Peripheral Vascular Disease

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There is little doubt that one of the greatest advances in the field of peripheral arterial disease was our ability to visualize problems wherever they occurred. This was possible because of the development of arteriography. One of the dramatic developments that made this possible was the observation by Forsmann in 1929 that a catheter could be threaded through a peripheral vein into the right heart. He also suggested the possibility of injecting a contrast agent through the catheter for imaging purposes. Because of this contribution, he was awarded the Nobel prize in 1953. Seldinger in 1953 pushed this concept even further by showing that it was possible to replace an intra-arterial needle with a catheter that could be manipulated within the arterial system.

These developments, along with the realization that arteries could be replaced, led to many of the early advances. One of the first methods used to replace segments of abdominal aorta was the use of homografts. Dubost et al in 1952 reported the replacement of an aortic aneurysm with a homograft. This procedure was rapidly followed by similar efforts in the United States by Julian et al and De Bakey et al. These homografts were initially used for the treatment of abdominal aortic aneurysms but did have serious problems related to size, according to the anatomy of the patient and late breakdown of the grafts themselves. Once it became obvious that arterial homografts were not an answer to the problem of arterial replacement, development of alternative methods moved ahead rapidly. Vorhees et al in 1952 reported the first application of an artificial prosthetic device for arterial replacement. This led to the development of other prosthetic materials such as Dacron, Teflon, and polytetrafluoroethylene. These grafts were and still are in widespread use for treatment of arterial problems.

All of these methods, for both the exposure of diseased anatomy and its correction, were developed in this time frame and remain in place even today. In the early phases of applying grafting techniques, one of the most difficult problems was related to the management of abdominal aortic aneurysms. The landmark study of Estes in 1950 pointed out the lethal nature of these lesions if left untreated. Although these lesions became recognized as a cause of death, it required the surgical application of developed techniques to show that resectional therapy was beneficial. Experience over the past 50 years has clearly demonstrated an improvement in long-term survival after aneurysm resection and replacement with prosthetic grafts. These grafts were also developed for bypassing areas of occlusion, both in the aortoiliac area and for femoral-popliteal occlusive disease.

A parallel advancement of great importance was the use of autogenous tissue to bypass areas of occlusion. The experience in the Korean conflict showed that limb survival secondary to arterial injury could be greatly improved by use of the saphenous vein as the bypass conduit. The saphenous vein was not only superior in terms of long-term patency but also was not as prone to infection as prosthetic devices when placed under less-than-optimal circumstances.

The use of autogenous veins for bypass grafting was applied with increasing frequency, particularly in areas distal to the inguinal ligament, where prosthetic grafts did not function as well in the long term. The concept of in situ versus reversed saphenous vein also emerged in this time frame. Using veins as reversed conduits, one did not have to deal with the issue of venous valves. However, when used in the in situ position, the valves had to be disrupted to permit unimpeded arterial flow. Although argument continues regarding the superiority of reversed saphenous vein over the in situ method, it is clear that when the vein is used to bypass lesions well below the knee, the in situ method offers some advantages in terms of sizing the anastomoses.

It should be noted that during this era there were also advances that at first glance did not appear to be very important, but in reality were a big influence on how these surgical procedures were successfully carried out. An obvious advance was the use of magnification in dealing with suturing blood vessels to ensure optimal coaptation. In addition, development of a variety of atrumatic vascular clamps represented a major advance. The development of monofilament vascular sutures also was a major advance in terms of ease of handling, with multiple sizes being available to fit the needs of the operative procedure at hand. Each of these technical innovations made the satisfactory performance of direct arterial surgery much simpler and better.

During this rapidly developing technological era with new approaches to aneurysmal and occlusive disease, the method of patient identification depended entirely on a well-taken history, palpation of pulses, and listening for
bruits. Although this was satisfactory in many respects, it did not offer the type of information that one often needed to assess the extent to which the physiology of blood flow had been either interfered with or restored to normal after an operative procedure. This lack of information led to the development of an entirely new area of study relating to the physiology of arterial blood flow and how it was affected by disease. In addition, it became important, since it was necessary to know to what extent the pathophysiology of arterial obstruction had been corrected.

