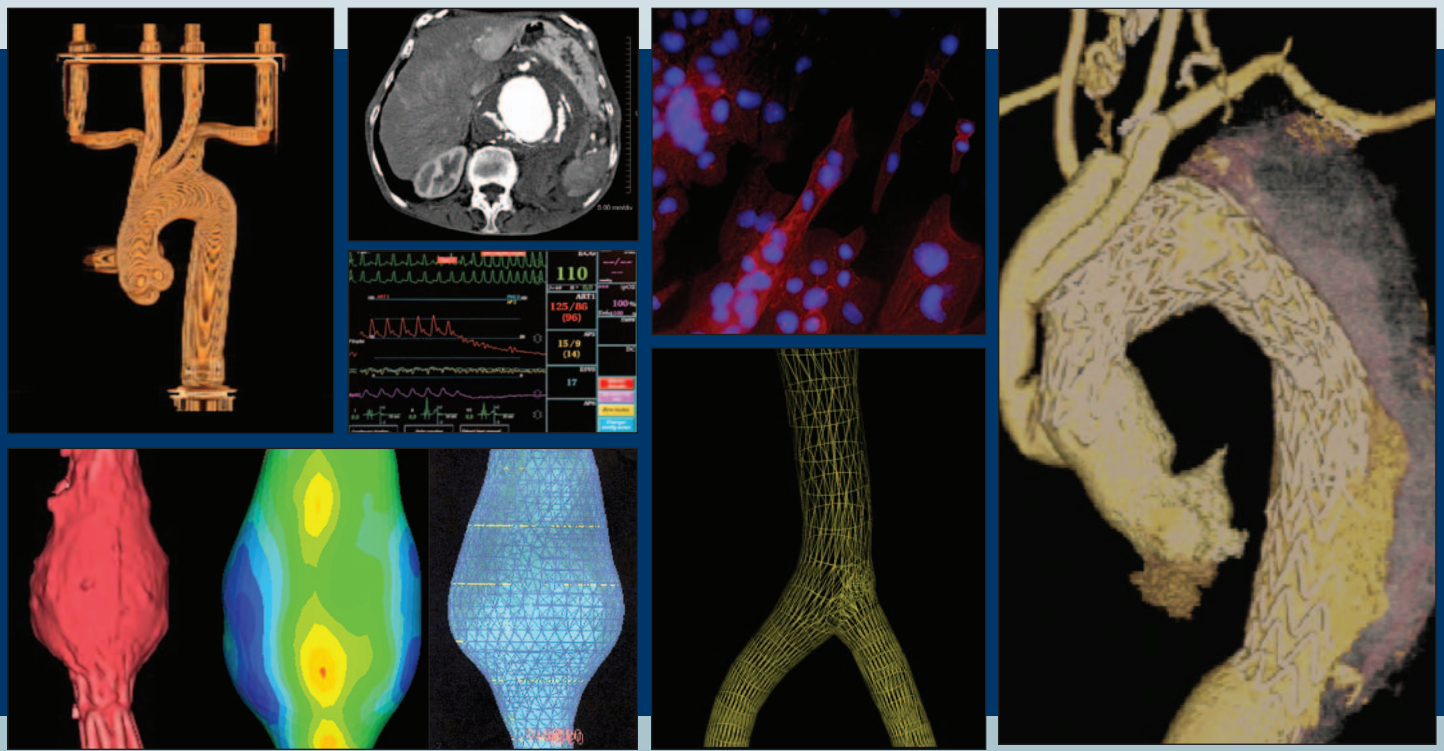
Supplement to

Endovascular TODAY

March 2009

LOOKING BEYOND



New Directions in Endovascular Treatment of Aortic Disease

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LOOKING BEYOND

New Directions in Endovascular Treatment of Aortic Disease

The current generations of endovascular abdominal and thoracic aortic stent grafts continue to produce favorable outcomes in appropriately selected patients, both in terms of immediate procedural success and the available long-term results.

Incremental advancements in operator experience, device materials, delivery systems, and related technologies such as imaging platforms have all contributed to the consistency and predictability of today's procedures. These devices are the result of nearly two decades of collaboration among innovative aortic specialists, researchers, engineers, regulatory representatives, and device manufacturers. Of course, despite the successes observed with current devices, industry continues to work with physicians to come up with new concepts and designs to bring even better results to the patient populations who are currently being treated, and also to provide new options for patients whose anatomies or disease states preclude them from undergoing endovascular or even surgical repair.

Medtronic, Inc., is very supportive of innovation through collaboration with physician partners and has therefore supported this supplement to highlight some of the emerging and future techniques in the field of aortic disease therapy. A group of cutting-edge clinicians and researchers have been invited to share their insights into the promise of truly "next-generation" approaches. These include in situ abdominal device fenestration, hybrid surgical and endovascular arch procedures, and rapid ventricular pacing to assist in thoracic stent graft placement. We also look at how translational technologies can augment endovascular procedures, detailing the potential uses of several new platforms. Next, the current research and potential for navigation systems and robotics are explored, followed by the role biological and cellular advances may play in aneurysm repair. Finally, we share an exciting look ahead to the possible applications of nanotechnology in endovascular therapy.

Medtronic, Inc., would like to express its sincerest gratitude for the continued commitment to research and innovation shown by these authors and the many groups currently working toward advancing the field of aortic therapy.

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Retrograde In Situ Fenestration in Abdominal Debranching Procedures

Visceral revascularization in elective and emergency aneurysm repair.

BY JÖRG TESSAREK, MD

The treatment of thoracoabdominal aneurysms involving the fourth aortic segment or the aortic arch remains a surgical challenge. Alternate methods have been developed and evaluated since the late 1990s.[1-3] However, despite all of the efforts to improve the overall outcome, the rate of perioperative morbidity and mortality remains high, with a reported 70% to 90% mortality in ruptured cases.[4,5] The use of branched and fenestrated grafts has offered a less-invasive therapeutic option for a select group of patients, but only for elective aneurysm repair.[5,6] A plethora of publications showing promising results for abdominal and thoracic hybrid procedures also reflect the variety of operative approaches that eliminate the risks of thoracoabdominal access and aortic cross-clamping. Prolonged organ ischemia is the main cause of complex, postoperative complications, including bowel ischemia, loss of kidney function, spinal cord ischemia, systemic inflammatory response, and fatal multiorgan failure.[7,8]

Retrograde in situ fenestration seems to be a feasible technique for simplifying visceral revascularization in abdominal debranching procedures. It was first used in 2002 as a bailout procedure for intraoperative occlusion of the superior mesenteric artery (SMA) caused by the migration of a thoracic endograft covering the orifice of the SMA after a previous mesenteric-celiac bypass. After using a tourniquet to fix the SMA, it was punctured 5 cm distal to its origin and distal to the origin of celiac bypass, using the needle to perforate the fabric of the graft and to insert a stiff, nonhydrophilic J-tip wire under fluoroscopic control using a mobile C-arm. A 5-F sheath was pushed forward, and the fabric puncture was dilated with a 6-mm balloon. To stabilize the position of the fenestration, a 6- X 18-mm balloon-expandable stent was placed under fluoroscopic control. This procedure can be performed in 4 minutes, with immediate restoration of blood flow after dilatation. Our patient survived without any symptoms of visceral malperfusion but died from myocardial infarction 3 years later.

TECHNICAL ASPECTS

Since our first experience in 2002, 13 patients have

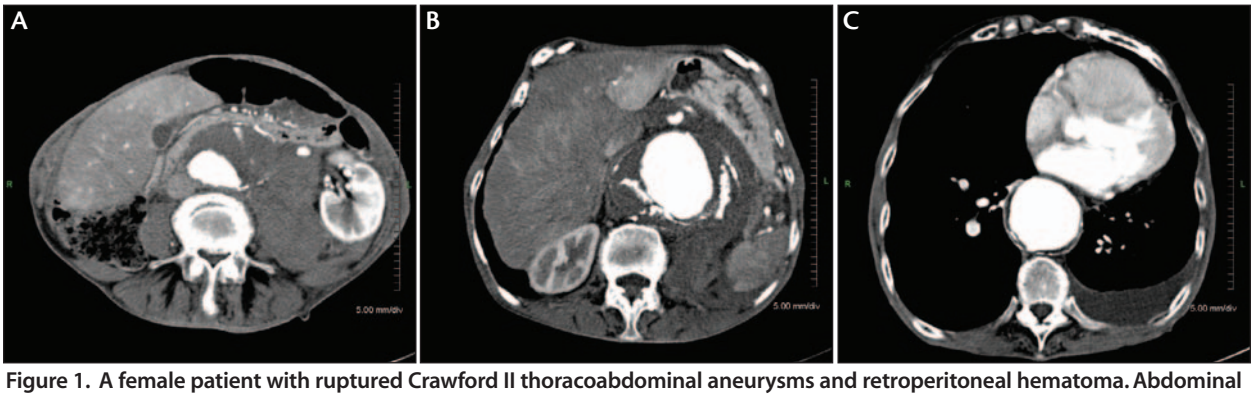

Figure 1. A female patient with ruptured Crawford II thoracoabdominal aneurysms and retroperitoneal hematoma. Abdominal segment with retroperitoneal hematoma (A). Thoracoabdominal segment with 9-cm diameter and periaortic hematoma (B). Thoracic segment of the aneurysm with a 6.5-cm diameter (C).

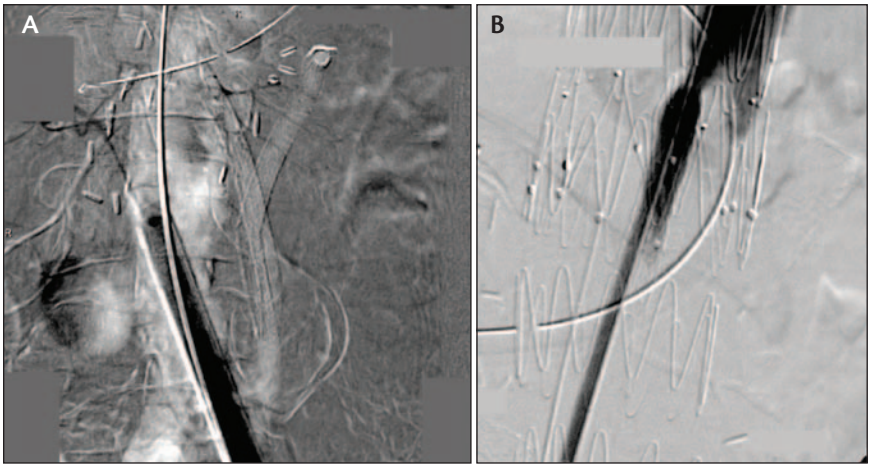

Figure 2. Intraoperative angiography of iliac-renal bypass and bridging device (A) and the in situ angiography (B). The Advanta V12 (Atrium Medical Corporation, Hudson, NH) shows a small waist at the level of fabric perforation and postdilatation.

been treated with this technique. Nine presented with symptomatic or ruptured thoracoabdominal aneurysms, and the other four were treated electively, showing an anatomy that was not suitable for fenestrated or branched endografts. This technique has not changed since 2002. In the elective debranching cases, the renal arteries were initially bypassed, and the endograft was then placed via femoral or iliac access. The exposed SMA (and in two cases, the celiac trunk) was punctured in a retrograde direction, followed by advancement of the starter wire. The needle was pushed forward, perforating the fabric of the graft, while the stiff wire was placed in a stable position inside the graft under fluoroscopic control.

After inserting an 8-F sheath to reach the inner lumen, the fabric was predilated with a 6-mm balloon, and a 6- to 8-mm covered stent (Advanta V12, Atrium Medical Corporation) was deployed in the target vessel with sufficient overlap. A 10- to 12-mm balloon can be used to flare the inner orifice, and when necessary, to adapt the visceral length of the covered stent to the diameter of the target vessel. In ruptured cases, the endografts were deployed after preparation of the SMA to exclude the aneurysm and prevent further bleeding. The SMA was then revascularized in the manner described previously. The bowel ischemia time was between 3 and 5 minutes. In the majority of ruptured cases, the collateral flow to the celiac trunk was estimated to be sufficient when a complete filling of the splenic, hepatic, and left gastric artery could be seen in the control angiography after stenting of the SMA. The celiac trunk was then ligated.

Five of the ruptured cases showed diffuse malperfusion of the abdominal organs due to hemorrhagic shock and extensive retroperitoneal hematoma. One presented with pre-existing segmental necrosis of the descending colon. With graft deployment, retrograde stenting, and stabilization of blood pressure and organ perfusion, the bowel showed normal color and was peristaltic in all the patients except for one.

RESULTS

Two intraoperative deaths occurred due to acute heart failure and hemorrhagic shock. All of the patients who survived rupture underwent a second-look procedure to avoid abdominal compartment syndrome and undetected delayed bowel ischemia, which none of the patients developed. Two patients showed severe ischemic pancreatitis with organ necrosis, leading to one death and prolonged intensive care >4 weeks in the other case. None of the patients had to be converted or had to undergo a thoracic cutdown.

DISCUSSION

With the fenestrated or branched technique, elective repair of thoracoabdominal aneurysms using local or regional anesthesia has become feasible, either using a percutaneous approach or through a small incision in the groin. Due to the need for exact planning and building of the graft, this is not an option for urgent or emergency cases. McWilliams et al[9] have described an in situ fenestration technique via percutaneous access to preserve antegrade perfusion of the subclavian artery while using standard endografts for thoracic aneurysm exclusion.

Retrograde fenestration in debranching procedures does not require preoperative 3D reconstructions and CT scan measurements to determine the localization of fenestrations. Even in stenotic vessels, the fabric puncture and stent placement can be performed safely and quickly. The technique is simple and decreases the ischemia time for the visceral organs from 10 to 15 minutes for conventional anastomosis down to 3 to 5 minutes. Retropancreatic manipulation is not necessary to expose an appropriate segment of the SMA. The endovascular deployment of the prosthetic material without exposure to the vicinity, such as pancreas or bowel, minimizes the risk of infection or pancreatitis, although this seems to be more common in patients with severe hypotension and hemorrhagic shock due to rupture organ ischemia

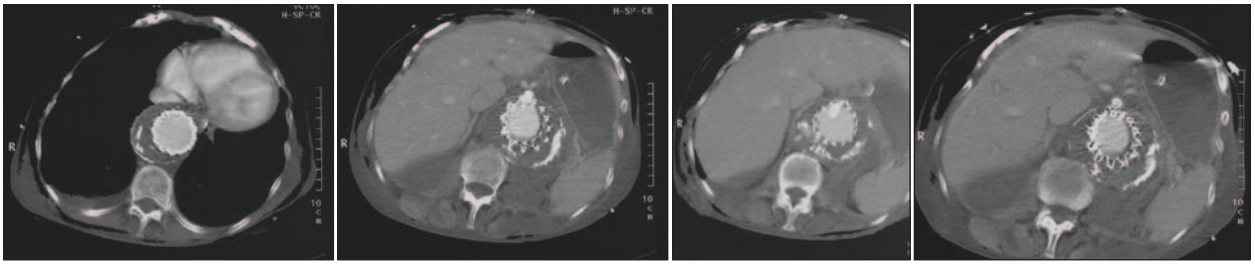

Figure 3. Computed tomography scan results at different levels 13 days after retrograde in situ fenestration and renal artery bypass showing patency of celiac trunk and SMA. The huge hematoma was asymptomatic.

(including ischemic pancreatitis). Depending on the anatomy, the celiac trunk may allow retrograde puncture and stenting as well.

The technical problems discovered arose from the anatomy of the SMA and the diameter of the aneurysm sac at the level of the visceral vessels. The puncture of the fabric was difficult in steep angulations because the tip of the needle had to be guided toward the fabric by digital compression of the aortic wall segment directly above the origin of the SMA. In huge aneurysms with no, or very little, thrombotic material on the dorsal side, the deployed stent graft was pushed backward while trying to puncture the fabric. The different grafts we used showed unique resistances to puncture and especially to sheath insertion. Due to the difference in fabric, the Valiant device (Medtronic, Inc., Minneapolis, MN), which is currently only available in Europe, could be punctured with low resistance, whereas the fabric of the Zenith device (Cook Medical, Bloomington, IN) was more resistant to the puncture and sheath insertion.

The basic principle of this technique is the same as hand-cut, in situ fenestration, or the early manufacturer-made fenestrated devices. The durability of the Advanta V12 covered stents used for these cases has been proven in our experience with 171 fenestrated and branched grafts. In contrast to the use of bare-metal stents in fenestrations, there are no signs of fabric or stent fatigue of covered stents in a follow-up period of up to 68 months. In addition to the ready availability of this in situ fenestrated graft, the advantages include the quick revascularization of the visceral perfusion without material exposure to a potentially hostile environment, and the elimination of time-consuming cannulation.

The fatal clinical outcome of four patients who experienced rupture was determined by rates of myocardial infarction in two of them, and necrotizing pancreatitis with multiorgan failure in the other two. Pulmonary complications were responsible for a prolonged stay in the intensive care unit for more than 40 days. None of the patients developed bowel ischemia or bowel infarction. All of the patients who experienced rupture underwent a second-look operation. The abdomen was left open for 1 to 2 days to eliminate the risk of an abdominal compartment after extensive retroperitoneal hematoma.

