

## Review

**QJM**

# Revascularization for cardiogenic shock

C.H. DAVIES

*From the Department of Cardiology, Oregon Health Sciences University, Portland, Oregon, USA*

## Introduction

Despite the availability of invasive circulatory monitoring, inotropes and thrombolysis, mortality from cardiogenic shock remains in excess of 50%, and continues to account for the deaths of between 7% and 11% of patients admitted with myocardial infarction.<sup>1–3</sup> In the majority of these patients, the problem is one of overwhelming left ventricular damage and, intuitively, revascularization should be the primary therapeutic strategy. However, attempts to prove this have been fraught with difficulty, and the randomized trial paradigm that revolutionized our approach to acute cardiology appears to have faltered. This review examines the features of cardiogenic shock that have hindered attempts to improve its outcome, discusses whether current evidence is sufficient to support a policy of revascularization and explores the potential value of approaches aimed at minimizing reperfusion damage.

## Diagnosis and aetiology

The development of cardiogenic shock is rarely unexpected, most patients who develop shock do so within 48 hours of admission, with only 10% shocked on arrival.<sup>2</sup> As would be expected, shock is associated with larger infarcts, prior infarction, diabetes and infarct extension.<sup>4,5</sup> The diagnosis itself is straightforward, with a systolic blood pressure <90 mmHg for more than 30 min in the absence

of hypovolaemia or other potential causes of hypotension. Additional features such as oliguria and impaired peripheral perfusion identify those at particularly high risk of death.<sup>6</sup> The widespread availability of bedside echocardiography has rendered the use of invasive haemodynamics, and in particular a requirement for a cardiac index of less than 2.2 l/min/m<sup>2</sup>, virtually obsolete in the decision-making process. Echocardiography readily identifies the mechanism of shock and those patients that might benefit from surgery for intra- or extra-myocardial rupture (Figure 1).<sup>4,7,8</sup>

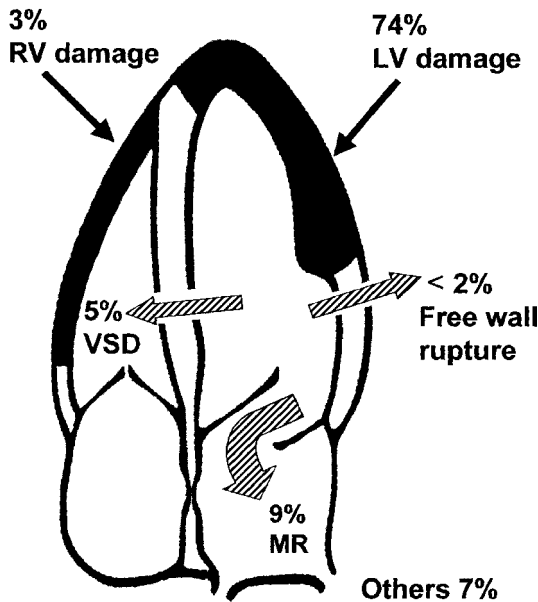
## Pathophysiology of shock due to overwhelming ventricular damage

We are then left with the largest group of patients, those with insufficient contracting myocardium to survive. This group comprises those patients with overwhelming left ventricular damage and the 50% of those with severe right ventricular damage that do not respond to fluid loading (whose prognosis is often worse than commonly perceived). The pathogenesis of shock in these patients can be considered at the level of the occluded epicardial artery, in the damaged microvasculature and in individual myocytes. This initiating insult is then compounded by a maladaptive endocrine response with additional damage produced by reperfusion and the myocardial depressant effects of hypotension itself.

*Address correspondence to Dr C.H. Davies, Department of Cardiology, Mail Code UHN 62, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201–3098, USA. e-mail: daviesc@ohsu.edu*

## Coronary occlusion

The initiating insult is persistent occlusion of an epicardial coronary artery,<sup>9,10</sup> reflected in the presence of ST segment elevation in 80% of patients.<sup>11</sup> The potential factors underlying thrombolytic failure in normotensive individuals have been recently reviewed,<sup>12</sup> but once shock develops, further intense

