Cardiogenic Shock Complicating Acute Coronary Syndromes

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Despite advances in the treatment of patients with acute coronary syndromes, in recent years, there has been no significant decrease in the incidence of cardiogenic shock[1-3]. Indeed, the occurrence of cardiogenic shock complicating acute myocardial infarction in Worcester, USA, remained relatively stable over a 23-year period (from 1975 to 1997), averaging 7.1 percent among patients with acute myocardial infarction[1]. The in-hospital death rates were relatively constant until the mid-to-late 1990s, averaging approximately 77 percent, 61 percent of patients with cardiogenic shock died in 1993 and 1995 and 59 percent in 1997[1]. Cardiogenic shock remains one of the major causes of death among patients with all types of acute coronary syndromes[4-6] and there is a growing interest in the identification of patients at risk for developing cardiogenic shock and in the exploration of different therapeutic approaches for its primary and secondary prevention.

Definition and diagnosis

Cardiogenic shock is a disorder caused by decreased systemic cardiac output in the presence of adequate intravascular volume, resulting in tissue hypoxia. The diagnosis itself is straightforward when there is a systolic blood pressure <90mm Hg in the absence of hypovolemia or other potential causes of hypotension. The reduction in systolic blood pressure leads to systemic signs of hypoperfusion, including altered mental state, cold clammy skin and oliguria.

In randomized trials[5-8] that enrolled patients with acute coronary syndromes, the definition of cardiogenic shock has been uniform and is defined as systolic blood pressure <90mm Hg for >1h that is:

- Not responsive to fluid administration
- Secondary to cardiac dysfunction, or
- Associated with signs of hypoperfusion or cardiac index< 2.2L/min/m^2 and pulmonary capillary wedge pressure> 18mm Hg

Also considered in this definition are:

- Patients with systolic blood pressure increase (>90mm Hg) within 1h after administration of inotropic agents, and
- Patients who died within 1 h of hypotension and met the other criteria of cardiogenic shock.

In equivocal circumstances, haemodynamic data derived from right heart catheterization may be useful in the diagnosis of cardiogenic shock. However, the widespread availability of bedside echocardiography has rendered the use of invasive haemodynamics in the decision-making process.

Etiology and pathophysiology

Left ventricular failure is the most common cause of shock among patients with acute coronary syndromes, associated with the loss of more than 40% of the contractile myocardium of the left ventricle[9,10]. It accounted for about 78% of cases in the SHOCK trial Registry[11], whilst 2.8% was attributed to isolated right ventricular failure In the same trial Registry

mechanical causes of shock (mitral regurgitation, ventricular septal rupture and tamponade) amounted to 12%. In-hospital Registry mortality was 60% and ventricular septal rupture was associated with a significantly higher mortality (87.3%) than all other causes[11].

Epidemiology

Cardiogenic shock can occur as a complication of all types of acute coronary syndromes, (unstable angina, acute myocardial infarction with or without-ST-segment elevation), however it is more common in myocardial infarction with ST-segment elevation[8]. The incidence of shock in unstable angina is about 2,9% and 2,1% in non-ST-elevation myocardial infarction[6]. In three large, international series of patients receiving thrombolytic therapy for acute myocardial infarction, the occurrence of cardiogenic shock ranged from 4,2% to 7,2%[5,7,8].

The median time to the occurrence of shock among patients with persistent-ST-segment elevation is 10h and most of the patients develop shock within the first 48h after acute myocardial infarction[5,8]. In the SHOCK trial Registry, shock onset occurred within 24h after acute myocardial infarction, in 74% of the patients with predominant left ventricular failure[12]. Mortality was slightly higher in patients developing shock earlier than later (62,6% vs 53,6%, p=0,022)[12]. Patients with acute ischemic syndromes without ST-segment elevation develop shock later (median time 76h after enrolment) than those with ST-segment elevation[8] suggesting a different etiology. In patients with ST-segment elevation, acute coronary artery occlusion may lead to massive necrosis and loss of a large amount of myocardium, whereas in patients without ST-segment elevation, shock may be a result of recurrent ischemia, or reinfarction[8]. Indeed, Holmes and his colleagues[8] found that patients with shock without ST-segment elevation had significantly more extensive coronary artery disease, and less TIMI grade 0 flow than patients with ST-elevation, this being consistent with the theory that ST-segment elevation usually results from acute coronary occlusion, whereas more preserved antergrade flow causes ischemia, ST-segment depression, or T-wave inversion, often without infarction.

