

Cardioprotection before revascularization in ischemic myocardial injury and the potential role of hemoglobin-based oxygen carriers

Daniel Burkhoff, MD, PhD,^a and David J. Lefer, PhD^b *New York, NY, and Shreveport, La*

Despite the availability of interventional catheterization for patients with acute coronary syndromes, there is an unavoidable delay until the occluded coronary artery(s) can be revascularized, during which time persistent ischemia may lead to irreversible myocardial damage despite subsequently high patency rates. Accordingly, there has been an intense effort to develop early interventions that will preserve the viability of ischemic myocardium before revascularization. A number of novel strategies have been studied, including hemoglobin-based oxygen carriers. These compounds transport oxygen in the plasma to help maintain more normal oxygen delivery to the myocardium supplied by a thrombosed vessel, and they also release oxygen to tissue more efficiently than intraerythrocytic hemoglobin. (*Am Heart J* 2005;149:573-9.)

Although new technologies have helped increase the speed with which acutely occluded coronary arteries can be revascularized,¹⁻⁶ many patients do not experience prodromal symptoms, or they ignore or are unsure of the meaning of their symptoms and delay going to the hospital. Sheifer et al found that almost 30% of 102339 patients older than 65 years with a confirmed myocardial infarction arrived at the hospital at least 6 hours after symptom onset.⁷ In addition, not all hospitals are equipped to manage patients efficiently when they present with an emerging myocardial infarction. Even under ideal conditions, with on-call availability of interventional catheterization teams at major clinical centers, there is an unavoidable 30- to 60-minute delay from presentation at an emergency department to the time the coronary artery is opened. Rogers et al found the median door-to-drug time for thrombolysis ranged from 42 to 45 minutes regardless of the invasive capability of the institution.⁸

When myocardium is deprived of oxygen-delivering arterial blood due to an atherothrombotic event (ie, unstable angina, non-ST-elevation myocardial infarction, ST elevation myocardial infarction), delayed reperfusion translates to necrosis of myocardial cells. Thus, although revascularization therapy has reduced the extent of

myocardial loss, it has not prevented myocardial infarction, despite subsequently high coronary patency rates. Unfortunately, traditional vasoactive agents such as β -adrenergic blockers, calcium-channel blockers, and nitrates provide little if any cardioprotective benefit in the setting of revascularization.⁹ Accordingly, salvage of ischemic myocardium represents an important unmet need, and an intense effort has been made to develop early interventions that will prolong the viability of cardiac myocytes before reperfusion can be established. These interventions, ideally, should be available outside the hospital to prevent or minimize myocardial injury. They should also be deliverable just before revascularization, which itself may trigger myocardial damage by inducing transient but profound ischemia. Hemoglobin-based oxygen carriers (HBOCs) enhance oxygen transport in the plasma to help maintain oxygen delivery to the microcirculation and also release oxygen to tissue more efficiently than intraerythrocytic hemoglobin.¹⁰⁻¹² Because these compounds can be infused outside the hospital and in the emergency department, they might be capable of salvaging ischemic myocardium before revascularization. In this article, we review available literature that supports a cardioprotective effect for HBOCs administered in the setting of acute myocardial ischemia.

Need for cardioprotection before reperfusion therapy

Coronary heart disease affects 14.2 million persons either as myocardial infarction (7.6 million persons) or as angina (6.6 million persons) and is the leading cause of death in the United States.^{13,14} Approximately 40% of these acute coronary events are recurrences.¹³ The Atherosclerosis Risk in Communities study, which examined cardiovascular disease through surveillance in

From the ^aDivision of Circulatory Physiology, Columbia University College of Physicians and Surgeons, New York, NY, and ^bDepartment of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, School of Medicine in Shreveport, Shreveport, La.

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Reprint requests: Daniel Burkhoff, MD, PhD, Division of Circulatory Physiology, Columbia University, Black Building 812, 650 W. 168th Street, New York, NY 10032.

