*Editorials*

## Primary Angioplasty — Enduring the Test of Time

THE role of mechanical reperfusion as compared with thrombolytic therapy for the treatment of acute myocardial infarction has remained controversial since Rentrop et al.[1] first reestablished perfusion in patients with myocardial infarction by dislodging the occluding coronary thrombus with a guide wire. Since then, considerable evidence has shown that thrombolytic agents are effective in restoring blood flow, improving left ventricular function, and reducing mortality from acute myocardial infarction. Primary treatment with percutaneous transluminal coronary angioplasty has been shown to have similar benefits, and controversy continues over what method is more effective.

Those who favor thrombolytic therapy emphasize its advantages over primary angioplasty: patients have greater access to it, treatment time is shorter, there is better evidence that infarct size is reduced, and success is less dependent on the physician's experience with the procedure. Critics of primary angioplasty are quick to identify problems with this interventional approach. The most notable drawback of primary angioplasty is its limited accessibility (only 20 percent of hospitals in the United States have catheterization laboratories, and even fewer have the capability 24 hours a day to perform primary angioplasty). Another limitation is the delay inherent in setting up the laboratory and mobilizing personnel, especially on nights and weekends.

Physicians' experience is also an important issue. The results of clinical trials in academic centers with large numbers of patients are often not duplicated in smaller hospitals, where there may be delays in getting the cardiac catheterization team to the laboratory, and where rates of restoration of normal coronary blood flow may be lower than the 90 to 95 percent success rates reported in the large clinical trials. Not only is the physician's experience important; the expertise of the technical and nursing staff in the cardiac catheterization laboratory is equally critical.

In recently revised American College of Cardiology–American Heart Association guidelines, it was suggested that primary angioplasty be considered an alternative to thrombolysis "if performed in a timely fashion (balloon inflation within 90 minutes of admission) by individuals skilled in the procedure (more than 75 procedures per year) and supported by experienced personnel in a laboratory environment (centers performing more than 200 [angioplasty] procedures per year [that] have cardiac surgical capabilities)."[2]

In addition, follow-up data have been limited, resulting in uncertainty about which approach yields better outcomes. A number of nonrandomized trials have failed to show a sustained benefit after primary angioplasty. For instance, in the Myocardial Infarction Triage and Intervention investigation there was no difference in outcomes during three years of follow-up between 1050 patients treated with primary angioplasty and 2095 who received thrombolytic therapy.[3] In this issue of the *Journal*, Zijlstra et al.[4] report on the first long-term follow-up (lasting five years) of the patients enrolled in a randomized trial in which primary angioplasty was compared with streptokinase for acute infarction. We applaud their effort and hope to see future reports from other investigators.

Although the numbers of patients were relatively small, Zijlstra et al. found that angioplasty was associated with a lasting benefit, with a favorable late mortality rate (13 percent for angioplasty vs. 24 percent for streptokinase), a lower reinfarction rate (6 percent for angioplasty vs. 22 percent for streptokinase), a lower incidence of heart failure, and lower total cost. These data strengthen the case for primary angioplasty. High rates of patency and improved coronary flow (grade 3, according to the Thrombolysis in Myocardial Infarction [TIMI] classification), with decreased rates of stroke, reinfarction, and recurrent ischemia, have been confirmed by Weaver et al.[5] in an analysis of pooled data from 10 randomized trials. Identification of high-risk left main coronary stenoses and patent infarct-related arteries is clearly an advantage of primary angioplasty. Avoiding the risk of hemorrhage associated with thrombolytic agents is also an advantage. The findings of Zijlstra et al. appear to confirm that an open artery with normal (TIMI grade 3) blood flow is a valuable goal, resulting in, as compared with the use of only thrombolytic agents, lower short-term and long-term morbidity and mortality — a benefit that is very likely to be cost effective because patients require fewer rehospitalizations.