More recent data[9] suggest that the timing of cardiogenic shock after onset of myocardial infarction provides important prognostic information. In 444 consecutive and not revascularised patients with ST and non ST-segment elevation myocardial infarction complicated by cardiogenic shock, development of shock later than 48h after myocardial infarction carries an extremely high 30-day mortality (more than 80%)[9].

Predictors of shock

As a result of the high mortality of cardiogenic shock, identification of subgroups of patients with acute ischemic syndromes who are at high risk of developing shock is important. Hasdai and his colleagues[14] analyzing data from the GUSTO-I trial revealed that certain demographic and clinical variables were strongly related to the development of cardiogenic shock in patients with persistent ST-segment elevation myocardial infarction. Age was the variable most strongly associated with shock: for every ten-year increase in age, the risk of developing shock was increased by 47%. Together with the patient's age, systolic blood pressure, heart rate and Killip class provided more than 85% of the predictive information[14].

Despite differences in the pathophysiology and clinical presentation of cardiogenic shock between patients with persistent ST-segment elevation myocardial infarction and patients with other acute coronary syndromes, the predictors of shock are quite similar. In another report of Hasdai and his colleagues[6], using data from the PURSUIT trial, it was shown that, patients with myocardial infarction were more likely to develop shock than were patients with unstable angina. In addition, patients with significant ST-segment depression in the initial electrocardiogram were more prone to the development of shock.

Management of shock

Attempts to improve outcome of cardiogenic shock need to take into account its multifactorial 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.

Supportive therapy

Whilst catecholamines acutely increase cardiac output, there is no evidence that they improve survival[15,16]. This point is underscored by the static mortality of

shock during the period of increasing inotrope use[1]. Inotropes do have a role in stabilizing patients during assessment or transfer and in situations where a reversible etiology has been identified; however as a treatment in isolation they should be regarded as essentially palliative. Levosimendan, a calcium sensitizer that increases myocardial contractility, has been shown to reduce mortality in patients with acute myocardial infarction complicated by heart failure[17]. However it has not been tried yet in patients with shock. Nitrates should be avoided because of their hypotensive effect. Administration of diuretics or fluids depends on left ventricular filling pressures values.

Patients with mechanical causes of shock should be first pharmacologically stabilized and the decision regarding the optimum timing for surgical intervention should be taken by the cardiologist and the surgeon together. Free wall rupture or pseudoaneurysm should be treated with prompt surgical repair[18]. In case of mitral regurgitation it is better to postpone the operation for 2-4 weeks if the patient can be stabilized after having been weaned from pharmacological and/or mechanical support[19]. Finally, recent data[20,21] suggest early surgical closure of post infarction ventricular septal defect using newer surgical techniques, (double patch approach), which have been shown to reduce in-hospital mortality.

Left ventricular assist devices

Circulatory support devices have been used to assist patients in cardiogenic shock due to acute myocardial infarction, usually as a bridge to cardiac transplantation. Although some successful series have been published[22,23], other reports have been less encouraging[24,25]. The disparity between the numbers of patients developing cardiogenic shock and the availability of donor organs, make this treatment option impossible for the majority of patients.

Thrombolytic therapy

The outcome of cardiogenic shock is closely linked to the patency of the culprit coronary artery[18]. Accordingly, reperfusion therapy with thrombolytic agents has decreased the occurrence of shock in acute myocardial infarction with persistent ST elevation[1]. GUSTO-I demonstrated that tissue-plasminogen activator is more efficacious than streptokinase in preventing shock[4]. However, new thrombolytic agents such as reteplase, which supposedly have higher reperfusion rates[19] and are associated with an incidence of shock similar to that observed with tissue-plasminogen-activator treatment[6].

When cardiogenic shock has already been established, thrombolytic therapy is often unsuccessful[20]. It has been suggested that the impaired fibrinolytic activity of thrombolytic therapy is in part related to the profound hemodynamic abnormalities that exist in these patients[21]. In order for a thrombolytic agent to dissolve an occlusive coronary thrombus, the agent must reach and then infiltrate the thrombus[22]. When mean arterial pressure falls below 65-70mm Hg, coronary blood flow begins to fall and ceases when mean arterial pressure drops below 30mm Hg[23].

