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VIEWPOINT
Acute cardiovascular care

Cardiogenic shock: do we need a paradigm shift?

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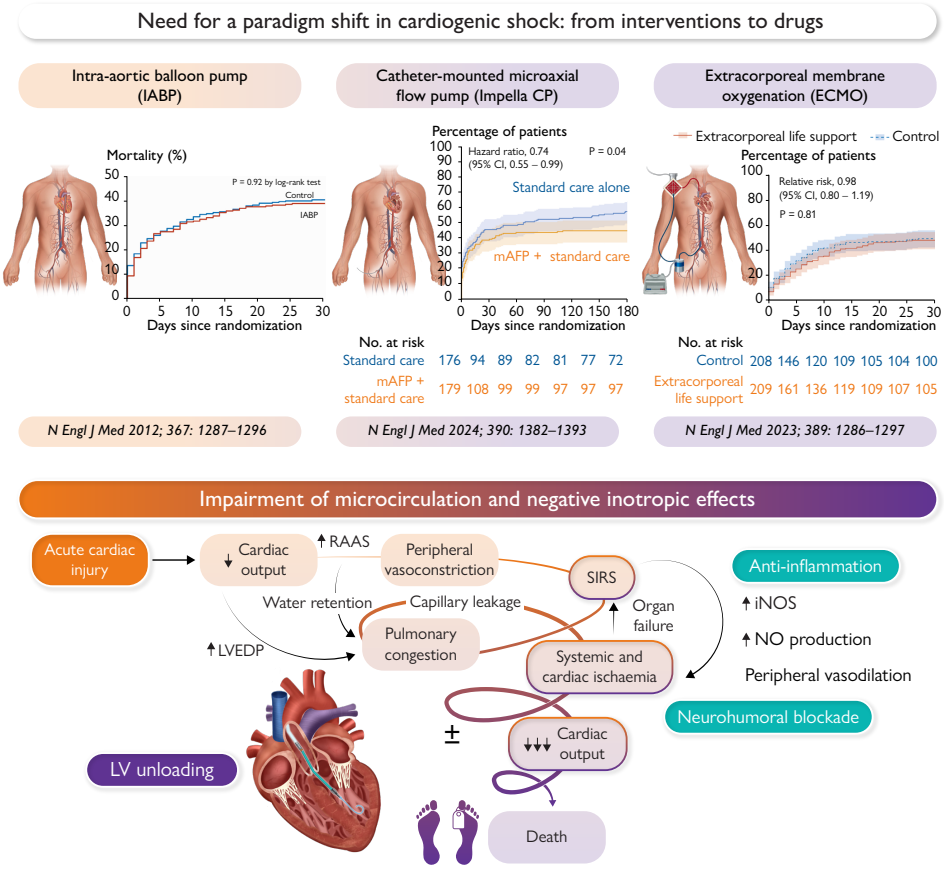
Graphical Abstract



The paradigm shift in the management of cardiogenic shock: moving from pure mechanical left ventricular unloading to neurohumoral and anti-inflammatory blockade with or without left ventricular mechanical assistance (red arrow). CI, confidence interval; iNOS, inducible nitric oxide synthase; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; mAFP, microaxial flow pump; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; SIRS, systemic inflammatory response syndrome.

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In 1962, a so far unknown young philosopher published a ground breaking book: *The Structure of Scientific Revolutions*.[1] Therein, Thomas S. Kuhn challenged the dominant linear course of scientific progress. Rather, he argued, science evolves in periods of normal science along a major paradigm and changes its course radically in scientific revolutions. Examples of this process are the change from Ptolemaic astronomy to Copernicus's heliocentric model or from Newton's mechanics to Einstein's relativity theory. In medicine, William Harvey's seminal book *De Motu Cordis* in 1616 is another example as it completely changed our view of the human body and its organs,[2] while the work of Robert Koch and Louis Pasteur revolutionized our understanding of contagious diseases.

In coronary artery disease, in particular as regards its acute manifestations, the *open-artery hypothesis* was the leading paradigm. As such, reopening of the occluded infarct-related artery initially with thrombolytics and later with primary percutaneous coronary intervention (pPCI) was a breakthrough. Indeed, compared to the times when President Dwight D. Eisenhower had his famous heart attack in 1956,[3] when over half of the patients who even reached a hospital died, in-hospital mortality for stable patients with acute coronary syndromes (ACS) could be massively reduced. Today, pPCI together with aspirin, $P2Y_{12}$ receptor blockers, heparin, rapid transport to heart attack centres, radial access, drug-eluting stents, and, if required, intravascular imaging reduced in-hospital mortality of ACS down to ~3%–5%. However, patients with cardiogenic shock complicated by ACS, which is the topic of this viewpoint, still have an unacceptably high mortality. Acute cardiac care and pPCI importantly improved survival (absolute improvement in 6-year survival of 13% compared with initial medical stabilization),[4] in-hospital or 30-day mortality has not changed ever since over the last two decades. Indeed, in spite of all the progress made since Eisenhower's heart attack, in the real world still one out of two patients with cardiogenic shock die within 30 days.

