

# Cardiogenic Shock Complicating Acute Myocardial Infarction

## Expanding the Paradigm

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Cardiogenic shock (CS) is the leading cause of death for patients with acute myocardial infarction (MI) who reach the hospital alive. Its incidence has remained constant for 20 years.<sup>1,2</sup> Rapidly re-establishing infarct-related artery (IRA) blood flow is essential in the management of patients with shock due to right ventricular or left ventricular (LV) failure. A strategy of early revascularization is superior to initial aggressive medical therapy.<sup>3-5</sup> Despite the advantages of early percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), once shock is diagnosed, the mortality rate remains high ( $\approx 50\%$ ) despite intervention, and half of the deaths occur within the first 48 hours.<sup>6-8</sup> This may be caused by irreversible extensive myocardial or vital-organ damage. New evidence suggests, however, that a systemic inflammatory response, complement activation, release of inflammatory cytokines, expression of inducible nitric oxide (NO) synthase (iNOS), and inappropriate vasodilation may play an important role not only in the genesis of shock but also in outcome after

shock. New insights and therapies are needed.

### Classic Shock Paradigm

The underlying pathophysiology of CS is profound depression of myocardial contractility, resulting in a vicious spiral of reduced cardiac output (CO), low blood pressure, further coronary insufficiency, and further reduction in contractility and CO. The classic paradigm predicts that compensatory systemic vasoconstriction with high systemic vascular resistance (SVR) should occur in response to the depression of CO (Figure 1).<sup>9</sup>

Autopsy studies have shown that the pathological basis of CS is extensive MI. Varying pathological stages of infarction confirm the stuttering and progressive nature of the myocardial necrosis as a corollary of the vicious spiral. Combined new and old infarctions consistently involve at least 40% of the LV myocardium in these autopsy specimens.<sup>10</sup>

### Observations That Challenge the Classic Paradigm

There are several observations derived from the SHOCK (SHould we emer-

gently revascularize Occluded Coronaries in cardiogenic shock?) trial and registry about patients with CS due to LV failure not easily explainable by our traditional concepts. These include the following:

- Average LV ejection fraction (EF) is only moderately severely depressed (30%), with a wide range of EFs and LV sizes noted.
- SVR on vasopressors is not elevated on average, with a very wide range of SVRs measured.
- A clinically evident systemic inflammatory response syndrome is often present in patients with CS.
- Most survivors have class I congestive heart failure (CHF) status.

Surprisingly, an average EF of 30% was observed in left ventriculograms and echocardiograms obtained soon after shock diagnosis in patients with confirmed shock in the SHOCK trial.<sup>3,11</sup> Although LV performance was measured most often on inotropic and intra-aortic balloon counterpulsation support, both of which increase EF, the hemodynamic measurements obtained concurrently document persistent hypotension, low CO, and high filling pressures.<sup>3</sup> Patients with remote MI or