Intra-aortic balloon pump (IABP)

The IABP is an intravascular, catheter-mounted counterpultation device with a balloon volume between 30 to 50ml. The device is inserted through the common femoral artery and positioned in the descending thoracic aorta. The balloon is inflated during cardiac diastole (set to inflate at the dicrotic notch of the arterial pressure waveform) and deflated during the isovolumetric phase of left ventricular contraction[24].

The diastolic inflation of the balloon augments the diastolic blood pressure and thereby increases the coronary artery perfusion and myocardial oxygen supply[25]. Systolic deflation of the balloon decreases systemic afterload and myocardial oxygen consumption. The net effect is a favorable shift in the myocardial oxygen supply/demand ratio, with a small increase in systemic perfusion.

Unfortunately clinical experience to date demonstrated that although patients can frequently be stabilized, they cannot subsequently be weaned and that the overall outcome remains unchanged[35,36]. Thus, the indication for IABP insertion in cardiogenic shock is to provide temporary hemodynamic stability until permanent therapy / treatment is effected.

Intra-aortic balloon pump-assisted thrombolysis

Experimental studies have demonstrated that augmentation of diastolic blood pressure by IABP increase both the rate and extent of coronary thrombolysis[21]. Nanas et al[36] showed that reperfusion and intraaortic balloon pump increased salvage of ischemic myocardium, more than that achieved by

reperfusion alone in a canine occlusion-reperfusion model.

Moreover, several clinical studies have suggested an improved outcome for patients with AMI complicated by cardiogenic shock that were treated with the combination of IABP and thrombolytic therapy[37,38]. Barron et al[39] found a significant reduction in mortality rates in patients who received thrombolytic therapy in combination with IABP (67%vs 49%). However there are no definitive data from randomized trials that can accurately answer this important question, thus the role of balloon-assisted thrombolysis in the management of shock remains undefined.

Interventional revascularisation

The discouraging results with thrombolytic therapy in patients with cardiogenic shock lead to an emerging interest in the use of interventional revascularization.

The information suggesting a benefit from interventional revascularization (the majority of which related to PTCA) is derived from three sources: small series, registry data and two randomized controlled trials.

There were several small single-center series[40-43] between 1985 and 2003, involving a total of 1303 patients with an in-hospital mortality of 50% or less. Although these are frequently presented as an improvement on the 90% mortality of historical controls, the limited number of patients and the likelihood of the selection bias make interpretation difficult.

The registry data derived from the $SMASH_R$[44], $SHOCK_R$[45,48], Californian[46] and Second National Registry[39] studies; with additional data from GUSTO-I trial[5,49] showed that revascularisation was associated with improved survival. Moreover, Berger and colleagues[47] showed that among GUSTO-I patients with cardiogenic shock, early revascularisation (within 30-days of myocardial infarction) was associated with marked reduction in mortality, independent of differences in baseline clinical characteristics between patients who did and who did not undergo early revascularisation, and this benefit was still apparent after 1 year.

However, the limitation of this type of data are illustrated by the fact that those patients selected to undergo catheterization in $SHOCK_R$ had lower mortality than those not selected (51% vs 85%) even if they were not subsequently revascularised[45]. Similarly, patients selected for aggressive treatment in GUSTO-I were younger, had a lower incidence of prior infarction and a shorter time to treatment[49].

Thus, despite data involving almost 27,000 patients, a definitive answer remained elusive, setting the scene of the two randomized trials. The first of these, SMASH[44] enrolled 55 patients over a 4-year period in nine European centers. 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 SHOCK[50], the second of the randomized trials, 302 patients with ST elevation were randomized within 36h of infarction and within 18h of the onset of shock. The comparison was made between immediate revascularisation and revascularisation preceded by a period of medical management (21% of patient in this latter group were subsequently revascularised). Mortality was not significantly different between the two groups at the primary end point of 30 days (47% vs 56%), but was reduced after 6-months (50% vs 63% $p<0.03$) and after 1 year (53% vs. 66%, $p<0.03$). It should be noted that benefit was limited in patients younger than 75 years, which is in accordance with both prior studies and clinical experience. In a recent sub-study of the SHOCK trial, Picard and his colleagues[51] found that both short- and long-term mortality appear to be associated with initial left ventricular systolic function and mitral regurgitation as assessed by echocardiography. The benefit of early revascularisation is noted regardless of baseline left ventricular ejection fraction or mitral regurgitation. The fundamental problem with both randomized trials is that they were underpowered, as the expectation by the registry studies of a 20% reduction of mortality was never proved (a trial of >1000 patients would be required to reliably detect the 9% difference that was actually found).