E-mail: db59@columbia.edu

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geographically defined patients aged 35 to 74 years, determined that 515 204 deaths annually between 1987 and 1994—or 1 out of every 5 deaths—were due to myocardial infarction.¹⁵ About half of these fatal events occurred outside the hospital.¹⁴ Although the mortality from acute coronary events has decreased substantially during the past 4 decades,^{16,17} the morbidity remains extremely high, particularly due to congestive heart failure after recurrent myocardial infarctions.¹⁸

Adults who survive a myocardial infarction remain at increased risk for heart failure as they age, and heart failure is the leading principal diagnosis for hospitalization among older adults.¹⁹ Of the approximately 550 000 new cases of congestive heart failure in the United States each year, about half are associated with coronary heart disease,^{14,18} and about 22% of males and 46% of females who experience myocardial infarction will be disabled with congestive heart failure within 6 years due to loss of functional myocardium, at an annual cost to Medicare in 1998 of \$3.6 billion.¹⁴ Hellermann et al found that 38% of 1658 patients who had had a myocardial infarction developed heart failure during a mean follow-up of 7.4 years; left ventricular systolic function was preserved (defined as ejection fraction $\geq 50\%$) in about 30%.¹⁸ Congestive heart failure with preserved left ventricular ejection fraction after myocardial infarction was associated with smaller infarct size.

The pathophysiologic mechanism of myocardial infarction is the acute rupture of an atherosclerotic plaque in an epicardial coronary artery, exposing endothelial tissue to a thrombogenic response, with formation of an intracoronary thrombus leading to severe obstruction of the vascular lumen. Necrosis of viable myocardial tissue begins within 15 minutes of loss of oxygen supply and occurs mainly during the 30 to 90 minutes after occlusive thrombosis is superimposed on a ruptured atheroma in an epicardial coronary artery.²⁰ Accordingly, revascularization during the period of acute regional ischemia can salvage myocardium, prevent extensive myocardial necrosis, and preserve left ventricular function. Indeed, many studies have shown improved survival, decreased infarct size, and better left ventricular function with earlier thrombolysis and reperfusion.^{21,22}

Unfortunately, the time from initial symptoms of an acute coronary syndrome to revascularization is often prolonged by a delay before an ambulance is called, during transport to the hospital, while emergency department assessment is performed, and until definitive therapy is provided. In one recently published study comparing coronary angioplasty with fibrinolytic therapy in acute myocardial infarction in the hospital setting, the median time from onset of symptoms to fibrinolysis was 169 minutes for those treated at referral hospitals and 160 minutes for those treated at invasive treatment centers.²³ The median time from onset of symptoms to angioplasty was longer: 224 minutes for those treated at

referral hospitals and 188 minutes for those treated at invasive treatment centers. Even when fibrinolysis was provided in the prehospital setting, the median treatment delay was 115 minutes after symptom onset.²⁴

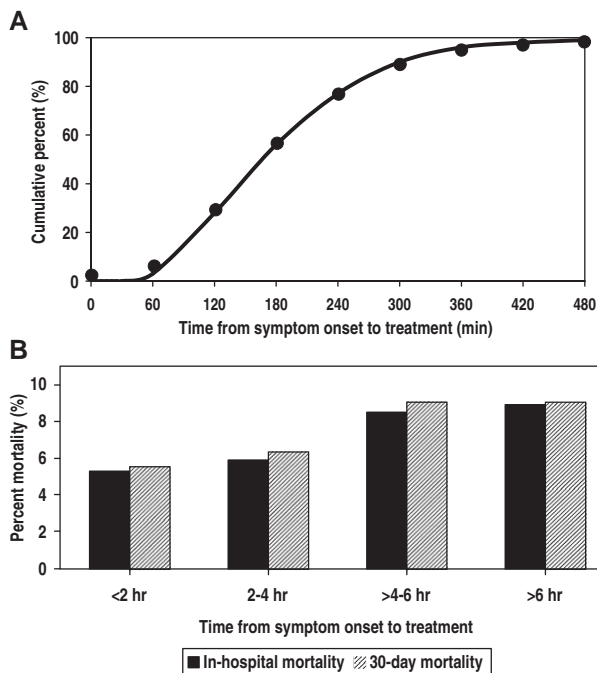
Because the minimal time between the onset of symptoms and revascularization is typically about 2 hours, early interventions that provide cardioprotection during this period may reduce the extent of myocardial necrosis. Newby et al evaluated the relationship between clinical outcomes and time of symptom onset to treatment, symptom onset to hospital arrival (presentation delay), and hospital arrival to treatment (treatment delay) in the GUSTO-1 trial.²⁵ The median time from the onset of symptoms to the initiation of revascularization for 50% of patients was almost 3 hours (Figure 1), which is a very long time with respect to myocardial loss; a similar relationship was noted between time of symptom onset to treatment and mortality.

