

REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Clinical applications of robotic technology in vascular and endovascular surgery

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Background: Emerging robotic technologies are increasingly being used by surgical disciplines to facilitate and improve performance of minimally invasive surgery. Robot-assisted intervention has recently been introduced into the field of vascular surgery to potentially enhance laparoscopic vascular and endovascular capabilities. The objective of this study was to review the current status of clinical robotic applications in vascular surgery.

Methods: A systematic literature search was performed in order to identify all published clinical studies related to robotic implementation in vascular intervention. Web-based search engines were searched using the keywords “surgical robotics,” “robotic surgery,” “robotics,” “computer assisted surgery,” and “vascular surgery” or “endovascular” for articles published between January 1990 and November 2009. An evaluation and critical overview of these studies is reported. In addition, an analysis and discussion of supporting evidence for robotic computer-enhanced telemanipulation systems in relation to their applications in laparoscopic vascular and endovascular surgery was undertaken.

Results: Seventeen articles reporting on clinical applications of robotics in laparoscopic vascular and endovascular surgery were detected. They were either case reports or retrospective patient series and prospective studies reporting laparoscopic vascular and endovascular treatments for patients using robotic technology. Minimal comparative clinical evidence to evaluate the advantages of robot-assisted vascular procedures was identified. Robot-assisted laparoscopic aortic procedures have been reported by several studies with satisfactory results. Furthermore, the use of robotic technology as a sole modality for abdominal aortic aneurysm repair and expansion of its applications to splenic and renal artery aneurysm reconstruction have been described. Robotically steerable endovascular catheter systems have potential advantages over conventional catheterization systems. Promising results from applications in cardiac interventions and preclinical studies have urged their use in vascular surgery. Although successful applications in endovascular repair of abdominal aortic aneurysm and lower extremity arterial disease have been reported, published clinical experience with the endovascular robot is limited.

Conclusions: Robotic technology may enhance vascular surgical techniques given preclinical evidence and early clinical reports. Further clinical studies are required to quantify its advantages over conventional treatments and define its role in vascular and endovascular surgery. (*J Vasc Surg* 2011;53:493-9.)

Emerging minimally invasive technologies have been embraced by many surgical disciplines over the past few years with a consequent reduction in morbidity and mortality, as well as allowing many patients unfit for conventional surgery to undergo treatment. The introduction of robotic technology to assist these minimally invasive procedures has been shown in many fields to significantly

improve outcomes.^{1,2} Robot-assisted surgery, also known as surgical telemanipulation or computer-assisted surgery, is being developed to overcome human limitations and eliminate impediments associated with conventional surgical and interventional tools.¹⁻⁵

Laparoscopic and endovascular interventions have both been introduced into the field of vascular surgery with definite advantages to the patient.⁶⁻⁹ There has been a recent interest in the application of robotic technology to enhance laparoscopic vascular procedures. The adoption of this technology may increase precision and dexterity in performing complex tasks and reduce training times in the challenging field of abdominal vascular surgery.¹⁰ Remote-controlled steerable catheter systems have recently been introduced for cardiac ablation procedures and may potentially improve endovascular skills in a similar way.^{11,12}

The objective of this article is to critically review the current literature available for clinical robotic vascular applications and discuss supporting evidence with regard

From the Division of Surgery, Department of Surgery and Cancer, Imperial College London.

Supported by an Imperial College Biomedical Research Centre Grant.

Competition of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/\$36.00

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doi:10.1016/j.jvs.2010.06.154

to robotic technologies and their application in vascular surgery.

