Thrombolysis: Go with the Flow

The experimental study by Prewitt and colleagues (see page 708) is the first to highlight the relationship between systemic blood flow and thrombolysis. In a canine model of pulmonary embolism, either pretreatment with hydralazine or opening a systemic arteriovenous fistula led to >50 percent increase in cardiac output compared with controls, and resulted in a parallel (>50 percent) increase in the rate of thrombolysis. In earlier experiments these investigators had shown hydralazine to lessen pulmonary vascular resistance and hypothesized that this effect would accelerate pulmonary artery thrombolysis. The equivalent results in the present study using an arteriovenous fistula, without attendant decrease in pulmonary artery pressure, strongly points to flow per se as a key determinant of clot dissolution therapy. These findings have important implications for clinical management of cardiogenic shock and future investigation of adjunctive pharmacotherapy to thrombolysis.

Cardiogenic Shock

In the setting of acute, massive myocardial injury or necrosis, the development of power failure and hypotension can be anticipated. Favorable interruption of the natural history of cardiogenic shock with a mortality in excess of 80 percent in historical controls has been suggested by recent series of patients undergoing direct coronary angioplasty. However, in patients with cardiogenic shock treated with intravenous thrombolysis, the results thus far have been disappointing. In the Gruppo Italiano per lo Studio della Streptochinasi (GISSI) trial, there was a 70 percent 30-day mortality for patients in Killip class 4 at time of presentation, irrespective of whether streptokinase or conventional therapy was given. Similarly, with intracoronary streptokinase in the multicenter registry of the Society for Cardiac Angiography, a 67 percent in-hospital mortality was reported for patients with cardiogenic shock. In light of the current study by Prewitt et al, a likely explanation for apparent failure of therapy is hypoperfusion. In the future, new approaches to thrombolysis in the setting of cardiogenic shock may do well to incorporate early intervention to maximize cardiac output. To this end, use of either intra-aortic balloon counterpulsation or percutaneous cardiopulmonary bypass has, in small series of patients, been accompanied by relatively favorable outcome.

Drug-Drug Interaction

For any drug that changes systemic or regional blood flow, a careful reassessment will be necessary before coupling the agent with thrombolytic therapy. As cited by Prewitt et al, an example which we did not anticipate was the negative interaction between tissue plasminogen activator and the prostacyclin analog Iloprost. In a pilot clinical trial we found very low infarct vessel patency (44 percent) for these two agents given concomitantly and only later did experimental studies confirm that Iloprost has the potential to decrease the plasma tPA level 30-40 percent, likely mediated via markedly increased hepatic blood flow and clearance. It is possible that this negative interaction is specific for the agents tested; a pilot study with streptokinase and prostaglandin E, suggested improved thrombolytic efficacy.

On the other hand, Rentrop et al have demonstrated that nitroglycerin given with intracoronary streptokinase improves left ventricular function beyond the level that each agent achieved as monotherapy. The mechanism for this interaction is not established, but may be due to nitroglycerin's amelioration of collateral blood supply, decreased afterload, or both. Likewise, the salutary effect for combined intravenous thrombolysis and captopril or thrombolysis with adenosine may, in part, be attributed to vasodilation and more extensive thrombolysis. Ongoing large scale clinical trials are testing the interaction of thrombolytic agents with angiotensin-converting enzyme inhibitors such as the International Studies of Infarct Survival (ISIS-4) and GISSI-3 trials. The facilitation of thrombolysis mediated by hydralazine verified in the present study suggests this may be a key method by which a vasodilator offers incremental benefit.

The study by Prewitt is fundamental to our understanding of how thrombolysis can be modulated. In order to accelerate infarct vessel recanalization in myocardial infarction, improvement in systemic blood flow and actual delivery of the plasminogen activator to the site of occlusion will be necessary. That thrombolysis in essence goes "with the flow," represents a significant, yet up until now neglected, future direc-
Identifying Patients with High Risk of High Cost

It has been shown for many types of health care services that a relatively small proportion of patients account for a disproportionately large share of resource use. This pattern appears again in the article by Oye and Bellamy in this issue (see page 685). For intensive care unit (ICU) patients, the high-cost group includes many patients who die. There is concern that large amounts of resources are being spent to treat chronically ill and/or elderly patients with acute illness or massively injured patients to salvage only a small proportion of these patients who are discharged alive from acute care hospitals. In some cases, families may demand this care in a futile attempt to save patients who are beyond help. For some ICU patients, the high cost far outweighs any benefit of these expenditures. Of course, it is one thing to see, ex post, that the medical care has been unsuccessful and quite another to predict outcome or cost in advance. Since it is the medical prognosis that is most helpful in guiding decision making, substantial efforts have been devoted to the development of models to predict the outcome of ICU care.1,2 These efforts have met with considerable success in predicting hospital mortality for groups of patients. From a somewhat different direction, interest has developed in the characterization of severity of illness and its relation to resource use. Driven largely by concerns about reimbursement based on diagnosis-related groups, systems have been developed to measure severity of illness so that the existence of resource use variability can be recognized in reimbursement.

Recent works, of which the article by Oye and Bellamy is an example, have begun to explore relationships among severity (as measured by predicted outcome), actual outcome, and resource use. Knaus et al2 found that, when severity was held constant, outcome improved with resource use at low levels of resource use.3 Other studies have emphasized the need to distinguish between actual outcome and predicted outcome. While it is true that many high-cost patients die, some patients who die are not high cost and some high-cost patients do not die. A finding first reported by Detsky et al,4 confirmed by Rapoport et al,5 and again reported in this issue by Oye and Bellamy, is that patients who have an outcome that is opposite to the predicted outcome tend to be high-cost patients.

Two implications of these findings might be noted. First, average resource use does not always rise with severity of illness (as measured by probability of mortality) for ICU patients. As severity of illness increases, average resource use rises and then falls, contrary to the (often implicit) assumption of most