We are thus left in the uncomfortable position of deciding whether or not to adopt an expensive and high-risk procedure on the basis of incomplete information. With the prospect of the significantly improved survival at 6 and 12 months, the evidence favours early revascularisation in selected patients, but this leads to the question of what selection criteria are appropriate. Based on the results of the SHOCK trial[50] the generally poor prognosis for elderly patients with shock underscores the need for careful consideration of revascularisation procedures in this age group. For patients younger than 75 years,

early revascularisation should be regarded favourable, especially if experienced cardiologists can do it promptly. A summary of the SHOCK trial[52] which has been recently published reported that in patients younger than 75 years of age, early revascularisation saves 20 lives at 6 months per 100 patients treated. According to these results, the current American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend the adoption of an early revascularisation strategy for patients <75 years of age with cardiogenic shock complicating acute ST elevation/Q-wave or new left bundle branch block myocardial infarction.

However, what these trials clearly demonstrate is that even with revascularisation, mortality remains unacceptably high and we need to focus on efforts to maximize myocardial salvage once reperfusion has been achieved.

Prospects for maximizing myocardial salvage

Attempts to improve myocardial salvage have focused on preventing and treating the no-reflow phenomenon (reducing the microvasculature damage) whilst maximizing the ischemic tolerance of the myocytes.

Prevention of no-reflow phenomenon

No-reflow phenomenon (decrease or cessation of the blood flow after restoration of an epicardial coronary artery occlusion) is caused by abnormalities at the level of microvasculature, although the exact mechanism is uncertain[53]. Platelet glycoprotein IIb/IIIa inhibitors prevent platelet and neutrophil adhesion, and are expected to prevent the no-reflow phenomenon by reducing the formation of microthrombi[54,55]. In a post hoc analysis of the PURSUIT trial, Hasdai and his colleagues[6] demonstrated that patients with shock (with unstable angina or non-ST elevation myocardial infarction) treated with eptifibatide had significantly reduced 30-day mortality (77,2% vs. 52,7% p = 0.001). Moreover, there is evidence of improved outcome of angioplasty with the use of abxicimab in cardiogenic shock[56-57]. Giri and his collegues[56] showed that abxicimab therapy improves the 30-day outcome of primary PTCA in acute myocardial infarction complicated by cardiogenic shock, especially when combined with coronary stenting (composite event rate of death, myocardial reinfarction and target vessel revascularisation 31% in abxicimab group vs. 63%, p=0.002). Further controlled trials[58,59] confirmed the clinical benefit of this group of platelet inhibitors and supported that their mechanism was not only related to better epicardial blood flow but was also related to less no-reflow phenomenon and better flow at the level of the microcirculation.

Myocyte protection

Once no-reflow phenomenon has been established, other treatment options are available. The two more intense studied agents, verapamil[60] and adenosine[61], have been claimed to prevent the no-reflow phenomenon when given intracoronary. Nicorandil[62], an ATP-sensitive K^+ channel opener results in a reduction of the no-reflow zone and improved left ventricular function following angioplasty in acute myocardial infarction. In addition, there has been renewed interest in the use of glucose/insulin/ potassium infusion, which aim to stimulate glycolytic activity whilst reducing free fatty acid consumption and consequently intracellular acidosis[63]. Finally, there is animal data to support the use of direct inhibititors of the Na^+/H^+ pump[64]. However, clinical experience with Na^+/H^+ inhibition has produced conflicting results[65,66].

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

Conclusion

Mortality of cardiogenic shock remains frustratingly high, while attempts to demonstrate benefit from revascularisation have been fraught with difficulty. We have arrived at a point where we should accept that in patients with shock, inotropes are essentially palliative, thrombolysis is of limited value and that evidence favours a policy of revascularisation in selected patients.

However, even with revascularisation, mortality remains high (>of 50%) and in order to make further progress, our attention must now shift from the open artery to maximizing microvascular integrity and optimizing myocardial protection. It seems that, although the previous two decades were the decades of reperfusion of large epicardial arteries, the first decade of the new millennium will be the decade of the microvasculature perfusion.