One of the major questions dealt with in this era was how one should study the arterial system and how this information should be used. Fortunately, a considerable amount of work was being done on the physiology of blood flow that could be applied to patient studies if methods were made available to provide this information. This required tools that could be applied to humans. The most common methods used by physiologists were plethysmographic, combined with some method of measuring intravascular pressures. Plethysmographic techniques were applied to humans and provided information on blood flow in the limbs and how it was affected by disease. At the same time, these methods could be used to estimate systolic pressures at several sites along the length of the limb. In addition, measurement of systolic pressures in the upper and lower limbs led to the concept of expressing these values as a ratio (the ankle/arm index, or AAI). It was noted that although absolute levels of pressure should be measured from both the upper arms and ankles, the level of the AAI was particularly useful in clinical practice.

One of the early concerns about both limb pressures and blood flow measurements was that they were indirect and did not, in most cases, affect what was done to the patient. However, it became apparent that the AAI was the best single evidence available concerning the prevalence of arterial occlusive disease and its severity. In addition, it was learned that changes in both the absolute levels of systolic pressure and the AAI could be used as markers of both improvement as well as failure of direct surgical procedures. It was also noted that an increase in the AAI in patients not treated surgically was associated with improvement of the collateral circulation, whereas a decrease was associated with disease progression. The practice of measuring systolic pressures was extended to the digits as well. The level of systolic pressures recorded could also be used to predict whether or not an ulcer was likely to heal.

Another advantage of toe pressures is that they were particularly useful in patients with diabetes, in whom medial calcification of the tibial-peroneal arteries could make the measurement of ankle systolic pressure unreliable. In fact, it is now a standard procedure to carry out pressure measurements from the toe in cases where calcification of the digital arteries has not occurred. These recommendations relative to the role of vascular studies in diabetic patients was arrived at by a consensus conference sponsored by the American Heart Association (AHA), with the results published in *Circulation*.

A major advance with regard to the study of arterial disease occurred when it was recognized that ultrasound could be transmitted through the skin. It was possible to obtain information concerning arterial blood flow patterns in health and disease by taking advantage of the Doppler effect. The earliest devices depended entirely on an audible interpretation by the observer of the backscattered, Doppler-shifted ultrasonic signal. The subjective nature of interpretation of the audible velocity signal limited its application to some degree. However, with audible output alone, the Doppler device became the most commonly used method to measure systolic pressures from the arm and ankle. Another problem was that proper use of the method depended on the skill of the examiner, who had to understand arterial anatomy as well as the significance of flow patterns that were observed in both health and disease. Nonetheless, despite the shortcomings of this method, these devices are in widespread use throughout the world for studying arterial flow patterns and the measurement of upper- and lower-limb systolic pressures.

As the field of ultrasound technology progressed, it became apparent that it would be possible to combine ultrasonic B-mode imaging with a pulsed-Doppler device for the study of peripheral arteries. There were several technical innovations that made this possible and that incorporated the pulsed Doppler, thus allowing selective sampling of blood flow at any point along the transmitted sound beam. In addition, development of the fast Fourier transform spectrum analyzer for depiction of both the frequency and amplitude of the backscattered Doppler signal was extremely important.

As technology improved and as we began to appreciate the medical need for a real-time combined imaging and Doppler system, it was apparent that this method could be extended beyond the carotid artery to the arteries of the limbs, the visceral vessels, and finally, to the intracranial arteries themselves. As a result of these developments, there were no arteries in the body that could not be accessed for study. With this new technology, it became possible to screen patients suspected of having disease, to document its severity, and to use the same methods to document the results of therapy. The technique has proved useful for follow-up of arteriosclerotic disease of the carotid and renal arteries as well as for patients who have undergone peripheral arterial grafting procedures.

Although this new technology has greatly improved how we evaluate patients, it has also had a remarkable effect on medical practice. This is most evident in the case of carotid artery atherosclerosis, for which duplex ultrasound scanning is now being used as the sole diagnostic test before carotid endarterectomy. This is now possible in up to 90% of patients, resulting in marked savings to the healthcare system and removing the patient from the risk of having a neurological event during the arteriogram. The risk has been estimated to be between 1% and 2%.