CURRENTLY AVAILABLE ROBOTIC SYSTEMS

Two advanced surgical robotic systems have been used in laparoscopic vascular surgery: the da Vinci (Intuitive Surgical Inc, Mountain View, Calif) and Zeus (Computer Motion Inc, Santa Barbara, Calif) systems.¹⁰ Of these, only the da Vinci system remains in current use for abdominal surgery, since the acquisition of Computer Motion by Intuitive Surgical and the corporate decision to stop production of the Zeus robot.⁵ Both systems are comprehensive master-slave surgical robots with similar capabilities.¹³ The da Vinci system consists of three components: the vision cart, the master surgeon console, and the robotic platform. The vision system has a dual light source and dual cameras, which generate a stereo image. The surgeon operates from a console, which is physically away from the patient. The surgeon console contains an image-processing computer, which provides a three-dimensional view of the operative field with adjustable magnification, a view port, instrument and camera arm clutches, and foot pedals for electrocautery. In addition, there is motion scaling, tremor elimination, and an ergonomic working position for the surgeon. Using manipulators, the surgeon's hand movements are digitally registered through sensors and then transferred to the robotic instrument cart. Two or three robotic instrument arms and a camera arm are mounted on this moveable cart. The articulating laparoscopic instruments provide seven degrees of freedom. The Zeus robotic system consisted of a surgeon control console and three separate robotic arms attached to the sidebars of the operating table; two arms held surgical instruments and the third arm was an AESOP voice-integrated control endoscope for visualization.

Two main types of endovascular interventional robots have been devised, with different mechanisms of action: electromechanical-based, such as the Sensei robotic navigation system (Hansen Medical, Mountain View, Calif) and magnetically controlled systems such as the Niobe magnetic navigation system (Stereotaxis, St. Louis, Mo).¹⁴⁻²⁰ The Sensei robotic catheter remote control system has been designed to facilitate navigation and positioning of catheters within the cardiovascular system. It consists of the surgeon's workstation, the remote catheter manipulator, and the steerable guide catheter (Artisan; Hansen Medical). The workstation, which is mobile, may be situated away from the patient and radiation source. It consists of a master console, with display screens, and the instinctive motion controller device, which is essentially a three-dimensional hand-operated joystick (Fig). Internal sensors transfer this motion to control computers and the slave remote control mechanism, which is mounted on the operating table, transmitting the surgeon's movements to the catheter. The Artisan robotic catheter consists of a flexible, multidirectional inner guide (11 F outer diameter, 8.5 F inner diameter) within a unidirectional outer guide sheath (14 F outer diameter, 11 F inner diameter). The outer guide sheath



Fig. The Sensei robotic navigation system master console with display screens and the hand-operated joystick.

provides stability and allows the entire system to rotate. This catheter system creates a workspace defined by a bend of up to 270° with 10 cm extension of the inner guide. The steerable catheter in the current Hansen system may be directed over an independent wire, but does not depend on that wire to maneuver within the vasculature. This system allows transmission of the operator's movements to remotely direct the catheter tip.

The function of the Niobe remote-controlled magnetic navigation system is based on a magnetic field created by two computer-controlled 0.08 T permanent magnets. Changing the orientation and intensity of these magnets, the orientation of the magnetic field changes, resulting in deflection of the catheter, which is equipped with magnetic implants in its tip. A computer-controlled catheter advancing system allows the operation to be remotely performed. The Niobe magnetic navigation system can be used with 7 to 8 F diagnostic and ablation catheters with up to 120 degrees bend radius. Use of the Niobe system requires a dedicated 0.014-inch-diameter coronary guidewire (Stereotaxis). The wire contains a magnet embedded in its tip that allows the tip to be deflected by the surrounding magnetic field, and is ad-

Table I. Clinical applications of robotic laparoscopic vascular and endovascular surgery

Robot-assisted laparoscopic aortic surgery	Robot-assisted aortic anastomosis	9 papers ²¹⁻²⁹
	Robot-assisted aortic dissection	1 paper ³⁰
	Total robot-assisted aortic surgery	1 paper ³¹
Robot-assisted laparoscopic applications as adjuncts to aortic endovascular surgical treatment	Repair of type II endoleak	1 paper ³⁴
	Hybrid TAAA repair	1 paper ³⁵
Other robot-assisted laparoscopic vascular applications	Splenic artery aneurysm repair	1 paper ³³
	Renal artery aneurysm repair	1 paper ³²
Robotic steerable endovascular catheter applications	Endovascular lower extremity arterial reconstruction	1 paper ³⁹
	Endovascular AAA repair	1 paper ¹²

AAA, Abdominal aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

vanced manually. It is not hydrophilic and does not have “memory.” The stiffness of the wire is less than most commonly used guidewires. A more recent robotic system to be developed using the same magnetic principal is the Maxwell Catheter Guidance, Control and Imaging system (Engineered Magnetics, Inc, Englewood, Calif), which uses eight electromagnets to again guide a magnetically tipped catheter. These are fixed magnets that can vary the direction of the magnetic field. This system is not hindered by the lag time associated with rotating the magnet and has a focused magnetic field.