As a continuation of the open-artery hypothesis, complete revascularization in those with multivessel disease has been the preferred approach. However, in the randomized CULPRIT-SHOCK trial, immediate complete revascularization in those presenting with multiple coronary lesions, against clinical intuition, did not improve outcomes compared to culprit artery only pPCI with a possible staged revascularization strategy. Indeed, immediate multivessel pPCI increased rather than decreased mortality in those presenting in cardiogenic shock.[5]

Another paradigm stated that unloading or haemodynamic support of the ischaemic left ventricle might provide benefit in cardiogenic shock (*Graphical Abstract*). First, the intra-aortic balloon pump has been evaluated in a randomized trial, but against all odds, the device did not change outcomes.[6] Subsequently, the ECLS-SHOCK trial in which 420 patients were randomized to venoarterial extracorporeal membrane oxygenation (or extracorporeal life support) or usual care, outcomes did not differ.[7] Next, catheter-mounted microaxial flow pumps (commonly Impella®) have been widely implanted into the left ventricle with a number of propensity-matched registries showing, again—although microaxial flow pumps reduce left ventricular (LV) filing pressures and are thus more effective on LV unloading—to the surprise of many and in spite of its favourable haemodynamic effects, either no benefit or even increased bleeding and mortality in unselected patients in clinical practice.[8] Yet recently, the DanGer Shock trial randomized 179 highly selected ST-elevation myocardial infarction patients without risk of neurological deficit to a microaxial flow pump and 176 to standard care.[9] While mortality was significantly reduced from 58.5% to 45.8% with effective LV unloading (with a relevant heterogeneity of results among the Danish and German population), the use of the microaxial flow pump was associated with a four-fold higher complication rate of 24.0%, but of only 6.2% with standard care. In particular, renal replacement therapy and bleeding were twice as common and limb ischaemia and sepsis were also markedly increased with LV unloading. Overall, this led to a remarkably low number needed to treat of 8, but an unusually high number needed to harm of 6 (*Graphical Abstract*).

Bleeding, a common complication in the ACS population—associated with markedly worse long-term outcomes beyond that of the DanGer Shock trial—may not only be related to the 14 F puncture site of the device, but also to haemostatic imbalance due to inflammation by the condition itself, by the shear stress exerted on white blood cells at the entry port and contact activation with the surface of the microaxial flow pump inducing eventually coagulation and platelet activation fostering simultaneously clots as well bleeding due acquired von Willebrand syndrome. By severe shear and stretch stress at the microaxial port and the device impeller itself, the device further induces haemolysis with release of free haemoglobin and haeme scavenging nitric oxide, fostering oxidative stress and inflammation.

Do we need a paradigm shift, rather than a paradigm change for cardiogenic shock after these overall disappointing results? Cardiogenic shock is neither a pure mechanical nor solely a haemodynamic problem. The acute coronary occlusion as well as the reduction of cardiac output has profound metabolic effects that are crucially involved in the downhill spiral eventually leading to circulatory arrest and death. First, cardiogenic shock is associated with and leads to massive activation of inflammation with an increase in neutrophils, reduced neutrophil-lymphocyte ratio, and elevated C-reactive protein plasma levels as a reflection of an activation of the NLRP3–interleukin pathway.[10] Although cooling with a target of 32–36°C conceptually might reduce inflammation, evidence for a benefit is low. On the other hand, in the ASSAIL-MI trial, tocilizumab, a monoclonal interleukin-6 antibody, increased myocardial salvage and reduced microvascular obstruction.[11] Furthermore, in the COMMA trial, pexelizumab, a monoclonal antibody against complement C5, even reduced mortality at 30 days independent of myocardial injury.[12] Second, underperfusion of vital organs leads to acidification of the body as reflected by a decrease in pH and increase in lactate plasma levels. Finally, leaky plasma membranes and dying cells as occurs in cardiogenic shock release an enzyme, i.e. dipeptidyl peptidase-3 (DPP-3) that digests angiotensins, interferes with the signal transduction of angiotensin receptors and exerts negative inotropic effects and as such may play a detrimental role in cardiogenic shock.[13] Of note, the DPP-3 blocking monoclonal antibody, procizumab, restored haemodynamics in a mouse model of coronary ligation, an exciting finding now confirmed in pigs, as well as in a rodent model of sepsis.[14] Furthermore, DPP-3 plasma levels are particularly elevated in patients at risk and with full-blown cardiogenic shock and are highly predictive of mortality. Interestingly, persistent elevations of DPP-3 at baseline and 24 h after pPCI are most notably associated with a massive increase in in-hospital mortality.[15]

What should be the future paradigm in the management of cardiogenic shock? Obviously, neither complete revascularization nor unselective mechanical circulatory support alone in a broader cardiogenic shock population has proved convincingly effective. Thus, early and timely inhibition of specific pathways fostering the downhill spiral during evolving shock, such as for instance the NLRP3–interleukin and complement pathway as well as of DPP-3 either alone or in combination, most likely together with LV unloading in selected patients must be considered going forward—indeed, hemo-metabolic unloading might be the future.

Declarations

Disclosure of Interest

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