CONCLUSION

Retrograde in situ fenestration seems to be a safe and feasible alterative to surgical anastomosis for the visceral arteries (Figures 1 through 3). This novel technique allows the performance of safe and time-saving revascularization of visceral arteries while avoiding a technically demanding conventional anastomosis. This new technique may represent significant improvement compared to the standard approach of surgical exposure and sutured anastomosis by reducing ischemia time and the potential risk for clamping damage of the target vessels and leaving no prosthetic material exposed to the retroperitoneal or retropancreatic space.

We keep this technique on hand as an alternative option to open thoracoabdominal and hybrid repair in elective or emergent cases when premanufactured fenestrated or branched grafts are not available or not suitable for the given anatomy. The follow-up for these patients has to be performed with the same accuracy as for fenestrated grafts, with ultrasound, x-ray of the stent grafts, computed tomography scan (if necessary), and control of renal function for detection of migration, stent fractures, and loss of renal function. The vicinity of the covered bridging devices to the stent struts of the main body or the sutures still has to be evaluated. Stent fractures and graft migration or rotation with the loss of target vessels are reported[10-17] in fenestrated and branched graft surveys. ■

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(Continued on page 13)

The Evolution and Future Directions of Hybrid Arch Repair

Endovascular technology has enabled a novel and less-invasive approach to the aortic arch that is evolving in many directions.

BY GRAYSON H. WHEATLEY III, MD

Endovascular technologies have successfully affected our approach to atherosclerotic aneurysms of the descending thoracic aorta (DTAA).[1] This less-invasive approach to the thoracic aorta has enabled patients with DTAA to benefit from a quicker, less painful recovery after treatment, and furthermore allows some high-risk patients who are not surgical candidates to receive treatment. Patients with diseases of the descending thoracic aorta other than atherosclerotic aneurysms (such as acute Type B aortic dissections with malperfusion and traumatic aortic transection) have also been successfully treated in an off-label fashion using thoracic endografting technologies (Table 1).[2] In fact, almost half of all thoracic endografting cases performed in the US are for aortic diseases other than DTAA or for aortic anatomies that are off label. Currently, clinical trials are being developed to better understand the safety and efficacy of many of these off-label uses.

Another area of development relating to endovascular treatment of the thoracic aorta is off-label repair of the aortic arch using thoracic aortic stent grafts. Hybrid arch repair—combining open surgical arch repair with thoracic endografting techniques—takes advantage of both a less-invasive surgical approach and endovascular technologies.[2,3] This approach has been used to treat atherosclerotic aneurysms of the aortic arch, chronic arch dissections with aneurysmal expansion of the false lumen, and penetrating ulcers of the aortic arch. Potential advantages of hybrid arch repair are numerous and include minimizing operative risk, lessening metabolic insult secondary to cardiopulmonary bypass (CPB), and avoiding a second operative surgery.

Because hybrid arch repair has only recently been developed and attempted in a limited number of patients, there is currently no consensus on patient selection and operative technique. Several small, single-center series and case reports have been published describing a variety of operative techniques.[4,5] As hybrid arch repair has evolved, four main factors have become significant in the conduct of the procedure and must be addressed when developing an operative plan (Table 2). The first factor to be addressed is the type of aortic pathology.

Aortic disease localized solely to the aortic arch, such

TABLE 1. COMPLEX AORTIC PATHOLOGIES AMENABLE TO THORACIC AORTIC STENT GRAFTING

- Atherosclerotic aortic aneurysms
- Uncomplicated acute Type B aortic dissections
- Acute Type B aortic dissections with malperfusion
- Chronic Type B aortic dissections with aneurysmal dilation of the false lumen
- Intramural hematomas
- Penetrating aortic ulcers
- Traumatic aortic transections
- Aortobronchial fistulae
- Aortoesophageal fistulae
- Aortic pseudoaneurysms
- Anastomic pseudoaneurysms

TABLE 2. FACTORS AFFECTING TYPE OF HYBRID ARCH REPAIR

- Extent of aortic arch disease (focal vs extensive)
- Involvement of cardiopulmonary bypass (on- vs off-pump)
- Revascularization of the great vessels
- Surgical versus endovascular repair of the aortic arch

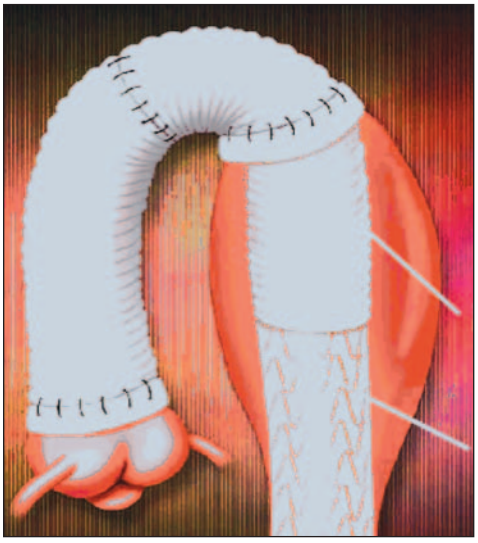

Figure 1. Hybrid Type I aortic arch repair.

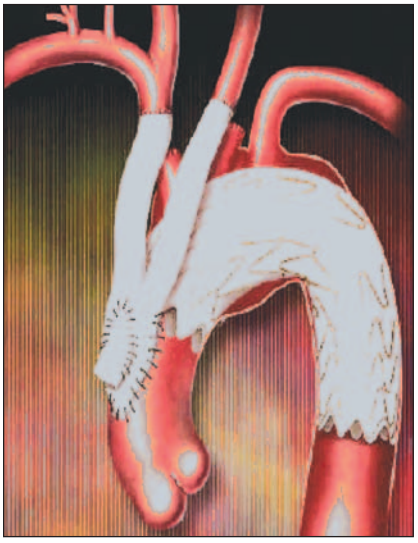

Figure 2. Hybrid Type II aortic arch repair.

as a focal arch aneurysm, can be treated with endovascular arch exclusion using a thoracic stent graft combined with debranching of the great vessels and is managed fundamentally differently than a diffuse aortic process such as an arch dissection extending into the descending thoracic aorta. When the dissection extends into the descending thoracic aorta, standard arch repair can be combined with endovascular stent grafting of the descending portion. The second factor that affects the type of hybrid arch repair to be performed is the role of CPB in the performance of the surgical component. Surgical approaches to the arch can involve off-pump technologies, CPB alone, and CPB combined with deep hypothermic circulatory arrest.[6]

The third factor to consider in the performance of hybrid arch repair is which great vessels are to be revascularized and what the method of revascularization will be. Controversy exists concerning the need to revascularize the subclavian artery in some patients. Certain patients require mandatory revascularization, and these criteria have been previously described. However, some surgeons believe that the subclavian artery can be selectively bypassed.[7] Finally, the role the endovascular stent graft plays in the hybrid arch procedure can vary. The stent graft can completely exclude the arch pathology, such as in focal aortic arch pathologies, or the stent graft can extend the surgical arch repair into the descending thoracic aorta.

Before outcomes of hybrid arch repair can be compared to open surgical repair, it is important to classify the different types of hybrid arch repair. Once a classification system is instituted, it will be possible to determine the safety and efficacy of different hybrid arch approaches so that techniques with superior results can be recognized. Discussing outcomes of hybrid arch repair in aggregate is not an accurate representation of this emerging approach to the aortic arch because there are so many varied procedures that fall under the umbrella of hybrid arch repair. With all the different surgical and endovascular approaches involved in performing hybrid arch repair, it is difficult to make important comparisons between one hybrid arch repair and another. Future success or failure of hybrid arch repair will rest on our ability to accurately compare different hybrid arch repair approaches to open surgical techniques.

CLASSIFICATION OF HYBRID ARCH REPAIR

Hybrid Type I

Hybrid Type I procedures are defined as repair of aortic arch pathology using standard arch replacement techniques in combination with endovascular stenting of the descending thoracic aorta (Figure 1). The endovascular portion of the procedure can be performed either simultaneous with the surgical arch repair or as a separately staged procedure. Hybrid Type I procedures are frequently called *frozen elephant trunk* procedures. If the thoracic aortic stent grafting component is performed as a simultaneous procedure at the time of the open arch repair, the endovascular stent graft is delivered antegrade through the open aortic arch into the descending thoracic aorta during deep hypothermic circulatory arrest (Hybrid Type Ia). However, if the endovascular repair is performed as part of a staged procedure, then the stent graft is delivered using a retrograde femoral approach (Hybrid Type Ib).

When using a staged approach, it may be helpful to place radiopaque markers or clips on the Dacron graft in the descending thoracic aorta to facilitate retrograde cannulation of the surgical graft. Regardless of the method and timing of delivery of the endovascular stent graft, the fundamental distinction of Hybrid Type I procedures is that the arch disease is repaired using standard open surgical techniques. The endovascular thoracic stent graft becomes an extension of the surgical repair into the descending thoracic aorta and a means of avoid-

ing a left lateral thoracotomy for repair of the arch disease extending into the descending thoracic aorta.

Patients undergoing Hybrid Type I procedures are deemed operative candidates for standard arch repair including the use of CPB and deep hypothermic circulatory arrest. It is frequently the secondary operative procedure that is avoided using this approach. Although there are many surgical techniques described for arch repair, all of them require CPB. The successful completion of a Hybrid Type I procedure depends on being able to land a thoracic stent graft into prosthetic surgical Dacron graft material in continuity with the arch repair. The surgical technique used for the arch repair can be variable. In addition, the type of thoracic aortic stent graft used is not significant. Although there may be a theoretical concern with durability in relation to landing bare-metal springs into the Dacron graft, in fact all three of the currently approved stent grafts can be used to interface with the surgical Dacron graft.

There may be some survival benefit to fully repairing the arch and descending thoracic aorta together (Hybrid Type Ia) as opposed to a secondary intervention several weeks later (Hybrid Type Ib). Both types of procedures are reserved for patients with arch disease that extends into the descending thoracic aorta. Some of the patients who undergo an elephant trunk procedure may have an adverse event in the interval between arch repair and endovascular thoracic stent grafting. In addition, some patients may be so debilitated after the initial open surgical arch repair that they never make it to the second stage of the procedure. The theoretical advantage of a Hybrid Type Ia approach versus a Hybrid Type Ib repair has yet to be determined and should be compared independently to staged open surgical elephant trunk repairs. Future studies will be necessary to determine both the early and late-term outcomes of Hybrid Type I procedures.

Hybrid Type II

Hybrid Type II procedures differ fundamentally from Hybrid Type I procedures with respect to the management of the aortic arch. In Hybrid Type II procedures, the arch is left intact and is completely excluded from arterial circulation using an endovascular stent graft (Figure 2). This approach involves landing the thoracic aortic stent graft in aortic zone 0 after a surgical revascularization of the great vessels. The debranching or revascularization of the great vessels can be performed either in an off-pump fashion using a side-biting cross-clamp on the ascending aorta or using nonarrested CPB assist. Hybrid Type II aortic arch repair implies a less-invasive approach because deep hypothermic circulatory arrest is avoided as well as possibly CPB. This theoretical advantage has yet to be substantiated; however, Hybrid Type II procedures may be a better alternative for high-risk surgical candidates who are deemed unable to undergo standard open surgical arch repair due to significant medical comorbidities.

Like Hybrid Type I procedures, Hybrid Type II procedures can be performed in a simultaneous (Type IIa) or a staged (Type IIb) fashion. When performed as a simultaneous procedure, the thoracic aortic stent graft is delivered in an antegrade approach through a separate conduit sewn to the Dacron bypass graft. This technique also involves a through-and-through guidewire to facilitate tracking of the thoracic aortic stent graft around the aortic arch. The antegrade, simultaneous approach is best for patients with challenging femoral access and can decrease operative mortality related to access complications. It is useful to place a radiopaque marker on the ascending aorta at the level of the origin of the great vessel bypass grafts to enhance accuracy of achieving proximal seal in the ascending aorta. It is also critically important to ensure that the diameter of the ascending aorta is compatible with available thoracic aortic stent graft sizes and that there is sufficient ascending aortic length to land a stent graft. If this is not the case, then it will be impossible to achieve proximal seal of the stent graft in the ascending aorta, and a proximal Type I endoleak will result. In extreme cases, the ascending aorta can be surgically replaced with an interposition tube graft prior to creating the great vessel debranching, thus creating a suitable landing zone in the Dacron graft.

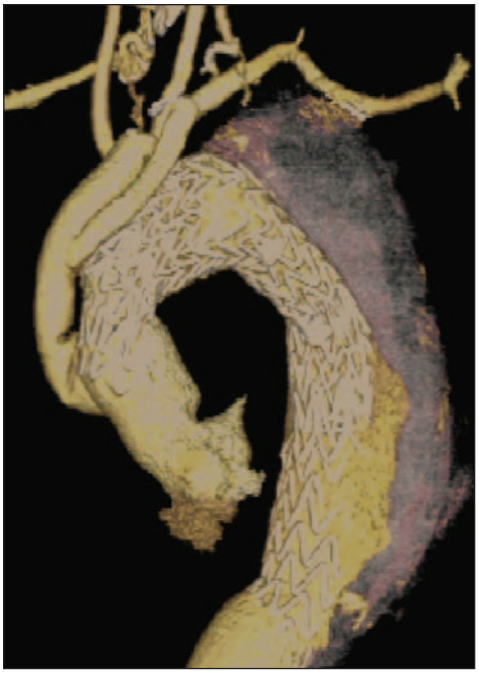

Figure 3. A 64-slice computed tomography reconstruction on a Hybrid Type II repair of a chronic aortic arch dissection extending into the descending thoracic aorta with revascularization of the great vessels.

For Hybrid Type IIb procedures, the thoracic aortic stent graft is delivered in a staged procedure. The advantage of this approach in high-risk patients is that it allows them to recover from the metabolic insult of the surgical debranching prior to compounding additional operative room time and intravenous contrast usage. The stent graft is delivered from a retrograde femoral approach, and, in patients with challenging femoral access, a retroperitoneal conduit can be placed. Again, it is useful to have a radiopaque marker placed on the ascending aorta at the level of the ascending aortic anastomosis to achieve an accurate proximal seal. There are many ways to revascularize the great vessels, and some of these approaches include direct end-to-end bypasses to each great vessel or a single bypass off the ascending aorta to the innominate artery followed by an extra-anatomic bypass to the other great vessels (Figure 3). Once again, no studies have yet looked at the differences in outcomes between Hybrid Type IIa and IIb procedures.

SUMMARY

Hybrid arch repair is emerging as potential treatment of patients with aortic arch disease. There are many different types of hybrid arch repairs described. Hybrid Type I procedures involve surgically replacing the aortic arch and extending the treatment into the descending thoracic aorta with an endovascular stent graft. Hybrid Type II procedures involve an off-pump surgical revascularization of the great vessels combined with total arch exclusion using a thoracic aortic stent graft. Outcomes for Hybrid Type I versus Type II procedures have yet to be compared, but in general, patients treated with a Hybrid Type II procedure are higher risk and have more medical comorbidities. Likewise, aggregate outcomes for Hybrid Type I and Type II procedures and open surgical outcomes are difficult to compare. However, based on several small single-center studies, hybrid arch repair procedures compare favorably with large single-center studies using open surgical repair techniques.

Developing an accurate classification system for hybrid arch procedures is the first step toward understanding the safety and efficacy of various techniques used for hybrid arch procedures and subsequently for comparison with standard open surgical arch repair. As these procedures continue to become refined with improvement in surgical and endovascular techniques, new generations of branched thoracic aortic stent grafts are being developed and may ultimately affect the endovascular treatment of aortic arch disease. However, we are still several years away from having the first branched thoracic aortic stent graft approved in the US, and until this time comes, hybrid arch repairs offer a less-invasive alternative to open surgical arch replacement. ■

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1. Dagenais F, Shetty R, Normand JP, et al. Extended applications of thoracic aortic stent grafts. Ann Thorac Surg. 2006;82:567-572.
2. Baraki H, Hagl C, Khaladj N, et al. The frozen elephant trunk technique for treatment of thoracic aortic aneurysms. Ann Thorac Surg. 2007;83:S819-S823.
3. Azizzadeh A, Estrera AL, Porat EE, et al. The hybrid elephant trunk procedure: a single-stage repair of an ascending, arch, and descending thoracic aortic aneurysm. J Vasc Surg. 2006;44:404-407.
4. Schumacher H, Bockler D, Bardenheuer H, et al. Endovascular aortic arch reconstruction with supra-aortic transposition for symptomatic contained rupture and dissection: early experience in 8 high-risk patients. J Endovasc Ther. 2003;10:1066-1074.
5. Zhou W, Reardon M, Peden EK, et al. Hybrid approach to complex thoracic aortic aneurysms in high-risk patients: Surgical challenges and clinical outcomes. J Vasc Surg. 2006;44:688-693.
6. Bergeron P, Mangialardi N, Costa P, et al. Great vessel management for endovascular exclusion of aortic arch aneurysms and dissections. Eur J Vasc Endovasc Surg. 2006;32:38-45.
7. Peterson MD, Wheatley GH 3rd, Kpodonu J, et al. Treatment of type II endoleaks associated with left subclavian artery coverage during thoracic aortic stent grafting. J Thorac Cardiovasc Surg. 2008;136:1193-1199.