For all these reasons, there has been an intense effort to develop early interventions that will preserve the viability of ischemic myocardium before revascularization. Such an intervention should be studied in patients with acute coronary syndromes in a carefully controlled clinical setting, where it must be shown in this population to (1) be safe; (2) save myocardium by altering myocardial metabolism, reducing myocardial oxygen demand, or increasing myocardial oxygenation; and (3) have a favorable impact on outcomes. The clinical effects would include reduction in postinfarction arrhythmias and acute mortality, maintenance of cardiac function and inotropic reserve, and limitation of the maladaptive postinfarction remodeling associated with increased ventricular volume, the most powerful predictor of subsequent mortality.²⁶ Finally, to provide the greatest benefit, such an intervention should be shown to be safe and effective when administered outside the hospital by emergency medical technicians or paramedics.

Cardioprotection by increasing myocardial oxygenation

The quantity of oxygen delivered to any tissue, including the myocardium, is determined by the volume of oxygen transported in blood and the rate of blood flow (Figure 2).²⁷ Approximately 8 mL of oxygen per 100 grams of myocardial tissue is delivered to the normal resting myocardium each minute. If the rate of flow falls to 0, the amount of oxygen available to the tissue also falls to 0, resulting in myocardial infarction. In very low flow settings, however, such as those that might be encountered during an atherothrombotic event, the viability of myocardial cells can be preserved for some time. Hemoglobin-based oxygen carriers provide a flow-based delivery system to increase the rate of oxygen delivery to tissues.

Figure 1



Time to symptom onset and relationship to mortality among patients experiencing acute coronary event. Essentially no patients began thrombolytic treatment before 60 minutes of symptom onset, and thrombolysis was initiated in only 20% within 120 minutes of symptom onset (A). Early thrombolysis was associated with lower overall mortality (B). Longer presentation and treatment delays were both associated with an increased mortality rate. Adapted from *J Am Coll Cardiol* 1996;27:1646-55.

Potential for hemoglobin-based oxygen carriers

Hemoglobin-based oxygen carriers enhance the oxygen-carrying capacity of blood and the delivery of oxygen to tissues by transporting oxygen in the plasma (Figure 3). Unlike blood, HBOCs do not need to be cross-matched and have a long shelf life. Accordingly, HBOC solutions have promise in the clinical setting of acute ischemia before patients reach the hospital.

Hemoglobin-based oxygen carriers are derived from bovine, human, or recombinant human hemoglobin.²⁸ Those that do not require refrigeration can be administered in the prehospital setting, and several have reached advanced stages of development and clinical testing. One such compound, HBOC-201 ([hemoglobin glutamer-250, (bovine)], Hemopure, Biopure Corporation, Cambridge, Mass), was approved for human use in South Africa in 2001. HBOC-201 is a bovine-derived, acellular, high-oxygen-affinity, modified hemoglobin that has been ultrapurified to remove any plasma proteins, red cell stroma, and potential pathogenic material.²⁹⁻³³

Figure 2

$$\text{Convective O}_2 \text{ delivery} = \text{coronary blood flow} \cdot \text{oxygen content of blood}$$

The rate at which oxygen can be delivered to the myocardium is determined by oxygen transport by the blood, or convective oxygen delivery, and oxygen diffusion within the tissue, or diffusive oxygen delivery. Convective oxygen delivery (mL O₂/min) is the product of the coronary arterial blood flow (mL/min) and the oxygen content of the blood (mL O₂/mL blood). Because the oxygen content of arterial blood ordinarily remains relatively constant, the primary determinant of oxygen delivery to the myocardium is coronary blood flow.

