REVIEW

Management of cardiogenic shock complicating acute myocardial infarction: towards evidence based medical practice

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The treatment of cardiogenic shock is the ultimate challenge of our ability to manage patients presenting with acute myocardial infarction. Despite advances in the treatment of infarcts with thrombolysis, there has been no significant decrease in the incidence of cardiogenic shock, which has remained at 7–10% during the last 20 years.^{1–5} Hospital mortality was over 90% in the 1970s⁶ and is still high, in the region of 45–80%, in the 1990s.^{1 7–9} Attitudes towards treatment of cardiogenic shock range from resignation, providing supportive measures only, to aggressive intervention. In the era of evidence based medical practice, are there data to support adoption of either extreme of approach?

Registry of cardiogenic shock patients

The largest prospectively identified registry of patients with cardiogenic shock so far analysed is from the GUSTO-I (global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries) trial.^{4 8 10} Of the 41 021 patients recruited into that study, 7.2% (2972) developed cardiogenic shock, with an overall 30 day mortality of 55%.⁸ For those undergoing coronary artery bypass grafting (CABG) the 30 day mortality was 29%, and for those having percutaneous transluminal coronary angioplasty (PTCA) it was 22%. On single factor comparison of one year mortality, the hazard ratio (after adjustments for baseline characteristics) for PTCA versus no PTCA was 0.81 (95% confidence interval (CI), 0.71 to 0.94; $p < 0.005$), suggesting that there may be medium term benefit with the PTCA management strategy. However, patients were not randomly allocated to revascularisation or conservative treatment in that study, and the better PTCA outcome could reflect selection bias. The hazard ratio for CABG versus no CABG was 1.08 (95% CI, 0.89 to 1.30; $p = 0.445$). It is unclear why the 30 day mortality advantage of CABG was not mirrored at one year.

The SHOCK (should we emergently revascularise occluded coronaries for cardiogenic shock) registry³ showed that patients selected to undergo coronary angiography had an improved outcome irrespective of whether they were revascularised or not. This type of selection bias may also be true for those

selected to receive PTCA or CABG in other observational studies.

Is prophylactic PTCA/CABG indicated?

Many uncontrolled observational studies assessing the role of coronary angioplasty or bypass surgery appear to advocate the interventional treatment approach. Of the 24 papers analysing the use of PTCA, involving 1257 patients,^{5 7 8 11–31} the overall mortality was 44%, as shown in table 1 (31% for successful PTCA and 81% for unsuccessful PTCA). Of the 28 papers reporting the effects of CABG on a total of 743 patients,^{5 7 8 20 31–54} the overall mortality was 42% (table 2). It is claimed that these figures show a more favourable outcome for intervention in comparison with conservative treatment in historical or contemporaneous controls. However, apart from the probable selection of less severely ill patients for intervention, there is another potential bias in that positive results (in favour of intervention) are more likely to have been reported or published.

GUSTO-I: is an invasive strategy better?

In the GUSTO-I cardiogenic shock subgroup analysis,⁸ it was suggested that the lower mortality in the American patient cohort “may have been due to the greater use of invasive diagnostic and therapeutic procedures”. However, further analysis suggests that this observation also reflects selection bias. First, the fact that the American patients with cardiogenic shock who were not revascularised had a lower mortality than their non-American counterparts (hazard ratio 0.73, $p < 0.001$) strongly suggests that the American cardiogenic shock population was an intrinsically lower risk group. Second, despite uniform recruitment criteria into the thrombolysis GUSTO-I study, the incidence of cardiogenic shock was 6.1% in the non-USA countries and 8.3% in the USA, so that 36% more patients were defined as having cardiogenic shock in the American population. It is possible that a lower threshold for classifying patients into the cardiogenic shock category was used by the American investigators if the criteria employed were insufficiently strict (for example, shock secondary to hypotensive agents such as opiates or β blockers was not excluded). Assuming

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Table 1 Papers reporting the use of PTCA in cardiogenic shock after acute myocardial infarction

