Hybrid approach to complex thoracic aortic aneurysms in high-risk patients: Surgical challenges and clinical outcomes

Wei Zhou, MD,a Michael Reardon, MD,b Eric K. Peden, MD,a Peter H. Lin, MD,a and Alan B. Lumsden, MD,a Houston, Tex

Background: Endovascular therapy is a less invasive alternative treatment for high-risk patients with thoracic aortic aneurysms. However, this technology alone is often not applicable to complex aneurysmal morphology. The purpose of this study was to evaluate the utility of hybrid strategies in high-risk patients who are otherwise unsuitable for endovascular therapy alone.

Methods: During an 18-month period, 31 high-risk patients (mean age, 69 years; range, 52-89 years) underwent combined open and endovascular approaches for complex aneurysms, including 16 patients with ascending and arch aneurysms and 15 patients with aneurysms involving visceral vessels. Among them, 11 patients had histories of aneurysm repairs. To overcome the anatomic limitations of endovascular repairs, various adjunctive surgical maneuvers were used, including aortic arch reconstruction in 3 patients, supra-aortic trunk debranching in 13 patients (including 8 patients who required aortas as inflow sources), and visceral vessel bypasses in 15 patients (including 10 patients who required bypasses to all 3 visceral branches). Additionally, carotid artery access was obtained in 1 patient, and iliac artery conduits were created in 12 patients.

Results: Technical success was achieved in all patients. There was one perioperative death (3.2%) due to postoperative bleeding. Two patients (6.4%) had immediate type II endoleaks, which were resolved by the 1-month follow-up. Other procedure-related complications occurred in three patients (9.6%), including renal bypass thromboses in two patients and retroperitoneal hematoma, which was successfully managed conservatively, in one patient. During a mean follow-up of 16 months, two patients died of unrelated causes, whereas the remainder of patients were asymptomatic, without aneurysm enlargement.

Conclusions: Our study highlights how hybrid strategies incorporating surgical and endovascular approaches can be used successfully in treating patients with complex thoracic aortic aneurysms. This combined approach potentially expands the field of endovascular stent grafting and is an attractive solution for patients with poor cardiopulmonary reserves. (J Vasc Surg 2006;44:688-93.)

If left untreated, thoracic aortic aneurysms (TAAs) with a diameter of more than twice the proximal uninvolved aorta are associated with a 2-year patient survival rate of less than 30%.1 Therefore, surgical repair is advocated for patients with large TAAs.2 However, conventional surgical treatment is typically associated with a prolonged operative time, significant blood loss, and hemodynamic instability.3 The significant morbidity and mortality associated with the open surgical approach have kindled interest in the development of an alternative treatment modality.

Endovascular repair, since its inception, has become a valuable therapeutic alternative in treating high-risk patients with TAA. It provides a less invasive and potentially safer strategy. The rapid evolution of catheter-based technology has laid the foundation for the treatment of TAAs.3-5 The recent Food and Drug Administration approval of the TAG thoracic endoprosthesis (WL Gore, Flagstaff, Ariz) further provides opportunities for patients who are not enrolled in clinical trials and who are unfit for open surgical repair. However, a large number of patients have been excluded from endovascular repair because of unfavorable anatomies, particularly an inadequate proximal landing zone (PLZ) and distal landing zone (DLZ). Endovascular repairs of arch aneurysms often require stent grafts that cross supra-aortic trunks, and treating thoracoabdominal aortic aneurysms near visceral vessels may require cov-
erating the celiac arteries, the superior mesenteric artery (SMA), and the renal arteries.

To increase the feasibility of endovascular repairs of TAAs, adjunctive open surgical bypasses may be required to provide adequate landing zones. The hybrid approach of combining endovascular repairs with adjunctive open surgical techniques may provide a valuable alternative for patients with TAAs, particularly for patients who are at high risk for open surgical aneurysmal repairs and who have unsuitable anatomies for endovascular approaches alone. The shift in the treatment paradigm of TAAs prompted us to review our use of hybrid approaches in treating high-risk patients with complex TAAs that involve supra-aortic trunks or visceral vessels. Specifically, technical considerations and clinical outcomes were analyzed.

PATIENTS AND METHODS

The hospital records of all patients who underwent a combined approach incorporating open surgical debranching and endovascular stent grafting between July 2004 and December 2005 were analyzed. All procedures were performed at the Methodist Hospital and the affiliated hospitals of Baylor College of Medicine, including St Luke’s Hospital, and the Michael E. DeBakey Veterans Affairs Medical Center.