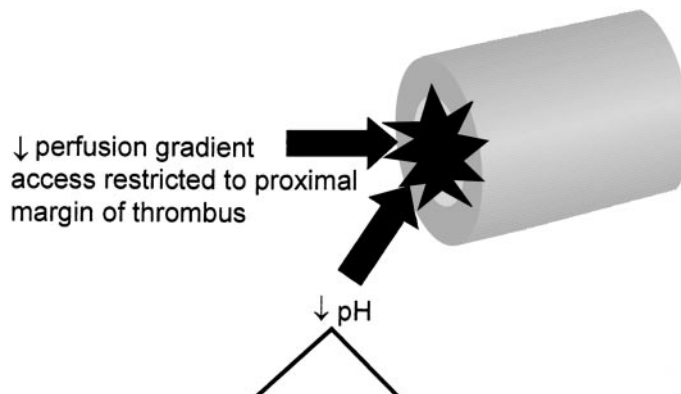


**Figure 1.** Apical four-chamber echo view with relative incidence of the mechanisms responsible for cardiogenic shock in the SHOCK 8 and MILIS 4 registries. MR, mitral regurgitation; VSD, ventricular septal defect.

thrombolytic resistance supervenes. This occurs due to failure of the lytic agent to gain access to the thrombus and a hostile biochemical environment<sup>13</sup> (Figure 2). In non-shocked patients, a pressure gradient exists between the proximal and distal margins of the thrombus, permitting both thrombolytics and their plasminogen substrate direct access to a large volume of clot via pores in the fibrin mesh. However, coronary blood flow falls off steeply below an aortic pressure of 85 mmHg,<sup>14</sup> and the pressure gradient declines, restricting access to only the proximal blood/clot boundary plane.<sup>15</sup> Under both *in vitro* conditions<sup>16</sup> and in animal models<sup>17,18</sup> this produces a substantial reduction in the rate of thrombolysis. In addition, acidosis impairs conversion of plasminogen to plasmin and produces disassociation of the streptokinase-plasminogen complex.<sup>19</sup>

## Microvascular damage

Following epicardial occlusion, platelet and neutrophil microthrombi aggregate in the capillaries and release vasoconstrictors, resulting in microvascular spasm. Leukocytes adhere to the endothelium via selectin and integrin receptors, producing endothelial dysfunction before migrating into the myocardium to produce direct myocardial damage. Combined with myocardial oedema, these events produce an additional impedance to flow at the level of the microvasculature which persists even after the restoration of epicardial flow (the 'no-reflow' phenomenon).



**Figure 2.** Mechanisms of thrombolytic resistance in cardiogenic shock.

## Myocyte necrosis and ischaemic dysfunction

Failure of perfusion results in necrosis of, on average, 50% of the left ventricular myocardium, although the range is surprisingly wide (35–66%).<sup>9,20,21</sup> Anaerobic metabolism results in accumulation of H<sup>+</sup> ions within the myocyte, activating the Na<sup>+</sup>/H<sup>+</sup> exchange system. This results in a net Na<sup>+</sup> influx which in turn is removed by the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, producing Ca<sup>2+</sup> influx, overload, hypercontracture and death. Gap-junction-mediated communication of this calcium overload may be responsible for the characteristic wave-front progression of necrosis. However, in addition to this irreversible damage, a proportion of the myocytes will be viable but not contracting due to varying degrees of stunning (impaired function despite restoration of flow) and hibernation (impaired function due to severely impaired flow).<sup>22</sup> Importantly, the timecourse of recovery of left ventricular myocardial function in shock (a component of which may extend over weeks<sup>23</sup>) parallels other situations where stunning occurs. This has implications for the protracted support that may be required if reperfusion were actually achieved.

## Neuroendocrine responses

Meanwhile, the fall in tissue perfusion induces a compensatory neuro-endocrine activation which attempts to maintain cardiac output by myocardial stimulation and increased peripheral resistance.<sup>24</sup> The ability of the remaining myocardium to generate a compensatory hyperkinesis<sup>25,26</sup> in response to this neuro-endocrine activation is probably responsible for the much of the variability in the degree of myocardial damage required to produce shock<sup>9,20,21</sup> and is particularly impaired in patients with multivessel disease.<sup>27</sup> Progressive myocardial depression then occurs by a combination of hypotension producing infarct extension,<sup>21</sup> the neuroendocrine activation producing direct myocardial damage<sup>20,28,29</sup> and an inappropriately high afterload.