What are the areas where this new technology has had a major impact? These include the carotid artery, the abdominal aorta and iliac arteries, and the arteries distal to the inguinal ligament. In addition, it is now possible to document the status of the renal arteries for the presence of atherosclerosis and fibromuscular hyperplasia, which are common causes for the development of hypertension. This same method has
been shown to be useful for the follow-up of disease and therapy for all of the above-mentioned areas.\textsuperscript{47,48}

How do these diagnostic methods impact the field of peripheral arterial disease and its management? The AHA has played a prominent role in bringing this information to the medical public. An example of their input can be read in the AHA Medical/Scientific Statement entitled Diagnosis and Treatment of Chronic Arterial Insufficiency of the Lower Extremities: A Critical Review.\textsuperscript{55} This document reviewed the current status of the field, with particular emphasis on which areas had level 1 evidence to support efforts currently used. This document represents a fair summary of the progress that has been made in the past 50 years, as well as suggestions where further work needs to be done.

In line with the scientific statement, there has been increasing interest in developing level 1 evidence for our approaches to the diagnosis and treatment of arterial vascular disease. One area where this plan has succeeded is in relation to the role of carotid endarterectomy in stroke prevention. Before 1913, stroke was believed to be secondary to intracranial vascular pathology. In that year, Ramsey Hunt\textsuperscript{56} suggested that occlusions of the cervical arteries were important in the causation of stroke. However, there is no doubt that it was the contributions of C. Miller Fisher\textsuperscript{57,58} who clearly detailed the role of the extracranial arteries in the pathogenesis of stroke. To approach this area from a surgical standpoint, Eastcott et al\textsuperscript{59} in London and DeBakey\textsuperscript{60} in the United States first reported the use of a new operation, carotid endarterectomy. Surgical interest in this area grew rapidly, but concerns were raised about the safety of the procedure and the lack of proof of its efficacy.\textsuperscript{61,62} These concerns became serious enough to warrant the initiation of randomized, clinical trials to compare the procedure with conventional medical therapy.\textsuperscript{63} Large, randomized trials were undertaken to examine this issue in patients with and without symptoms. There were two large trials in symptomatic patients and one in patients who were free of symptoms. These were the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).\textsuperscript{64–66} Both of these trials proved without question that carotid endarterectomy was better than conventional medical therapy for the prevention of stroke. Level 1 evidence is now in with regard to this issue. The large National Institutes of Health–supported trial of Asymptomatic Carotid Surgery (ACAS) was also a randomized trial and showed a benefit from carotid endarterectomy in selected patients.\textsuperscript{54} This is also level 1 evidence, but the results are more controversial than those in the NASCET and ECST trials.

With introduction of the balloon catheter by Fogarty et al\textsuperscript{67} in 1963, the potential for transluminal treatment of arterial embolization and thrombosis was introduced. Instead of the standard methods of replacement or bypass grafting, the opportunity to restore patency by transluminal dilatation methods was brought to our attention by Dotter and Judkins\textsuperscript{68} in 1964. The “Dotter” technique of enlarging the site of arterial narrowing was improved by introduction of the balloon catheter by Gruentzig and his colleagues\textsuperscript{69} in 1974. It appeared to work, with the creation of a local dissection followed by remodeling.\textsuperscript{70} The best results were obtained with disease of the common iliac arteries, but the results were, in general, disappointing in arteries distal to the inguinal ligament.\textsuperscript{71,72} Use of balloon angioplasty alone has been modified by the addition of a stent to hold the dilated segment in place, thereby preventing “rebound” stenosis.\textsuperscript{73} There has been an increasing number of intraarterial stents developed for use in every area where atherosclerotic narrowing and occlusion develop. This field is moving very quickly, but its final use in areas such as the carotid arteries, renal arteries, and lower-extremity arteries, remains to be determined.

Another area of treatment that is emerging is endovascular therapy of abdominal aortic aneurysms.\textsuperscript{74} This form of therapy appears to be safer for the patient who may pose a serious risk for open repair, but long-term results will need to be determined before this method finds a permanent place in our therapy for this very important problem.

There is little doubt that one of the major problems facing all forms of intervention in the arterial system is that of neointimal hyperplasia. This represents the single most important problem influencing the long-term results of interventional procedures.\textsuperscript{75} There have been extensive efforts to control this process, but none have proved successful in preventing this from occurring.