Contemporary practitioners, both at academic centers and in the "real world" of community practice, show continued enthusiasm for interventions to restore coronary perfusion in patients with acute myocardial infarction. Much has changed since 1990, when the study by Zijlstra et al. was begun. More effective thrombolytic agents and the expanding role of platelet glycoprotein IIb/IIIa receptor inhibitors, which block platelet aggregation, have improved the success of thrombolytic therapy. Recent data from several trials suggest that the greatest potential for early reperfusion in cases of acute myocardial infarction is achieved with fibrinolytic agents in the presence of platelet glycoprotein IIb/IIIa receptor inhibitors. Both the TIMI 14 and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries IV (GUSTO IV) pilot trials showed that a combination of thrombolysis (with

recombinant or nonrecombinant tissue plasminogen activator) and treatment with abciximab (a IIb/IIIa receptor inhibitor) improved reperfusion rates.[6,7]

Primary angioplasty has also changed. Early experience with balloon angioplasty alone was extremely favorable, but more recent clinical trials have shown the superiority of coronary stenting in improving the early and long-term success rates of the procedure and in reducing rates of reocclusion and restenosis.[8-10] In the Primary Angioplasty in Myocardial Infarction stenting trial, the rate of target-vessel revascularization six months after intervention was significantly lower after stenting than after balloon angioplasty alone (7.5 percent vs. 17 percent, $P<0.001$).[10] Likewise, concomitant use of platelet glycoprotein IIb/IIIa receptor inhibitors has further reduced the incidence of early complications of stenting.[11,12] One ongoing trial in which stenting is being compared with balloon angioplasty and the use of the IIb/IIIa antagonist abciximab in a multifactorial design should help determine the efficacy of each of these newer approaches.

The advances in both thrombolysis and primary angioplasty should not be viewed independently. The use of combined thrombolysis and angioplasty has been studied for nearly 20 years, and several large clinical trials (the TIMI, Thrombolysis and Angioplasty in Myocardial Infarction, and European Cooperative Study Group trials) have failed to show a benefit with this approach. However, preliminary results of the Plasminogen-Activator Angioplasty Compatibility Trial (PACT) suggest that combination therapy is superior to angioplasty alone and have challenged us to look again at combination therapy.[13] An approach that uses pharmacologic therapy to open the infarct-related artery rapidly in the emergency room and thus permits safe and more complete reperfusion by angioplasty later is clearly attractive and promising.[13,14]

It is time to move on and stop debating the relative merits of thrombolytic strategies and invasive strategies; we now need to deal constructively with the lessons we have learned from both. We know that early opening of a coronary artery with reestablishment of normal blood flow, no matter how it is achieved, results in improved early and late outcomes. Primary angioplasty has proved to be effective both in the short term and in the long term. Our challenge for the future is to enhance reperfusion further by optimizing both pharmacologic and mechanical techniques.

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# THE PARADOX OF OSTEOPATHY

IN the spring of 1864, Andrew Taylor Still, a rural Kansas practitioner, watched helplessly as the best medications then available failed to save his three children from spinal meningitis. Bitterly disappointed, Still set out to devise an alternative healing practice. He eventually based his new system on the idea that manipulation of the spine could improve blood flow and thus improve health by allowing the body to heal itself. His philosophy included a healthy dose of moralism; patients were forbidden to consume any liquor and, as part of the break from existing practices, were also forbidden to take any medicine.[1] Still founded a school to teach his new system of osteopathy in Kirksville, Missouri, in 1892.

Osteopathy was not the only system of spinal manipulation to be created in the late 19th century. Chiropractic, established in 1895 by Daniel David Palmer, aimed to relieve obstruction in the nerves rather than

in the blood vessels. Osteopathy and chiropractic initially shared several characteristics. Both were founded when Americans freely chose from many systems of healing. Both were home-grown American systems created at about the same time by messianic midwesterners. Both systems were seen by many midwesterners as preferable to the reductionist European model of laboratory-based medicine, which was established most firmly on the eastern seaboard and was fast becoming the standard.