Rapid Ventricular Pacing to Facilitate Thoracic Stent Graft Deployment

An overview of current rationale, techniques, indications, and results.

BY FRANÇOIS DAGENAIS, MD; ERIC DUMONT, MD; AND PIERRE VOISINE, MD

The Stanford group initially proposed the use of thoracic stent grafts to treat aneurysms of the descending aorta.[1] Over time, the indications for use of thoracic stent grafts expanded to diseases such as traumatic tears, Type B aortic dissections, and arch pathologies.[2,3] The experience with thoracic stent grafts, especially in high-risk patients, demonstrates a decrease in perioperative mortality and paraplegia rates compared to a standard open procedure.[4,5] Moreover, graft technology has substantially evolved since the initial custom-made thoracic devices. Improvements in graft conformability, trackability, and device deployment systems have allowed for the expanding use of thoracic stent grafts in challenging angulated aortic anatomy and have made it possible to treat more proximal arch diseases combined with extra-anatomical bypasses. However, to minimize perioperative complications and to avoid unintended coverage of important aortic side branches, accuracy in stent graft deployment is paramount in these complex procedures. We describe the emerging role of rapid ventricular pacing as an adjunct for thoracic stent graft deployment.

GRAFT DEPLOYMENT CHARACTERISTICS AND TECHNIQUES

First-generation pusher-rod systems tracked poorly and required forceful maneuvers to deploy the graft in the arch or in angulated anatomy, which occasionally led to inaccuracy in stent graft positioning. Furthermore, the prolonged arch manipulations may have contributed to the higher stroke rate found in earlier series.[6] Developments of newer generations of thoracic stent grafts have enhanced the precision of stent graft deployment. The middle-to-outward deployment system of the Gore TAG device (W. L. Gore & Associates, Flagstaff, AZ) allows for rapid deployment even in angulated anatomy. The capture tip of the TX2 system (Cook Medical, Bloomington, IN) permits the stent graft to be unsheathed yet allows repositioning of the stent graft before final deployment. The Xcelerant delivery system of the Talent and Valiant stent grafts (Medtronic, Inc., Minneapolis, MN) has significantly decreased the deployment forces and allows for progressive controlled release of the stent graft for precise placement.

Systemic hypotension has been traditionally used to facilitate deployment of thoracic stent grafts and still remains a common technique. Adenosine-mediated cardiac arrest has been suggested to improve stent graft deployment accuracy in short-neck circumstances, and in Type B dissection and arch deployment.[7,8] However, variability in the dose-effect relationship, and the occasionally prolonged periods of hypotension, have led endovascular specialists to seek a more reliable adjunctive technique to optimize stent graft deployment accuracy. Since 2006, we have used rapid ventricular pacing for thoracic stent graft deployment.

RATIONALE FOR RAPID VENTRICULAR PACING

Thoracic stent graft procedures with a proximal landing zone in the arch are exposed to a high-pressure and high-cardiac-output environment. In addition, the angulated arch may further jeopardize the accuracy of stent graft deployment. The high cardiac output contributes significantly to the "windsock" effect and the backward stent graft movement observed during arch deployments. Decreasing blood pressure with vasodilating agents further increases the cardiac output and, consequently, the cardiac output-mediated windsock effect during deployment.

Cardiac output may be temporarily abolished by induced ventricular fibrillation, bicaval inflow occlusion, adenosine arrest, or rapid ventricular pacing. Adenosine

arrest and rapid ventricular pacing offer the advantage of ease of use. As opposed to adenosine arrest, rapid ventricular pacing is basically an on-off switch; thus, the duration of the cardiac arrest is controlled. Unfortunately, the duration of the heart arrest with adenosine is highly variable. An unplanned ventricular ejection during arch deployment may be catastrophic, especially because the stroke volume in this circumstance will be significantly higher considering a high left ventricular end diastolic volume. In addition to the control of the cardiac arrest period, rapid ventricular pacing offers a quick return to normal hemodynamics after discontinuation of pacing.

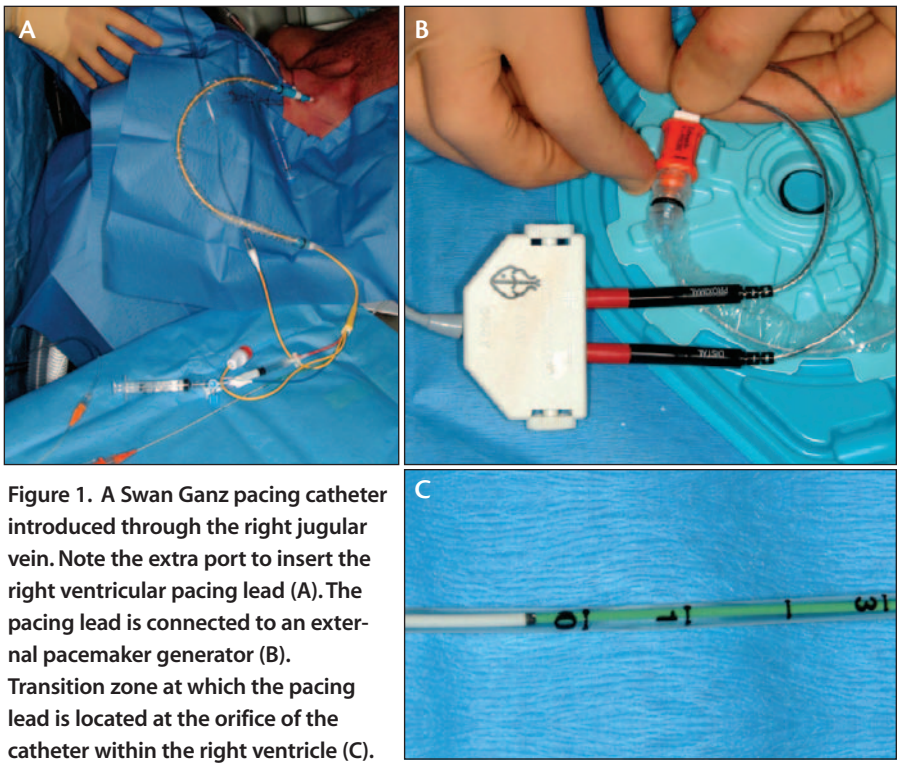

Figure 1. A Swan Ganz pacing catheter introduced through the right jugular vein. Note the extra port to insert the right ventricular pacing lead (A). The pacing lead is connected to an external pacemaker generator (B). Transition zone at which the pacing lead is located at the orifice of the catheter within the right ventricle (C).

Maintenance of at least normal systemic pressure during thoracic stent graft procedures is often overlooked. Prolonged hypotension during thoracic stent graft operations has been shown to contribute to spinal cord hypoperfusion, which may lead to spinal cord ischemia.[6] Rapid ventricular pacing may thus minimize changes in hemodynamics and optimize medullary blood flow, especially in procedures in which the left subclavian artery is covered and the descending aorta is fully paved by stent grafts. Furthermore, prolonged hypotension after deployment may render a patient with limited cardiac reserve unstable.

In addition to improving the precision of achieving the stent graft landing site, rapid ventricular pacing decreases aortic trauma by minimizing the shear stress during the graft apposition to the aortic wall. This advantage is especially important in the presence of a diseased aortic wall, such as in Type B dissection or in a heavily atherosclerotic aortic arch. Complications such as retrograde Type A dissections or embolic strokes are less likely to occur with a graft apposed to the aortic wall under zero aortic pressure and flow.

RAPID VENTRICULAR PACING TECHNIQUE AND INDICATIONS

Technique

Use of rapid ventricular pacing mandates general anaesthesia. External defibrillator pads are positioned and connected to an external defibrillator. A Swan Ganz pacing catheter (Edwards Lifesciences, Irvine, CA) is inserted through a right percutaneous jugular vein approach, with its distal lumen positioned in the pulmonary artery (Figure 1A). A pacing lead is inserted into the right ventricular port of the catheter. The distal end is connected to an external pacemaker generator (Figure 1B). The lead is located at the orifice of the Swan Ganz catheter within the right ventricle when the white-green transition zone has reached the 0 marker (Figure 1C). Usually within the next 5 cm, the lead tip should contact the right ventricle wall and induce pacing. The pacemaker is programmed in an asynchronous mode, and the right ventricle is stimulated up to 220 bpm to ensure good lead capture and the abolishment of the cardiac output (Figure 2). During the procedure, the systemic blood pressure is kept at normal to supranormal values of the patient's preoperative baseline value to ensure quick hemodynamic recovery after pacing periods. Pacing is commenced immediately before graft deployment or ballooning and ceased once the maneuver is terminated. Pacing may be repeated if further stent grafts or balloon dilatations are required.

Indications

Although rapid ventricular pacing offers minimal advantages in patients with isolated lesions of the mid-

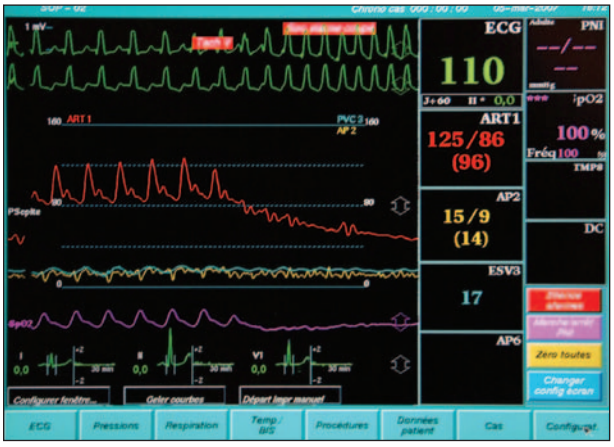

Figure 2. Rapid ventricular pacing at 220 bpm demonstrating complete abolishment of the arterial pressure (red curve).

Figure 3. Incorrect sensing of the pacemaker resulting in an inadvertent ejection during the asystolic period (red curve).

descending aorta with good proximal and distal landing zones, we believe that one should be familiar with the technique in such cases.

We currently use rapid ventricular pacing for all aortic arch and Type B dissection stent graft procedures. Moreover, rapid ventricular pacing may be useful for deployment in angulated aortic anatomy. In such circumstances, pacing during balloon dilatation minimizes the risk of stent graft migration.

RESULTS AND PITFALLS OF RAPID VENTRICULAR PACING

Few investigators have proposed the use of rapid ventricular pacing for thoracic stent graft procedures.[9-11] Nienaber and colleagues[9] reported the use of rapid ventricular pacing in 27 patients treated for various thoracic diseases and compared the level of hypotension, the hemodynamic recovery, and the procedure time to two other groups in which the thoracic stent grafts were deployed either with adenosine (n=16) or with induced hypotension (n=27). They observed more pronounced hypotension, an enhanced hemodynamic recovery, and shorter procedure length within the rapid ventricular pacing group. Our institutional experience shows similar results among 62 patients treated with rapid ventricular pacing since 2006. More specifically, we utilized rapid ventricular pacing to deploy thoracic stent grafts in 19 consecutive patients with complicated type B dissection. The technical success rate was 100%. No early mortality or paraplegia was encountered. Furthermore, no retrograde type A dissection developed during the perioperative period; a complication was reported in 2% of patients in a recent meta-analysis.[12]

From a hemodynamic standpoint, rapid ventricular pacing was very well tolerated in our cohort of patients. This finding is further supported by the percutaneous aortic valve literature. Hemodynamic recovery after rapid ventricular pacing in this setting is excellent, even in the presence of significant ventricular dysfunction.[13] Although we use rapid ventricular pacing in an asynchronous mode, we have not observed ventricular fibrillation in our patients. We believe that the asynchronous mode minimizes the risk of inadvertent ejection due to inappropriate sensing during rapid ventricular pacing (Figure 3). Furthermore, placement of the ventricular lead should be done meticulously to avoid a possible right ventricular perforation; this complication, however, is not encountered in our cohort.

Although rapid ventricular pacing facilitates graft positioning in difficult situations, one should not compromise on anatomical prerequisites to select patients for thoracic stent grafting. A proximal and distal neck of at least 15 to 20 mm should be respected to ensure a good midterm outcome.

CONCLUSION

Accuracy in thoracic stent graft deployment depends on many factors, such as the landing zone in the thoracic aorta, the presence of a tortuous aorta, the graft type and deployment mechanism, the experience of the operator, and the quality of imaging. Use of rapid ventricular pacing reduces the windsock effect during stent graft deployment. Furthermore, rapid ventricular pacing allows the graft to appose to the aortic wall under zero aortic pressure and zero cardiac output, thus minimizing aortic wall shear stress in fragile aortas. Moreover, the technique of rapid ventricular pacing is easy, safe, and reproducible. Rapid ventricular pacing should be considered as a useful adjunct to enhance the precision of thoracic stent graft deployment and to minimize aortic trauma in dissected aortas. ■

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1. Dake MD, Miller DC, Semba CP, et al. Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms. N Engl J Med. 1994;331:1729-1734.
2. Duebener LF, Lorenzen P, Richart G, et al. Emergency endovascular stent-grafting for life-threatening acute type B aortic dissections. Ann Thorac Surg. 2004;78:1261-1267.
3. Dagenais F, Normand JP, Turcotte R, et al. Changing trends in management of thoracic aortic disease: where do we stand with thoracic endovascular stent grafts? Can J Cardiol. 2005;21:173-178.
4. Leurs LJ, Bell R, Degrieck Y, et al, EUROSTAR; UK Thoracic Endograft Registry collaborators. Endovascular treatment of thoracic aortic diseases: combined experience from the EUROSTAR and United Kingdom Thoracic Endograft registries. J Vasc Surg. 2004;40:670-679.
5. Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. Ann Thorac Surg. 2008;85(suppl):S1-41.
6. Nienaber CA, Kische S, Ince H. Thoracic aortic stent-graft devices: problems, failure modes, and applicability. Semin Vasc Surg. 2007;20:81-89.
7. Fang TD, Lippmann M, Kakazu C, et al. High-dose adenosine-induced asystole assisting accurate deployment of thoracic stent grafts in conscious patients. Ann Vasc Surg. 2008;22:602-607.
8. Hashimoto T, Young WL, Aagaard BD, et al. Adenosine-induced ventricular asystole to induce transient profound systemic hypotension in patients undergoing endovascular therapy. Dose-response characteristics. Anesthesiology. 2000;93:998-1001.
9. Nienaber CA, Kische S, Rehders TC, et al. Rapid pacing for better placing: comparison of techniques for precise deployment of endografts in the thoracic aorta. J Endovasc Ther. 2007;14:506-512.
10. Pornratanarangsi S, Webster MW, Alison P, et al. Rapid ventricular pacing to lower blood pressure during endograft deployment in the thoracic aorta. Ann Thorac Surg. 2006;81:e21-e23.
11. Moon MC, Dowdall JF, Roselli EE. The use of right ventricular pacing to facilitate stent graft deployment in the distal aortic arch: a case report. J Vasc Surg. 2008;47:629-631.
12. Parker JD, Golledge J. Outcome of endovascular treatment of acute type B aortic dissection. Ann Thorac Surg. 2008;86:1707-1712.
13. Webb JG, Pasupati S, Achtem L, et al. Rapid pacing to facilitate transcatheter prosthetic heart valve implantation. Cathet Cardiovasc Interv. 2006;68:199-204.

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tioned herein. Dr. Tessarek may be reached at joerg.tessarek@sfh-muenster.de.

1. Anderson JL, Berce M, Hartley DE. Endoluminal aortic grafting with renal and superior mesenteric artery incorporation by graft fenestration. J Endovasc Ther. 2001;8:3-15.
2. Park JH, Chung JW, Choo IW, et al. Fenestrated stent-grafts for preserving visceral arterial branches in the treatment of abdominal aortic aneurysm: preliminary experience. J Vasc Interv Radiol. 1996;7:819-823.
3. Anderson JL, Adam DJ, Berce M, et al. Repair of thoracoabdominal aortic aneurysms with fenestrated and branched endovascular stent grafts. J Vasc Surg. 2005;42:600-607.
4. Derrow AE, Seeger JM, Dame DA, et al. The outcome in the United States after thoracoabdominal aortic aneurysm repair, renal artery bypass, and mesenteric revascularization. J Vasc Surg. 2001;34:54-61.
5. Cowan JA Jr, Dimick JB, Henke PK, et al. Surgical treatment of intact thoracoabdominal aortic aneurysms in the United States: hospital and surgeon volume-related outcomes. J Vasc Surg. 2003;37:1169-1174.
6. Semmens JB, Lawrence-Brown MM, Hartley DE, et al. Outcomes of fenestrated endografts in the treatment of abdominal aortic aneurysm in Western Australia (1997-2004). J Endovasc Ther. 2006;13:320-329.
7. Svensson LG, Crawford ES, Hess KR, et al. Experience with 1509 patients undergoing thoracoabdominal aortic operations. J Vasc Surg. 1993;17:357-368.
8. Black SA, Wolfe JH, Clark M, et al. Complex thoracoabdominal aortic aneurysms: endovascular exclusion with visceral revascularization. J Vasc Surg. 2006;43:1081-1089.
9. McWilliams R, Murphy M, Hartley D, et al. In situ stent-graft fenestration to preserve the left subclavian artery. J Endovasc Ther. 2004;11:170-174.
10. Muhs BE, Verhoeven EL, Zeebregts CJ, et al. Mid-term results of endovascular aneurysm repair with branched and fenestrated endografts. J Vasc Surg. 2006;44:9-15.
11. Faruqi RM, Chuter TA, Reilly LM, et al. Endovascular repair of abdominal aortic aneurysm using a pararenal fenestrated stent graft. J Endovasc Surg. 1999;6:354-358.
12. Chuter TA, Rapp JH, Hiramoto JS, et al. Endovascular treatment of thoracoabdominal aortic aneurysms. J Vasc Surg. 2008;47:6-16.
13. Roselli EE, Greenberg RK, Pfaff K, et al. Endovascular treatment of thoracoabdominal aneurysms. J Thorac Cardiovasc Surg. 2007;133:1474-1482.
14. Greenberg RK, Haulon S, Lyden SP, et al. Endovascular management of juxtarenal aneurysms with fenestrated endovascular grafting. J Vasc Surg. 2004;39:279-287.
15. Greenberg RK, Haulon S, O'Neill S, et al. Primary endovascular repair of juxtarenal aneurysms with fenestrated endovascular grafting. Eur J Vasc Endovasc Surg. 2004;27:484-491.
16. Ziegler P, Avgerinos ED, Umscheid T, et al. Fenestrated endografting for aortic aneurysm repair: a 7-year experience. J Endovasc Ther. 2007;14:609-618.
17. O'Neill S, Greenberg RK, Haddad F, et al. A prospective analysis of fenestrated endovascular grafting: intermediate-term outcomes. Eur J Vasc Endovasc Surg. 2006;32:115-123.