## Reperfusion injury

Paradoxically, reperfusion is associated with a burst of free radical production, further neutrophil adhesion and complement formation.<sup>30</sup> In addition, the restoration of free fatty acid metabolism precedes that of glucose oxidation. This further depresses intracellular pH and the potential for calcium overload via an activated Na<sup>+</sup>-H<sup>+</sup> exchanger.<sup>31</sup>

As a result, the proportion of viable myocardium actually falls during the first 2 h of reperfusion<sup>32</sup> and apoptotic mechanisms may be particularly prominent here.

## Management of shock due to overwhelming left ventricular damage

Attempts to improve the outcome of cardiogenic shock need to address this multi-faceted pathophysiology: circulatory support is required during restoration of reperfusion at both the macro- and microvascular levels, while at the same time attempts are made to limit ongoing myocyte necrosis and minimize reperfusion damage.

## Inotropes and supportive therapies

Whilst catecholamines<sup>33,34</sup> and other agents<sup>35</sup> increase cardiac output acutely, there is no evidence that they improve survival. This point is underscored by the static mortality of shock during the period of increasing inotrope use.<sup>1</sup> Indeed, the role of catecholamine excess in the pathogenesis of shock suggests that inotropes will accelerate myocardial dysfunction, due to the rapid development of  $\beta$ -adrenoceptor desensitization,<sup>36</sup> and the need for dosage escalation. Inotropes do have a role in stabilizing patients during assessment or transfer, and in situations where a reversible aetiology has been identified; however, as a treatment in isolation, they should be regarded as essentially palliative. Similar comments can be applied to the use of mechanical ventilation and haemofiltration in the absence of a remediable cause of shock. The inappropriately high peripheral resistance in cardiogenic shock has been viewed as a potential target for vasodilators, although in practice the prevailing hypotension makes these of no practical use.<sup>37</sup>

## Mechanical LV assist devices and transplantation

The use of mechanical ventricular assist devices, usually as a bridge to transplantation, remains experimental. Although successful series have been published,<sup>38–40</sup> other reports have been less encouraging.<sup>41–43</sup> The mismatch between the numbers of patients developing cardiogenic shock and the availability of donor organs means that this will never be an option for the majority of patients.

## Myocardial reperfusion

Reperfusion, either chemically or mechanically, is intuitively the rational approach to a condition caused by arterial occlusion, a fact appreciated for almost a century.<sup>44</sup> However, for this to become a realistic option, flow must be restored at both the epicardial and microvascular levels while attempts are made to minimize myocyte injury. As a result, progress to establish reperfusion as a viable strategy has been frustratingly slow.

## Thrombolysis

As the absolute benefits of successful medical treatments tend to be accentuated in high-risk subgroups of cardiovascular trials, one might predict that thrombolysis would be particularly efficacious in patients at such a high risk of death. This effect is seen up to a point in the FTT thrombolytic meta-analysis, where some of the highest absolute benefits occurred in those with a systolic BP <100 mmHg (66 lives saved per 1000) or heart rate >100/min (33 lives/100).<sup>45</sup> Judging by their overall mortality of <35%, however, this group fell short of established cardiogenic shock and the subgroup with established shock (both BP <100 mmHg and heart rate >100/min and a 60% mortality) failed to show benefit.<sup>46</sup> This meta-analysis defined the clinical lower limit limit of thrombolytic efficacy, where the biochemical effects of thrombolytic resistance negate the high-risk subgroup effect. This important conclusion is also apparent in the one trial to specifically include shocked patients<sup>47</sup> and has not been altered by subsequent trials using more aggressive lytic regimens.<sup>2,48–50</sup> Further support for the futility of thrombolysis in shock is derived from SHOCK<sub>R</sub>,<sup>7</sup> where patients receiving thrombolysis had a similar mortality to thrombolytic-eligible patients (61%) who did not receive thrombolysis (71%,  $p = 0.334$ ).