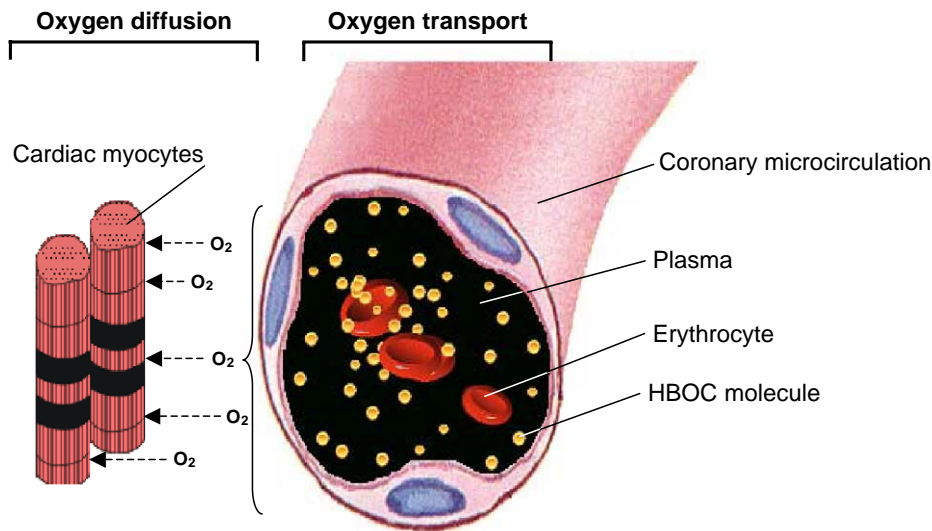
During the manufacturing process, glutaraldehyde cross-linking and polymerization stabilize the hemoglobin molecule, which increases its vascular persistence as well as the efficiency of oxygen transport to tissue. One unit of HBOC-201 contains 30 g of hemoglobin, which should increase the total plasma hemoglobin by 1 g/dL in a person of average size,²⁹ similar to that produced by 1 to 2 units of packed red blood cells.³⁴

Tissue oxygenation with HBOCs

Oxygen transport, or convective oxygen delivery, is promoted by intravascular volume expansion after infusion of HBOCs, which increase the mean arterial pressure³⁵ and functional capillary density.³⁶ This is clinically important, as microvascular transport studies have shown that maintenance of an open and fully perfused microvasculature is more critical than the oxygen supply as a determinant of survival in shock. Oxygen transport is also affected by the viscosity of these compounds. HBOC-201 contributes to increased blood flow by reducing blood viscosity during hemodilution (the viscosity of HBOC-201 is 1.3 cP vs 3.8 cP for blood at 37°C).³⁷ An investigational maleimide-polyethylene glycol-conjugated human HBOC (Hemospin, Sangart, Inc, San Diego, Calif) has a viscosity of 3 cP, which may improve flow by increasing capillary transmural pressure.³⁶ The viscosity of an investigational *o*-raffinose-polymerized human HBOC purified from outdated donated blood (Hemolink, Hemosol, Inc, Ontario, Canada) is 1.1 cP, whereas that of an investigational glutaraldehyde-polymerized human HBOC (PolyHeme, Northfield Laboratories, Inc, Evanston, Illinois) is 2.1 cP.³⁸

Oxygen diffusion, or diffusive oxygen delivery, is promoted primarily by the P₅₀ (oxygen tension at 50% saturation of blood) of HBOCs. This is clinically important, as the P₅₀ value affects the ability of hemoglobin to release oxygen to tissues. As the P₅₀ increases, oxygen affinity decreases; as the P₅₀

Figure 3



Hemoglobin-based oxygen carriers enhance the oxygen-carrying capacity of blood and the delivery of oxygen to tissues by transporting oxygen in the plasma.