Over the course of the 20th century, medicine as practiced by M.D.'s (sometimes called allopathy) has come to dominate U.S. health care. Chiropractic and osteopathy, initially parts of a pluralistic medical system, have taken very different paths. Chiropractors have generally remained focused on spinal manipulation for a limited set of conditions, particularly those that are often resistant to allopathic therapy, such as back pain. Osteopaths, on the other hand, have worked hard to employ the entire therapeutic armamentarium of the modern physician, and in so doing they have moved closer to allopathy.[2]

The move toward assimilation became explicit in California in the early 1960s, when the California Medical Association and the California Osteopathic Association merged in what has been called the osteopathic profession's darkest hour.[3] By attending a short seminar and paying $65, a doctor of osteopathy (D.O.) could obtain an M.D. degree; 86 percent of the D.O.'s in the state (out of a total of about 2000) chose to do so. The College of Osteopathic Physicians and Surgeons became the University of California College of Medicine, Irvine. Many osteopaths feared that the California merger was the wave of the future and that the profession would not survive. But it did, and in so doing it may have become even stronger. D.O.'s are now licensed in all 50 states to prescribe drugs, deliver babies, perform surgery — in short, to do anything that M.D.'s can do. Despite national recognition, osteopathy is still a regional phenomenon in ways that mirror its historical origin. The ratio of D.O.'s to the population varies by a factor of almost 3, from a low of 7.7 per 100,000 population in the West to a high of 20.4 per 100,000 in the Midwest; the number is 8.5 per 100,000 in the South and 18.3 per 100,000 in the Northeast. M.D.'s are far more evenly distributed throughout the country.[4]

Osteopathy was originally created as a radical alternative to what was seen as a failing medical system. Its success at moving into the mainstream may have come at a cost — the loss of identity. Most people — including physicians — know very little about the field (most people know more about chiropractic[5]). Many people — even osteopaths — question what osteopathy has to offer that is distinctive.

Those who claim that osteopathy remains a unique system usually base their argument on two tenets. One is the holistic or patient-centered approach, with a focus on preventive care, that they say characterizes osteopathy. That claim to uniqueness is hard to defend in the light of the increasing interest paid to this approach within general internal medicine and other areas of allopathic medicine. The other, potentially more robust, claim to uniqueness is the use of osteopathic manipulation as part of the overall therapeutic approach. In osteopathic manipulation, the bones, muscles, and tendons are manipulated to promote blood flow through tissues and thus enhance the body's own healing powers. The technique, based on the idea of a myofascial continuity that links every part of the body with every other part, involves the "skillful and dexterous use of the hands" to treat what was once called the osteopathic lesion but is now referred to as somatic dysfunction.[6] Osteopathic manipulation is not well known (or practiced) by allopathic physicians, but for decades it has stood as the core therapeutic method of osteopathic medicine.

In this issue of the *Journal,* Andersson et al. report a comparison of osteopathic spinal manipulation, a form of osteopathic manual therapy, with standard care for patients with low back pain.[7] Patients were randomly assigned to standard care (72 patients) or to treatment including manipulation (83 patients). Pain, functional ability, and the patients' satisfaction with their treatment were assessed with a variety of measures. After 12 weeks, there was significant improvement in both groups, and there was no difference between the two groups in any of the primary outcome measures. However, patients given standard therapy without osteopathic manipulation used significantly more medication and more physical therapy.

Some claim that osteopathic physicians are more parsimonious in their use of medical technology. Thus, they can provide more cost-effective medical care and reduce the need for medications, which, although effective, can have serious side effects. The specific mechanism that would account for any improvement in back pain directly related to osteopathic manipulation is unclear, but the most important studies will be those that test whether the technique works in clinical practice. Part of the success of osteopathic manipulation for patients with back pain may come from the fact that physicians who use osteopathic manipulation touch their patients.