## Intra-aortic balloon pumping

The combination of reduced afterload, increased diastolic pressure available for coronary perfusion and improved cardiac output makes the use of an intra-aortic balloon pump (IABP) an attractive option in cardiogenic shock. Unfortunately, early experience demonstrated that although patients can frequently be stabilized, they cannot subsequently be weaned, and that the overall outlook remains unchanged.<sup>51–55</sup> Two randomized trials have also failed to demonstrate benefit from the use of an IABP,<sup>56,57</sup> although strictly speaking the patients enrolled fell short of the criteria for cardiogenic shock. Neither was there evidence of benefit from

the use of balloon pumping in the patients developing cardiogenic shock in GUSTO-1<sup>58</sup> nor in SHOCK<sub>R</sub> once the confounding effects of cardiac catheterization had been adjusted for.<sup>58</sup> Pooling of all of the above data still fails to demonstrate any benefit.<sup>59</sup> There is thus no indication for IABP insertion in cardiogenic shock except in combination with more definitive treatment, or to provide stability during investigation.<sup>60</sup>

## Intra-aortic balloon-pump-assisted thrombolysis

In canine models, the thrombolytic resistance encountered in shock is substantially reversed by intra-aortic balloon pumping.<sup>18,61,62</sup> This effect is not mediated by significant increases in coronary flow, suggesting that the benefit was due to the augmentation of diastolic pressure or to a doubling of the number of pressure waves in each diastolic period. One attraction of a combination of thrombolysis and IABP ('balloon-assisted thrombolysis') is that it does not require transfer of patients to a regional centre or the provision of 24-h interventional facilities. Nevertheless, enthusiasm has been tempered by the potential for haemorrhagic complications: IABP insertion was an independent predictor of severe bleeding in the TAMI-1 trial of alteplase<sup>63</sup> and of moderate bleeding in GUSTO-1.<sup>64</sup> Surprisingly, this has not been a consistent finding<sup>65</sup> and the availability of balloons which can be inserted through smaller puncture sizes has promoted a re-evaluation of this combination.

The clinical evidence for balloon-assisted thrombolysis is derived from three retrospective series and the prospective data from SHOCK<sub>R</sub>. In the first of these, Stomel *et al.*<sup>66</sup> examined the records of 64 patients treated with either thrombolysis or IABP alone or the two in combination. Mortality was similar for patients receiving either treatment in isolation (70%) but reduced (32%) in those who receiving both. Kovak *et al.* have reported similar findings, with an in-hospital mortality of 93% for thrombolysis alone but 37% for balloon-assisted thrombolysis.<sup>67</sup> Of the 21 178 patients who developed cardiogenic shock in the Second National Registry of Myocardial Infarction, mortality was lower in patients receiving a combination of thrombolysis and balloon pumping when compared to thrombolysis alone (49% vs. 69%).<sup>68</sup> Lastly, in the 857 patients in SHOCK<sub>R</sub>, the combination of IABP and thrombolysis was associated with a 46% mortality compared to 76% for patients who received neither ( $p < 0.001$ ), but this result was potentially confounded by younger age, earlier

onset of shock and a higher frequency of revascularization in patients in the combined treatment group.<sup>69</sup>

The combination of a coherent scientific rationale combined with these encouraging studies made this a promising avenue of investigation, and the publication of the randomized TACTICS trial was eagerly awaited. Unfortunately, this has now been abandoned due to poor recruitment, and the role of balloon-assisted thrombolysis in the management of shock remains undefined. It remains worth considering if interventional facilities are not immediately available, particularly for the 10% of patients who present in shock, as only a single dose of thrombolytic is required, thus minimizing the haemorrhagic risk. A variant on this theme is the use of inotropes to increase the blood pressure transiently to a point at which thrombolysis might be effective. This is potentially a more logical use of inotropes than our current practice, and is supported by evidence from a canine model.<sup>62</sup> To date, this has only been investigated in a small series of eight patients, of whom reperfusion was demonstrated in six,<sup>70</sup> and the role of this approach must await further studies.

## Mechanical revascularization

The information suggesting a benefit from mechanical revascularization (the majority of which relate to PTCA) can be considered in three sections: small case series, registry data and the two randomized controlled trials (Table 1).