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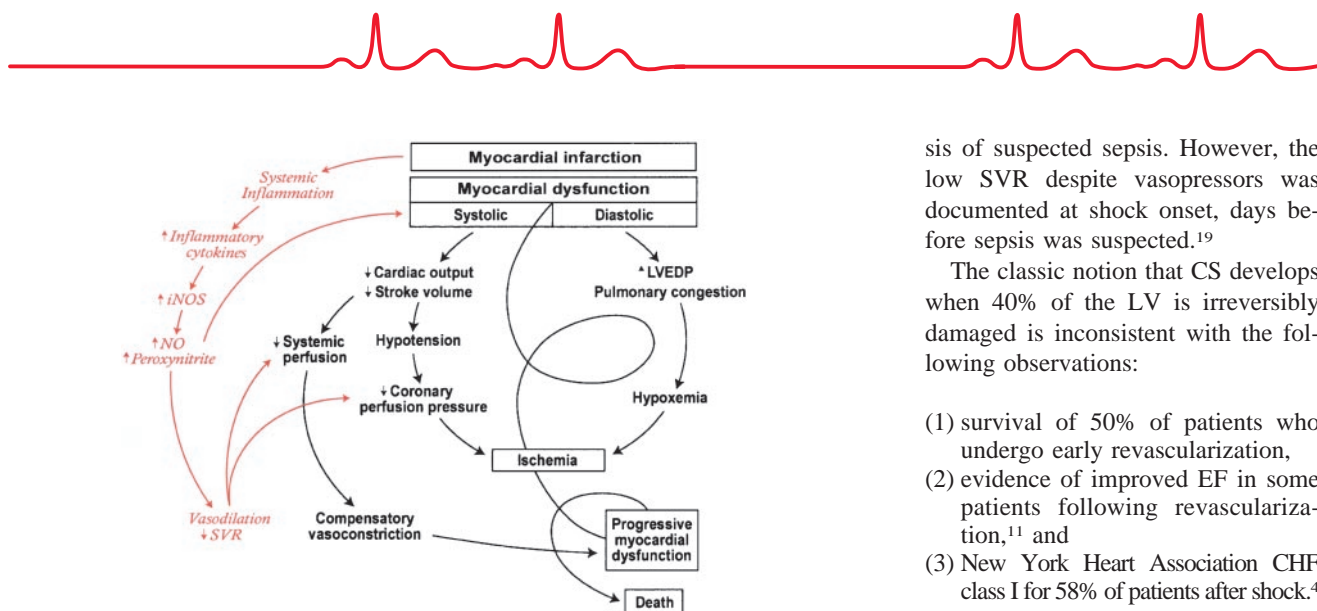
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**Figure 1.** Classic shock paradigm, as illustrated by S. Hollenberg, is shown in black. The influence of the inflammatory response syndrome initiated by a large MI is illustrated in red. LVEDP indicates left ventricular end-diastolic pressure. Reprinted with permission from *Harrison's Principles of Internal Medicine*.<sup>9</sup>

dilated cardiomyopathy and mild to moderate chronic CHF often have EFs considerably lower than this and are not in shock.<sup>12</sup> These observations highlight the role of ventricular dilation to maintain stroke volume and peripheral vascular and neurohormonal adaptation in chronic CHF. However, an EF in the low 30s is not uncommon in uncomplicated patients with recent MI who do not have CHF.<sup>13</sup>

The classic notion that acute reduction in CO leads to compensatory vasoconstriction was not confirmed in many patients in the SHOCK registry and trial (Menon et al<sup>14</sup> and Hochman et al, unpublished data, 2002). SVR varied widely but on average was not elevated at  $\approx 1350$  to  $1400 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$  despite vasopressor use.

Cotter et al<sup>15,16</sup> categorized acute heart failure patients according to cardiac power and demonstrated its importance in risk stratification and selection of therapy. Cardiac power, the product of cardiac index and mean arterial pressure, is a useful prognostic indicator in chronic heart failure.<sup>17</sup> Acute heart failure patients with very high SVR and reduced CO have high cardiac power indices, in contrast to most shock patients, who have low cardiac power. In both the SHOCK trial and the SHOCK registry, cardiac power was the hemodynamic variable most strongly associated

with mortality.<sup>18</sup> A small subset of patients in the SHOCK registry was clinically diagnosed with CS without hypotension, based on systemic hypoperfusion, low CO, and elevated ventricular filling pressures. In these patients, blood pressure was maintained by elevated SVR.<sup>14</sup> Their in-hospital mortality rate (although high at 43%) was lower than the rate of those patients with classic hypotensive shock (66%), despite the 2 groups having the same LVEF (34%), cardiac index ( $1.9 \text{ L/min per m}^2$ ), and pulmonary capillary wedge pressure (25 mm Hg). The ability to vasoconstrict vascular beds that supply nonvital organs is an important compensatory response to a reduction in CO. Vasodilators (endogenous and exogenous) interfere with this critical response, which is needed to maintain flow to the cerebral and coronary circulations. Cardiac power is also prognostically important because it reflects myocardial reserve adequate to generate flow, albeit reduced, in the face of high resistance.

