Editorial

Cardiogenic shock: have we really found the magic potion?

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The aetiology of cardiogenic shock following an acute myocardial infarction is multi-factorial. It predominantly arises in the setting of a large myocardial infarction that results in diminished stroke volume and a cardiac output that does not meet ensuing demand. Patients with prior myocardial infarction and extensive coronary artery disease are especially vulnerable due to the inability of the remote myocardium to compensate. Strategies to enhance outcome are focused on early definition of coronary anatomy and emergent revascularization while simultaneously providing haemodynamic support with intra-aortic balloon pulsation and vasopressor therapy. The goal of this approach is to restore infarct artery patency, salvage jeopardized myocardium; and prevent irreversible vital end-organ injury. The NHLBI supported SHOCK trial conclusively established the utility of this invasive strategy in a randomized prospective trial.1 At 12-months an early revascularization strategy resulted in a treatment benefit of 13 lives saved per 100 patients treated.2 An interaction between treatment strategy; outcome and age <75 vs ≥75 years was also noted (interaction P=0.03). An 18% absolute difference in survival in favour of an early revascularization strategy was observed for patients aged <75 years with cardiogenic shock within 36 h of an acute ST-elevation myocardial infarction.3

Despite the utilization of an aggressive early revascularization strategy mortality with cardiogenic shock remains staggering. The 30-day mortality rate for patients in the early revascularization arm of the SHOCK trial receiving percutaneous intervention was 45%.4 A similar 46% mortality rate was reported in the SHOCK registry4 with consistent results observed in the National Registry of Myocardial Infarction (NRMI). Further research in this critical area is clearly warranted. While the promise of LVAD and other mechanical support devices is self-evident, it is unlikely that these devices will significantly alter outcome at the level of the community hospital in the near future.

The SHOCK Investigators and others were impressed by the heterogeneity of shock in the setting of predominant left ventricular failure.5–7 Clinical presentation in many patients masqueraded as a sepsis syndrome. Systemic vascular resistance in the majority of patients with cardiogenic shock were noted to be within the low to normal range and a role for a reactive systemic inflammatory state mediated by inflammatory cytokines was postulated.

Cotter and colleagues have hypothesized a pivotal role for excess nitric oxide in the setting of cardiogenic shock. In their conceptual model shock is no longer purely a response to a critical loss of pump function. Nitric oxide mediated myocardial dysfunction and decrease in systemic vascular resistance have a crucial role in shock genesis and progression. Despite previous harm with NO synthase inhibition in the setting of septic shock,
Cotter and colleagues were the first investigators to explore the adjunctive use of NO synthase inhibition in the setting of cardiogenic shock. In their original report, Cotter et al. L-NMMA (N^6- monomethyl L-arginine) a non-specific NO synthase inhibitor to 11 consecutive patients with cardiogenic shock greater than 24 h post percutaneous revascularization. All patients received IABP counterpulsation, catecholamine support and mechanical ventilation prior to study drug initiation. The investigators reported 64% thirty-day survival in this small group of patients. Administration of L-NMMA in this study was associated with a 43% immediate rise in mean arterial and a 148% increase in urine output in this group of patients without any adverse reactions noted.

In this issue of the journal, Cotter and colleagues extend their experience with NOS inhibition by performing a single center randomized prospective clinical trial with L-NAME (N^6-Nitro-L-Arginine-Methyl Ester Hydrochloride) in the treatment of refractory cardiogenic shock. The study appears exploratory in that no preset treatment effect or sample size is reported. Although a safety committee aborted the trial after 30 patients, no formal methodology for interim review of the data is reported. It is also remarkable that the authors were able to enroll all consecutive patients without any refusals in this clinical setting.