There were 31 small single-centre series between 1985 and 1999, involving a total of 1267 patients with an in-hospital mortality of 50% (many only available as abstracts). Although these are frequently

presented as an improvement on the 90% mortality of historical controls, the small numbers of patients and the likelihood of selection bias makes interpretation difficult. What these data do confirm is that PTCA for patients in cardiogenic shock is technically feasible, but that unsuccessful PTCA carries a very high mortality. One interesting observation is that in those studies examining longer-term prognosis, the benefits of revascularization are still apparent at 6 and 12 months.<sup>71-76</sup>

The registry data is derived from the SHOCK<sub>R</sub>, Worcester, MITRA, Californian and Second National Registry studies, with additional data from the four publications relating to shock from GUSTO-1 (Figure 4). SHOCK<sub>R</sub> was first published in 1995,<sup>7</sup> with an update in 1999,<sup>77</sup> and now includes a total of 1380 patients. Those undergoing revascularization (which was by PTCA in 69%) had a lower mortality than those managed conservatively (41% vs. 79%). In addition, the use of revascularization increased over time, and was paralleled by a reduction in mortality in both SHOCK<sub>R</sub> and the Worcester registry.<sup>1</sup> A similar pattern emerges in MITRA,<sup>3</sup> the Second National Registry<sup>68</sup> and in GUSTO-1.<sup>2,78</sup> Importantly, the one-year follow-up data from GUSTO-1 confirm the impression from the smaller studies that the prognosis of patients who were successfully revascularized remains favourable (with 88% of those alive at 30 days surviving at one year).<sup>79</sup> Subgroup analysis of the GUSTO-1<sup>80</sup> and GUSTO-3<sup>50</sup> data by country also reveals improved survival for the more intensively treated patients in the USA compared to elsewhere (50% vs. 66%). However, the limitations of this type of data are illustrated by the fact that those patients selected to undergo catheterization in SHOCK<sub>R</sub> had a lower mortality than those not

**Table 1** Sources of evidence for potential benefit of revascularization in cardiogenic shock

	Patient numbers	Revascularized mortality	Not revascularized mortality
Case series	1058	48%	NA <sup>a</sup>
<i>Registeries</i>			
Californian <sup>96</sup>	1122	33%	68%
SMASH <sub>R</sub> <sup>43</sup>	51	50%	74%
Worcester <sup>1</sup>	644	NA <sup>b</sup>	NA <sup>b</sup>
MITRA <sup>3</sup>	837	52%	73%
SHOCK <sub>R</sub> <sup>7,77</sup>	1380	41%	79%
GUSTO-1 <sup>2,78-80</sup>	2972	43%	61%
National Registry-2 <sup>68</sup>	21 718	47%	69%
<i>Randomized trials</i>			
SMASH <sub>T</sub> <sup>43</sup>	55	69%	78%
SHOCK <sub>T</sub> <sup>81</sup>	302	47%	56%

NA, not available. <sup>a</sup>Mortality for non-revascularized patients not available for the majority of these studies. <sup>b</sup>Absolute mortality data not available from the Worcester study.

selected (51% vs. 85%), even if they were not subsequently revascularized. Similarly, patients selected for aggressive treatment in GUSTO-1 were younger, had a lower incidence of prior infarction and a shorter time to treatment.<sup>78</sup> Those being considered for aggressive management thus constitute a subgroup with an intrinsically favourable outlook, with the suspicion that the sickest patients either died before revascularization could be undertaken, or were rejected as being unsalvageable. The data examining mortality between countries are equally problematic, as the incidence of shock was higher in the USA and the mortality in medically-managed patients lower, further fuelling suspicion that a lower-risk population was revascularized. These studies illustrate that in a condition with a high intrinsic mortality, even small changes in inclusion characteristics can translate into marked variations in outcome—a fact that can also be inferred from the wide differences in mortality between individual studies.

Thus, despite data involving almost 27 000 patients, a definite answer remained elusive, setting the scene for the two randomized trials. The first of these, SMASH,<sup>43</sup> enrolled 55 patients over a 4-year period in nine European centres. Virtually all of the patients in the invasive arm underwent PTCA, with only one undergoing bypass surgery. The study was terminated prematurely due to inadequate recruitment, with no significant mortality difference between the invasive and non-invasive groups (69% vs. 78%). In a small parallel registry, the differences between invasive and non-invasive groups were more marked (50% vs. 74%), again emphasizing the preselection that must have been present in previous series.