Translational Technologies in EVAR: Multimodality Interventions

Optimizing tomorrow's tools in the preclinical laboratory.

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An estimated 43,000 to 47,000 people die annually in the US from aortic disease.[1] Endovascular aneurysm repair (EVAR) is increasingly performed as an alternative to open surgery for the treatment of aortic disease. In addition to the treatment of aneurysms, EVAR of dissections, trauma, pseudoaneurysms, and intramural hematoma has been reported.[1-4] EVAR has the potential to reduce acute morbidity and mortality for specific indications and target populations. For example, thoracic endovascular stent graft deployment has reportedly lower rates of paraplegia than open surgery.[1,3,4]

Technology continues to evolve in its potential to treat more complex clinical scenarios that are accompanied by difficult anatomy.[2,5,6] For example, the experimental use of stent grafts has been reported in cases with shorter necks, which include planned coverage of the subclavian artery (in up to 20% of thoracic stent graft procedures, the majority of which will require brachiocephalic revascularization).[2,7] In addition, reports of combined surgical and endovascular procedures suggest the potential for extension of stent graft applications to the aortic arch, ascending aorta, and thoracoabdominal aortic pathologies.[8,9] Side-branched and fenestrated aortic stent grafts may mitigate some of these problems for inoperable patients, but in general, EVAR procedures can be prone to poor visualization and difficult anatomy requiring large quantities of contrast.[5,6,10,11] Techniques to reduce contrast requirements and facilitate visualization could counter these limitations and improve EVAR outcomes.

The combinations of imaging modalities that are used in endovascular interventions have been a fertile area of research and application during the past decade. Certainly,

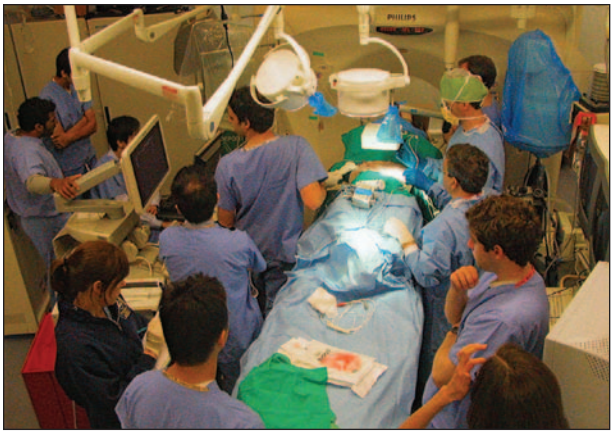

Figure 1. Multimodality interventional translational suite: electromagnetic (EM) tracking, ultrasound, fluoroscopy, and computed tomography (CT) imaging during a preclinical nonsurvival procedure examining the accuracy of navigational paradigms using smart interventional devices enabled with the medical equivalent of GPS.

the use of more than one modality (or fused modalities) either simultaneously or in sequence has tremendous appeal because it provides key information during different stages of endovascular procedures (Figure 1). Exactly when this information adds vital clinical value is also an area of debate and interest. The combination of intravascular ultrasound and fluoroscopy, CT and fluoroscopy, magnetic resonance imaging (MRI) and fluoroscopy, and fluoroscopy and cone beam CT are being studied for vascular therapies such as EVAR. The recent optimization of rotational angiography adds a new twist to this paradigm as well, offering postprocessed CT from rotational angiography

(Human images by cvSim.)

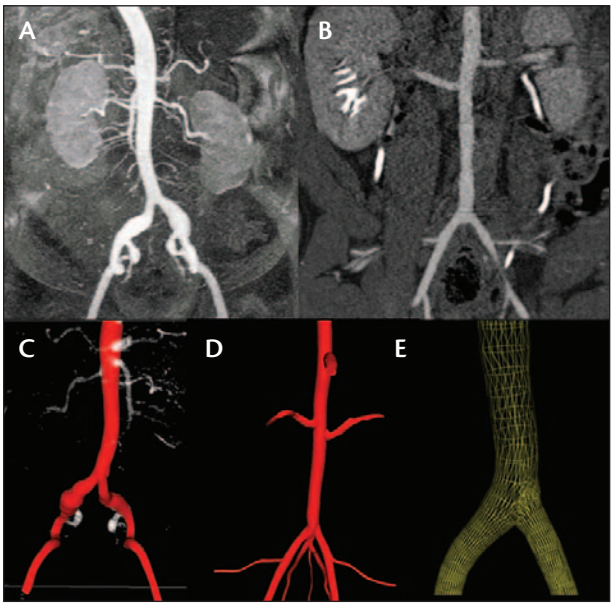

Figure 2. Human CT angiography (A), swine CT angiography (B), and 3D volume rendering of human (C) and swine (D) abdominal aortoiliac region. A simulation tool (cvSim, Cardiovascular Simulation, Inc., Stanford, CA) was used to generate 3D images (C,D) and computational grid for swine (E) that allows for flow and force evaluations.

source data in rapid, clinically relevant time frames and with clinically relevant fields of view.

Navigation tools may also be the bridge between imaging modalities. EM and optical tracking can provide the backbone for an array of imaging techniques within and among different modalities. Smart guidewires equipped with EM sensors can correlate position and orientation information in real time to display multiparametric data from different modalities with real-time updates. Advances in cross-sectional imaging or MRI contrast may eventually localize functional or lesion characteristics, such as vulnerable plaque. This type of geometric localization could be used in real time during standard revascularization procedures via the registration and fusion tool of the tracked guidewire. The interventional surgeon, cardiologist, or radiologist can have multimodality volumetric information at his or her fingertips or wire tips. Standard endovascular devices can be manipulated in a specially equipped fluoroscopy suite for preprocedural imaging, such as positron emission tomography (PET) or MRI, without requiring the PET or MRI to be physically present. In addition, 3D reconstruction of anatomic relationships coupled with real-time positional information for the body and interventional devices during delivery of an aortic stent graft could provide meaningful intraoperative data (Figure 2). The real-time 3D display of spatial relationships for devices and patient anatomy, including critical anatomic sites such as vessel origins or bifurcations, can assist in guiding the manipulation and deployment of devices. Determining when this helps in a cost-effective manner is key.

EM TRACKING

Although commonly referred to as the GPS system for medical instruments, these medical positioning systems use locally placed EM field generators instead of satellites to locate sensor coils incorporated within devices such as guidewires, catheters, needles, or ultrasound transducers. These devices are emerging as a component of the multimodality imaging suite for use in routine image-guided interventions.

Until recently, EM tracking systems were highly susceptible to metal interference with bulky sensor coils and were typically not accurate enough for routine use in the standard metallic medical environment. Accuracy may have been adequate for motion capture in the entertainment or gaming industry but was not acceptable for medical applications. Modern technology uses smaller sensors and more accurate field generators and is also less susceptible to metal interference than older systems. EM tracking systems consist of the field generator or transmitter that sends out weak EM pulses (typically under 100 µT) from multiple transmission coils. These EM signals induce small currents in sensors (typically small coils) placed within the working space (approximately 500 X 500 X 500 mm) near the field generator. The signals are transmitted by wires to the position sensor unit that decodes the position and orientation of the sensor relative to the transmitter. Passive EM tracking systems are also becoming available, which rely on a technology such as radiofrequency identification that uses the position sensor to wirelessly power the tracking ele-

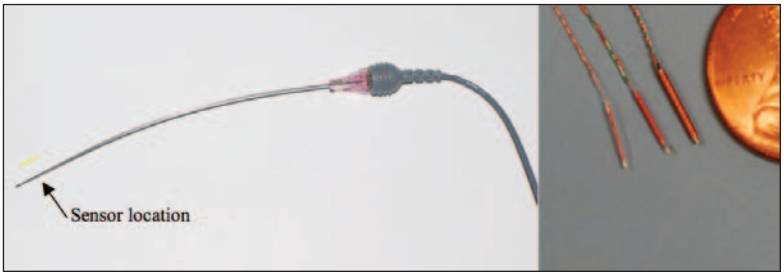

Figure 3. Tracked 22-gauge fine aspiration biopsy needle (sensor is embedded within the tip of the stylette) (A). Sensor coils used in EM tracking (Traxtal Inc., Toronto, Canada) (B).

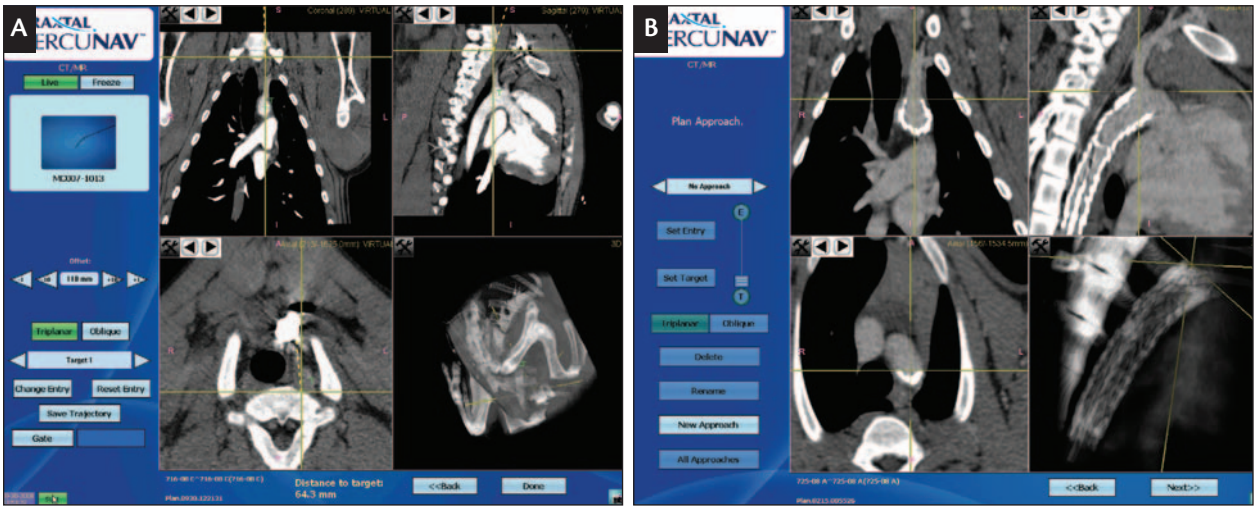

Figure 4. Preprocedure EM tracking showing position of guidewire in aorta/branch of the subclavian (A) and postprocedure image of deployed stent graft positioned at the preoperative target site (B).

ment with a pulse of EM energy and then transmits its location. Sensors are now small enough to be embedded within the tips of many instruments including needles, guidewires, stents, and stent grafts as well as catheters or transducers and a variety of other minimally invasive instruments (Figure 3). Accuracy in the lab and in rigid anatomy has a range of 1 to 2 mm; however, the clinical accuracy in mobile soft tissue (such as liver or lung tissue) drops to 3 to 5 mm in breathing patients but can be partially corrected with dynamic motion compensation, gating, or image processing techniques.[12]

These tracking devices are usually integrated as part of image-guided intervention systems that use the position information from the instrument to display the location on preprocedural images (such as CT, PET, or MR) or in combination with live images (such as ultrasound or fluoroscopy). This combination of modalities is displayed with real-time updates at about 30 frames per second. Recent systems make use of tight integration with imaging devices and streaming source data to provide a reliable and highly connected system that is suitable for interventions (Figure 4). In addition to EVAR, other clinical and experimental preclinical applications of this approach include guiding devices for ablation, biopsy, vascular access, bronchoscopy, prostate biopsy and therapies, laparoscopic ultrasound, 4D ultrasound, respiratory tracking for radiation therapy, endoscopy, and surgery. Image-guided interventional systems are also widely used in cranial surgery, ear, nose, and throat procedures, and orthopedics.[13,14]

EM TRACKING NAVIGATION FOR EVAR

Accurate deployment of thoracic aortic stent grafts requires fluoroscopy and several angiograms. Multimodality navigation may facilitate rapid, accurate placement and decrease contrast and radiation dose. Custom equipment including hydrophilic guidewires, catheters, and stent graft shafts with integrated EM coil sensors enabled real-time endovascular tracking with an experimental version of a commercially available tracking system (Traxtal Inc.). Stent graft deployment is feasible in swine using EM tracking for positioning. For this approach, the target was selected using a preprocedure CT angiogram of the thoracic aorta, and stent grafts were advanced and accurately deployed without fluoroscopy using real-time EM tracking as the sole source of guidance (Figure 5).[15]

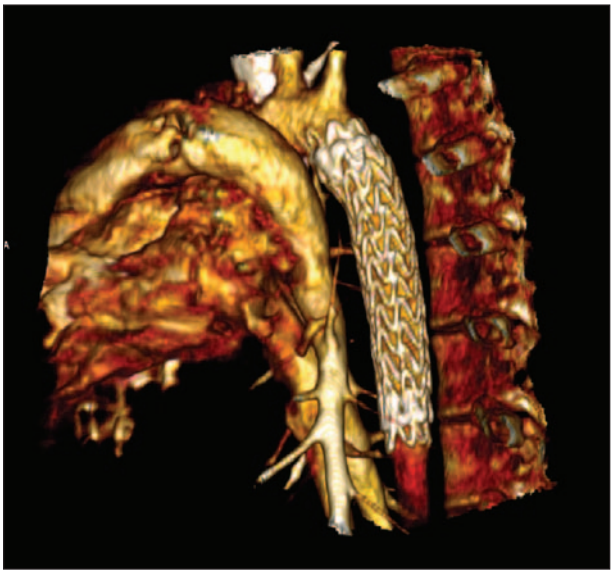

Figure 5. Intraoperative 3D volume rendering of EM-tracked thoracic stent graft after CT angiography. Image generated intraoperatively with OsiriX imaging software.

(Courtesy of Hansen Medical.)

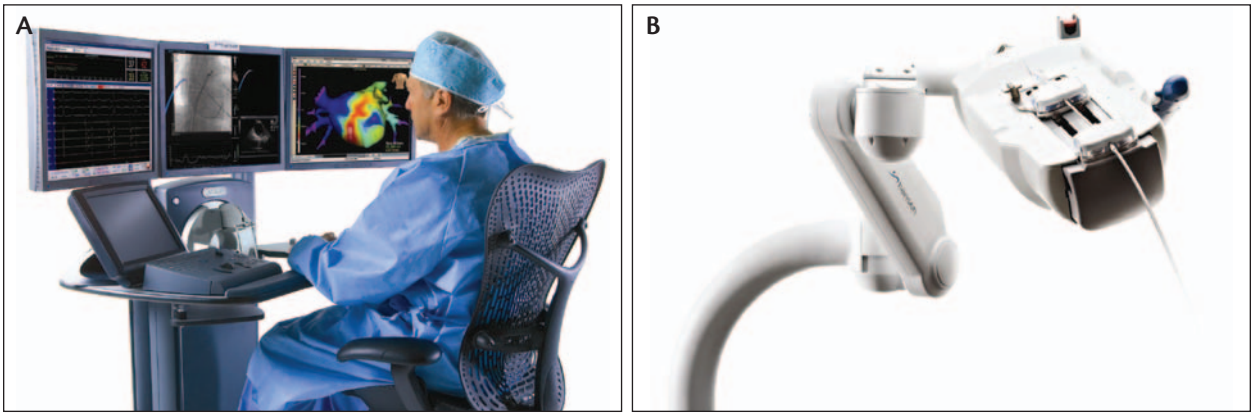

Figure 6. The Sensei control workstation (Hansen Medical, Mountain View, CA) allows the physician to control catheter positioning and provides force feedback (A). The mechanically positioned robotic drives the Artisan control catheter for manipulations within the vasculature (B).