METHODS

The literature was systematically searched to identify all published studies related to robotic implementation into vascular interventions. A public domain database (MEDLINE) was searched using a Web-based search engine (PubMed) for articles published between January 1990 and November 2009. The keywords used were “surgical robotics,” “robotic surgery,” “robotics,” “computer-assisted surgery,” and “vascular surgery” or “endovascular.” Case reports, patient series, and prospective studies reporting laparoscopic vascular and endovascular treatments for patients using robotic technology were identified. Included articles were retrieved, reviewed, and summarized in this review. Seventeen articles reporting on clinical applications of robotics in laparoscopic vascular and endovascular surgery were detected (Table I). These clinical papers were critically reviewed. In view of the expected heterogeneity of data, no meta-analysis was planned. An evaluation and critical overview of other evidence for or against the use of robotic technology in this field was also undertaken.

RESULTS

Applications in laparoscopic vascular surgery. The first report on robot-assisted laparoscopic aortic surgery was published in 2002; Wisselink et al used the Zeus robotic system to construct the proximal aortic anastomosis of an aortobifemoral bypass from a console remote from the operating table in two patients with aortoiliac occlusive disease.²¹ Our systematic search of the literature identified nine studies reporting on robot-assisted laparoscopic surgery for infrarenal aortic pathologies.²¹⁻²⁹ They are either case reports or case series, and after excluding publications

with duplicate cases, four papers reporting on a total of 162 patients remained (Tables I and II).^{22,24,27,28} The Zeus and da Vinci system was used to perform the aortic anastomosis in 15 and 147 cases, respectively. Of the 162 procedures, 137 were performed for aortoiliac occlusive disease, 21 for abdominal aortic aneurysms (AAAs), and two for repair of a common iliac artery aneurysm; the type of operation was not clarified in two cases. The conversion rate ranged from 3% to 20%, with technical problems related to the robotic system and bleeding from the lumbar arteries being the most common reasons for conversion. Morbidity rates ranged from 3% to 20%. One perioperative death from myocardial infarction was described, yielding an overall mortality rate of 0.6%. Only one comparative study of conventional laparoscopic and robot-assisted aortic surgery was identified, which demonstrated shorter anastomosis time in the robotic group, even though the total operating time was longer in this group because of technical complexity with the robotic device.²⁸

Recent reports have extended the application of robotic technology beyond the construction of the aortic anastomosis (Table I). It has been proposed that surgical robotic techniques allow greater visualization and facilitate aortic dissection, and this should encourage a move toward fully laparoscopic robotic aortic surgery.³⁰ A technique of using robotic surgery as a sole modality for repair of an AAA with sac exclusion and obliteration has been described.³¹ Furthermore, robotic devices have been used in other complex reconstructive arterial procedures, expanding their use beyond the aorta. Complete renal artery aneurysm resection and reconstruction has been reported.³² Intraoperative mixed-reality technology and the da Vinci surgical system have also been used to reconstruct a splenic artery aneurysm, obviating the need for splenectomy.³³ A further step in the applicability of robotic surgery is to treat complications of and complement endovascular procedures. Robotic ligation of an inferior mesenteric artery for the treatment of a persistent type II endoleak after endovascular aneurysm repair has been reported.³⁴ Computer-assisted robotic technology has also been used as an adjunct to hybrid surgical debranching and endovascular repair of a thoracoabdominal aortic aneurysm.³⁵