In the second of the randomized trials, SHOCK<sub>T</sub>,<sup>81</sup> 302 patients with ST elevation were randomized within 36 h of infarction and within 18 h of the onset of shock (Box 1). Strictly speaking,

#### **SHOCK trial: eligibility criteria**

- ST elevation
- Systolic BP < 90 mmHg for > 30 minutes
- Evidence of peripheral hypoperfusion
- Onset of shock < 36 hours post MI
- < 18 hours after the onset of shock

**Box 1**

the comparison was between immediate revascularization (of which 64% was by PTCA) and revascularization preceded by a period of medical management (21% of patients in this latter group were subsequently revascularized). Mortality was not significantly different between the two groups at the primary end point of 30 days (47% vs. 56%), but was reduced by the secondary end-points of 6 months (50% vs. 63%,  $p < 0.03$ ) and 1 year (53% vs. 66%,  $p < 0.03$ ). Looked at optimistically, this equates with needing to treat approximately eight patients to prevent one death at 6 months, but conversely the absolute difference in numbers between the two groups is too small for this type of analysis to be meaningful (an extra five deaths in the intervention group against 10 in the medically-managed group between 30 days and 6 months). It should be noted that benefit was concentrated in those below 75 years of age, which is in accord with both prior studies and clinical experience. The caveat that the ongoing improvements in PTCA technology result in trials underestimating the benefits of intervention is frequently cited when a PTCA trial fails to deliver the expected results. Although favourable results from the use of both abciximab and stenting<sup>82,83</sup> have been described in the context of shock, only stenting appeared to confer additional benefit in SHOCK<sub>T</sub>.<sup>84</sup> More important perhaps was the frequent use of thrombolysis (63%) and balloon pumping (86%) in the medical therapy group, which may have attenuated the apparent benefit from revascularization.

With the benefit of hindsight, the fundamental problem with both randomized trials is that they were underpowered, as the expectation generated by the registry studies of a 20% mortality reduction never materialized (to reliably detect the 9% difference that actually occurred would require a trial of >1000 patients). The enormous effort to randomize the 300 patients in SHOCK should not be underestimated, and there is no realistic prospect of a 1000-patient trial ever being undertaken (the HEROICS trial has been abandoned). In addition, the registry data and published opinion remind us that most major US centres now regard revascularization for cardiogenic shock as the norm.

We are thus left in the uncomfortable position of deciding whether to adopt an expensive and high-risk procedure on the basis of incomplete information. On balance, with the prospect of significantly improved survival at 6 and 12 months, the evidence favours early revascularization in selected patients, but this begs the question of what selection criteria are appropriate. Criteria based on the measurement of cardiac reserve have been proposed,<sup>85</sup> but these are based on studies of only 28 patients, with no evidence that they can predict

suitability for revascularization. The inclusion criteria for SHOCK<sub>T</sub> provide a starting point (Box 1) and shocked patients falling outside these should not be considered for revascularization, whereas patients falling within them should be discussed with a regional cardiology centre. However, many cardiologists would feel that the optimal time window for intervention is significantly less than the 18-h duration of SHOCK<sub>T</sub> and that a 10-h ceiling would be more appropriate.

However if they tell us anything at all, what these trials clearly demonstrate is that even with revascularization, mortality remains unacceptably high, and this serves to focus attention on efforts to maximize myocardial salvage once reperfusion has been achieved.

## Prospects for maximizing myocardial salvage

Attempts to improve myocardial salvage have centred on reducing platelet and neutrophil adhesion/migration whilst maximizing the ischaemic tolerance of the myocyte.

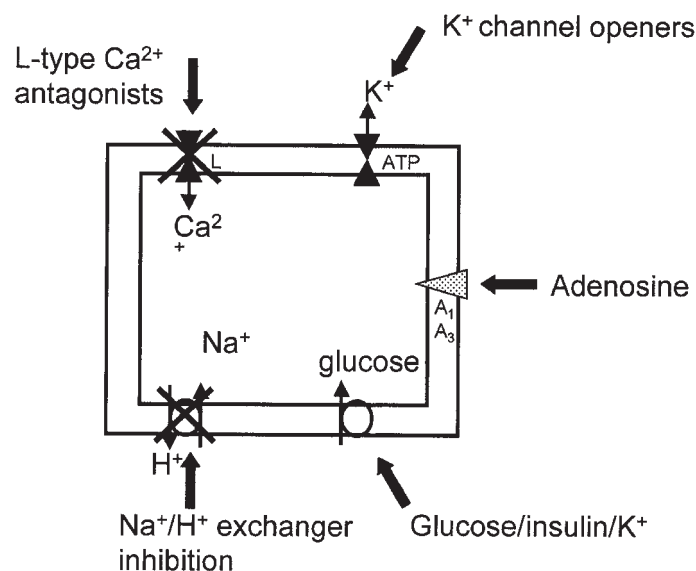
### Neutrophil and platelet function

Abciximab prevents platelet and neutrophil adhesion, and might be expected to mitigate against the no-reflow phenomenon by reducing the formation of microthrombi. There is some preliminary evidence of improved outcomes in cardiogenic shock angioplasty with the use of abciximab,<sup>86</sup> although as noted above, this was not apparent in retrospective analysis of the SHOCK data. For