REAL-TIME MRI GUIDANCE FOR EVAR

Endovascular repair of aortic aneurysms using MRI guidance has proven feasible as well. Custom stent grafts with integrated MRI receiver coils (antennae) facilitate deployment of the grafts. Imaging with 1.5-T MRI provides detailed anatomy that may translate into improved accuracy of positioning and deployment while eliminating the radiation associated with the procedure as currently performed under fluoroscopy.

ROBOTICS FOR EVAR

The first recorded clinical application of medical robotics was for the positioning of a needle for a brain biopsy in 1985.[16] During the 20 years since then, robotics have been applied to many medical specialty fields including urology, orthopedics, radiosurgery, and cardiac surgery. The concept of a vascular interventional robot (including applications in cardiac surgery) was described in a recent overview article.[17] In cardiac surgery, the da Vinci robot (Intuitive Surgical, Inc., Sunnyvale, CA) was initially used for mitral valve repair, but other cardiac applications include resynchronization, revascularization, and tissue ablation.[18] The da Vinci master/slave system provides motion scaling, as well as an ergonomic workstation the clinician can use to control two laparoscopic, robotic arms.[19] The da Vinci system consists of a surgeon's console, a patient side cart with three or four robotic arms, and specialized instruments that can be inserted through 1- to 2-cm operating ports. Early experience with the da Vinci system for laparoscopic aortoilliac procedures was presented in 2008.[20] The investigators successfully completed procedures (mostly for arterial occlusive disease) in 97 of 100 consecutive patients using the robotic systems. Investigators concluded that robotic aortoilliac surgery had a high technical success rate and appeared to be safe. Another robotic system that has recently been applied to cardiovascular procedures provides joystick control of a precision mechanical device to position vascular instruments such as guidewires or catheters (Figure 6) (Hansen Medical). In 2008, Hansen Medical announced the system was used to aid deployment of stent grafts for treatment of an abdominal aortic aneurysm in a 78-year-old patient.[21]

CONCLUSION

The development and optimization of EVAR techniques and technology may lead to improved safety and clinical outcomes particularly with continued improvement in diagnosis, visualization, and placement accuracy combined with decreased contrast requirements and procedural times. The emergence of new minimally invasive techniques and applications requires rigorous premarket translational study (preclinical and clinical) with consideration of special training requirements and cost. ■

This study is supported in part by the NIH Intramural Research Program.

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1. Svensson LG, MD, Kouchoukos NT, Miller, DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using stent-grafts. Ann Thorac Surg. 2008;85(suppl 1):1S-41S.
2. Hodgson KJ, Matsumura JS, Ascher E, et al; SVS/SIR/SCAI/SVMB Writing Committee. Clinical competence statement on thoracic endovascular aortic repair (TEVAR)–multispecialty consensus recommendations. A report of the SVS/SIR/SCAI/SVMB Writing Committee to develop a clinical competence standard for TEVAR. J Vasc Surg. 2006;43:858-862.
3. Schumacher H, Böckler D, von Tengg-Kobligk H, et al. Acute traumatic aortic rear: open versus stent-graft repair. Semin Vasc Surg. 2006;19:48-59.
4. Wellons ED, Milner R, Solis M, et al. Stent-graft repair of traumatic thoracic aortic disruptions. J Vasc Surg. 2004;40:1095-1100.
5. Malina M, Dirven M, Sonesson B, et al. Feasibility of a branched stent-graft in common iliac artery aneurysms. J Endovasc Ther. 2006;13:496–500.
6. Greenberg RK, West K, Pfaff K, et al. Beyond the aortic bifurcation: branched endovascular grafts for thoracoabdominal and aortoiliac aneurysms. J Vasc Surg. 2006;43:879–886; discussion 886–887.
7. Makaroun MS, Dillavou ED, Kee ST, et al. Endovascular treatment of thoracic aortic aneurysms: results of the phase II multicenter trial of the GORE TAG thoracic endoprosthesis. J Vasc Surg. 2005;41:1-9.
8. Kaviani A, Greenberg R. Current status of branched stent-graft technology in treatment of thoracoabdominal aneurysms. Semin Vasc Surg. 2006;19:60-65.
9. Chen IM, Wu FY, Shih CC. Banding technique for endovascular repair of arch aneurysm with unsuitable proximal landing zone. Circ J. 2008;72:1981-1985.
10. Bleyn J, Schol F, Vanhandenhove I, et al. Side-branched modular endograft system for thoracoabdominal aortic aneurysm repair. J Endovasc Ther. 2002;9:838–841.
11. Chuter TA, Gordon RL, Reilly LM, et al. An endovascular system for thoracoabdominal aortic aneurysm repair. J Endovasc Ther. 2001;8:25–33.
12. Krucker J, Xu S, Glossop N, et al. Electromagnetic tracking for thermal ablation and biopsy guidance: clinical evaluation for spatial accuracy. J Vasc Interv Radiol. 2007;18:1141-1150.
13. Kaspersen JH, Sjolie E, Wesche J, et al. Three-dimensional ultrasound-based navigation combined with preoperative CT during abdominal interventions: a feasibility study. Cardiovasc Interv Radiol. 2003;26:347-356.
14. Schichor C, Witte J, Scholler K, et al. Magnetically guided neuronavigation of flexible instruments in shunt placement, transsphenoidal procedures, and craniotomies. Neurosurg. 2008;63(supp1 1):ONS121-127; discussion ONS127-128.
15. Abi-Jaoudeh N, Dake MD, Pritchard, WF, et al. Electromagnetic tracking navigation for thoracic aortic stent graft deployment. J Vasc Interv Radiol. 2009;20(supp):S94.
16. Kwoh, YS, Hou J, Jonckheere EA, et al. A robot with improved absolute positioning accuracy for CT guided stereotactic brain surgery. IEEE Trans Biomed Eng. 1988;35:153-160.
17. Da L, Zhang D, Wang T. Overview of the vascular interventional robot. Int J Med Robot. 2008;4:289-294.
18. Murphy DA, Miller JS, Langford DA. Endoscopic robotic mitral valve surgery. J Thorac Cardiovasc Surg. 2007;133:1119-1120; author reply 1120.
19. Guthart GS, Kenneth Salisbury JJ. The intuitive telesurgery system: overview and application. Paper presented at: IEEE International Conference on Robotics and Automation. 2000.
20. Stádler P, Dvorácek L, Vitásek P, et al. Is robotic surgery appropriate for vascular procedures? Report of 100 aortoiliac cases. Eur J Vasc Endovasc Surg. 2008;36:405-406.
21. Riga CV, Bicknell CD, Cheshire NJW, et al. First use of robotic technology for endovascular aneurysm repair. J Endovasc Ther. In press.

Navigation and Robotics for Endovascular Treatment of Aortic Disease

Early experience with robotic and navigational technology for applications in endovascular therapy.

BY CELIA V. RIGA, BSc, MRCS; COLIN D. BICKNELL, MD, FRCS; MOHAMAD HAMADY, FRCR; AND NICHOLAS J. W. CHESHIRE, MD, FRCS

The advent of endovascular therapy has revolutionized the treatment of aortic disease by decreasing the mortality and morbidity of traditional operative approaches and treating patients unable to withstand traditional surgery because of age, health, or likelihood of cardiac or pulmonary complications.[1,2] The number of minimally invasive endovascular procedures has steadily risen as a result of increased operator experience, the availability of more sophisticated and versatile endovascular tools, and advances in imaging modalities.

Endovascular intervention, however, is not applicable to all. Anatomical factors such as short landing zones, arch and visceral vessel involvement, tortuosity, and angulation, as well as poor visualization of key aortic regions, limit its uptake. New-generation and custom-made fenestrated devices have allowed the treatment of more complex aortic pathology, but the procedure can still be technically challenging and time consuming, as long fluoroscopic times often occur. Even with these devices, anatomical factors still present many challenges.

Our studies at Imperial College have focused on the integration of new technology to enhance aortic and aortic branch endovascular procedures. Our long-term goals are to develop reliable methods for three-dimensional (3D) navigation in the vascular tree, which may be used in conjunction with robotic steerable catheter systems. Integration of these technologies with novel stent graft designs will increase the number of patients who can undergo a total endovascular method of treatment with improved overall clinical outcomes and a high degree of staff and patient safety.

Figure 1. The Sensei robotic system (Hansen Medical, Mountain View, CA) workstation is shown outside the angiography suite during cannulation of the short contralateral limb of an infrarenal Endurant stent graft (Medtronic, Inc., Minneapolis, MN).

ROBOTIC CATHETERIZATION

Conventional endovascular catheters have limited shape range and flexibility, take time to change over, and rely on operator skill to maneuver the catheter tip and maintain stability at target sites. Therefore, guidewire positioning and passage of stents through an unstable guiding catheter can be technically demanding in the presence of complex anatomy. Difficult cannulation may also lead to traumatic injury to vessels. Instrumentation within the aorta and especially around the aortic arch carries a significant risk of embolization.

Stroke has been reported as a complication of thoracic stenting in up to 9% of cases.[3-5] A variety of manually shapeable and steer-

able sheaths and guide catheters have been developed to overcome some of the difficulties of standard catheter technology. These manually controlled catheters traditionally rely on an experienced physician's ability to either manually shape the distal catheter tip prior to introduction or, in the case of steerable catheters, to apply varying amounts of curvature via a steerable catheter's handle (via pull wires). The tip curvature is then used in combination with insertion and torque to manipulate the distal tip of the catheter in the desired fashion. This manual control has limitations, and the amount of fine maneuverability and stability over the distal tip is often insufficient for performing complex vessel cannulation and other therapeutic procedures. It is hoped that a robotic, steerable catheter system may overcome some of the difficulties of precise cannulation, catheter stability, and trauma to vessels.

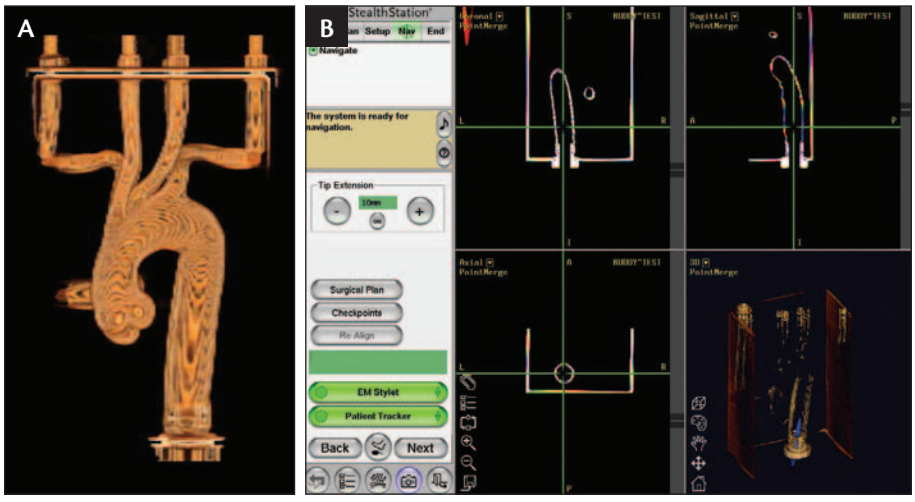

Figure 2. A pulsatile silicon arch model representing an angulated type III aortic arch (A). The Stealth electromagnetic navigation system (Medtronic, Inc.) combines cross-sectional imaging with electromagnetic tracking of microposition sensors located at the tip of an endovascular wire (B). The operator can use the cross-sectional images to navigate through the aorta and the arch in this pulsatile silicon model successfully and accurately with minimal contact with the vessel wall and without fluoroscopic guidance.

At present, fenestrated stent graft technology has shown encouraging short- and midterm results in selected patients.[6-8] However, despite a custom-made device design, the implantation procedure can be challenging. These devices mandate precise alignment of the bespoke windows with the branch vessel ostia and subsequent cannulation of the target vessels. Complicating factors in fenestrated stent grafting include tortuous iliac vessels, which cause significant problems with catheter control and manipulation; the presence of thrombus and calcification, which may lead to embolization with prolonged attempts at cannulating branch vessels; aberrant renal vessels and tortuosity; and angulation of the aorta above or at the level of the fenestrated segment, which can lead to graft rotation and significant misalignment of fenestrations with vessel ostia, preventing easy and safe target vessel cannulation.

Robotic systems have already been used in a variety of surgical procedures, demonstrating improved precision, stability, and dexterity while operating. An endovascular robotic system has advantages over conventional catheterization because it allows accurate cannulation of vessels and stable positioning of the catheter for the introduction of diagnostic and therapeutic endovascular tools. It has been used successfully for cardiac mapping and ablation procedures.[9]

The Hansen Sensei robotic system (Figure 1) is one steerable robotic system designed to facilitate the physician's ability to control and precisely position and manipulate catheters within the vascular system. This control is provided via a master-slave electromechanical system that controls a guide catheter and sheath (Artisan catheter, Hansen Medical) from a remote workstation. This robotic system allows and visualizes precise positioning of the steerable catheter tip at a desired point while enabling the physician to remain seated away from the x-ray radiation source. The Artisan catheter is composed of a flexible inner guide (11-F outer diameter, 8.5-F inner diameter) within a steerable but stable outer guide (14-F outer diameter, 11-F inner diameter). This intuitive catheter system replicates the hand movement of the motion controller delivering control in three dimensions and with seven degrees of freedom via a 3D hand-operated joystick at the workstation.

A limitation of remote catheter control systems is the lack of mechanical feedback the operator receives from manual catheter manipulation and hence the inability to assess the amount of force that is being applied to the target tissues. However, visual feedback of force applied to the catheter tip can be obtained (eg, Intellisense Fine Force Technology, Hansen Medical). Damage or perforation of the vessel wall can be avoided, thereby improving the safety of the device.

Imperial College Healthcare NHS Trust has installed the first robotic system in the UK specifically for clinical use in the vascular tree. Early experimental studies have investigated the use of this system, documenting where the system may be advantageous. Our in vitro experimental work using silicon phantom pulsatile flow models has shown that through precise manipulation and stable positioning in complex anatomical configurations, use of the robotic system results in faster vessel cannulation times and a decrease in the number of movements required for each task.[10,11] There does not seem to be an advantage to robotic cannulation over and above conventional methods when performing simple tasks.

Following standardized training with this robotic system and after rehearsing the procedure in a laboratory environment in August 2008, we were able to undertake the first human case of robotically assisted endovascular aneurysm repair to assess the feasibility of using this novel and innovative approach in a clinical setting.[12] The robotic catheter easily cannulates the contralateral limb of an infrarenal stent graft (Endurant) (Figure 1) and navigates through the aorta to allow passage of a stiff wire without the need for conventional catheter and wire manipulation. This first-in-the-world use of a robotic endovascular system for vascular intervention is a breakthrough, but clearly its role lies in more complex procedures. This system has the potential to simplify more complex procedures and increase safety, thus decreasing procedure times, radiation exposure, and possibly maximizing the number of patients that are able to undergo a totally endovascular aneurysm exclusion. We are extending its use to more complex fenestrated stent graft procedures and are using the system to provide a platform of stability for in situ fenestrated stent placement.

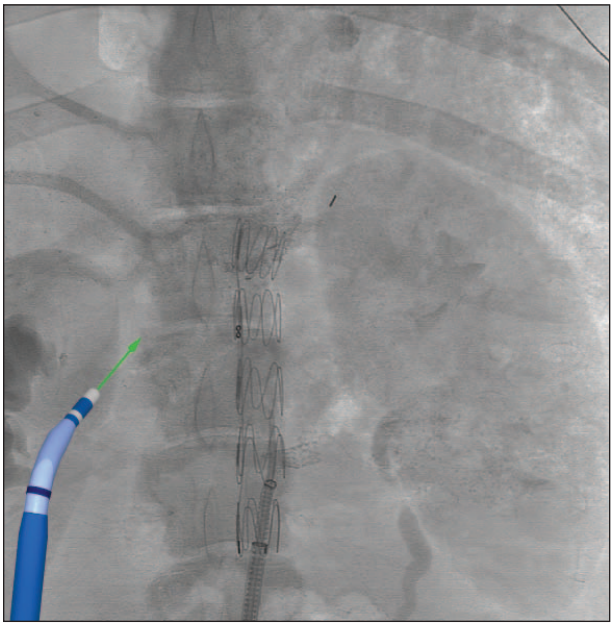

Figure 3. Successful antegrade in situ fenestration of an aortic stent graft (16-mm iliac extension covered stent; Endurant, Medtronic, Inc.) with subsequent stenting of the left renal artery in a porcine model. The robotic catheter can be seen in position, adjacent to the orifice of the left renal artery.

3D NAVIGATION TECHNIQUES

A crucial development to extend the range of minimally invasive, image-guided endovascular work will be the ability to navigate through the vascular tree using real-time 3D imaging techniques. Although a number of navigational devices have been developed and used successfully by several other surgical disciplines, such as cranial, orthopedic, and ear, nose, and throat surgery, as well as electrophysiology procedures, they have not yet been applied in endovascular therapy.