Table II. Case series of robotically-assisted laparoscopic vascular procedures

Author	Kolvenbach et al ²⁸	Desgranges et al ²⁷	Diks et al ²⁴	Städler ²²
Year	2003	2004	2007	2009
Number of patients	10	5	17	130
Robot	Zeus	Da Vinci	Zeus 5, Da Vinci 12	Da Vinci
Operation	10 AAA	5 AOD	17 AOD	115 AOD, 11 AAA, 2 CIAA, 2 other
Conversion (number)	2 (hand-assisted)	1 (open)	3 (open)	3 (mini or full laparotomy)
Reason for conversion	NR	External conflicts between robotic arms	1 technical robot problem, 1 bleeding lumbar, 1 difficult dissection	1 difficulty excluding CIAA, 2 bleeding (lumbar, anastomosis)
Operative time (min)	242 (mean)	188 (mean)	365 (median)	215 (median)
Clamping time (min)	96 (mean)	75 (mean)	86 (median)	43 (median)
Blood loss (mL)	NR	540 (mean)	1000 (median)	380 (median)
Morbidity (number [cause])	1 (ARF)	1 (ischemic colitis)	1 (bleeding from prosthesis)	3 (MRSA infection, 1 incisional hernia, 1 graft occlusion)
Mortality (number [cause])	None	None	1 (MI)	None
Hospital stay (days)	7 (mean)	8 (mean)	4 (median)	5 (median)
Follow-up (months)	NR	8 (mean)	18 (median)	NR

AAA, Abdominal aortic aneurysm; AOD, aortoiliac occlusive disease; ARF, acute renal failure; CIAA, common iliac artery aneurysm; MI, myocardial infarction; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported.

Supporting evidence for the use of robotic systems in laparoscopic vascular surgery. Robotic instrumentation was initially evaluated in animal models with the implantation of infrarenal aortic grafts.¹⁰ The results obtained from this study showed that both da Vinci and Zeus robotic systems were effective in performing aortic anastomoses with the surgeon operating from a console away from the operating table. Another animal study investigated the hypothesis that robotic systems, with improved imaging and surgeon dexterity, might facilitate aortic laparoscopic procedures.³⁶ Comparison of the performance of robot-assisted and standard laparoscopic surgery revealed the superiority of the former, as evidenced by shorter procedure, suturing and clamping times, and less blood loss. The feasibility of robotic-assisted aortic anastomosis has also been tested in the thoracic aorta of animal models using the closed-chest technique.^{37,38} Of interest, the anastomosis time and hemostasis were found to be comparable between running suture techniques using the da Vinci system and interrupted nitinol clips.³⁷

Applications in endovascular surgery. Remotely controlled steerable catheter navigation and catheterization of the arterial system is a novel approach in the field of endovascular surgery. Two articles have been published documenting clinical use of robotic endovascular catheters.^{12,39} A case of successful use of the Niobe magnetic navigation system for the endovascular treatment of peripheral arterial disease in a symptomatic male with gangrenous toe ulceration has been reported.³⁹ From our unit, following experiments in *in vitro* silicon models and animal studies, a robotic-assisted endovascular aneurysm repair was accomplished in a 78-year old man with a 5.9-cm infrarenal AAA.¹² The robotic catheter was used to navigate within the aneurysm sac and access the contralateral limb of the bifurcated stent graft. In our institution, a clinical trial

approved by the Regional Ethics Committee is underway to assess the feasibility of using the robotic system *in vivo* and determine its safety and performance in clinical cases of fenestrated stent grafting.

Supporting evidence for the use of robotic endovascular catheters. Experience with computerized robotically-controlled catheter systems was initially obtained in cardiac ablation and mapping for the treatment of arrhythmias. Early investigations in animal models demonstrated the feasibility and safety of navigation within cardiac chambers and facilitation of transseptal puncture; no intracardiac damage associated with catheter manipulation occurred.⁴⁰ In another animal study, the robotic catheter system was evaluated for its ability to navigate within the heart and precision in ablation as compared with conventional ablation catheters.⁴¹ This study demonstrated reduced navigation time and precision targeting associated with the use of the robotically controlled system. The transition to application of the Sensei robotic catheter system in humans was associated with promising results.^{11,42} Preliminary experience of remote navigation for catheter ablation for the treatment of a variety of cardiac arrhythmias demonstrated its safety and clinical efficacy, as well as reduction in radiation exposure. Furthermore, results similar to conventional approaches for cardiac ablation were demonstrated.^{11,42}