decreases, oxygen affinity increases. The lower affinity of HBOC-201 for oxygen (the P_{50} of HBOC-201 is 40 ± 6 mm Hg vs 27 mm Hg for intraerythrocytic hemoglobin) increases its ability to offload oxygen to tissues compared with native hemoglobin³⁷; HBOC-201 offloads oxygen approximately 3 times greater than intraerythrocytic native hemoglobin.^{30,39} Hemospan has a P_{50} of about 5 mm Hg,³⁶ which is below that of native hemoglobin and, accordingly, Hemospan will not increase oxygen delivery to tissue. The P_{50} of Hemospan will, however, increase its ability to onload oxygen in the pulmonary capillary bed, which might provide some use in clinical settings of decreased lung function but not in the setting of cardioprotection. Hemolink has a P_{50} of 34 mm Hg, and PolyHeme has a P_{50} of 29 mm Hg.³⁸

In summary, most HBOCs provide plasmatic oxygen delivery, with advantages over intraerythrocytic hemoglobin because they enhance tissue oxygenation by convective and diffusive oxygen delivery.

Potential cardioprotective use of HBOCs

Animal models have been used to assess the potential use of HBOCs in acute tissue ischemia. Erni et al and Contaldo et al have shown that a solution containing liposome-encapsulated human hemoglobin improves oxygenation of ischemic hamster skin-flap tissue.^{40,41} Studies of HBOC-201 in animal models of skeletal muscle ischemia have shown that HBOC-201 can maintain tissue oxygen tension when it is infused after acute blood loss⁴² or before acute arterial occlusion^{30,43,44} and

can improve the homogeneity of local tissue oxygenation.⁴⁵ Loke et al studied the effect of HBOC-201 on myocardial oxygen consumption and substrate use in permanently instrumented dogs.⁴⁶ Myocardial oxygen consumption and coronary blood flow increased, and there was a shift in cardiac metabolism from using free fatty acid to using lactate and glucose. The metabolic changes were independent of the HBOC-201-induced change in hemodynamics.

Burmeister et al studied the effect of HBOC-201 on infarct size in a rat model of myocardial ischemia reperfusion.⁴⁷ HBOC-201 was infused intravenously 15 minutes before (prophylactic group, $n = 8$) or after (treatment group, $n = 8$) occlusion of the left coronary artery, followed by reperfusion. The infarct size was then quantified by computed planimetry and the results compared with those of a control group ($n = 8$), which received saline infusions before and after coronary occlusion, followed by reperfusion. The infarct size as a percentage of the area at risk was $62.2\% \pm 15\%$ in the control group, $43.4\% \pm 9\%$ in the prophylactic group ($P < .025$ compared with the control group), and $61.9\% \pm 10\%$ in the treatment group (difference not significant compared with the control group). The results demonstrate that prophylactic infusion of HBOC-201 can reduce the infarct size in experimental myocardial ischemia.

Strange et al investigated the potential cardioprotective effects of HBOC-201 in a canine model of myocardial ischemia reperfusion.⁴⁸ Thirty minutes after infusion

of HBOC-201 ($n = 9$) or 0.9% saline vehicle ($n = 8$) equivalent to 10% of the estimated total blood volume, a coronary artery was completely occluded by ligation for 90 minutes, which was followed by 270 minutes of reperfusion. Hemodynamic data and peripheral blood samples were obtained at baseline, at 60 minutes after coronary occlusion, and at 60, 120, and 270 minutes of reperfusion. At 270 minutes of reperfusion (360 minutes from baseline), cardiectomy was performed and the area-at-risk determined by incubating the tissue with triphenyltetrazolium chloride (TTC vital stain), which stains viable myocardium red whereas infarcted myocardium remains unstained, appearing pale yellow. These areas were then measured. Finally, myocardial tissue samples were taken for histologic analysis of polymorphonuclear leukocytic infiltration.