References

1. Goldberg RJ, Samad NA, Yarzebski J, et al: Temporal trends in cardiogenic shock complicating acute myocardial infarction. N Engl J Med 1999; 340: 1162-1168.
2. Holmes DR, Califf RM, Van de Werf F, et al, for the GUSTO-I investigators. Difference in the countries' use of resources and clinical outcome for patients with cardiogenic shock after myocardial infarction: results from the GUSTO trial. Lancet 1997; 349: 75-78.
3. Hochman JS, Sleeper LA, Godfrey E et al, for the SHOCK trial study group. Should we emergently revascularise occluded coronaries for cardiogenic shock: an international randomised trial of emergency PTCA/CABG trial design. Am Heart J 1999; 137: 313-321.
4. Menon V, Hochman JS: Management of cardiogenic shock complicating acute myocardial infarction. Heart 2002; 88: 531-537.
5. Holmes DR, Bates ER, Kleiman NS, et al: Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. J Am Coll Cardiol 1995; 26: 668-674.
6. Hasdai D, Harrington RA, Hochman JS, et al: Platelet glycoprotein IIb/ IIIa blockade and outcome of cardiogenic shock complicating acute coronary syndromes without persistent ST-segment elevation. J Am Coll Cardiol 2000; 36: 685-692.
7. Hasdai D, Holmes DR, Topol EJ, et al: Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase: results from GUSTO III. Eur Heart J 1999; 20: 128-135.
8. Holmes DR, Beger PB, Hochman JS, et al: Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. Circulation 1999; 100: 2067-2073.
9. Lindholm MG, Kober L, Boesgaard S, Torp-Pedersen C, Aldershvile J, on behalf of the TRACE study group. Cardiogenic shock complicating acute myocardial infarction. Prognostic impact of early and late shock development. Eur Heart J, 2003; 24: 258-265.
10. Killip T: Cardiogenic shock complicating myocardial infarction. J Am Coll Cardiol 1989; 14: 47-48.
11. Alonso DR, Scheidt S, Post M, Killip T: Pathophysiology of cardiogenic shock: quantification of myocardial necrosis, clinical, pathologic and electrocardiographic correlations. Circulation 1973; 48: 588-596.
12. Hochman JS, Buller CE, Sleeper LA, et al, for the SHOCK investigators. Cardiogenic shock complicating acute myocardial infarction-Etiologies, management and outcome: A report from the SHOCK trial Registry. J Am Coll Cardiol. 2000; 36: 1063-1070.
13. Webb JG, Sleeper LA, Buller CE, et al, for the SHOCK investigators. Implications of the timing of onset of cardiogenic shock after acute myocardial infarction: A report from the SHOCK trial Registry. J Am Coll Cardiol. 2000; 36: 1084-1090.
14. Hasdai D, Califf RM, Thompson TD, et al: Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol. 2000; 35: 136-143.
15. Richard C, Ricome JL, Rimailho A, et al: Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. Circulation 1983; 67: 620-626.
16. Gage J, Rutman H, Lucido D, Lejemtel. Additive effects of dobutamine and amrinone on myocardial contractility and ventricular performance in patients with severe heart failure. Circulation 1986; 74: 367-373.
17. Moiseyev VS, Poder P, Andrejevs, et al: Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction (RUSSLAN) Eur Heart J. 2002; 23: 1422-1432.
18. Lopez-Sendon J, Gonzalez A, Lopez De Sa E, et al: Diagnosis of subacute ventricular wall rupture after acute myocardial infarction: sensitivity and specificity of clinical, hemodynamic and echocardiographic criteria. J Am Coll Cardiol 1992; 19: 1145-1153.
19. Pretre R, Ye Q, Grunenfelder J, et al: Operative results of "repair" of ventricular septal rupture after acute myocardial infarction. Am J Cardiol 1999; 84: 785-788.
20. Tanaka H, Hasegawa S, Sakamoto T, Sunamori M: Post-infarction ventricular septal perforation repair with endoventricular patch plasty using double patches and gelatin-resorcinol-formaldehyde biological glue. Eur J Cardiothorac Surg 2001; 19: 945-948.
21. Labrousse L, Choukroun E, Chevalier JM et al: Surgery for post infarction ventricular septal defect (VSD): risk factors for hospital death and long term results. Eur J Cardiothorac Surg 2002, 21: 725-731.
22. Hendry PJ, Masters RG, Mussivand TV, et al: Circulatory support for cardiogenic shock due to acute myocardial infarction: a Canadian experience. Can J Cardiol 1999; 15: 1090-1094.
23. Magovern JA, Sussman MJ, Goldstein AH, et al: Clinical results with the AB-180 left ventricular assist device. Ann Thorac Surg 2001; 71: S121-124.
24. Boehemer JP, Pae WP, Silber D, et al: Poor outcome with left ventricular assist devices as a bridge to transplant following myocardial infarction with cardiogenic shock. J Am Coll Cardiol 1999; 33: 208A (abstract).
25. Gacioch GM, Ellis SG, Lee L, et al: Cardiogenic shock complicating acute myocardial infarction: the use of coronary angioplasty and the integration of the new support devices into patient management. J Am Coll Cardiol 1992; 19: 647-653.
26. Bengtson JR, Kaplan AJ, Pierer KS, et al: Prognosis in cardiogenic shock after acute myocardial infarction in the interventional era. J Am Coll Cardiol 1992; 20: 1482-1489.
27. Noble S, Mc Tavish D. Reteplase: a review of its pharmacological properties and clinical efficacy in the management of acute myocardial infarction. Drugs 1996; 52: 589-605.
28. Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico. Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. Lancet 1986; 1: 397-401.
29. Prewitt RM, Gu S, Garber PJ, Ducas J: Marked systemic hypotension depresses coronary thrombolysis induced by intracoronary administration of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1992; 20: 1626-1633.
30. Becker RC: Hemodynamic, mechanical, and metabolic determinants of thrombolytic efficacy: a theoretic framework for assessing the limitations of thrombolysis in patients with cardiogenic shock. Am Heart J 1993; 125: 919-929.
31. Mueller H, Ayres SM, Conklin EF, et al: The effects of intra-aortic counterpulsation on cardiac performance and metabolism in shock associated with acute myocardial infarction. J Clin Invest 1971; 50: 1885-1900.