Patient selection criteria. All patients presented with complex TAAs that were evident on computed tomographic (CT) scans. These patients were all deemed unsuitable for open surgical repairs because of high surgical risks; this category included patients who could not tolerate aortic cross-clamping or open thoracotomy and patients who had multiple prior aneurysmal repairs. Significant medical comorbidities and surgical risks included chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, diabetes, hypertension, and prior multiple aneurysmal repairs. Because of significant open surgical risks, these patients were evaluated for endovascular treatments. However, none of the patients was deemed to be an endovascular candidate on initial evaluation as a result of inadequate landing zones. Among them, 16 patients (52%) required endograft landing in the aortic arch; these included 11 patients landing in zone 0 and 5 patients in zone 1 to achieve a proximal seal, which would have compromised the left carotid artery and inominate artery flow. Additionally, 15 patients (48%) had short DLZs that required endografts covering the celiac and SMA. Among them, ten patients required endografts covering the renal artery as well as the celiac and SMA. Patients who presented with acute or chronic aortic dissections or traumatic transactions were excluded from the study. Similarly, patients who presented with connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, were not included in the study.

Surgical techniques. Custom-made multibranched grafts were fashioned so that the branches were sutured to the supra-aortic or visceral vessels in an end-to-side fashion, and the main trunks were anastomosed to the aorta for supra-aortic trunk bypasses or to the iliac arteries for visceral vessel bypasses. In addition, the main trunks were anastomosed to the aortic grafts in patients with concomitant or prior aortic reconstructions. The main trunks were also used for stent-graft insertions in selected patients who received concomitant endovascular repairs. After adjunctive surgical procedures, the origins of the bypassed aortic branches were ligated or coiled to prevent potential type II endoleaks. Subsequently, the stent grafts were inserted either immediately or in a staged fashion. Cerebrospinal fluid drainage catheters were placed for all patients with prior descending thoracic or abdominal aortic aneurysm repairs. A pressure of less than 10 mm Hg was maintained. A guidewire was advanced into the aorta under fluoroscopic guidance, and a stiff Meier wire (Boston Scientific, Oakland, NJ) was exchanged. A 24F introducer sheath was then inserted over the Meier wire, followed by a TAG stent-graft insertion. After the position was confirmed angiographically, the stent graft was deployed in a standard fashion. Completion angiograms were performed after the procedures.

RESULTS

Patient information and aneurysm morphologies. A total of 31 patients presented with complex TAAs of various morphologies, including 8 patients with aortic arch aneurysms, 2 patients with ascending aortic pseudoaneurysms, and 18 patients with thoracoabdominal aortic aneurysms (TAAAs), including a Crawford classification of type I in 3 patients (16.7%), type III in 8 patients (44.4%), and type IV in 7 patients (38.9%). Additionally, three patients presented with total aortic aneurysms that involved both the ascending and descending aortas (Table I). The mean diameter of the aneurysms was 6.2 cm (range, 5.5–7.4 cm). All patients were deemed at high risk for open surgical repairs. Ten patients (32%) presented with severe chronic obstructive pulmonary disease that prohibited open thoracotomy, and 29 (94%) patients had significant coronary artery disease that prohibited aortic cross-clamping. Additionally, 11 (35%) patients had previous aortic aneurysm repairs that significantly increased surgical challenges. Other risk factors included congestive heart failure (n = 2; 6%), diabetes (n = 6; 19%), hypertension (n = 21; 68%), and renal insufficiency (n = 4; 13%).

On the basis of the anatomic selection criteria, these patients were not suitable for endovascular repairs as a result of inadequate landing zones. A total of 16 patients had insufficient PLZs, including 8 patients with arch aneurysms, 3 patients with total aortic aneurysms, 2 patients with ascending pseudoaneurysms, and 3 patients with

<table>
<thead>
<tr>
<th>Aneurysmal morphology</th>
<th>No. patients</th>
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<tr>
<td>Arch aneurysms</td>
<td>8</td>
</tr>
<tr>
<td>Ascending pseudoaneurysms</td>
<td>2</td>
</tr>
<tr>
<td>Thoracoabdominal aneurysm</td>
<td>18</td>
</tr>
<tr>
<td>Total aortic aneurysms</td>
<td>3</td>
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TAAAs (type I). Among the patients with inadequate PLZ, 11 patients required endografts covering both the innominate artery and the common carotid artery (CCA), therefore significantly compromising cerebral perfusions. Conversely, 15 patients lacked adequate DLZs, including 8 patients with type III TAAAs and 7 patients with type IV TAAAs. Additionally, 13 patients had insufficient access arteries for stent-graft deployments.