Techniques to visualize in three dimensions and navigate through the vascular tree may be through continuously acquiring 3D imaging during the procedure; for example, with magnetic resonance imaging, by integrating multiplanar 3D reconstructions of the vascular anatomy with real-time intraoperative imaging, or by navigating via 3D preoperative image reconstructions with the tip of the catheter identified via an electromagnetic sensor. These last two image-guided navigation systems visualize the internal anatomy in real time without the need for continuous image acquisition. The Stealth Station (Medtronic, Inc.) combines cross-sectional imaging with electromagnetic tracking of microposition sensors located at the tip of various stylets. Preprocedural MR or CT images are fused with on-table angiographic images and then loaded onto custom-developed tracking, registration, navigation, and rendering software. Wires, catheters, and stent graft devices can therefore be manipulated with guidance from the previously acquired CT scan and simultaneous real-time angiography. The application of multimodality, image-fusion techniques allows one to integrate information of different image datasets into the actual interventional procedure. Electromagnetic systems that allow tracking of the tip of a device via small detector coils show a trajectory path view in real-time motion.

Three-dimensional navigation systems used in conjunction with a steerable robotic catheter system may allow safe and accurate positioning of endovascular tools within the aorta and its branches. Utilization of these technologies may potentially improve patient safety when complex anatomical configurations are tackled, such as the carotid origin, where instrumentation using conventional techniques carries a significant risk of embolization. This technology will also potentially allow

accurate positioning of catheters during fenestrated or branched stenting, as well as in situ fenestrated stent grafting, which may potentially increase the applicability of endovascular therapy to a greater patient population. Although 3D navigation systems coupled to steerable catheter systems is an attractive proposition, this technology must be optimized for use in the vascular tree before any clinical applications. Current 3D navigation systems that co-register with preoperative imaging do not compensate for elastic organ or tissue deformations, assuming that anatomic structures and instruments are rigid bodies. In endovascular procedures in particular, possible sources of inaccurate navigation are the arterial contractility and the respiration-dependent movements of the arteries themselves.

We have installed an electromagnetic Stealth Station in our institution, specifically for the development of these advanced applications, in association with Medtronic, Inc. Our early studies have focused on the applicability of this system in the arterial tree using pulsatile flow models (Figure 2). We envisage that further refinement of this system will soon allow in vivo work.

Advances in image-guided and minimally invasive procedures have led to an increasing use of imaging data for diagnostic and therapeutic interventions, as well as planning, simulation, procedure rehearsal, and training. In endovascular therapy, current fluoroscopic methods lead to loss of 3D information, which can result in difficulties in positioning of guidewires and stents. Long fluoroscopic exposure times may also be hazardous for both the patient and medical personnel involved in the procedure. Navigation technology has been used successfully in electrophysiology, resulting in significant reductions in fluoroscopic times without compromising efficacy or safety. In addition, although experience with this system is limited, a number of studies have shown a reduction in overall procedure times.[13,14] Integration of robotic and navigational strategies may allow complex endovascular procedures to be refined and gain wider acceptance for the treatment of vascular disease.

POTENTIAL APPLICATIONS OF ROBOTIC AND NAVIGATIONAL TECHNOLOGY: IN SITU FENESTRATED STENT GRAFTING

Endovascular aneurysm repair has clear benefits with regard to mortality (a reduction of two-thirds in the EVAR Trial 1) and immediate postoperative complications, making it a viable option for people who are at increased risk from traditional surgery. However, the anatomy of the aneurysm neck excludes many from this approach. Fenestrated custom-made stents produced from CT data have allowed the endovascular treatment of more complex aneurysm configurations in the abdominal aorta, such as short-necked infrarenal and thoracoabdominal aneurysms. This method of a totally endovascular approach to complex abdominal and thoracoabdominal aneurysms is limited by the inherent delay involved in bespoke manufacturing of the fenestrated devices. The development of a system to allow in situ fenestration[15,16] (on-table localization of vessels, puncture of a standard graft, and vessel cannulation and stenting through the graft in an antegrade fashion) will overcome the difficulties seen with manufactured fenestrated stents and allow this technology to be applicable to a wider range of patients, including those who require urgent treatment.

Our early in vivo work has shown that the use of these technologies is feasible in a large porcine model and that antegrade in situ fenestration is possible using a robotic steerable catheter and 3D rotational angiography (Figure 3).[17] The stable, precise localization of the tip of the robotic steerable catheter allows easy passage of a customized needle through graft material with confirmation of position in the renal vessel before dilation and stenting. This technique needs accurate 3D imaging to be certain of the needle position in relation to the ostia of the renal vessel. A technique to accurately locate catheters in relation to the target vessel origin is essential before this technique can progress. We hope that further refinement of this technique using 3D navigational technology, as well as developments in stent graft design, will allow in situ fenestration to progress and become a viable alternative to manufactured fenestrated stent grafting.

CONCLUSIONS

Integration of robotic and navigational techniques into clinical practice may lead to improved catheter accuracy, stability, and safety in comparison with conventional techniques, while minimizing radiation exposure. By maximizing the use of existing technologies while developing new approaches to treating these challenging cases, we are hoping to improve overall clinical outcomes and reduce the high mortality and morbidity rates associated with aortic disease. It is clear from initial trials we have performed in vitro and in vivo that there may well be an extended role for this system elsewhere in the vascular tree. With increasing experience with these methods, we may well be able to maximize the applicability of minimally invasive endovascular technology to treat a larger cohort of patients with vascular disease. ■

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(Continued on page 31)

Biologic Considerations in the Treatment of Abdominal Aortic Aneurysms

Where do we go from here?

BY DANIEL M. ALTERMAN, MD, AND SCOTT L. STEVENS, MD

The focus of this article is to describe biologic considerations for treating abdominal aortic aneurysms (AAAs). Opportunities for biologic manipulation to improve endovascular aneurysm repair (EVAR) will be delineated by anatomic locale. Sites for biologic therapy will include endograft landing zones, aneurysm sac, and aortic wall.

The treatment of AAAs has a history of continual evolution and has undergone a particularly dramatic change in recent years. The writings of Galen from the second century give perhaps the first description of an AAA, "When the arteries are enlarged, the disease is called an *aneurysm* . . . If the aneurysm is injured, the blood gushes forth, and it is difficult to staunch it."[1] For many centuries, recognition of aneurysmal disease was hampered by social taboo that prohibited violation of the body's interior. Historically, most aneurysms were attributed to syphilitic disease.

In 1825, Home attempted treatment of a peripheral aneurysm with acupuncture in an effort to induce thrombosis.[2] Most treatment efforts thereafter were directed at inducing thrombosis of the aneurysm sac. A variety of means were used including acupuncture, electrical current through indwelling pins or wiring placed in the vicinity, injection of vinegar or iron solution, or even packing of the aneurysm sac with copper, silver, or iron wiring.[2,3] The consensus for the future of aneurysm treatment was quite pessimistic as evidenced by Osler's statement that, "There is no disease more conducive to clinical humility than aneurysms of the aorta."[1] The 1950s ushered in the modern era of aneurysm treatment with advancements by Oschner, Dubost, Cooley, and Debakey. Initial efforts focused on human aortic allografts, but these quickly proved unsuitable. A viable synthetic graft was then sought, and the popular choice became Dacron, which can be impregnated with materials such as collagen to decrease porosity.[1]

In 1991, Parodi reported on the feasibility of intraluminal exclusion of an AAA.[4] The goal was isolation of the aneurysm sac from systemic pressure thus alleviating the forces causing expansion and rupture. Since that time, enthusiasm and use of endovascular therapy for aneurysm treatment has grown briskly. Early use of the endovascular approach was limited to hybrid devices custom made by physicians using graft material sutured to available stents. In the interim 18 years, numerous manufactured devices have been in use and in various phases of product testing. These devices have undergone continuous modifications as new needs are identified based on growing clinical experience and lessons learned from previous models.

Although it is clear that endovascular technology and outcomes have improved over time, ways to improve durability are less clear. EVAR offers great benefits in the perioperative and early postoperative phase in terms of morbidity and mortality, but the tradeoff comes in dealing with long-term aneurysm problems as well as the need for

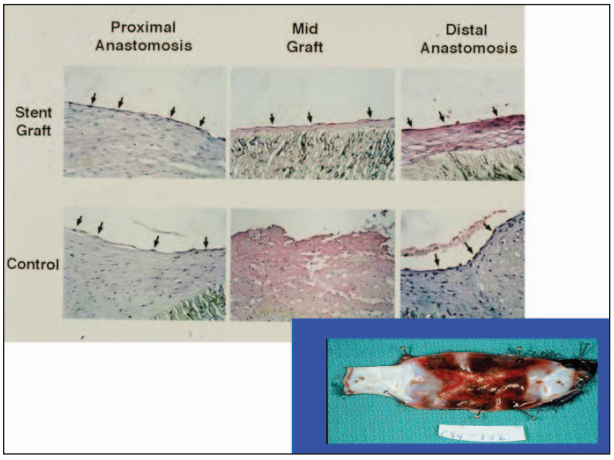

Figure 1. Specimens from our research lab demonstrating the hospitable nature of a healthy artery for endovascular grafts.

commitment to ongoing follow-up device imaging. The enthusiasm for EVAR has also been tempered with the knowledge of its high cost and need for reintervention.[5,6]

Early generations of aortic endografts suffered technical setbacks with problems such as fabric erosion, incomplete fixation, graft migration, and transgraft porosity issues leading to collection of ultrafiltrate in the aneurysm sac.[7-9] Modifications have solved some of these issues, and the newer-generation stent grafts have shown improved durability and outcomes.[10] Given these challenges, it is clear that there is still considerable room for improvement and new directions. Current aortic endograft technology relies almost exclusively on mechanical interaction between the device and the native vessels to afford graft stability and ultimately incorporation. Grafts have been sequentially modified with better fixation mechanisms and improved coating of the surface to minimize graft porosity. However, these inherent limitations manifest over time with the eventual need for reintervention, revision, or explantation. What then is the next direction for improving on an optimized structural system? We believe that therapies customized for both individual vascular wall biology and the systemic response of vascular disease should serve this goal.

VESSEL WALL BIOLOGY AND EVAR

Work from our vascular research lab at the University of Tennessee has focused on the relationship of vessel wall biology and healing of intraluminal grafts. In experimental models, intraluminal placement of a polytetrafluoroethylene (PTFE) aortic graft when compared with a PTFE interposition graft was associated with earlier endothelization and earlier organization of a basement membrane (Figure 1). Also noted was complete coverage of endothelium in the intraluminal graft compared with only partial coverage in the interposition graft with the remainder being lined with red blood cells, fibrin, and debris.[11,12] A similar animal model compared PTFE interposition graft with intraluminal graft on a balloon or self-expanding stent. This also demonstrated that the intraluminal grafts had superior endothelium ingrowth and less intimal hyperplasia. These interposition grafts had greater cell proliferation activity and higher cell content of platelet-derived growth factor.[13] Similar findings were noted even after experimental injury with an aortic balloon.[14] The key is that local production of platelet-derived growth factor was associated with the degree of intimal hyperplasia.[15] These animal models confirm that a healthy arterial tissue bed is associated with graft incorporation and healing. Graft healing is influenced by the environment, and a healthy vessel is a hospitable locale. Selection of hospitable landing zones for an endovascular graft is thus critical. The clinical application of this concept becomes difficult when healthy landing zones share "high-rent real estate" with critical branch vessels.

Figure 2. Biofixation analogy of an oak tree growing into a fence.

THERAPEUTIC APPLICATIONS

Targeted therapy to influence graft healing and incorporation may focus on the local hormonal and cytokine milieu. In cell culture, endothelial cells of the human aorta can be stimulated by vascular endothelial growth factor and heparin while minimizing smooth muscle cell proliferation. Heparin has also been identified as an inhibitor of smooth muscle cell proliferation but has less effect when the cells are actively dividing.[16] Vascular endothelial growth factor (previously identified as vascular permeability factor) has been shown to play a prominent role in intimal hyperplasia following experimental injury.[17] In human and porcine aorta cell culture, basic fibroblast growth factor is capable of inducing graft healing as evidenced by a dose-dependent neointimal formation.[18] Placing growth factors on the graft could improve EVAR success and durability by providing biofixation and seal (Figure 2).

The hormonal milieu has profound effects on vascular biology. Previously, gender differences in cardiac and vascular disease were attributed to a protective effect of estrogen and were thought to be a rationale basis in support of hormone replacement therapy (HRT). This dogma has been challenged by findings of increased association with coronary and thromboembolic events.[19,20] Previous reports from our research lab have found an association with HRT and a decreased primary patency for iliac angioplasty and stent placement compared with women who were not taking HRT.[21] This was true with estrogen alone and estrogen plus progestin therapy. Estrogen and progestins have an impact on vascular tissue remodeling; matrix metalloproteinases (MMP) are inducible and have

isoform modification in response to estrogen and progestin. These enzymes are capable of degrading elastic fibers such as interstitial collagens and have been implicated in the pathogenesis of aneurysm formation.[22] These responses include increased levels of membrane type 1 MMP and MMP-2. In the presence of interleukin-1, estrogen upregulates the activity of MMP-3. Tissue inhibitor of MMP does not appear to be induced by estrogen leaving unbalanced gene activation in favor of type IV collagen degradation with subsequent remodeling.[23,24]

The net effect of the changes in collagenase activity may lead to improved vascular smooth muscle motility with easier migration through a collagen type IV lattice. The lack of inhibitory enzyme induction may promote intimal hyperplasia and is a potential explanation for the poorer outcomes noted previously with peripheral artery intervention in women taking HRT. This imbalance between MMPs and their inhibitors may impede healing of an endograft and may also promote aneurysmal degeneration. Changes in MMP gene expression that occur in the setting of inflammatory cytokines also suggest a therapeutic target, because manipulation of the gene expression appears to alter the healing pathway.

Enzymatic degradation of key structural elements of the aortic wall has been implicated in playing a key role in aneurysm formation. The previously mentioned membrane type 1 MMP and MMP-2, as well as MMP-7, MMP-9, and MMP-12 have also been evaluated for this potential role. There appears to be a correlation between aortic wall expression of MMP-9 messenger RNA and aneurysm size. It has also been noted that patients with an AAA have increased plasma levels of MMP-9.[25,26] Experimentally induced aortic aneurysm in mice via elastase infusion can be attenuated by inhibition of MMP-9 with doxycycline treatment.[27] A similar experiment in a rat demonstrated that periaortic infusion reduced the need for elevated systemic doxycycline levels in order to produce the same inhibition.[28] This study points to the endograft as a potential delivery vehicle for targeted doxycycline therapy of the vessel wall.

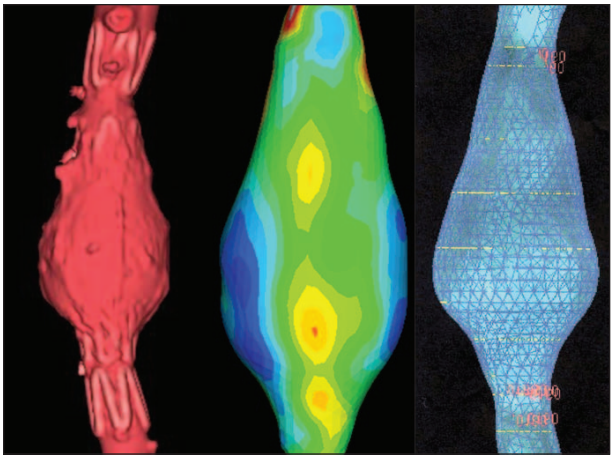

Figure 3. Aneurysm model from our research lab demonstrating the relationship of wall stress to sac contents, distance, and systemic blood pressure.

Systemic therapy to manipulate MMP expression has been encouraging. In vitro studies have demonstrated decreased expression of MMP-2 and MMP-9 when human vascular cells are treated with doxycycline.[29] These findings prompted an evaluation of the short-term effects of doxycycline therapy before aneurysm repair. After only 1 week of therapy, MMP-2 and MMP-9 were significantly suppressed in the aneurysmal aortic wall compared with untreated controls.[29] Similar findings were demonstrated with reduction in MMP-9 mRNA and suppression of posttranslation activation of MMP-2.[30] Several other compounds are known to inhibit MMPs in both broad and focused spectrums (HMG-CoA reductase, statins, marimastat, and others). An unanswered question is whether long-term therapeutic or even prophylactic administration of these or related compounds would tip the scales toward stability of the aortic wall and if these compounds could affect long-term success of EVAR. Preliminary work in this field is intriguing. A cohort of patients undergoing EVAR was randomized to doxycycline or placebo for 6 months after EVAR. Decreased plasma levels of MMP-9 were found in the treatment group as well as reduced aortic neck dilatation. However, there was no reduction in aneurysm sac size.[31] These findings urge continued evaluation of inhibitors such as doxycycline to better define their potential role as primary, secondary, or local therapy for arterial aneurysm treatment. A better understanding of these interactions may improve graft-vessel interaction as well as serve as a foundation for systemic therapy to both prevent and treat aortic aneurysm disease.