32. Nanas JN, Moulopoulos SD: Counterpulsation: historical back-ground, technical improvements, hemodynamic and metabolics effects. Cardiology 1994; 84: 156-167.
33. Kern MJ, Aguirre F, Bach R, et al: Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. Circulation 1993; 87: 500-511.
34. Flaherty JT, Becker LC, Weiss JL, et al: Results of a randomized prospective trial of intra-aortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarction. J Am Coll Cardiol 1985; 6: 434-446.
35. Goldberger M, Tabak SW, Shah PK: Clinical experience with intra-aortic balloon counterpulsation in 112 consecutive patients. Am Heart J 1986; 111: 497-502.
36. Nanas JN, Nanas SN, Kontoyannis DA, et al: Myocardial salvage by the use of reperfusion and intraaortic balloon pump: Experimental study. Ann Thorac Surg 1996; 61: 629-634.
37. Prewitt RM, Gu S, Schick U, et al: Intra-aortic balloon counterpulsation enhances coronary thrombolysis induced by intravenous administration of a thrombolytic agent. J Am Coll Cardiol 1994; 23: 794-798.
38. Sanborn TA, Sleeper LA, Bates ER, et al: Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: A report from the SHOCK Trial Registry. Should we emergently revascularized Occluded Coronaries for cardiogenic shock? J Am Coll Cardiol 2000; 36 (3 Suppl A): 1123-1129.
39. Barron HV, Every NR, Parsons LS, et al: The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: Data from the National Registry of myocardial infarction 2. Am Heart J 2001; 141: 933-939.
40. Moosvi AR, Khaja F, Vilanueva L, Gheorghiade M et al: Early revascularization improves survival in cardiogenic shock complicating acute myocardial infarction. J Am Coll Cardiol 1992; 19: 907-914.
41. Hibbard MD, Holmes DRJ, Bailey KR, et al: Percutaneous transluminal coronary angioplasty inpatients with cardiogenic shock. J Am Coll Cardiol 1992; 19: 639-646.
42. Antoniucci D, Valenti R, Santoro GM, et al: Systematic direct angioplasty and stent-supported direct angioplasty therapy for cardiogenic shock complicating acute myocardial infarction: in-hospital and long-term survival. J Am coll Cardiol 1998; 31: 294-300.
43. Lindholm MG, Aldershvile J, Sundgreen C, et al: Effect of early revascularisation in cardiogenic shock complicating acute myocardial infarction. A single center experience. Eur J Heart Fail 2003; 5: 73-79.
44. Urban P, Stauffer JC, Bleed D, et al: A randomized evaluation of early revascularisation to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock-(S)MASH. Eur Heart J 1999; 20: 1030-1038.
45. Webb JG, Sanborn TA, Sleeper LA, et al, for the SHOCK investigators. Percutaneous coronary intervention for cardiogenic shock in the SHOCK Trial Registry. Am Heart J 2001; 141: 964-970.
46. Edep ME, Brown DL: Effect of early revascularisation on mortality from cardiogenic shock complicating acute myocardial infarction. Am J Cardiol 2000; 85: 1185-1188.
47. Berger PB, Tuttle RH, Holmes DR, et al: One-year survival among patients with acute myocardial infarction complicated by cardiogenic shock, and its relation to early revascularisation. Results from GUSTO-I. Circulation 1999; 99: 873-878.
48. Hochman JS, Boland J, Sleeper LA, et al: Current spectrum of cardiogenic shock and effect of early revascularisation on mortality. Results of an International Registry. SHOCK Registry Invastigators. Circulation 1995; 91: 873-981.