A clinically overt systemic inflammatory response syndrome as evidenced by fever, elevated white blood cell count, and low SVR, was observed in many patients with confirmed shock complicating acute MI in the randomized SHOCK trial. These findings often led to a secondary clinical diagno-

sis of suspected sepsis. However, the low SVR despite vasopressors was documented at shock onset, days before sepsis was suspected.<sup>19</sup>

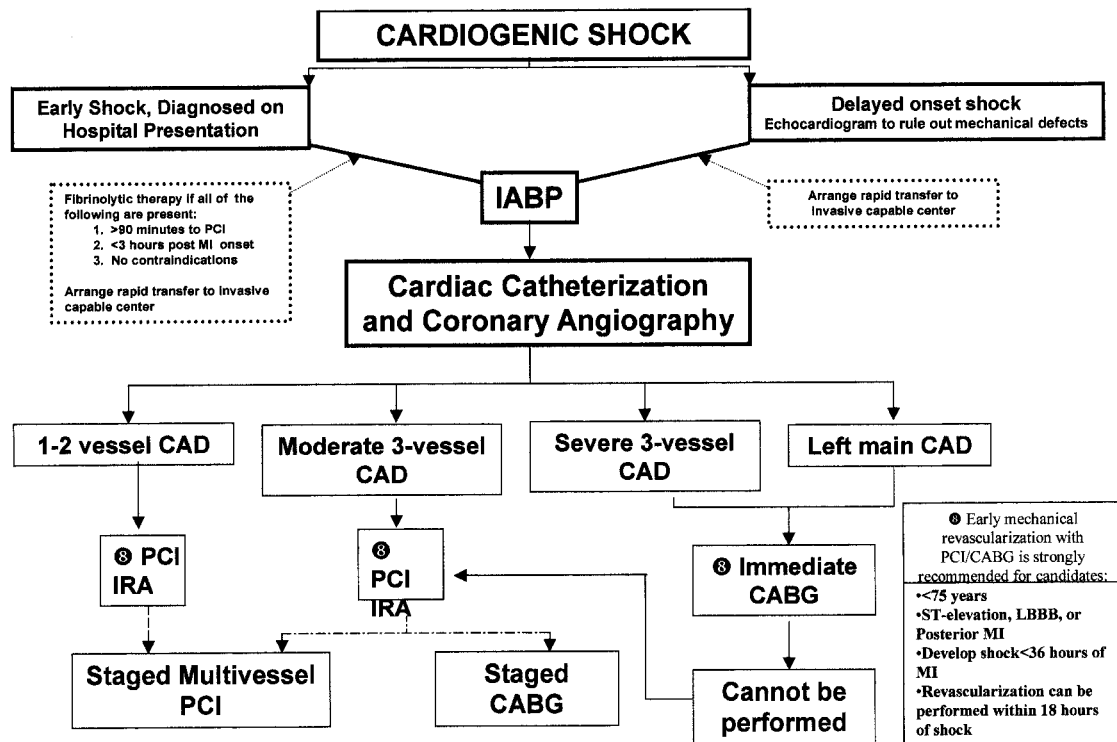
The classic notion that CS develops when 40% of the LV is irreversibly damaged is inconsistent with the following observations:

- (1) survival of 50% of patients who undergo early revascularization,
- (2) evidence of improved EF in some patients following revascularization,<sup>11</sup> and
- (3) New York Heart Association CHF class I for 58% of patients after shock.<sup>4</sup>

Resolution of severe ischemia and/or neurohormonal-inflammatory abnormalities explain the complete reversibility of the shock state in some patients. The wide variation in EF, LV size, and SVR in the SHOCK trial suggests that the pathophysiology of shock varies among patients.

### A New Paradigm

A systemic inflammatory response syndrome occurs in the setting of a number of noninfectious, major systemic insults, including trauma, cardiopulmonary bypass, pancreatitis, and burns.<sup>20,21</sup> Patients with large MIs often have elevation of body temperature, white blood cell count, complement, interleukins, C-reactive protein, and other inflammatory markers. NO, synthesized at low levels by endothelial and myocardial cell endothelial nitric oxide (eNOS), is a cardioprotective molecule.<sup>22,23</sup> In contrast, many cell types express iNOS at pathological levels after trauma or exposure to inflammatory mediators (ie, bacterial lipopolysaccharide, tumor necrosis factor- $\alpha$ , and interleukin-1).<sup>24</sup> Such expression may lead to toxic levels of NO and the cytotoxic NO-derived species, peroxynitrite, formed by reaction with superoxide. In experimental models, high iNOS and NO levels are seen after MI and subsequent reperfusion.<sup>25</sup> Release of cytokines by the heart after MI has been documented in patients. These levels markedly increase after primary PCI in acute MI patients but not in control patients.<sup>26</sup> This suggests that in patients post-MI, activation of inflam-