**Adjunctive open surgical techniques for endografting.** To overcome the limitations of endovascular repairs, various adjunctive surgical maneuvers were used to render the endovascular strategy a feasible option (Table II). Among the 16 patients with inadequate PLZs, 3 patients received arch reconstruction and endovascular stent grafting for concomitant ascending and descending aortic aneurysms, including 2 patients who had elephant trunk creations. Seven patients received ascending aorta to supra-aortic trunk bypasses (Fig 1, A), and one patient received a descending aorta to supra-aortic trunk bypass (Fig 1, B) before endograft placement. Additionally, 13 CCA to CCA bypasses and 25 CCA to subclavian artery bypasses were performed (Fig 1, C) to facilitate endovascular repairs. Furthermore, 15 patients underwent a total of 40 visceral vessel bypasses, including 15 patients who received iliac artery to celiac and SMA bypasses and 10 patients who received additional iliac artery to renal artery bypasses (Fig 2). Finally, 13 patients did not have adequate access because of insufficient access vessel diameters, including 1 patient who required the use of a carotid artery as an access vessel for the stent-graft repair of an ascending aortic pseudoaneurysm and 12 patients who required iliac artery conduit creations.

**Endograft placement.** All patients received TAG endovascular prostheses to repair their complex TAAAs, including 21 (68%) patients who received endovascular stent grafting immediately after debranching procedures and 10 (32%) patients who underwent endovascular TAA repairs as second-stage procedures. The average time interval between the staged procedures was 32 days, ranging from 7 to 93 days. Eight patients had endograft placements in an antegrade fashion immediately after arch debranchings or reconstructions (Fig 1, A), and the remainder had stent-graft placement in a retrograde fashion (Fig 1, B). In patients receiving immediate endovascular repairs, custom-made Dacron (DuPont, Wilmington, Del) bypass grafts with appropriate configurations were sutured to 14-mm Dacron trunks in an end-to-side fashion. The bypass grafts were used as inflows for supra-aortic or visceral vessels, and the 14-mm trunks were anastomosed to the aortas or iliac arteries and used as conduits for stent-graft insertions. At the completion of the procedures, the stumps of the 14-mm trunks were oversewn.

**Clinical outcomes.** Technical success, which was defined by aneurysmal exclusion without type I or III endoleak, was achieved in all patients. There was one perioperative death (3.2%) secondary to delayed postoperative bleeding. Perioperative complications occurred in six patients (19.2%; Table III). One patient (3.2%) developed a retroperitoneal hematoma after placement of the iliac conduit, and this was resolved with conservative management. One patient (3.2%) had prolonged ileus. In addition, two patients (6.4%) developed right renal graft thrombosis with transient renal failure and increasing creatinine levels that required temporary hemodialysis. Both patients recovered renal function. Moreover, two patients (6.4%) had immediate type II endoleaks, which were resolved by the 1-month follow-up, as illustrated by the CT scans. There was no incidence of stroke or paraplegia in our series. All patients underwent CT scan surveillance every 6 months. During a mean follow-up of 16 months (range, 3-24 months), two patients (6.7%) died of unrelated causes, including one patient who died as a result of myocardial infarction 10 months later and one who died as a result of metastatic lung cancer 14 months later. All remaining patients were asymptomatic without aneurysm enlargement.

**DISCUSSION**

Complex TAAAs that involve supra-aortic trunks or visceral vessels pose a significant therapeutic dilemma for high-risk patients, because endovascular therapy alone is often not feasible as a result of unsuitable anatomicies. Adjunctive surgical techniques can overcome the major limitations of inadequate landing zones and render the endovascular treatment a valuable therapeutic option for high-risk patients, as demonstrated by our series. Our series also highlights the

<table>
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<th>Endovascular limitations</th>
<th>Adjunctive surgical techniques</th>
<th>No. procedures</th>
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<tbody>
<tr>
<td>PLZ (n = 16)</td>
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<td>Arch debranching</td>
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<td>Ascending aorta to innominate bypass</td>
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<tr>
<td>Descending aorta to innominate bypass</td>
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<tr>
<td>CCA-CCA</td>
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<td>13</td>
</tr>
<tr>
<td>CCA-SCA or SCA-CCA</td>
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<td>25</td>
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<td>DLZ (n = 15)</td>
<td>Visceral debranching</td>
<td></td>
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<td>Iliac to celiac artery bypass</td>
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<td>Iliac to SMA bypass</td>
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<td>Iliac to renal artery bypass</td>
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<tr>
<td>Inadequate access vessel</td>
<td>Carotid access</td>
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<tr>
<td>(n = 13)</td>
<td>Iliac conduit</td>
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PLZ, Proximal landing zone; DLZ, distal landing zone; CCA, common carotid artery; SCA, subclavian artery; SMA, superior mesenteric artery.
effective alternative of a hybrid approach for TAAs by demonstrating the excellent technique successes and satisfactory outcomes.