Author	Year	Number in study	Mortality (%)
Heuser ¹¹	1986	10	40
Disler ¹²	1987	07	57
Landin ¹³	1988	34	41
Laramée ¹⁴	1988	39	41
Lee ¹⁵	1988	24	50
Verna ¹⁷	1989	07	14
Shaw ¹⁸	1989	09	33
Meyer ¹⁹	1990	25	47
Lee ¹⁶	1991	69	45
Bengston ²⁰	1992	14	43
Gacioch ²¹	1992	25	44
O'Neill ²²	1992	27	30
Hibbard ²³	1992	45	44
Moosvi ²⁴	1992	38	47
Yamamoto ²⁵	1992	26	62
Seydoux ²⁶	1992	21	43
Himbert ⁷	1994	18	78
Hochman ⁹	1995	55	60
Morrison ²⁷	1995	17	53
Eltchaninoff ²⁸	1995	33	36
Holmes ⁴	1997	565	22
Antoniucci ²⁹	1998	66	26
Calton ³⁰	1999	18	28
Perez-Castellano ³¹	1999	65	71
Total		1257	44

Table 2 Papers reporting the use of CABG in cardiogenic shock after acute myocardial infarction

Author	Year	Number in study	Mortality (%)
Dunkman ³²	1972	15	40
Mundth ³³	1973	33	61
Miller ³⁴	1974	12	58
Mills ³⁵	1975	10	0
Cascade ³⁶	1975	03	67
Willerson ³⁷	1975	03	67
Keon ³⁸	1977	21	67
Johnson ³⁹	1977	05	60
Erich ⁴⁰	1977	03	67
Bardet ⁴¹	1977	04	50
O'Rourke ⁴²	1979	06	67
Subramanian ⁴³	1980	20	45
DeWood ⁴⁴	1980	19	42
Kirklin ⁴⁵	1985	04	0
Phillips ⁴⁶	1986	34	24
Laks ⁴⁷	1986	50	30
Athanasuleas ⁴⁸	1987	13	62
Guyton ⁴⁹	1987	09	22
Bolooki ⁵⁰	1989	07	43
Beyersdorf ⁵¹	1991	11	55
Bengston ²⁰	1992	17	12
Allen ⁵²	1993	66	09
Quigley ⁵³	1993	05	80
Himbert ⁷	1994	05	40
Hochman ⁹	1995	16	19
Holmes ⁴	1997	338	29
Donatelli ⁵⁴	1997	08	50
Perez-Castellano ³¹	1999	06	91
Total		743	45

that the same percentage of patients with acute myocardial infarction (6.1%) developed cardiogenic shock in the USA as in the other countries, the actual number of patients with cardiogenic shock in the American cohort would be less, and the mortality for the American patients with cardiogenic shock would then become 67.5%—not very different from the figure of 66% obtained in the non-American cohort.⁵⁵ The recommendation for more invasive diagnostic and therapeutic strategies for managing cardiogenic shock cannot be upheld on the basis of the GUSTO-I investigators' interpretation of their data.

Consecutive patients revascularised

Only two published studies have entered unselected consecutive patients with cardiogenic shock after acute myocardial infarction into a strategy of coronary angiography and revascularisation, and they came to opposite conclusions. The first of these⁷ showed mortalities for those with successful reperfusion of 70% and with unsuccessful reperfusion or medical treatment of 80%; these figures were generally higher than in other cardiogenic shock cohorts. It would appear from that study that in unselected patients the mortality associated with revascularisation was not as low as suggested by previous reports with potential selection bias. In the other series²⁹ where PTCA was performed in a consecutive cohort of patients, an inpatient hospital mortality of 26% was reported (17 of 66 patients). The success rate of PTCA was 94% and this group had an overall mortality of 21%. The mortality in this study compares favourably with other series and this would seem to support an interventional approach to treatment. Although a consecutive series excludes preselection bias of those patients most likely to survive, the incidence of cardiogenic shock in this cohort was higher than in previous studies (66 of 364, or 18% of all patients admitted with acute myocardial infarction), which again raises the possibility that the physicians had used permissive criteria for diagnosing cardiogenic shock. Such conflicting outcomes suggest that it is essential to rely on randomised controlled trials to determine whether interventional strategies should be advocated for all patients with cardiogenic shock after acute myocardial infarction.