**Figure 2.** Recommendations for initial reperfusion therapy when CS complicates acute MI. Early mechanical revascularization with PCI or CABG is strongly recommended for suitable candidates <75 years of age and for selected elderly patients (see text). Eighty-five percent of shock cases are diagnosed after initial therapy for acute MI, but most patients develop shock within 24 hours. Intra-aortic balloon pump (IABP) is recommended when shock is not quickly reversed with pharmacological therapy, as a stabilizing measure for patients who are candidates for further invasive care. Dashed lines indicate that the procedure should be performed in patients with specific indications only. Recommendations for staged CABG and multivessel PCI are discussed in the text, as are definitions of moderate and severe 3-vessel CAD. LBBB indicates left bundle-branch block.

matory cytokines leads to high levels of iNOS, NO, and peroxynitrite, all of which have multiple deleterious effects.

### Effects of High Levels of NO and NO-Derived Species (eg, Peroxynitrite)

- Direct inhibition of myocardial contractility
- Suppression of mitochondrial respiration in nonischemic myocardium
- Effects on glucose metabolism
- Proinflammatory effects
- Reduced catecholamine responsiveness
- Induction of systemic vasodilation

The mechanism of the detrimental effect of high NO levels is unclear, but it may result from a direct effect of NO on myocardial contractility by uncoupling of calcium metabolism,<sup>27,28</sup> through effects on glucose metabolism,<sup>27</sup> or through  $\beta$ -adrenergic re-


sponsivity.<sup>29</sup> High levels of iNOS are associated with LV dysfunction and higher mortality in mice with MIs.<sup>30,31</sup> In animal models, NO production by iNOS is deleterious during ischemia-reperfusion.<sup>27,28</sup> Induced iNOS expression and high NO levels during ischemia may mediate myocardial stunning. Furthermore, stimulation of iNOS expression by interleukins could explain the observation of new or worsening hypotension after primary PCI in some patients.

A marked variability in the responsiveness of the inflammatory system has been reported, supporting the concept that systemic inflammation may play a large role in some patients but not in others in the genesis and persistence of shock. Liuzzo et al<sup>32</sup> reported an enhanced inflammatory response to PCI in patients with severe unstable angina that was highly variable and

related to baseline, pre-PCI levels of interleukin-6 and C-reactive protein. In patients with acute coronary syndrome, elevated inflammatory markers, including white blood cell count and C-reactive protein, are independently associated with mortality.<sup>33</sup>

### Beneficial Effects of Inhibiting Inflammatory Mediators and iNOS

Experimentally, iNOS knockout mice were shown to survive MI better than wild-type mice.<sup>31,34</sup> In ischemia-reperfusion models, inhibition of NO synthase appears to have favorable metabolic, antistunning, and coronary blood flow effects.<sup>27,28</sup> Cotter and colleagues<sup>35</sup> administered a non-isoform-specific NOS inhibitor, *N*<sup>G</sup>-monomethyl-L-arginine (L-NMMA), to 11 patients with persistent shock despite vasopressors, intra-aortic balloon



pump, and PCI. Urine output and blood pressure increased markedly, and 72% survived to 30 days. Cotter et al<sup>36</sup> subsequently reported a reduction in 30-day mortality from 67% to 27% with a similar NOS inhibitor, *N*<sup>G</sup>-nitro-L-arginine methyl ester, in a small randomized trial of 30 patients.

Inhibition of the complement cascade at the C5 level results in, among other effects, a reduction of the excess iNOS response to ischemia and reperfusion and could theoretically inhibit the genesis of shock. Preliminary results of the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) study demonstrate that inhibition of C5 was associated with lower rates of shock and death in high-risk patients undergoing primary PCI, despite an absence of effect on infarct size.<sup>37</sup>