Osteopathic manual therapy is claimed to be useful for treating a wide range of conditions, from pancreatitis to Parkinson's disease, sinusitis, and asthma. Some leading osteopaths say that manual therapy should be part of almost every visit to an osteopathic physician. A recent president of the American Osteopathic Association claimed that he "almost always turned to [osteopathic manipulation] before considering any other modality," and he asserted that 90 percent of his patients got better with osteopathic manipulation alone.[8] Such claims underscore a raging debate within osteopathy and a disconnection be-

tween its theories and its practice. A 1995 survey of 1055 osteopathic family physicians found that they used manual therapy only occasionally; only 6.2 percent used osteopathic manipulation for more than half of their patients, and almost a third used it for fewer than 5 percent.[9] The more recent their graduation from medical school, the less likely practitioners were to use osteopathic manipulation, a finding consistent with the view that osteopathic practice is moving closer to allopathic practice. A decreasing interest in osteopathic manipulation may also indicate that more physicians enter osteopathic medical school not as a result of a deeply held belief in the osteopathic philosophy but after failing to be admitted to allopathic medical schools.[10] The osteopathic physicians who are more committed to osteopathic manipulation tend to be more likely than their colleagues to have a fundamentalist religious orientation.[10]

With or without manipulation therapy, osteopathic medicine seems to be undergoing a resurgence. Although the number of allopathic medical schools in the United States has remained stable since 1980, at about 125, the number of osteopathic medical schools has increased from 14 to 19. The number of graduates each year has increased at an even more disproportionate rate. The number of graduates of allopathic medical schools has increased only slightly, from 15,135 in 1980 to 15,923 in 1997, whereas the number of graduates of osteopathic medical schools has almost doubled, from 1059 to 2009, over the same period. Osteopathic medical schools have not done as well as allopathic medical schools in recruiting underrepresented minorities and women, and students entering osteopathic medical schools have somewhat lower grade-point averages and lower scores on the Medical College Admission Test. On the other hand, the ratio of applicants to those admitted is higher for osteopathic medical schools, 3.5 applicants for each person admitted, as compared with 2.4 for allopathic medical schools.[11-13]

Overall, osteopathic medical schools have come to resemble allopathic medical schools in most respects; some students even share classes. Graduates of osteopathic medical schools more often than not go on to residency training in allopathic programs.[14] An evaluation of performance on the certifying examination of the American Board of Internal Medicine in the 1980s noted that although physicians from osteopathic medical schools did not do as well as those from allopathic programs, overall they "did well" and could be an "untapped reservoir of talented physicians" for internal medicine.[15]

Although they constitute only about 5 percent of U.S. physicians, osteopaths may be disproportionately important for the health care system by virtue of their distribution in terms of specialty and location: 60 percent of graduates of osteopathic medical schools select generalist fields.[16] Because osteopathic education is more community-based than allopathic education, and because osteopathic schools are smaller, osteopathic education may be able to adapt more quickly to new approaches to health care delivery.[17] Many more osteopaths than allopaths (18.1 percent vs. 11.5 percent) select rural areas in which to practice.[18] One osteopathic medical school found that 20 percent of its graduates were practicing in underserved communities.[19]

At the end of the century, osteopathy continues its uneasy dance with allopathy, but only one partner is really paying attention. The resurgence in the numbers of osteopaths should not mask the precarious position of osteopathy. At its birth, osteopathy was a radical concept, rejecting much of what allopathic medicine claimed was new and useful. Today, osteopathic medicine has moved close to the mainstream — close enough that in general it is no longer considered alternative medicine. The long-term survival of osteopathic medicine will depend on its ability to define itself as distinct from and yet still equivalent to allopathic medicine. That argument may best be articulated not in theoretical terms, but by demonstrating treatment outcomes. The paradox is this: if osteopathy has become the functional equivalent of allopathy, what is the justification for its continued existence? And if there is value in therapy that is uniquely osteopathic — that is, based on osteopathic manipulation or other techniques — why should its use be limited to osteopaths?

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## The Allocation of Cadaveric Kidneys

WITH the discovery of cyclosporine and anti–T-cell antibodies and the successful application of HLA matching, short-term and long-term graft-survival rates for cadaveric kidney transplants have improved dramatically. Nonetheless, there are more than 40,000 people in the United States waiting for a kidney transplant, with an ever-widening gap between supply and demand. The organ shortage has fueled the ongoing debate about how cadaveric kidneys should be allocated. This frequently rancorous debate has pitted patient against patient, physician against physician, smaller hospitals against larger institutions, and politicians from states with large multiorgan-transplantation programs against those from states with smaller programs.