Randomised controlled studies

The SHOCK trial randomly allocated patients with cardiogenic shock to early revascularisation (PTCA or CABG) or medical treatment, and the results showed no significant difference in the primary end point of 30 day mortality between the two groups (46.7% *v* 56.0%, *p* = 0.11).⁹ These results from the randomised cohort were considered to be representative of other non-randomised patients in the registry. The suggestion from previous uncontrolled studies that PTCA/CABG confers better outcome and should be offered to all patients with cardiogenic shock is not borne out by this randomised trial, and is likely to reflect selection biases in favour of intervention groups in observational studies.

The SMASH (Swiss multicenter angioplasty for shock) trial, comparing initial strategies of coronary angioplasty with medical treatment, also showed a non-significant mortality difference (69% *v* 78%; relative risk 0.88, 95% CI, 0.6 to 1.2).⁵⁶ The comparatively higher mortality in this study reflected the inclusion of sicker patients, who remained hypotensive despite inotropic support and volume replacement. This study was terminated early because of difficulties in patient recruitment.

These two studies are the first well conducted randomised controlled trials of treatment in cardiogenic shock. The results have

exposed the unreliability of previous uncontrolled trials that suggested that PTCA or CABG would result in a major reduction in mortality in patients with cardiogenic shock. In the light of such neutral controlled trial results, it is natural to try to find something positive in further analyses, but this process may be as treacherous as reliance on results from uncontrolled observational studies. Setting aside the result for the primary endpoint, and basing their view on the lower mortality observed in the revascularisation group at six months, the authors of the SHOCK trial concluded that "early revascularisation (should) be strongly considered for patients with acute myocardial infarction complicated by cardiogenic shock." This position is rather precarious if we note that between 30 days and six months after randomisation, there were only five extra deaths in the PTCA/CABG group and 10 in the medical treatment group. Overreliance on such small numbers may be risky. In the accompanying editorial,⁵⁷ there was an attempt to make something positive out of "a negative trial," as shown by the statement that "the 17% relative reduction in overall mortality at 30 days . . . is clinically relevant and therapeutically worthwhile since it represents 93 lives saved per 1000 patients treated," while ignoring the fact that this could have been due to chance alone ($p > 0.05$).

If angioplasty and bypass surgery in patients with cardiogenic shock were low risk procedures, then the above recommendations might well be adopted into routine clinical practice. However, it is known that the operative risks are substantial in such patients, and when the extensive infarct processes are completed, revascularisation is unlikely to achieve much myocardial salvage. When the considerable cost in terms of physical and emotional stress brought about by the interventions is also taken into account, the adoption of a blanket strategy of early revascularisation to all patients with cardiogenic shock must await more convincing evidence of benefit.

We are, however, unlikely to see many more large scale randomised controlled trials of revascularisation for cardiogenic shock in the future unless there is a major injection of research funding. Unlike trials of drug treatment in myocardial infarction, conducting controlled trials on patients with cardiogenic shock is notoriously difficult. For instance, the 302 patients in the SHOCK trial took most of the past decade to recruit, and by nearly half as many trialists; this contrasts greatly with nearly 200 times as many patients recruited in half the time in the contemporary ISIS-4 trial (fourth international study of infarct survival).^{57a} It is therefore crucial to formulate a rational approach to the management of cardiogenic shock based on all available information on the subject. Currently, it is safe to state that early revascularisation should be advocated in *selected* cases, but the question is how to select these cases.

Diagnostic criteria

As with any other clinical conditions, the first crucial step in management is arriving at the correct diagnosis.⁵⁸ As illustrated above in the analysis of the subgroup with cardiogenic shock in the GUSTO-I trial, differences in diagnostic criteria can lead to important differences in outcome. They may also play a role in the differences in mortality in various study cohorts (for example, SHOCK versus SMASH trial results). In most of these studies the prespecified criteria for diagnosing cardiogenic shock did not exclude the contributory role of hypotensive agents (such as opiates or angiotensin converting enzyme (ACE) inhibitors) or negative inotropic agents (β blockers, verapamil), which are often used in patients with acute myocardial infarction. In some studies, the contribution of tachyarrhythmias, bradyarrhythmias, or relative hypovolaemia (for example, in infarction of the right ventricle) may have allowed the inclusion of patients with potentially reversible causes of shock, who tend to have a better prognosis. In non-randomised studies, other sources of bias may confound the results, such as the failure to exclude patients with cardiogenic shock who died before angiography, and allowing them to be included in the group treated conservatively; or failure to account for differences in the baseline characteristics of the group selected for intervention—these patients may be younger and have less co-morbid illness or previous infarction.