the future, inhibition of leucocyte adhesion using a monoclonal antibody directed against the integrin receptor is being investigated in the HALT-MI,<sup>87</sup> while complement inhibition has been shown to improve myocardial salvage in animal models of reperfusion.<sup>88</sup>

### Myocyte protection (Figure 3)

Pharmacological attempts to mimic the powerful protection afforded by the preconditioning phenomenon using adenosine have demonstrated a reduction in infarct size,<sup>89</sup> while its intracoronary use has been claimed to mitigate against the no-reflow phenomenon. Both nicorandil,<sup>90</sup> an ATP-sensitive K<sup>+</sup> channel opener, and the L-type calcium antagonist verapamil<sup>91</sup> result in a reduction of the no-reflow zone and improved left ventricular function following angioplasty in acute MI, although the precise mechanisms underlying this remain unclear. In addition, there has been renewed interest in the use of glucose/insulin/potassium infusions, which aim to stimulate glycolytic activity whilst reducing free fatty acid consumption and consequently intracellular acidosis.<sup>92</sup> Lastly, there is a substantial body of animal evidence to support direct inhibition of the Na<sup>+</sup>-H<sup>+</sup> exchanger.<sup>31</sup> Clinical experience with Na<sup>+</sup>-H<sup>+</sup> exchanger inhibition, however, has produced conflicting results. Initial results in patients undergoing primary PTCA showed improvements in left ventricular function,<sup>93</sup> but no evidence of benefit was apparent in a larger unselected group of patients in the GUARDIAN trial.<sup>94</sup> These disappointing results probably reflect the need to initiate exchanger inhibition prior to the ischaemic insult—a strategy unlikely to prove viable in the context of shock.



**Figure 3.** Potential mechanisms for myocyte protection.

Thus the potential for improving myocardial salvage following reperfusion already exists, although much remains to be done before this emerges as a coherent clinical strategy.<sup>95</sup> At present, clinical use is restricted to the use of adenosine and verapamil for angiographic no-reflow.

## Conclusions

Mortality from cardiogenic shock remains frustratingly high, while attempts to demonstrate benefit from revascularization have been fraught with difficulty. We have arrived at a point where we should accept that in shocked patients, inotropes are essentially palliative, that thrombolysis is of no value and that on balance, the evidence favours a policy of revascularization in selected patients. We still lack a sound basis on which to perform this selection. However, even with revascularization, mortality remains in excess of 50%, and in order to make further progress, our attention must now shift from the open artery to one of maximizing microvascular integrity and optimizing myocardial protection.

## Trials glossary

AMISTAD, acute myocardial infarction study of adenosine; FTT, fibrinolytic therapy trialists collaborative group; GISSI, gruppo Italiano per lo studio della streptochinasi nell'infarcto miocardio; GUSTO, global utilization of streptokinase and tPA for occluded arteries; GUARDIAN, guard during ischaemia against necrosis; HEROICS, how effective are revascularization options in cardiogenic shock; INJECT, international joint efficacy comparison of thrombolytics; MILIS, multicenter investigation of limitation of infarct size; MITRA, maximal individual therapy of acute myocardial infarction; TAMI, thrombolysis and myocardial infarction; SHOCK, should we emergently revascularize occluded coronary arteries for cardiogenic shock [trial (SHOCK<sub>T</sub>) and registry (SHOCK<sub>R</sub>)]; SMASH, Swiss multicenter trial of angioplasty for shock [trial (SMASH<sub>T</sub>) and registry (SMASH<sub>R</sub>)]; TACTICS, thrombolysis and counterpulsation to improve cardiogenic shock survival (confusingly, there is also a TIMI trial in unstable angina with the same acronym).

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