ENDOTENSION MANAGEMENT

Management of endotension (defined as pressurization of the aneurysm sac without a demonstrable leak) and optimization of aneurysm sac pressure is evolving. A general goal of EVAR is to exclude the aneurysm sac from systemic pressure. Discontinuity of proximal graft attachment (type I endoleak), backbleeding from branch vessels (type II endoleak), failure of a modular component (type III endoleak), or graft porosity (type IV endoleak) have all been evaluated to play a role in exclusion failure and potential aneurysm rupture. Even with aneurysm sac exclusion, work from our research lab suggests that systemic pressure may affect sac pressure indicating the importance of systemic treatment of the aneurysm sac.[32] Surveillance for these complications, particularly with respect to endotension, can prove difficult. Issues facing the patient are repeated exposure to radiation from serial computed tomography scans,

repeated loads of potentially nephrotoxic dye, and cost. Pressure within the aneurysm sac depends on systemic arterial pressure, the contents of the sac, and the distance from the leak as measured (Figure 3).[33] It is possible to draw conclusions on sac pressure from computed tomography findings.[34] An implantable microchip has been evaluated to measure aneurysm sac pressures by external communication with the chip. It has no battery and is powered by external radiofrequency. This device has a reported sensitivity of 0.94 and a specificity of 0.80 for detection of type I or type III endoleaks.[35] It may suffer limitations due to potential sac pressure heterogeneity. On the horizon are fillable sac anchoring aortic endografts that use injectable agents to stabilize the aneurysm.

ROLE REVERSAL

Coronary stents serve as a dramatic example of biologics having an impact on vascular therapy. Restricted by seemingly irreducible restenosis rates from tissue ingrowth, bare-metal coronary stents were eclipsed by stents coated with biologics that reduce tissue ingrowth. It is paradoxical that biologics to increase tissue ingrowth might be used to knock down barriers in EVAR.[36,37]

CONCLUSION

General principles adopted by vascular surgeons for successful open aneurysm repair with prosthetic grafts include placement to a healthy tissue bed with an adequate supply of fibroblasts, smooth muscle cells, and elements to promote ingrowth, sealing of proximal and distal ends, and a laminar coating with neointima. These same fundamental tenets apply to durable endovascular therapy. All successful aneurysm repairs must effectively address vessel wall biology. Historically, advances in aneurysm therapy have followed a staccato pattern in which progress is based on insights into disease mechanisms. As aortic aneurysm therapy evolves by engaging biologics, count on more elegant, less morbid, and more durable outcomes. ■

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1. Cooley DA. Aortic aneurysm operations: past, present, and future. Ann Thorac Surg. 1999;67:1959-1962, 1979-1980.
2. Schechter DC. Flashbacks: electrical treatment of aneurysms. Pacing Clin Electrophysiol. 1979;2:234-245.
3. Szilagyi DE. The problem of healing of endovascular stent grafts in the repair of abdominal aortic aneurysms. J Vasc Surg. 2001;33:1283-1285.
4. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg. 1991;5:491-499.
5. Brooks MJ, Brown LC, Greenhalgh RM. Defining the role of endovascular therapy in the treatment of abdominal aortic aneurysm: results of a prospective randomized trial. Adv Surg. 2006;40:191-204.
6. Rutherford RB. Randomized EVAR trials and advent of level I evidence: a paradigm shift in management of large abdominal aortic aneurysms? Semin Vasc Surg. 2006;19:69-74.
7. Acosta S, Ogren M, Bengtsson H, et al. Increasing incidence of ruptured abdominal aortic aneurysm: a population-based study. J Vasc Surg. 2006;44:237-243.
8. Haider SE, Najjar SF, Cho JS, et al. Sac behavior after aneurysm treatment with the Gore Excluder low-permeability aortic endoprosthesis: 12-month comparison to the original Excluder device. J Vasc Surg. 2006;44:694-700.
9. Zarins CK, Arko FR, Crabtree T, et al. Explant analysis of AneuRx stent grafts: relationship between structural findings and clinical outcome. J Vasc Surg. 2004;40:1-11.
10. Brown LC, Greenhalgh RM, Kwong GP. Secondary interventions and mortality following endovascular aortic aneurysm repair: device-specific results from the UK EVAR trials. Eur J Vasc Endovasc Surg. 2007;34:281-290.
11. Ombrellaro MP, Stevens SL, Sciarrotta J, et al. Effect of intra-arterial environment on endothelialization and basement membrane organization in polytetrafluoroethylene grafts. Am J Surg. 1997;174:29-32.
12. Ombrellaro MP, Stevens SL, Kerstetter K. Healing characteristics of intraarterial stented grafts: effect of intraluminal position on prosthetic graft healing. Surgery. 1996;120:60-70.
13. Ombrellaro MP, Stevens SL, Sciarrotta J, et al. Effect of balloon-expandable and self-expanding stent fixation on endoluminal polytetrafluoroethylene graft healing. Am J Surg. 1997;173:461-466.
14. Weatherford DA, Ombrellaro MP, Schaeffer DO, et al. Healing characteristics of intraarterial stent grafts in an injured artery model. Ann Vasc Surg. 1997;11:54-61.
15. Ombrellaro MP, Stevens SL, Schaeffer DO, et al. The role of platelet-derived growth factor in intraluminal stented graft healing. J Am Coll Surg. 1997;184:49-57.
16. Weatherford DA, Sackman JE, Reddick TT. Vascular endothelial growth factor and heparin in a biologic glue promotes human aortic endothelial cell proliferation with aortic smooth muscle cell inhibition. Surgery. 1996;120:433-439.
17. Callow AD, Choi ET, Trachtenberg JD, et al. Vascular permeability factor accelerates endothelial regrowth following balloon angioplasty. Growth Factors. 1994;10:223-228.
18. van der Bas JM, Quax PH, van den Berg AC, et al. Ingrowth of aorta vascular cells into basic fibroblast growth factor-impregnated vascular prosthesis material: a porcine and human in vitro study on blood vessel prosthesis healing. J Vasc Surg. 2002;36:1237-1247.
19. Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med. 2003;349:535-545.
20. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin replacement study (HERS) research group. JAMA. 1998;280:605-613.
21. Timaran CH, Stevens SL, Grandas OH, et al. Influence of hormone replacement therapy on the outcome of iliac angioplasty and stenting. J Vasc Surg. 2001;33(2 Suppl):S85-92.
22. Wassef M, Baxter BT, Chisholm RL, et al. Pathogenesis of abdominal aortic aneurysms: a multidisciplinary research program supported by the national heart, lung, and blood institute. J Vasc Surg. 2001;34:730-738.
23. Grandas OH, Mountain DH, Kirkpatrick SS, et al. Regulation of vascular smooth muscle cell expression and function of matrix metalloproteinases is mediated by estrogen and progesterone exposure. J Vasc Surg. 2009;49:185-191.
24. Grandas OH, Mountain DJ, Kirkpatrick SS, et al. Effect of hormones on matrix metalloproteinases gene regulation in human aortic smooth muscle cells. J Surg Res. 2008;148:94-99.
25. McMillan WD, Pearce WH. Increased plasma levels of metalloproteinase-9 are associated with abdominal aortic aneurysms. J Vasc Surg. 1999;29:122-127, 127-29.
26. Tamarina NA, McMillan WD, Shively VP, et al. Expression of matrix metalloproteinases and their inhibitors in aneurysms and normal aorta. Surgery. 1997;122:264-271, 271-272.
27. Pyo R, Lee JK, Shipley JM, et al. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. J Clin Invest. 2000;105:1641-1649.
28. Sho E, Chu J, Sho M, et al. Continuous periaortic infusion improves doxycycline efficacy in experimental aortic aneurysms. J Vasc Surg. 2004;39:1312-1321.
29. Thompson RW, Baxter BT. MMP inhibition in abdominal aortic aneurysms. Rationale for a prospective randomized clinical trial. Ann N Y Acad Sci. 1999;878:159-178.
30. Curci JA, Mao D, Bohner DG, et al. Preoperative treatment with doxycycline reduces aortic wall expression and activation of matrix metalloproteinases in patients with abdominal aortic aneurysms. J Vasc Surg. 2000;31:325-342.
31. Hackmann AE, Rubin BG, Sanchez LA. A randomized, placebo-controlled trial of doxycycline after endoluminal aneurysm repair. J Vasc Surg. 2008;48:519-526.
32. Skillern CS, Stevens SL, Piercy KT, et al. Endotension in an experimental aneurysm model. J Vasc Surg. 2002;36:814-817.
33. Xenos ES, Stevens SL, Freeman MB, et al. Distribution of sac pressure in an experimental aneurysm model after endovascular repair: the effect of endoleak types I and II. J Endovasc Ther. 2003;10:516-523.
34. Pacanowski JP, Stevens SL, Freeman MB, et al. Endotension distribution and the role of thrombus following endovascular AAA exclusion. J Endovasc Ther. 2002;9:639-651.
35. Ohki T, Ouriel K, Silveira PG, et al. Initial results of wireless pressure sensing for endovascular aneurysm repair: the APEX trial—acute pressure measurement to confirm aneurysm sac exclusion. J Vasc Surg. 2007;45:236-242.
36. Tamburino C, Angiolillo DJ, Capranzano P, et al. Long-term clinical outcomes after drug-eluting stent implantation in unprotected left main coronary artery disease. Catheter Cardiovasc Interv. 2009;73:291-298.
37. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. J Am Coll Cardiol. 2006;48:1304-1309.

Nano and the Future of Endovascular Medicine

A look at the medical advances we expect in the coming decades.

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Statistics recently released by the American Heart Association show that cardiovascular disease is responsible for one in every 2.8 deaths in the US alone, and the estimated US health care cost of cardiovascular disease as of 2009 is $475 billion.[1] In addition, atherothrombosis is increasing across the globe, and it is estimated that atherothrombotic diseases will be the leading cause of death worldwide by 2020. As engineers, we are motivated by these statistics, and by harnessing nanoscale fabrication, we have numerous opportunities to improve endovascular medicine.

THE "NANO" IN NANOMEDICINE

All biological materials contain nanoscale structures, and we generally use the term *nano* to describe man-made structures with at least one critical feature <1 micron in size.[2] Fundamentally, natural structures are composed of nanoscale features assembled "bottom-up" from biochemical reactions into micro- and macrostructures; thus, molecules from chemistry are the original "nano." Biomimetic, man-made nanostructures can be engineered from "top-down" hierarchical manufacturing techniques that add and remove material through a variety of techniques. We cannot describe these techniques with sufficient detail here, but the interested reader is referred to comprehensive sources on micro- and nanofabrication.[3-6] One feature of successful nanotechnologies, whether natural or synthetic, is a functional interface with larger micron-scale and macro-scale components.

Nanoscale features can directly interact with the functional units of vascular biology (Table 1).[7] By working on the scale of our cells and their constituents, tissue engineers may soon be able to construct biologically accurate engineered tissues that function because their structure mimics nature more accurately than ever before.

In the coming decades, we can expect to see stent designs that integrate seamlessly with the body and avoid provoking an immune response.[8,9] Hybrid stents or grafts using man-made materials as well as living materials may enable enhanced structural and biological function in patients with diseased cardiovascular tissues and even allow doctors to wirelessly monitor the health and material properties of high-risk vessels in vivo. With advances in pluripotent cell manipulation, patient-specific vessels may be produced using a patient's own cells or DNA to eliminate immune response concerns. Smaller tools enabled by micro- and nanotechnology will lead to ever-smaller stents and grafts and more effective remote microsurgical techniques and tools.[10]

We predict advances in three major categories: (1) man-made tissues assembled with precision from the nanoscale up, (2) synthetic-biological hybrid technologies that improve the viability of currently existing synthetic grafts, and (3) a new cadre of nanoimaging and nanofabricated surgical tools (Figure 1).

TABLE 1. COMMON DIMENSIONS IN VASCULAR TISSUE

Red blood cells (width)	8 µm
Collagen fiber diameter	0.5–3 µm
Collagen fibril diameter	10–300 nm
Microfibrils of elastin fiber diameter	10 nm
Smooth muscle cell (width)	15–20 µm

Dimensions range from microns at the cellular level to nanometers at the subcellular level.[7]

NANOFABRICATION FOR BIOLOGICALLY ACCURATE CULTURE ENVIRONMENTS

The engineering of replacement vessels using nanotechnology holds exciting potential for tissue engineers. Early successes in engineered vessels were constructed

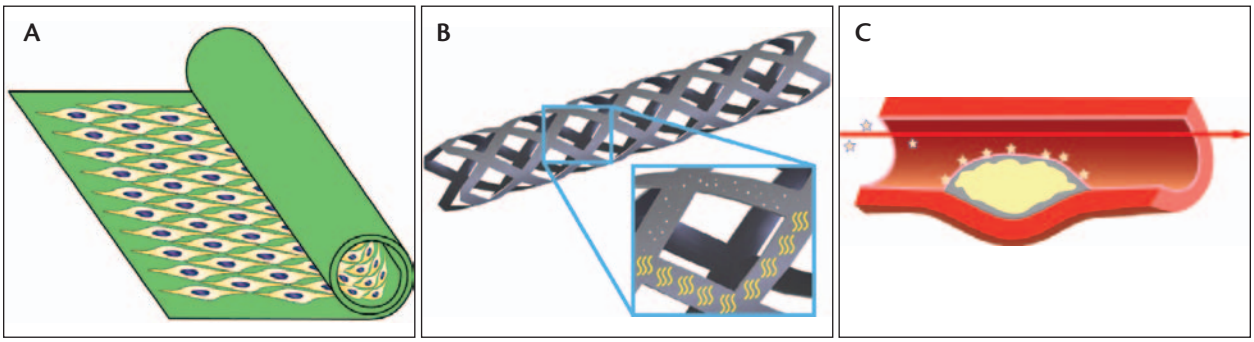

Figure 1. Technological innovations leveraging nanotechnology are expected in three categories with examples of anticipated or current technologies in engineered tissues assembling cells and proteins into physiologically correct microstructures (A). Hybrid stents combining nanotopography or functionalized surfaces to promote integration with native tissues and augmented for improved material properties (B). Medical tools that use nanostructures or devices for improved imaging and ablation of diseased tissues (C).

from layers of various cell types and then rolled together to form vessel-like structures.[11] The function of vascular tissue strongly follows its structural form. The basic unit of vascular tissue is the medial lamellar unit (MLU) shown in Figure 2.[12] Fabricating structures with repeating MLUs having equivalent mechanical and biological function will be essential. Structurally accurate MLUs using nanostructured matrices will need to provide the same biochemical cues and mechanical integrity as the elastin, collagen, and matrix of native tissue to provide the strength, elasticity, adhesion, and permeability required for proper vascular cell function. Techniques such as protein patterning and electrospinning have the potential to generate sheets of organized elastin underneath regions of properly off-axis aligned smooth muscle cells between collagenous nests (Figure 3).[13,14] Current micro- and nanofabrication techniques lend themselves to the fabrication of repeating unit systems, so sheets of hundreds of thousands of MLUs could conceivably be arranged and then rolled or stacked into functional media layers ready to take their place inside an engineered vessel.[15-17]

Polymer stiffness has also been shown to affect cell adhesion and motility.[18] Therefore, polymers with appropriate stiffness, structure, and biochemical/protein binding sites are expected to provide a healthy environment for cardiovascular cell types to grow and proliferate in a manner that better mimics cell behavior in vivo. Toward this goal, researchers are currently working on various pieces of the vascular tissue engineering puzzle such as engineering artificial extracellular matrix (ECM) polymers with custom mechanical and biochemical properties.[19,20] The effects of mechanical stimulation, nano- and micropatterned textures, and specific binding proteins on the organization, morphology, and function of cells have also been investigated. Protein patterning can enhance alignment of endothelial cells, and in addition, surface texture patterning has been shown to improve not only cell alignment but also adhesion properties.[21-24] For example, Figure 4 shows the patterning of HL1 atrial myoblasts on microcontact-printed stripes of ECM proteins (gelatin-fibronectin blend) for cardiovascular tissue graft applications.[25] Technologies like dip-pen lithography can be used to "write" ECM proteins into specific shapes using technology similar to those currently used for rapid prototyping of plastic parts.[26] Fundamentally, these techniques provide nanoscale spatial control of the cell culture environment and will enable the creation of structurally equivalent engineered tissues.

NEXT-GENERATION SYNTHETIC NATURAL VESSEL HYBRIDS AND STENTS

The first implementation of nanotechnology in clinical procedures may involve the creation of nanostructured stents to enhance their long-term function (an area of interest to stent and stent graft manufacturers) and possibly the development of hybrid grafts that involve cultured tissue within modified endovascular tools. An example of this augmented/hybrid technology was recently demonstrated when scientists strengthened arterial vein grafts using electrospun wraps of polymer nanofibers.[27] Knowing that arteries experience higher pressures than veins, these researchers used electrospinning nanotechnology to improve the mechanical properties of a graft.