How to select cases for cardiac interventions

From our current understanding of the pathophysiological processes involved in cardiogenic shock, the data from the SHOCK and SMASH trials may now be used as a basis for formulating a rational approach to management. An obvious but key point in this consideration is that the most fundamental objective of revascularisation is to relieve coronary arterial stenoses in order to improve perfusion and function of the myocardial regions in jeopardy. Evidence of myocardial jeopardy and viability is vital for successful revascularisation. This implies that late presentation and delayed revascularisation after diagnosis will make the intervention less likely to be beneficial. Unfortunately cardiogenic shock often presents rather late after the onset of myocardial infarction.¹⁴⁹ Those with early presentation (less than six hours after the onset of infarction) and with features suggestive of ongoing ischaemia should be seriously considered for revascularisation, whereas those with late presentation are likely to benefit from revascularisation only if significant amounts of myocardium can be shown to be in jeopardy and still salvageable.

The SHOCK data suggest that younger patients (< 75 years old) are more likely to benefit from revascularisation. This observation is consistent with the concept that natural attrition throughout adult life effectively leads to the eventual loss of 35% of cardiomyocytes in the heart,⁵⁹ while it is also known that cardiogenic shock often occurs once there is

loss of more than 40% of left ventricular myocardium through infarction.⁶⁰ Thus, comparatively, older patients have less room for myocardial loss before pump failure occurs and are more susceptible to cardiogenic shock with smaller infarcts; they are also less likely to have a sizeable amount of salvageable myocardium than their younger counterparts.

If death is the endpoint to prevent, then identifying the individual patients who are most likely to die will require an accurate and reliable predictive indicator. Using a logistic regression modelling technique, the GUSTO-I investigators showed that "cardiac output measurements were of greatest prognostic significance" even when demographic and clinical variables were included in the analysis.⁶¹ This is consistent with the concept that, in the absence of life threatening arrhythmia, the most important determinant of mortality is cardiac pump function, as it is inadequate pumping that leads to circulatory collapse and cardiogenic shock. In cardiogenic shock, a more important feature than the cardiac function at baseline resting states is the reserve pumping capability of the failing heart.⁶²⁻⁶³ Availability of this mechanistic information alone would help clinicians to select, on an individual basis, which patients should receive invasive treatment. This information may be used in conjunction with the more probabilistic information contained in the risk factors derived from multivariate analysis of other patient cohorts.⁶¹

In a consecutive unselected series of cardiogenic shock patients,⁶⁴ it has been shown that if the baseline resting cardiac power output (arterial pressure $\times$ flow output, expressed in watts) is below 0.4 W after optimising the filling pressures, none of these patients will survive on medical treatment alone; those with cardiac power output still falling below the normal resting level for an average sized adult (< 1 W) with maximal inotropic stimulation were also found to be non-survivors with medical treatment alone. The reason why cardiac power output or left ventricular stroke work⁶⁴ are better indicators than cardiac output or other variables is because the function of the heart pump is not only to generate flow but also pressure, and these variables incorporate both flow and pressure generating capacity.⁶²⁻⁶³ Because of the clear separation between the non-survivors (who had inadequate cardiac reserve at the time of evaluation) and survivors (with adequate reserve), it is possible to triage patients according to their cardiac reserve status. Patients with poor reserve are the ones who will need to be considered for aggressive interventions if death is to be prevented.