49. Berger PB, Holmes DR, Stebbins AL et al: Impact of an aggressive invasive catheterization and revascularisation strategy on mortality in patients with cardiogenic shock in the Global Utilization of StreptoKinase and Tissue Plasminogen Activator for Occluded Coronaries Arteries (GUSTO I) trial. An observational study. Circulation 1997; 96: 122-127.
50. Hochman JS, Sleeper LA, Webb JG, et al, for the SHOCK investigators. Early revascularisation in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999; 341: 625-634.
51. Picard MH, Davidoff R, Sleeper L et al, for the SHOCK Trial. Echocardiographic predictors of survival and response to early revascularization in cardiogenic shock. Circulation 2003; 107: 279-288.
52. Menon V, Fincke R: Cardiogenic shock: a summary of the randomized SHOCK. Congest Heart Fail 2003; 9: 35-39.
53. Shereif HR, Kloner RA: No-reflow phenomenon. Circulation 2002; 105: 656-662.
54. Topol Ej, Yadav JS: Recognition of the importance of embolization in atherosclerotic vascular disease. Circulation 2000; 101: 570-580.
55. Williams MS, Coller BS, Vaananen HJ, et al: Activation of platelets in platelets rich plasma by rotablation is speed dependent and can be inhibited by abciximab (c7E3 Fab; Reopro). Circulation 1998; 98: 742-748.
56. Giri S, Mitchel J, Azar RR, et al: Results of primary percutaneous transluminal coronary angioplasty plus abciximab with or without stenting for acute myocardial infarction complicated by cardiogenic shock. Am J Cardiol 2002; 89: 126-131.
57. Antoniucci D, Valenti R, Migliorini A, et al: Abciximab therapy improves 1-month survival rate in unselected patients with acute myocardial infarction undergoing routine infarct artery stent implantation. Am Heart J 2002; 144: 315-322.
58. Montalescot G, Barragan P, Wittenberg O, et al: Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001; 344: 1895-1903.
59. Antoniucci D, Valenti R, Migliorini A, et al: Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation. Am J Cardiol 2002; 90: 353-357.
60. Taniyama Y, Ito H, Ivakura K, et al: Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. J Am Coll Cardiol. 1997; 30: 1193-1199.
61. Engler R: Consequences of activation and adenosine –mediated inhibition of granulocytes during myocardial ischemia. Fed Proc. 1987; 46: 2407-2412.
62. Ito H, Taniyama Y, Iwakura K, et al: Intravenous nicorandil

can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol. 1999; 33: 654-660.
63. Apstein CS. Glucose-insulin-potassium for acute myocardial infarction: remarkable results from a new prospective, randomized trial . Circulation 1998; 98: 2223-2226.
64. Avkiran M: Rational basis for use of sodium-hydrogen exchange inhibitors in myocardial ischemia. Am J Cardiol 1999; 83: 10-17G.
65. Erhardt LR: GUARD During Ischemia Against Necrosis (GUARDIAN) trial in acute coronary syndromes. Am J Cardiol 1999; 83: 23-25G.
66. Zeymer U, Suryapranata H, Monassier JP, et al: The Na^+/H^+ exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. Results of the Evaluation of the Safety and Cardioprotective Effects of Eniporide in Acute Myocardial Infarction (ESCAMI trial) J Am Coll Cardiol 2001; 38: 1644-1650.