Prior to study discontinuation, the investigators randomized 30 patients with refractory cardiogenic shock following acute coronary syndrome despite revascularization with percutaneous intervention, IABP support and vasopressor use. Patients were randomized on a 1:1 basis to receive L-NAME (1 mg/kg bolus and 1 mg/kg/h IV for 5 h with supportive care or supportive care alone). The supportive care provided appears to be state of the art. The observed 30-day mortality rate despite IABP and attempted revascularization of the infarct related artery was 67% in the control arm. Although higher than previously stated studies, this outcome is not unexpected given the presence of persistent shock despite revascularization and IABP placement prior to randomization in this group. Remarkably thirty-day mortality in the study arm receiving L-NAME was only 27%. This translates into 40% absolute mortality difference, a highly statistically significant result (P=0.008) despite a small study sample (n=30). Other secondary outcomes including measured haemodynamic parameters, time on mechanical ventilation as well as need for IABP support are also favoured strongly by the experimental treatment.

The mortality benefit reported in this trial is rather dramatic and unexpected. To place this in perspective; the SHOCK trial was unable to show a pre-specified 20% mortality benefit of early revascularization over initial medical stabilization at 30 days using a sample size of 302 (46.7% vs 56%, P=0.11). How and why did these patients derive the magnitude of benefit described from this treatment?

Koreny et al. evaluated 118 consecutive patients with cardiogenic shock complicating an acute coronary syndrome. Acute renal failure defined as urine volume <20 ml/h associated with an increase in serum creatinine ≥0.5 mg/dL or >50% the baseline value was observed in 33% of the study population with an in-hospital mortality of 87%. Multi-variate logistic regression analysis identified acute renal failure as the only independent predictor of mortality. Similarly, in the GUSTO trial oliguria was the strongest predictor of 30-day mortality among patients with cardiogenic shock (OR 3.42; 95% CI (2.80; 4.17)).

In contrast renal perfusion at baseline for patients in the current study appears remarkably intact. Despite being relatively elderly (65±13 years) significantly diabetic (47%), on mechanical ventilation (100%) and exposure to contrast (100%) and in florid shock; urine output at baseline in the treatment group was 122±75 cc an hour. Perhaps this reflects a benefit of the unconventional treatment with large volumes of fluid (180±103 cc/h) and diuretic. An even greater augmentation of urine output is seen with initiation of study drug. This protection of renal function however surprising may have played a role in the treatment benefit reported in this study.

The haemodynamic response to L-NAME also deserves scrutiny. Consistent with their earlier observations; NOS inhibition appears to result in a dramatic and instantaneous rise in mean arterial pressure. This suggests a strong pathognomonic role for over-expressed NO in the genesis of hypotension in this setting. The rise in mean arterial pressure results in a substantial increase in systemic vascular resistance and afterload and consequently an expected fall in cardiac index. With time cardiac index recovers and mean arterial pressure is maintained. How does this phenomenon take place? One explanation is that NOS inhibition has a positive effect on the contractile recovery of salvaged ventricular myocardium. Salvage however appears unlikely given the 53% epicardial TIMI-3 flow and poor microvascular perfusion reported in these patients. Details of a follow-up angiogram as well as a follow-up echocardiogram would shed further light on this issue.
The results of the current study should in no way influence current clinical practice. A number of critical issues demand clarification and further research is clearly indicated. We have little information regarding the dose-response and optimal timing of the study drug. Important adverse reactions in other organ systems may have also been missed given the small number of patients studied.

In conclusion, the results of the current study by Cotter et al. are both startling as well as provocative. The mortality benefit if confirmed represents the potential for a dramatic breakthrough in the treatment of cardiogenic shock. The proposed modality of benefit though poorly understood represents a shift in the clinical paradigm of shock onset and reversal. Our enthusiasm should be tempered by the extremely limited single centre experience with this agent. Small studies are prone to randomly find very positive benefits that even when confirmed in larger studies appear relatively modest in size. Cautious optimism is warranted and a thoughtful well designed, randomized multi-centre trial is clearly warranted. In this regard, a larger confirmatory trial (SHOCK-2) is currently being designed to study the promising role of NO synthase inhibition in the setting of cardiogenic shock.7

References