Initially reported by Parodi et al in 1991, the endovascular repair of abdominal aortic aneurysms was an important surgical milestone in vascular surgery. Because of its early success, a similar interest for endovascular stent grafting of the descending and thoracoabdominal aorta ensued, and the first successful endovascular TAA repair, performed by Dake and colleagues, was reported in 1994. Since then, endovascular therapy has evolved into a valuable therapeutic modality in treating patients with TAAs. Compared with the substantial morbidity and mortality rates associated with open surgical repair of TAAs, endovascular intervention has fewer procedure-related complications, a shorter convalescence, and minimal neurologic deficits. Despite promising results of endovascular TAA repairs, anatomic unsuitability, particularly inadequate landing zones, often excludes patients from endovascular interventions. The general anatomic inclusion criteria are fusiform TAAs 5 cm or larger in maximal diameter; saccular aneurysms at least 20 mm distal to the origin of the left CCA and 20 mm proximal to the origin of the celiac artery; and proximal and distal neck diameters 18 mm or larger and 42 mm or smaller. These anatomic inclusion criteria are deemed necessary to ensure successful stent-graft treatment and
CCA, and zone 2 involves the origin of the left subclavian innominate artery, zone 1 involves the orifice of the left landing zones. Briefly, zone 0 involves the origin of the aortic arch.7,10 Castelli and colleagues10 treated six high-risk patients required endografts landing in zone 0, and five patients required endografts landing in zone 1 to achieve a proximal seal. All 16 patients received adjunctive surgical procedures to ensure an adequate PLZ and protect the cerebral circulation. Aortic arch replacements were necessary in three patients because of the presence of concurrent ascending aortic aneurysms. Ascending aortas were used as inflow sources in patients with relatively normal-appearing ascending aortas, whereas a descending aorta was used as an inflow source in one patient with multiple prior surgical repairs of ascending aneurysms. Extreme caution is warranted when inserting the 24F stent-graft delivery sheath through the bypass graft. Re-enforcing the aortic anastomosis is often necessary. Our perioperative death was caused by immediate postoperative bleeding due to disruption of the aortic anastomosis.

Visceral debranching to ensure adequate landing zones for endovascular repair of TAAs has been reported by several series.12,14 Fulton and colleagues12 successfully treated 10 patients with type IV thoracoabdominal aortic and pararenal aortic aneurysms by using a combined approach of a visceral bypass and endovascular stent grafting. Similarly, Moore et al15 reviewed the use of adjunctive surgical techniques in patients who received endovascular procedures with suboptimal anatomy or intraoperative technical problems. They reported that 31.5% of patients required adjunctive surgical procedures and concluded that despite advances in endovascular technology, hybrid techniques will continue to be required to achieve good overall success rates. Additionally, Kotsis and associates14 treated four patients with thoracoabdominal aortic aneurysms by using the combined approach. In our series, 15 patients with thoracoabdominal aortic aneurysms received adjunctive visceral debranching procedures. The most common perioperative complication was renal graft occlusion (6.4%), which was likely due to technical errors.

Antegrade stent graft placements immediately after debranching procedures have been described previously.16 In our series, most stent grafts (67.7%) were placed immediately after debranching procedures by using bypass grafts as conduits to avoid separate incisions or additional anesthesia. Among the patients who received immediate endovascular repairs, seven patients (33%) had endoluminal grafts deployed via an antegrade fashion, particularly when ascending aortas were used as inflow sources (Fig 1). Typically, a custom-made multiple-branched graft was constructed. The side limbs were used for supra-aortic vessel inflows, and the large main trunk was anastomosed to the ascending aorta and used as a conduit for stent-graft insertion. This antegrade approach is particularly useful for patients with proximally located arch aneurysms, because using the retrograde approach would require the stent graft

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**Table III. Clinical outcomes and follow-up**

