DEVICE THERAPY

Where next in cardiogenic shock owing to myocardial infarction?

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Refers to Ahmad, Y. *et al. JAMA Intern. Med.* http://dx.doi.org/10.1001/jamainternmed.2015.0569 | Khera, R. *et al. JAMA Intern. Med.* http://dx.doi.org/10.1001/jamainternmed.2014.7856

Intra-aortic balloon pumping has recently been shown to be ineffective in treating cardiogenic shock due to myocardial infarction. Other, more potent percutaneous pumps have been developed, and their use is growing substantially, but they have not been studied in randomized trials. Two new reports provide provocative information about these devices.

Cardiogenic shock occurring in the setting of myocardial infarction is still associated with high mortality and remains a major treatment challenge for clinicians. Long-recognized limitations of pharmacological therapies motivated the development of percutaneous mechanical circulatory assist devices. Such devices include intra-aortic balloon pumps (IABPs), extracorporeal blood pumps, and catheter-based miniature blood pumps.[1] These devices are collectively referred to as percutaneous ventricular assist devices (pVADs). Until around 2014, IABPs were a mainstay of therapy for cardiogenic shock. However, meta-analyses and the completion of a landmark randomized controlled study showing no benefit of IABPs in cardiogenic shock associated with myocardial infarction[2] have resulted in their demotion in treatment guidelines.[3,4] In parallel, the usage of various pVADs has increased. Two new studies now provide additional information that more broadly confirms IABP futility,[5] but question the efficacy and cost-effectiveness of particular pVADs.[6]

IABPs became the standard of care before the introduction of governmental oversight of devices in the USA, and these devices were never subjected to rigorous testing of safety and efficacy. IABPs achieved widespread acceptance on the basis of data showing improved coronary perfusion, modest increases in cardiac output, anecdotal reports of clinical successes, and large registry data suggestive of safety and efficacy. Such data were obtained from nonrandomized, controlled, or uncontrolled studies, which provided mixed results. The IABP-SHOCK II study[2] was the first randomized, controlled study of IABPs in patients with myocardial infarction and showed no benefit. In view of certain limitations of the IABP-SHOCK II trial—such as a lower than expected mortality, raising questions about the severity of shock, and the high rate of late insertion of IABPs after percutaneous coronary intervention—many clinicians continue to use IABPs on the basis of personal experience and support from some of the earlier, nonrandomized studies. Ahmad *et al.* went further than in previous meta-analyses by introducing an 'inequality index' aimed at accounting for the differences in baseline characteristics between IABP and control populations in the previous studies.[5] They found that the majority of the variability in outcomes between studies was explained by the inequalities between the IABP and control patients; after accounting for these differences, beneficial and detrimental effects of IABP therapy were eliminated. Accordingly, these findings further support the latest changes in treatment guideline recommendations, which have downgraded IABP use to class II[4] or class III[3] in the USA and Europe, respectively.

> "...investigators should focus on high-quality studies of cardiogenic shock pathophysiology..."

With recognition of the limited circulatory support offered by IABPs, more potent approaches to providing percutaneous haemodynamic support started to emerge, including extracorporeal pumps (such as TandemHeart®; CardiacAssist, USA) and transaortic valvular micropumps (such as the Impella® class of devices; ABIOMED, USA). Early, small studies confirmed superior haemodynamic support provided by such approaches compared with IABPs. However, no appropriately powered, randomized, controlled study to investigate whether these devices improve survival has yet been completed.

Accordingly, Khera *et al.* examined use patterns, outcomes, and costs associated with IABPs and pVADs between 2007 and 2012 using data obtained from the National Inpatient Sample.[6] pVADs in this study were restricted to Impella® and TandemHeart® devices. The study included patients receiving devices for any indication, not only cardiogenic shock; some data specific to cardiogenic shock were provided. They found a significant increase in the number of hospitals using pVADs (from 72 to 477) and that pVAD use for cardiogenic shock increased markedly from 1,506 to 19,913 per million hospital discharges.[6] Concomitantly, IABP use for cardiogenic shock decreased from ~287,500 to 220,000 per million hospital discharges. Consistently with previous studies, mortality in the overall population of patients with cardiogenic shock was 47.5%. The investigators concluded (after propensity matching) that mortality and costs were higher in patients who received a pVAD than in those with an IABP. However, the analysis is limited by the exclusion from the mortality analysis of patients who received both an IABP and a pVAD. This exclusion is critical, because a patient with cardiogenic shock who was treated with both devices would typically have received the IABP first and then, if failing to improve, treatment would have been 'escalated' to the use of a pVAD, often late in the course of treatment. Under the assumption that a substantial number of those patients who did not respond well to IABP therapy died, such censoring eliminates a potentially large number of deaths from the IABP group. Regardless, a previous analysis derived from the same National Inpatient Sample database over a similar time period (without censoring this group) concluded that IABP use was associated with higher costs and mortality than short-term mechanical circulatory support (which included the Impella® and TandemHeart® devices).[7]

This latter study also highlights the point that clinicians currently have more pVAD options for treating cardiogenic shock, which raises the problem of data pooling. In addition to different flow capacities, the part of the circulation from which blood is taken (femoral vein, right or left atria, superior vena cava, or left ventricle) and to which it is returned (femoral artery, axillary artery, or central aorta) differ according to the pVAD. These differences influence overall haemodynamic effects and the degree of ventricular unloading (Figure 1).[1] The latter has a substantial effect on myocardial oxygen demand, which has been shown to influence infarct size and long-term ventricular function in animal models. The expanded use of extracorporeal membrane oxygenation for cardiogenic shock (excluded from these previous utilization studies) raises other questions, not only associated with its very different haemodynamic effects, but also because of its effects on blood components and systemic inflammation. Pooling of cardiogenic shock outcomes obtained with different devices is clearly problematic.