The question of which intervention is optimal requires further study, but the absence of myocardial contractile reserve suggests that such patients are unlikely to have enough viable myocardium for revascularisation to have a major impact on survival. Suitable patients would therefore require mechanical circulatory support⁶⁵⁻⁶⁷ as a bridge to cardiac transplantation⁶⁸⁻⁷⁰ or, in a small proportion, to allow stunned myocardium to recover.⁷¹⁻⁷² Ongoing studies such as HEROICS (how

effective are revascularisation options in cardiogenic shock?) and TACTICS (thrombolysis and counterpulsation to improve cardiogenic shock survival) will provide further insight into these issues. On the other hand, if aggressive interventions are not indicated, then objective physiological information about prognosis is helpful in avoiding futile and undignified struggles against the inevitable.

Technologically, the measurement of cardiac reserve does not require unusually sophisticated equipment. As described previously,⁶⁴ it requires measurement of pressures and cardiac output using Swan-Ganz catheter systems available in all modern coronary care or intensive care units. However, for clinicians without access to such equipment, a simple bedside rule of thumb may help: if the blood pressure on maximal inotropic stimulation fails to exceed 100/70 mm Hg and the patient is still clinically hypoperfused (oliguric, peripherally shut down, diaphoretic), then it is highly unlikely that the cardiac output has exceeded 5.5 l/min to give a power output value of > 1 W. Such patients would fall into the category of non-survivors on medical treatment alone.

Patients who are responsive to inotropic stimulation and show adequate cardiac reserve (power output > 1 W), and who present early after the onset of acute myocardial infarction, may be suitable for early revascularisation to salvage the still viable myocardium. Alternatively, they may have extensive stunned myocardium that could recover in due course without revascularisation, given sustained inotropic support.⁷¹⁻⁷² Those who present late with cardiogenic shock and have adequate cardiac reserve may not require acute prophylactic revascularisation, because with optimal medical treatment these patients are likely to survive the acute episode,⁶⁴ and interventions may be planned subsequently if indicated to prevent further cardiac events.

Prevention is the best policy

Once cardiogenic shock has occurred the prognosis is dire, even with revascularisation.⁹ Major efforts should therefore be directed towards preventing shock after the onset of acute myocardial infarction.⁷³ Appropriate treatment of every infarct is a prerequisite in this task. There is a suggestion that, compared with thrombolysis, primary angioplasty reduces the incidence of eventual heart failure,⁷⁴ but whether this will affect the incidence of cardiogenic shock is at present unknown. The use of stents and platelet inhibitors may further enhance the successes of primary angioplasty.²⁹⁻⁷⁵⁻⁷⁸

Prevention should also include identification of the preshock state followed by treatment aimed at preventing deterioration into cardiogenic shock—that is, relief of ischaemia, control and prevention of arrhythmias, optimisation of haemodynamic variables by inotropic support, and the use of glucose–insulin–potassium infusions to support viable myocardial function.⁷⁹⁻⁸⁰

A major objective of treating the preshock syndrome is to prevent the occurrence of a vicious cycle whereby systemic arterial hypotension leads to further coronary hypoperfusion, which in turn results in worse hypotension, and so on. Agents likely to aggravate this tendency are widely used in the treatment of acute myocardial infarction. Opiates, angiotensin converting enzyme (ACE) inhibitors, β blockers, nitrates, and calcium antagonists need to be used very cautiously in these patients because they can precipitate cardiogenic shock.⁸¹⁻⁸² It is important to highlight that treatment for cardiogenic shock (at the severe extreme of the spectrum of heart failure) is different from treatment for heart failure, because nowadays ACE inhibitors and β blockers are indicated for the treatment of heart failure⁸³⁻⁸⁶ but should be avoided in true cardiogenic shock, and they may precipitate shock if the patient is in the preshock state. Right ventricular involvement in infarction has a poor prognosis⁸⁷⁻⁸⁸ and requires careful adjustments of right and left ventricular preloads with invasive monitoring.

Conclusion

The results of the SMASH and SHOCK studies have not suggested that there is an absolute indication to proceed with prophylactic revascularisation in patients with cardiogenic shock, but selected high risk patients who are likely to benefit from interventions should be diligently identified and offered appropriate intervention, either acutely or electively. Rather than relying on subjective impressions, physiological and objective means of selecting and categorising these patients should be adopted in clinical practice. A major thrust in therapeutic efforts should be directed at preventing the onset of cardiogenic shock if at all possible.

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