One of the most important developments in our understanding of peripheral arterial atherosclerosis was the devastating impact of cigarette smoking.\textsuperscript{76} In addition, diabetes was recognized as a major contributing factor to the development of severe peripheral arterial disease. A fact that is poorly understood is that the distribution of atherosclerosis is different for the diabetic and nondiabetic. This is also important from a clinical standpoint.\textsuperscript{77–79} It is also known that the presence of peripheral arterial atherosclerosis is a powerful predictor of cardiovascular mortality.\textsuperscript{80} In this regard, the finding of an abnormal AAI is an important marker of atherosclerosis in other arterial beds.\textsuperscript{81}

There also appears to be a relationship between the surface changes of the atherosclerotic plaque and the development of thrombosis.\textsuperscript{82} Development of a thrombus on the surface of a plaque may lead to total occlusion and/or the release of embolic material from that site. It is not surprising that many antithrombotic strategies have been proposed and implemented. One of the earliest strategies of immense importance was the development and use of heparin.\textsuperscript{83–85} This has its greatest application for therapy during the acute event period or during interventional procedures. For long-term therapy, coumarin remains the most commonly used agent for both arterial and venous problems. It is also clear that antiplatelet agents are of great importance in the prevention of primary and secondary cardiovascular events.\textsuperscript{86} Newer and more powerful antiplatelet agents are appearing that may be even more useful, particularly during interventional procedures. In addition, the availability of low-molecular-weight heparin is beginning to change our therapeutic approach to both arterial and venous disease.\textsuperscript{87}

As with other areas of arterial circulation, prevention of atherosclerosis would remove the need for both expensive
and potentially dangerous forms of therapy. In this regard, it is hoped that basic research in the pathogenesis of diabetes—both types 1 and 2, with their profound influence on the arterial system—will provide some understanding of this very complex disorder. Although we understand the implications of the disease and its effects on arterial circulation, it is unfortunate that we have not been able to definitively reduce the incidence of vascular complications in any of the major arterial beds.

There is and hopefully will continue to be research into the pharmacotherapy of intermittent claudication. There is some hope in this regard, as evidenced by the approval of cilostazol by the US Food and Drug Administration for the treatment of stable intermittent claudication. It is also hoped that work will continue into the role of gene-based therapy to improve collateral circulation to the limbs.

Although there have been dramatic improvements in the application of endovascular therapy for the treatment of occlusive arterial disease, its ultimate impact remains to be determined. Whereas some devices may shorten time in the hospital, the cost of follow-up studies and management of long-term complications remain to be sorted out. At the moment, it appears that most of these methods do not provide any substantial savings, either in the short or long term. Randomized trials, whenever possible, should be used to validate these new therapies. One area that stands out as both contentious and difficult is the issue of carotid stents. Successful completion of the randomized trials of endarterectomy versus conventional medical therapy has shown that the operation can be done at low risk, yet there remains the possibility that carotid stents may do as well, if not better. Unfortunately, the risk of arteriography is nearly equal to the risk of endarterectomy, and this will have to be factored into the role of this new therapy. A good cost analysis of these two approaches must be done.

There is universal agreement that the response of the arterial wall to injury remains a real challenge to the future. If this process can be either prevented or controlled, the long-term results of therapy will be greatly improved, be it surgery or endovascular means. Unfortunately, to date, none of the proposed methods have been successful. It is the opinion of these authors that the peripheral arterial circulation is an ideal site for these studies to be done. Routine and regular surveillance is possible for the entire limb and can provide quantifiable evidence of the response to injury and how it is being modified. The areas where research needs to be done are with angioplasty, with or without stents, and the use of venous bypass grafts, both of which are easily studied by ultrasonic methods. Work on 3D ultrasonic imaging that can quantify both the sites of restenosis, as well as monitor changes over time, will permit a realistic look at this problem. While it is clear that thrombolysis is useful for therapy of acute embolic events, its role in the therapy of chronic, occlusive arterial disease remains an important issue.

During this period of arterial bypass grafting for the treatment of arterial occlusive disease, the search for the satisfactory small-bore arterial prosthesis has been very disappointing. It is generally agreed that there have been no developments with prosthetic materials that have matched those achieved by venous grafts.

References

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