So, where do we go from here? Many publications about cardiogenic shock start with the statement that mortality remains high despite all efforts, and end with the statement that randomized studies are needed. Several principles might guide us until appropriate trials are completed. First, the pathophysiology of cardiogenic shock is only partially understood. Generically, haemodynamic factors are a critical component of the pathophysiology; restoration of more normal blood flows and pressures (arterial and venous, systemic and pulmonary) as can be achieved to varying degrees by pVADs is still a viable primary therapeutic target. Second, haemodynamic responses to pVAD support vary between patients; the factors governing these responses need to be determined. Therefore, identification of better-defined subgroups of cardiogenic shock might lead to enrolment stratification, which might increase success of future studies. Third, how to match a specific patient with the optimal form of haemodynamic support is currently unknown. Fourth, pooling of data obtained with different devices ignores their fundamental differences at many levels. Finally, although the role of inflammation is recognized as being important, the results of one negative clinical trial of an inducible nitric oxide synthase inhibitor[8] seem to have halted progress in clinical studies of this potentially critical contributing mechanism. Improved outcomes might be achievable only by simultaneously addressing both haemodynamic and inflammatory mechanisms.

Nevertheless, randomized studies are extremely difficult to execute, for example owing to low enrolment despite appropriate funding.[9] Even the process of obtaining informed consent at a time of critical illness poses an absolute and unavoidable obstacle. Until further randomized studies are executed, my opinion is that investigators should focus on high-quality studies of cardiogenic shock pathophysiology and the physiological effect of potential therapies such as pVADs. Results will inform the optimal inclusion and exclusion criteria of outcome trials.

Meanwhile, what should practising clinicians do? Ahmad *et al.* state very simply what I believe is on every clinician's mind: "In the challenging clinical situation of acute myocardial infarction complicated by cardiogenic shock, there is an understandable desire to do something rather than appear to do nothing."[5] Guidelines and expert opinions are vague, which necessarily leads to development of local practice algorithms. Such algorithms for pVAD use are probably based on considerations such as familiarity and experiences with specific devices, their ease of use, adverse event profile, economics, and—perhaps most notably—their capacity acutely to improve haemodynamic status.

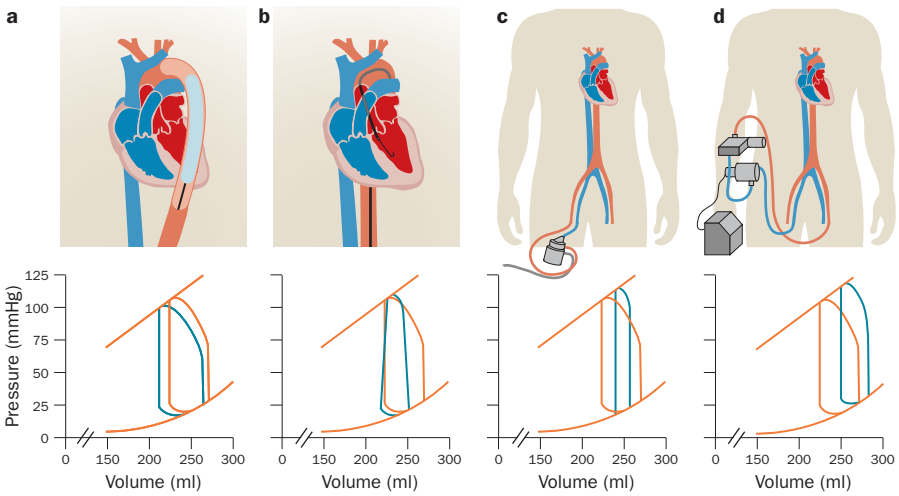

Figure 1 | Haemodynamic effects and ventricular unloading with pVADs. Haemodynamic effects differ between pVADs, which affects the degree of ventricular unloading.[1] These differences can be recognized on ventricular pressure–volume loops ('on-pump' loops shown in blue). **a** | Intra-aortic balloon pump. **b** | Impella® device (ABIOMED, USA). **c** | TandemHeart® (CardiacAssist, USA). **d** | Extracorporeal membrane oxygenation. Abbreviation: pVAD, percutaneous ventricular assist device. Upper panels modified from Thiele, H. *et al*. Management of cardiogenic shock. *Eur. Heart J.* **36** (20), 1223–1230 (2015), by permission of OUP and the ESC.

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Competing interests
D.B. declares that he is an employee of HeartWare International, and a consultant to BackBeat Medical, CardiacImplants, DC Devices Inc., and Sensible Medical. He has received grant support from Abiomed, is on the Heart Failure Advisory Board of the Sorin Group, and is the founder of PVLoops LLC.

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