The myocardial area-at-risk was similar in the HBOC-201- and saline-infused groups, but the area of infarction relative to the area-at-risk and to the entire left ventricle was significantly ($P < .01$) smaller in the HBOC-201 group. Analysis of blood samples taken at 270 minutes of reperfusion showed significantly ($P < .05$) lower elevation of creatine kinase (CK)-MB and troponin I levels—both markers of myocardial necrosis—in the HBOC-201 group. Histologic analysis demonstrated that polymorphonuclear leukocytic infiltration was significantly ($P < .01$) greater in the saline group. The investigators concluded that HBOC-201 infusion before acute coronary occlusion reduces the extent of ischemia-reperfusion injury in the canine myocardium. Thus, HBOC-201 provides an “oxygen bridge” until perfusion can be reestablished by thrombolysis or angioplasty.⁴⁸

In the only published report of its direct effect on myocardial oxygenation, HBOC-201, but not Ringer's solution, restored myocardial tissue oxygen tension (tPO_2) in a canine model of acute anemia accompanied by 90% stenosis of the left anterior descending coronary artery.⁴⁹ The median myocardial tPO_2 , measured with a flexible microelectrode, decreased from 21 to 7 mm Hg after coronary stenosis when Ringer's solution was infused before stenosis. Low tPO_2 values were paralleled by dysfunctional left ventricular contractility. In contrast, the median myocardial tPO_2 remained unchanged when HBOC-201 was infused before stenosis and increased to nearly baseline values when HBOC-201 was infused after stenosis.

The mechanism by which HBOC-201 increases myocardial oxygenation in the setting of coronary occlusion remains to be elucidated. Standl speculated that HBOCs can reach poststenotic or poorly perfused tissues with the plasma stream, where erythrocytes are not able to pass.⁵⁰ Although an HBOC-201 molecule is reportedly 1/1000th the size of an erythrocyte,⁵¹ there is currently no evidence that HBOCs can traverse totally occluded vessels. It is speculated that the mechanism is more likely enhanced oxygen delivery via collateral blood

flow, especially in the setting of complete coronary occlusion. If this proves to be correct, the judicious administration of agents known to improve collateral flow might enhance the effect of oxygen-saturated HBOCs on ischemic myocardium. In addition, it should be noted that the effect on collateral flow as well as any potential cardioprotective benefit of HBOCs may be altered substantially when infused with fibrinolytic agents. Alternatively, it is possible that the use of these compounds may be limited to patients with at least some preserved coronary flow (eg, those with preexisting collaterals, those with non-ST-segment-elevation infarctions, or before revascularization).

All animal studies of HBOCs in acute ischemia use surrogate markers of injury to evaluate efficacy, and only limited data from humans have been published suggesting that HBOC-201 can ameliorate myocardial ischemia. Niquille et al reported the case of a 64-year-old man with a past history of myocardial infarction who developed acute myocardial ischemia, associated with progressive hypotension, tachycardia, and a new 2-mm ST-T-segment depression on monitored standard leads II and V5, during surgery to revise an aortofemoral graft.⁵² The patient had been enrolled as a subject in a trial to evaluate the intraoperative efficacy and safety of HBOC-201, which was infused during the surgery as an alternative to blood transfusion. After the start of the infusion, systemic arterial blood pressure increased slightly and the heart rate decreased with rapid normalization of the ST-T-segment abnormalities. The authors noted that the beneficial effect of HBOC-201 may have been related to its ability to improve tissue oxygenation.

A multicenter European phase II pilot safety study of HBOC-201 in the setting of elective angioplasty and stent procedures was recently initiated. This randomized, 3-arm, double-blind, placebo-controlled, dose-finding trial will assess the safety of HBOC-201 in adult patients with coronary artery disease. Approximately 45 patients will be evenly randomized to receive placebo or 15 or 30 g of HBOC-201 before percutaneous coronary interventions. Patients will be monitored until discharge from the hospital and at 30 days postinfusion. Preliminary results should be available in 2004.

Conclusions

Cardioprotective interventions are needed before revascularization procedures to reduce adverse outcomes that result from the unavoidable delay between the onset of symptoms of an acute coronary event and revascularization. Ideally, patients experiencing atherothrombotic events should have access to cardioprotection before reaching the hospital. This currently is an unmet need, although preclinical and clinical research to identify safe and effective interventions is underway.

Potential strategies and agents include hemoglobin-based oxygen carriers, which increase myocardial oxygenation to provide an oxygen bridge until coronary perfusion is reestablished.

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