Research in animal and laboratory models investigating robotic-assisted endovascular surgical procedures has been undertaken in our institution. *In situ* fenestration of an abdominal aortic stent graft with subsequent stent deployment in the right renal artery was successfully achieved in a large mammalian model with the Sensei robotic system, demonstrating the technical feasibility of this method.⁴³ Another study, comparing conventional endovascular catheters with steerable robotic catheter technology in fenestrated stent grafting using an anthropomorphic pulsatile

phantom model, demonstrated significant reductions in procedure times and increased stability at the catheter tip with robotic cannulation techniques. Overall, four-vessel cannulation times were reduced from 12 to 20 minutes using conventional catheters to less than 5 minutes using robotic technology. Improvement in operator performance was also shown, despite minimal exposure of the operators to this novel technology.⁴⁴

DISCUSSION

Although there are only a few reports on robot-assisted laparoscopic aortic surgery, contemporary results are encouraging. Only one comparative study of laparoscopic and robotic vascular procedures was identified, which demonstrated advantages in the time taken to complete the aortic anastomosis.²⁸ Although the whole procedure time was increased, one would think that the setup times may be decreased as staff become more familiar with this technology. Considering endovascular robotic catheter usage, the procedure is in its infancy, and further cases need to be undertaken before definite conclusions can be made. A literature search and analysis has demonstrated potential advantages of robotic-assisted technology over conventional vascular procedures. Even though the current evidence to support integration of robotic technologies into widespread clinical practice is insufficient, the existing results from preclinical and clinical research are promising.

Robotic technology may enhance surgery by extending human capabilities. These systems can translate a surgeon's movements into precise real-time movements of the robotic instruments inside a patient's body. The robot can manipulate tools more accurately and steadily, by incorporating hardware and software filters, which eliminate physiological tremor. Additionally, the surgeon sits at the console distal to the patient and uses a master control manipulator that sends commands to the robotic instruments performing the surgical procedure or endovascular intervention. In cases of remotely-controlled catheter navigation systems, the comfort and ergonomics of the operator is significantly increased, and surgical intervention performed from the workstation located away from the operating site is associated with significantly reduced fluoroscopy exposure for the surgeon.

Robotic surgical systems used in laparoscopic surgery can scale movements so that surgeon's movements are transformed into micromotions inside the patient (motion scaling). The additional introduction of extra degrees of freedom at the end of the instruments enhances dexterity and precision and facilitates actions that cannot be made by conventional laparoscopic instruments. Additionally, these systems afford improved vision. High-definition, three-dimensional views, with depth perception and adjustable magnification, are now possible, providing surgeons with capabilities to identify and dissect anatomic structures and perform vascular anastomoses. Another advantage is the restoration of natural hand-eye coordination; in robotic-assisted laparoscopic techniques, the fulcrum effect is eliminated, which makes instrument manipulation more intuitive.

Table III. Benefits and limitations of robot-assisted laparoscopic vascular surgery

<i>Potential advantages</i>	<i>Potential disadvantages</i>
Scaled movements	Cumbersome systems
Extra degrees of freedom	Long set-up time
Elimination of tremor	Mechanical problems
Hand-eye coordination	Absence of tactile feedback
Elimination of fulcrum effect	High cost
Ergonomic position	Not established method
Three-dimensional visualization	
Telemanipulation/surgery	
Shortened learning curve	

These benefits provided by advanced laparoscopic robotic technology and its applications in vascular surgery have led to the presumption that robotics may be of value in overcoming the long learning curve associated with conventional laparoscopic instrumentation in performing vascular anastomoses. It may be postulated that robotic manipulation does not require as much practice and maintenance of skills as conventional laparoscopic surgery. However, other authors have found that robotic assistance does not improve laparoscopic performance nor does it shorten the learning curve.^{45,46} Nevertheless, robotic surgery offers increased dexterity and visualization, which are essential in overcoming difficulties inherent to conventional laparoscopic vascular surgery (Table III). Learning curves, training programs, and assessment systems have not as yet been established, and the importance of training and experience with the robotic instrumentation has not been adequately investigated. An experimental animal model has been designed using standardized and reproducible training methods for clinical introduction of the da Vinci robotic system in visceral and vascular surgery.⁴⁷ This training program was shown to allow evaluation of surgical performance, while shortening and optimization of the learning curve was also demonstrated. Furthermore, another study evaluated the transfer of training in robotic-assisted microsurgical vascular anastomosis.⁴⁸ Both fully-trained surgeons and surgical trainees achieved technical feasibility of performing a robotic-assisted microvascular anastomosis and demonstrated the ability to equally master the robotically assisted procedure.