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<tr>
<th>Clinical outcome</th>
<th>Underlying etiology</th>
<th>No. patients (%)</th>
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<tbody>
<tr>
<td>Technical success</td>
<td>Bleeding</td>
<td>31 (100%)</td>
</tr>
<tr>
<td>Perioperative mortality</td>
<td>Retroperitoneal hematoma</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Perioperative morbidities</td>
<td>Transient renal failure</td>
<td>2 (6.4%)</td>
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<td></td>
<td>Type II endoleak</td>
<td>2 (6.4%)</td>
</tr>
<tr>
<td></td>
<td>Prolonged ileus</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Follow-up mortality (mean, 16 mo)</td>
<td>Metastatic lung cancer</td>
<td>1</td>
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proper circumferential seals. Therefore, aortic arch aneurysms and aneurysms involving visceral vessels are generally excluded from endovascular interventions as a result of inadequate landing zones and the risks of obstructing flows to important aortic branches. By using a combined surgical and endovascular approach, an adequate landing zone may be created.7,10 Castelli and colleagues10 treated six high-risk patients with distal aortic arch or thoracoabdominal aortic aneurysms by using hybrid approaches and achieved 100% technical success rate. Similarly, Criado and associates7 reviewed their 4-year experiences of treating patients with aortic arch and descending TAAs, including eight patients who received adjunctive cervical reconstruction, and reported satisfactory outcomes. Thus, high-risk patients who would otherwise be unsuitable for endovascular repairs are potentially qualified for endovascular interventions with adjunctive surgical techniques.

To categorize endovascular repairs of TAAs, Criado and colleagues7,11 mapped the thoracic aorta into five landing zones. Briefly, zone 0 involves the origin of the innominate artery, zone 1 involves the orifice of the left CCA, and zone 2 involves the origin of the left subclavian artery, whereas zones 3 and 4 include the descending thoracic aorta. More importantly, a stent graft landing in zone 1 will compromise the left CCA flow, and one landing in zone 0 compromises both the left CCA and innominate artery flows. Using the same mapping system, we examined our high-risk patients with complex TAAs. Eleven patients required endografts landing in zone 0, and five patients required endografts landing in zone 1 to achieve a proximal seal. All 16 patients received adjunctive surgical procedures to ensure an adequate PLZ and protect the cerebral circulation. Aortic arch replacements were necessary in three patients because of the presence of concurrent ascending aortic aneurysms. Ascending aortas were used as inflow sources in patients with relatively normal-appearing ascending aortas, whereas a descending aorta was used as an inflow source in one patient with multiple prior surgical repairs of ascending aneurysms. Extreme caution is warranted when inserting the 24F stent-graft delivery sheath through the bypass graft. Re-enforcing the aortic anastomosis is often necessary. Our perioperative death was caused by immediate postoperative bleeding due to disruption of the aortic anastomosis.

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to be deployed in a very proximal location with the stiff portion of the guidewire placed near an aortic valve and, potentially, the right atrium. Placing the proximal piece of the stent graft through an antegrade approach, conversely, provides maximum precision with minimal cardiac irritation.

In our series, technical success was achieved in all patients. However, there was one perioperative death due to delayed suture line bleeding at the aortic anastomosis in a patient with an arch aneurysm. Two residual type II endoleaks were resolved at 1 month, as was evident on follow-up CT scans. There was no aneurysmal-related mortality over an average of 16 months of follow-up. Two patients died of unrelated causes (myocardial infarction and metastatic lung cancer), and all remaining patients were asymptomatic without aneurysm enlargement. Although hybrid procedures decrease the magnitude of operations with relatively low perioperative mortality in high-risk patients, the complication rate remains high (19.2%), as demonstrated in our series. The most common complication was renal graft thrombosis, which occurred in two patients (6.4%), who required temporary hemodialysis. We suspected that the acute angles and the potential kick of the renal bypass grafts might be contributing factors. Additionally, one patient developed a retroperitoneal hematoma after an iliac conduit access, and another patient had prolonged ileus. We did not encounter clinical evidence of stroke or paraplegia in our series. Admittedly, detailed evaluation by the neurology team and head CT scan were not routinely performed for our postoperative patients unless clinically indicated. Most of our TAAAs were type III and type IV (83.3%). There was no type II TAAA, which is associated with the highest paraplegia rate, in our series.

In conclusion, the combined approach of surgical debranching and endovascular stent grafting provides a unique opportunity for high-risk patients with TAAAs who would otherwise not be endovascular candidates. This combined technique is useful in expanding the aortic territory that can be grafted. Although some of these adjunctive procedures remain major operations, they avoid the requirements of aortic cross-clamping and the potential need for hypothermic circulatory arrest. Until branched aortic endografts become available, debranching techniques combined with aortic stent grafting provide a valuable alternative for the management of complex thoracic aneurysms.

AUTHOR CONTRIBUTIONS
Conception and design: WZ
Analysis and interpretation: WZ
Data collection: WZ, MR, EKP, PHL, ABL
Writing the article: WZ
Critical revision of the article: WZ, MR, PHL, ABL
Final approval of the article: WZ, MR, EKP, PHL, ABL
Statistical analysis: PHL
Obtained funding: ABL, MR, PHL
Overall responsibility: WZ

REFERENCES