To address the problems of inadequate supply and inequitable distribution, Congress enacted the National Organ Transplant Act in 1984. A private, nonprofit organization, the United Network for Organ Sharing (UNOS), holds the contract to operate the national Organ Procurement and Transplantation Network. Currently, regional organ-procurement organizations cooperate to distribute and share organs across the country under the supervision of UNOS. Current UNOS organ-allocation policy for kidneys takes HLA-antigen matching, time spent on the waiting list, the presence or absence of medical urgency (as indicated by technical reasons why the patient cannot undergo dialysis), and geographic area into account.

The most important determinants of the results of kidney transplantation are the degree of HLA-A, B, and DR matching and the total amount of time during which the organ is preserved before transplantation, particularly cold-ischemia time.[1-6] HLA matching has not always been universally accepted as a determinant of outcome, except for transplantations involving so-called complete six-antigen matching between donor and recipient or zero mismatching (an absence of HLA-A, B, and DR mismatches).[7,8] Because grafts are preferentially assigned to patients with relatively frequent HLA specificities, HLA matching has also been criticized for diverting organs, which are obtained mainly from white donors, from minority recipients, particularly blacks, with variant genotypes and from other hard-to-match recipients. As a result of a recent policy change, kidneys must now be distributed nationally when there is complete phenotypic HLA matching and when there are no HLA-A, B, or DR mismatches; other kidneys are shared within organ-procurement areas, which cover widely varying geographic areas. This new policy has increased the number of and percentage of HLA-matched transplants available for blacks and members of other minority groups.[6,9,10] The role of HLA matching in the allocation of cadaveric kidneys and its effects on costs remain controversial. National sharing of organs on the basis of HLA matching requires organs to be transported long distances. This may lead to increased cold-ischemia time, with a potential for delayed graft function and the need for dialysis after engraftment. It also requires additional time for cross-matching at the transplantation center that receives the organ. All of these requirements increase the cost of kidney transplantation. However, HLA matching improves both short-term and long-term graft survival.

In this issue of the *Journal*, Schnitzler et al.[11] analyze the economic implications of various HLA-matching criteria for cadaveric renal transplantation. They studied patients who received a first cadaveric kidney transplant in 1991 through 1997, a period when cyclosporine was widely used. On the basis of various simulations, they concluded that HLA-based allocation of kidneys at the local level (i.e., the level of the organ-procurement organization) produced the largest estimated cost savings, when the duration of cold ischemia was taken into account. A national allocation program was not estimated to produce additional savings, because the additional costs associated with longer cold-ischemia times were greater than the savings associated with minimizing HLA mismatching. Nonetheless, other data suggest that when graft survival is taken into account, a mixture of local and national systems for the allocation of kidneys — similar to current policies — remains a reasonable approach. By analyzing data from the UNOS renal-transplant registry from 1987 through 1996, Hata and colleagues[6] demonstrated that despite longer mean periods of cold ischemia, the HLA-matched kidneys that were allocated on a national basis had a significantly better one-year graft-survival rate (88 percent) than kidneys with at least one HLA mismatch (81 percent).

The report by Schnitzler et al. provides an important example of the kind of data on which decisions about the allocation of organs should be based. "Sickest first and widest distribution" — which is a

fair reading of the current federal organ-allocation rule — is not and should not be applicable to all forms of organ transplantation. For example, current organ-preservation technology does not permit the wide distribution of donor lungs or hearts without substantial detriment to the integrity of the organ. Therefore, the current policy of assigning these life-sustaining organs to the sickest patients within a region remains sound. This method of allocating hearts and lungs for transplantation is acknowledged implicitly in the organ-allocation rules of the Department of Health and Human Services as an exception to the general policy.

With respect to life-enhancing organs (such as the kidney), as distinct from life-sustaining organs (such as the heart and lung), "sickest first" has no medical meaning except in unusual circumstances. In our view, the current hybrid system of regional distribution for most kidneys and national allocation for those with no HLA-A, B, or DR mismatches provides the best and most economical balance between efficacy and equity. Most important, these sensitive decisions, which are not only medical but also, ultimately, political, should be based on evidence such as that offered by Schnitzler et al.

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