Stents can likewise be augmented to contain or even deliver these nanofabricated vessel units to the damaged tissue sites. In this way, tissue engineering holds potential for the creation of stenting technologies that do more than mechanically brace a vessel. Next-generation stents may include nanotopography or engineered protein

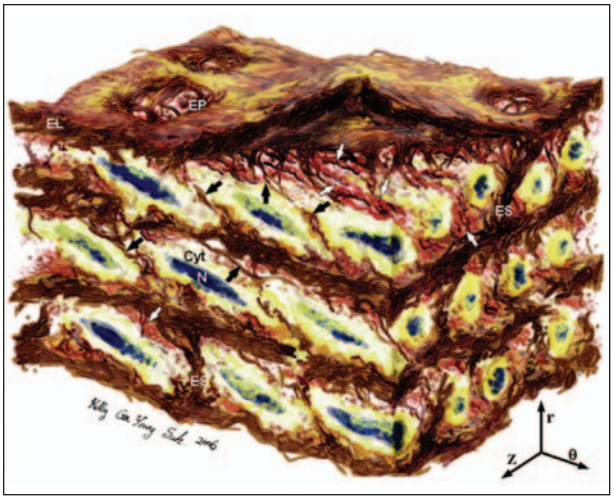

Figure 2. A medial lamellar unit consists of smooth muscle cells (yellow with blue nuclei) surrounded by elastin (brown) and collagen (red), which strengthen and reinforce the vessel while providing compliance. Smooth muscle cells are oriented slightly off orthogonal from flow (z-direction). Elastin takes the form of lamellar sheets, radial struts, and interlamellar fibers. Parallel collagen fibers and fiber bundles are densely packed around smooth muscle cells. (Reprinted with permission from O'Connell MK, Murthy S, Phan S, et al. Matrix Biology. 2008;27:177.)

coatings that enhance healing and the reformation of endothelial lining in the vessel, or they may incorporate preformed endothelial layers or MLUs inside the artificial structures necessary for bracing the weakened vessel. Nanotechnology certainly holds promise for making stents antithrombogenic without drug coatings through the design of the stent surfaces. For example, neural probes incorporating multiscale ladder features demonstrated that encapsulation and foreign body response is markedly reduced in regions of interest (Figure 5).

Additionally, the integration of micro- and nanosensors could allow hybrid smart stents to both sense the onset of aneurysm development and communicate information about vessel diameter, material properties, or chemical signaling to vascular surgeons. Stents that double as wireless antennae have been developed for communicating data from implanted micro- and nanosensors.[28] Such devices when coupled with micro- and nanoforce and displacement sensors could give vascular surgeons a whole new level of postprocedural vascular monitoring ability.

TOOLS FOR NANOMEDICINE

Several imaging and material property measurement tools have been miniaturized into catheter-delivered devices. Ultrasound probes have been developed that can fit inside a standard catheter.[29] Cantilever-based stiffness probes have been optimized for use with living tissue and can be deployed in vivo.[30] Catheter-based devices for imaging or tissue property investigation will lead to improved visualization of the injured vascular tissue, and this spatial information about vessel wall thickness and stiffness will enable better microvascular surgery planning.

Innovative imaging tools using tagged cell-specific nanoparticles offer the ability to actively track and ablate dangerous cells such as cancer cells or diseased endothelial cells.[31-33] Cells endocytose the gold particles or surround the particles without injury, but when electromagnetic fields are introduced, those particles can be made to vibrate and thus be imaged to show the location of the targeted cells in the body. Higher levels of energy can lead to the extreme heating of the particles and localized

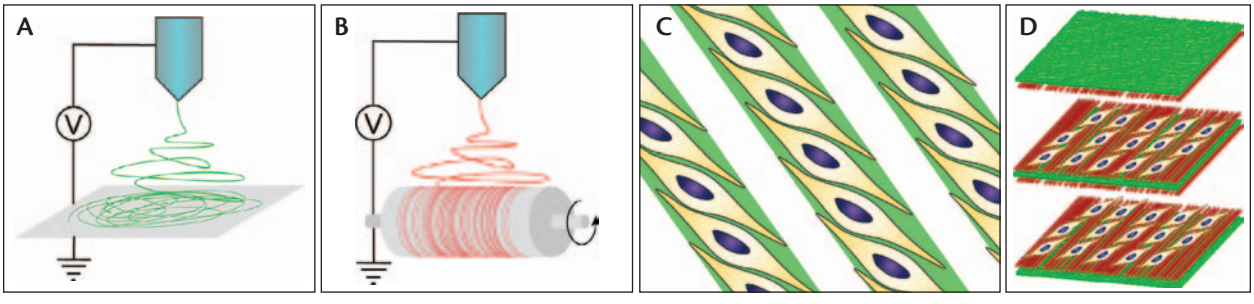

Figure 3. Artificial MLU and microfabrication techniques that make its fabrication possible. Electrospinning thick layers of elastin on plates generates a strong mesh for simulating each elastin lamella (A). Electrospinning collagen on a rotating drum creates aligned cords that accurately simulate the collagen strands that surround each smooth muscle cell in the regions between lamellae (B). Microcontact printing can be used to guide smooth muscle cell attachment in a physiological arrangement (C). By repeating the processes of protein deposition and cell patterning, it would be possible to create sheets of MLUs that are ready to be rolled into vessels (D). Attention to the alignment of the collagen strands and alignment of the smooth muscle cells will lead to artificial vessels that accurately replicate natural vessel structure.

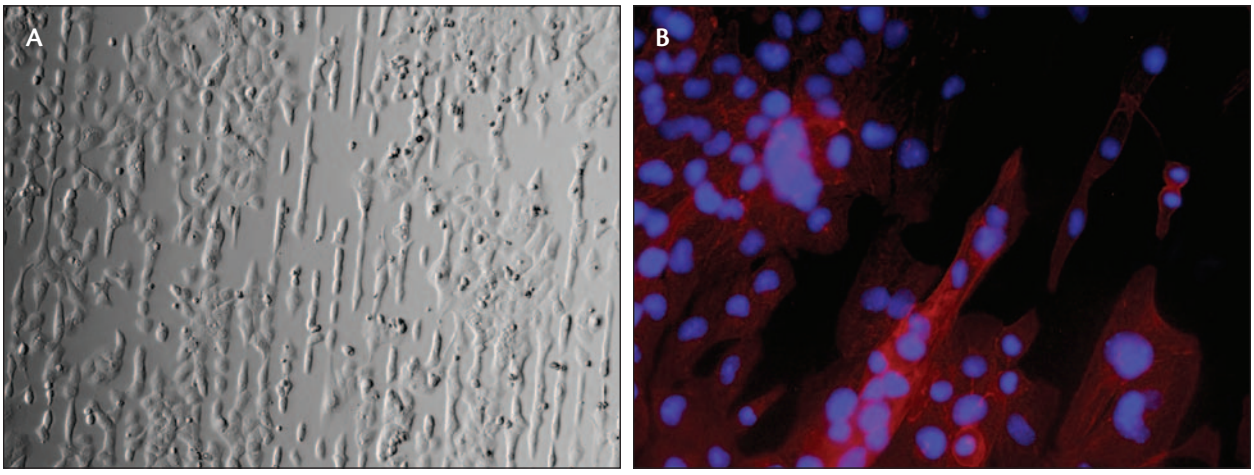

Figure 4. A bright field image (A) and a fluorescent image (B) stained for nuclei and cytoplasmic actin show that HL1 atrial myoblasts patterned on ECM proteins (gelatin-fibronectin blend) mimic the alignment of cardiomyocytes found in vivo.

destruction of dangerous cells. These techniques could be refined to deliver particles selectively to plaques or scar tissue, to locate diseased vessel surfaces, and ultimately to ablate necrotic plaques or tissues.

CONCLUSION

Nanotechnology holds promise in enabling surgical tools and procedures coupled with delivery of nanoengineered MLUs, stents, or whole tissue grafts to provide powerful treatment options. These new stents and biologically engineered vessels that mimic native tissues hold the potential to further reduce invasiveness of current techniques, minimize damage to nondiseased tissue, and improve physiological function by potentially growing and responding to normal neuronal, hormonal, and biochemical cues. As medical research on the nanometer scale advances, we can expect exciting transformations in the field of endovascular medicine. ■

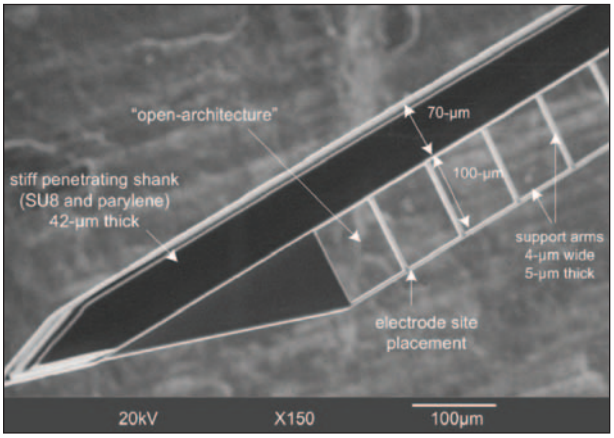

Figure 5. Scanning electron microscope of a neural probe tip with open ladder-like architecture. The electrodes are located on subcellular scale support arms, which evoke a less significant encapsulation response. By altering feature scale, immune response was diminished, and this approach will prove useful for future vascular surgery devices. (Reprinted with permission from Seymour J, Kipke D. Materials Research Society Symposium Proceedings. 2006.)

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1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics 2009 update. A report from the American Heart Association statistics committee and stroke statistics subcommittee. Circulation. 2008:119:e21-e181 [published online ahead of print December 15, 2008].
2. Whitesides GM. The 'right' size in nanobiotechnology. Nat Biotechnol. 2003;21:1161-1165.
3. Madou M. Fundamentals of microfabrication. Boca Raton, FL: CRC Press; 1997.
4. Xia Y, Whitesides GM. Soft lithography. Ann Rev Mat Sci. 1998;28:153-184.
5. Bhushan B. Handbook of Micro/Nano Tribology. Boca Raton, FL: CRC Press; 1999.
6. Geisse NA, Feinberg AW, Kuo P-l, et al. Micropatterning approaches for cardiac biology. In: Khademhosseini A, Borenstein J, Toner M, et al, eds. Micro and Nanoengineering of the Cell Microenvironment: Technologies and Applications. Boston, MA: Artech House; 2008:341-360.
7. Alberts B, Bray D, Lewis J, et al. Molecular Biology of the Cell. New York: Garland Publishing; 1994.
8. Seymour JP, Kipke DR. Neural probe design for reduced tissue encapsulation in CNS. Biomaterials. 2007;28:3594-3607.
9. Wise KD, Sodagar AM, Ying Y, et al. Microelectrodes, microelectronics, and implantable neural microsystems. Proc IEEE. 2008;96:1184-1202.
10. Isenberg BC, Williams C, Tranquillo RT. Small-diameter artificial arteries engineered in vitro. Circ Res. 2006;98:25-35.
11. Fuchs JR, Nasseri BA, Vacanti JP. Tissue engineering: a 21st century solution to surgical reconstruction. Ann Thorac Surg. 2001;72:577-591.
12. Wolinsky H, Glagov S. A lamellar unit of aortic medial structure and function in mammals. Circ Res. 1967;20:99-111.
13. Liao S, Li B, Ma Z, et al. Biomimetic electrospun nanofibers for tissue regeneration. Biomed Mater. 2006;1:R45-53.
14. Sarkar S, Lee GY, Wong JY, et al. Development and characterization of a porous micropatterned scaffold for vascular tissue engineering applications. Biomaterials. 2006;27:4775-4782.
15. L'Heureux N, Paquet S, Labbe R, et al. A completely biological tissue-engineered human blood vessel. FASEB J. 1998;12:47-56.
16. Griffith LG, Swartz MA. Capturing complex 3D tissue physiology in vitro. Nat Rev Mol Cell Biol. 2006;7:211-224.
17. Edelman ER. Vascular Tissue Engineering:designer arteries. Circ Res. 1999;85:1115-1117.
18. Pelham RJ, Wang Y-l. Cell locomotion and focal adhesions are regulated by substrate flexibility. PNAS. 1997;94:13661-13665.
19. Heilshorn SC, DiZio KA, Welsh ER, et al. Endothelial cell adhesion to the fibronectin CS5 domain in artificial extracellular matrix proteins. Biomaterials. 2003;24:4245-4252.
20. Straley KS, Heilshorn SC. Independent tuning of multiple biomaterial properties using protein engineering. Soft Matter. 2009;5:114-124.
21. Khademhosseini A, Langer R, Borenstein J, et al. Microscale technologies for tissue engineering and biology. PNAS. 2006;103:2480-2487.
22. Boateng S. Peptides bound to silicone membranes and 3d microfabrication for cardiac cell culture. Adv Mat. 2002;14:461-463.
23. Miller DC, Webster TJ, Haberstroh KM. Technological advances in nanoscale biomaterials: the future of synthetic vascular graft design. Expert Rev Med Devices. 2004;1:259-268.
24. Norman J, Desai T. Methods for fabrication of nanoscale topography for tissue engineering scaffolds. Ann Biomed Eng. 2006;34:89-101.
25. White SM, Constantin PE, Claycomb WC. Cardiac physiology at the cellular level: use of cultured HL-1 cardiomyocytes for studies of cardiac muscle cell structure and function. Am J Physiol Heart Circ Physiol. 2004;286:H823-829.
26. Mironov V, Boland T, Trusk T, et al. Organ printing: computer-aided jet-based 3D tissue engineering. Trends in Biotech. 2003;21:157-161.
27. El-Kurdi MS, Hong Y, Stankus JJ, et al. Transient elastic support for vein grafts using a constricting microfibrillar polymer wrap. Biomaterials. 2008;29:3213-3220.
28. Takahata K, DeHennis A, Wise KD, et al. Stentenna: a micromachined antenna stent for wireless monitoring of implantable microsensors. Proc IEEE EMBS. 2003;25:3360-3363.
29. Yeh DT, Oralkan O, Wygant IO, et al. 3-D ultrasound imaging using a forward-looking CMUT ring array for intravascular/intracardiac applications. IEEE Trans Ultrason Ferroelectr Freq Control. 2006;53:1202-1211.
30. Yang S, Saif T. Reversible and repeatable linear local cell force response under large stretches. Exp Cell Res. 2005;305:42-50.
31. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5:161-171.
32. Lukyanenko V. Delivery of nano-objects to functional sub-domains of healthy and failing cardiac myocytes. Nanomedicine. 2007;2:831-846.
33. Yang X. Nano- and microparticle-based imaging of cardiovascular interventions: overview. Radiology. 2007;243:340-347.

(Continued from page 22)

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1. EVAR Trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomized controlled trial. Lancet. 2005;365:2179-2186.
2. Bavaria JE, Appoo JJ, Makaroun MS, et al. The Gore Tag Investigators. Endovascular stent grafting versus open surgical repair of descending thoracic aortic aneurysms in low-risk patients: a multicenter comparative trial. J Thorac Cardiovasc Surg. 2007;133:369-377.
3. Czerny M, Grimm M, Zimpfer D, et al. Results after endovascular stent graft placement in atherosclerotic aneurysms involving the descending aorta. Ann Thoracic Surg. 2007;83:450-455.
4. Feezor RJ, Martin TD, Hess PJ, et al. Risk factors for perioperative stroke during thoracic endovascular aortic repairs (TEVAR). J Endovasc Ther. 2007;14:568-573.
5. Thompson M, Ivaz S, Cheshire N, et al. Early results of endovascular treatment of the thoracic aorta using the Valiant endograft. Cardiovasc Interv Radiol. 2007;30:1130-1138.
6. Bicknell CD, Cheshire NJ, Riga CV, et al. Treatment of complex aneurysmal disease with fenestrated and branched grafts. Eur J Vasc Endovasc Surg. 2009;37:175-181.
7. Chuter TA, Rapp JH, Hiramoto JS, et al. Endovascular treatment of thoracoabdominal aortic aneurysms. J Vasc Surg. 2008;47:6-16.
8. Greenberg RK, Haulon, S, Lyden SP, et al. Endovascular management of juxtarenal aneurysms with fenestrated endovascular grafting. J Vasc Surg. 2004;39:279-287.
9. Kanagaratnam P, Koa-Wing M, Wallace DT, et al. Experience of robotic catheter ablation in humans using a novel remotely steerable catheter sheath. J Interv Cardiol Electrophysiol. 2008;21:19-26.
10. Cheshire NJ, Bicknell CD, Riga CV. Will the Hansen Robotic System for remotely controlling catheters and guidewires be useful for endovascular procedures: early clinical experience. Presented at the 35th VEITH Annual Symposium, New York, November 2008.
11. Riga CV, Bicknell CD, Cheshire NJ, et al. Robotic endovascular catheters improve accuracy, reduce time and minimize radiation exposure for visceral vessel and fenestrated stent cannulation.Presented at the British Society of Interventional Radiology (BSIR) Annual Meeting, November 2008.
12. Riga CV, Bicknell CD, Cheshire NJ. First use of robotic technology for endovascular aneurysm repair. J Endovasc Ther. In press.
13. Khongphatthanayothin A, Kosar E, Nademanee K. Nonfluoroscopic three-dimensional mapping for arrhythmia ablation: tool or toy? J Cardiovasc Electrophysiol. 2000;11:239-243.
14. Dickfeld T, Calkins H, Zviman M, et al. Anatomic stereotactic catheter ablation on three-dimensional magnetic resonance images in real time. Circulation. 2003;108:2407-2413.
15. McWilliams RG, Murphy M, Hartley D, et al. In situ stent-graft fenestration to preserve the left subclavian artery. J Endovasc Ther. 2004;11:170-174.
16. Tse LW, Bui BT, Lerouge S, et al. In vivo antegrade fenestration of abdominal aortic stent-grafts. J Endovasc Ther. 2007;14:158-167.
17. Riga CV, Bicknell CD, Wallace D, et al. Robot-assisted in situ fenestration stent grafting [published online ahead of print October 30, 2008]. Cardiovasc Interv Radiol. doi:10.1007/s00270-008-9459-5.

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UC200905027EN