### Current Recommendations

In the randomized SHOCK trial, a strategy of early revascularization resulted in 132 lives saved at 1 year per 1000 patients treated as compared with initial medical therapy followed by no or late revascularization as clinically determined.<sup>4</sup> This magnitude of benefit is comparable to that of CABG versus medical therapy for patients with left main coronary stenoses. Recommended selection of initial reperfusion for CS is outlined in Figure 2. Most patients in the SHOCK trial had severe multivessel disease, and of those revascularized in the early revascularization group of the SHOCK trial, 40% underwent CABG. This is in marked contrast to the low and decreasing rate of CABG for shock in the National Registry of Myocardial Infarction (NRMI).<sup>38</sup>

The preferred treatment is PCI of the IRA for patients with 1- to 2-vessel coronary artery disease (CAD) and suitable lesions. Moderate 3-vessel disease, ie, 100% IRA occlusion, <90% stenosis in 2 other major vessels, or more severe lesions in second-order vessels, may be treated with PCI of the IRA and staged complete revascularization, as indicated. Glycopro-

tein IIb/IIIa antagonists and stents are recommended. Immediate CABG is the preferred treatment for severe 3-vessel or left main CAD. If CABG cannot be performed, single-vessel or multivessel PCI may be attempted. Distal embolization in the non-IRA territories during PCI may be disproportionately harmful in the setting of shock or recent shock. Therefore, CABG is generally preferred to PCI when revascularization of the non-IRA artery is clinically indicated in the week after shock. However, early multivessel PCI may be warranted when shock persists despite PCI of the IRA, when CABG cannot be performed.

Despite the American College of Cardiology/American Heart Association<sup>39</sup> revised guidelines class I recommendation for early revascularization in patients younger than age 75, NRMI data suggest that most patients did not receive this therapy as recently as 2001.<sup>38</sup> According to NRMI data, mortality has decreased in hospitals that perform early revascularization, but not in those that do not.<sup>38</sup> Although the small cohort of elderly patients in the SHOCK trial had a surprisingly low mortality rate in the initial medical stabilization group and did not appear to benefit from a routine strategy of early revascularization, the nearly 20% of the elderly who were clinically selected for early revascularization in the SHOCK registry appeared to have improved survival.<sup>40</sup> Therefore, individualized judgments must be made regarding the elderly; those with good prior functional status and less severe, early shock may be suitable candidates. For those <75 years of age, all subgroups enrolled in the SHOCK trial, based on clinical, hemodynamic, and echocardiographic characteristics,<sup>4,11</sup> derived benefit from early revascularization. However, patients with pre-existing severe comorbidities, life-shortening illnesses, cardiomyopathy and CHF, lack of vascular access, and anoxic brain damage are unsuitable for early revascularization and were excluded. Patients who develop shock early or late after MI ( $\leq 36$  hours) and who are revascularized

within 12 to 18 hours of shock onset derive benefit.<sup>3,4</sup> Patients with very prolonged duration of CS may be unsuitable. Because of the potential adverse effects of sympathomimetic amines, early intra-aortic balloon counterpulsation is recommended for all patients who are candidates for further therapy beyond comfort care.<sup>39</sup>

The observation in the SHOCK trial and registry that only 14% and 9% of shock patients, respectively, presented to the hospital in shock, but that almost half developed it rapidly after admission, raises the concern of an iatrogenic component of shock. Negative inotropic and vasodilating agents may cause hypotension and initiate the vicious spiral of CS in patients with large MIs, multivessel disease, and marginal hemodynamic compensation.

In summary, immediate stabilization followed promptly by early revascularization is indicated when shock due to pump failure complicates acute MI. Data on ventricular function, systemic resistance, and systemic inflammatory response syndrome observed in some patients with LV failure in the SHOCK trial and registry suggest that CS complicating acute MI is often not simply due to extensive infarction and ischemia with reduced ventricular function but also involves inflammatory mediators. These mediators induce iNOS expression, increasing NO and peroxynitrite levels, resulting in further myocardial dysfunction and failure of an appropriate peripheral circulatory response. Experimental and preliminary clinical studies demonstrate improved survival when iNOS is absent or inhibited. Further investigation is needed to evaluate the inflammatory and excess iNOS component of CS, and promising new therapies that target these pathways need testing to try to reduce the persistently high mortality rate despite emergency revascularization. SHOCK-2 (SHould we inhibit nitric Oxide synthase in patients with Cardiogenic shock?) is being designed to test an NO inhibitor, L-NMMA, in a well-powered randomized trial of patients with persistent shock despite a patent IRA.

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