours	Slow clearance Elevated for several days
Central/mixed venous saturation	>65-70%	<60-65% or abnormally high

CA: cardiac arrest; MAP: mean arterial pressure; TTM: target temperature management; AKI: acute kidney injury; CA: cardiac arrest; EGDHO: early goal-directed hemodynamic optimization; IHCA: in-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; MAP: mean arterial pressure; NIRS: near infra-red spectroscopy; NSE: neural serum enolase; pVT: pulseless ventricular tachycardia; ROSC: return of spontaneous circulation; TTM: target temperature management; VF: ventricular fibrillation.

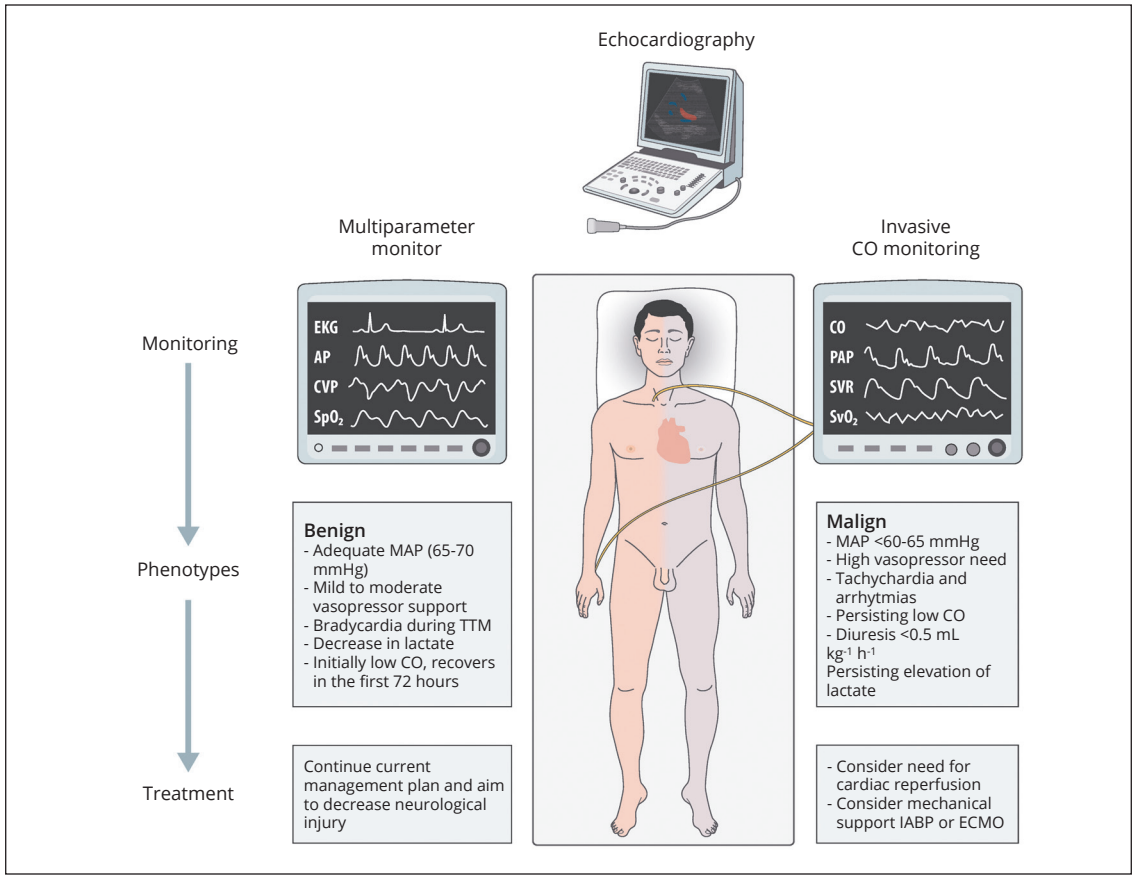

Figure 1.—Approach to postcardiac arrest myocardial dysfunction.

sampling, blood gas analysis and drug administration. Advanced cardiac output monitoring should be considered in patients with a malign form of cardiogenic shock, and the choice of a specific device/technology should be based on local availability and expertise.

The best treatment strategy to optimize cardiac function is still debated. Faster lactate clearance and improved outcomes were observed when a higher MAP was achieved using fluid over vasopressors.[55] Even if it is not possible to exclude that this is feasible in less severely injured patients, abundant fluid resuscitation in the first hours after resuscitation is frequent and remarkably well tolerated.[9, 23] Vasopressors are used to target MAP and limit positive fluid balance. No specific drug demonstrated a clear advantage; however, the use of adrenaline is likely best avoided. In a recent randomized controlled pilot trial, the use of adrenaline compared to noradrenaline in AMI patients resulted in more tachycardia, refractory cardiogenic shock, multiple organ dysfunction and mortality, probably due to catecholamine overload and stress cardiomyopathy.[15, 56, 57] Currently, noradrenaline is the first-line vasopressor to maintain target MAP. One should, however, be careful using unopposed α-1 induced vasoconstriction, since elevated afterload may impair stroke volume, cardiac output and cerebral perfusion. A combined approach using vasopressors and inotropes, as guided by continuous SvO_2 measurements, has been tested in the Neuroprotect post-CA trial and resulted in clear improvements in cerebral perfusion and oxygenation during the first 12 hours of ICU stay.[37] Other inotropes have been proposed (*e.g.* levosimendan, PDE-III inhibitors) and represent valid alternatives in selected patients.[11]

Mechanical circulatory support (*e.g.* intra-aortic balloon pump, percutaneous ventricular assist device and extracorporeal life support) should be promptly inserted in selected patients when pharmacological therapies fail.[21, 58]

Fast-track coronary angiography (CAG) and percutaneous coronary intervention (PCI) are indicated for patients presenting ST-segment-elevated myocardial infarction (STEMI) on postresuscitation ECG.[59, 60] Early reperfusion is associated with improved survival and good neurological outcomes.[61] In patients without STEMI, non-coronary causes of CA should be excluded.[59, 60] If alternative causes are not identified, delayed CAG and PCI are indicated, ideally within two hours, since an acute critical coronary occlusion could be identified in up to one third of the patients.[61] The role of CAG and PCI in this group of patients is less well established, and recent evidence does not support any clear impact on CA outcome.[62]

Key messages

- Postcardiac arrest myocardial dysfunction frequently complicates postresuscitation care and adversely impacts survival and neurological outcome.
- Clinical criteria to define cardiogenic shock are not validated in cardiac arrest population; indeed, low cardiac output is frequent and not independently associated with mortality or adverse outcome.
- Two distinct hemodynamic phenotypes could be observed in patients with PCAMD and low cardiac output at admission: a "benign" and a "malign" form of myocardial dysfunction and cardiogenic shock.
- Evidence on best treatment strategy for hemodynamic optimization after cardiac arrest is scarce; actual recommendations are largely based on general principles of hemodynamic support in critically ill patients.

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