Similarly, whereas conventional endovascular procedures require skill and experience to navigate and catheterize target vessels, the endovascular robotic system is designed to facilitate the operator's ability to manipulate and position the catheter, potentially decreasing the learning curve. Even though learning curves in integrating this new technology have not been investigated, research from our institution has shown significantly improved overall performance using the robotic system, despite minimal operator exposure to this technology.⁴⁴ Even though the data for the Hansen system are not yet mature enough, in our preclinical study, the less experienced groups reached the same high-standard technical performance as highly experienced operators using robotic technology, something

Table IV. Benefits and limitations of robotic applications in endovascular interventional surgery

<i>Potential advantages</i>	<i>Potential disadvantages</i>
Accurate positional control	Considerable cost for system and disposable catheters
Enhanced catheterization through complex anatomy	No tactile feedback
Reduced requirements for catheter exchanges	Longer set-up times
Enhanced catheter stability	Requires greater technical backup
Reduced contrast/fluoroscopy time	
Reduced fluoroscopy exposure for the operator	
Reduced manual skill required and shorter learning curve	
Increased operator comfort	

which may impact on training and learning curves in the future.⁴⁴ Endovascular interventional robots enable surgeons to manipulate the catheter in three dimensions. Therefore, steerable catheters may be driven into tortuous vessels with difficult anatomy. Potentially, success rates and patient safety may be increased with a decrease in procedure and fluoroscopic times (Table IV).

There are, of course, several limitations to the application of robotics in laparoscopic vascular and endovascular surgery (Tables III and IV), the most obvious of these being the high cost of the systems. The da Vinci system costs approximately \$1.5 million with maintenance fees of about \$125,000 per year. Cost comparisons between robotic surgery, laparoscopic, and open techniques differ markedly, due to variation in costs from hospital to hospital and between health systems and the choice of economic model used.⁴⁸ All, however, consistently demonstrate that robotic surgery is more expensive, although a full economic model, which includes quality-of-life adjustment, has not been performed. There are no data regarding the cost-effectiveness of robotic endovascular catheter systems. The systems are again costly (over \$600,000) with high maintenance costs of approximately \$60,000 to \$80,000. An additional cost is that of disposable high-tech catheters, which are again expensive; the Hansen catheter costing upwards of \$1500. The Niobe system also requires refurbishment of the interventional electrophysiology lab. Disadvantages are also associated with the cumbersome nature and complexity of the robotic systems. The systems are large, although decreasing in size with each generation and may compete with space limitations of the operating room. The setup of the system may be time consuming, before the staff is fully trained. Mechanical and practical problems, such as interference between the robotic arms, may also add difficulties. Another potential disadvantage of current robotic technology is the absence of tactile feedback on which surgical skill is strongly dependent. In the case of the endovascular robot, lack of force-feedback information enhances the risk of vascular damage and perforation,

because a certain amount of stiffness of the active steerable catheter is required for navigation and orientation. In order to reduce these risks, a force quantification system (Intellisense Technology, Hansen Medical) has been developed, allowing constant measurements of catheter-tissue contacts.

Specific clinically established contraindications to the applications of robotic technology in vascular procedures have not been described, and the same principles as conventional procedures for aortic and peripheral arterial disease should apply. The contraindications to robotically steerable catheters are therefore those that at present preclude safe endovascular therapy, often related to access difficulties. For the Da Vinci system, the contraindications are those that also apply to laparoscopic repair of the aorta.

The enhancement of laparoscopic vascular surgery with robotic systems has not been widely adopted by vascular communities, and its role is not fully established. Experience is restricted to a few centers around the world, which have demonstrated technical feasibility with satisfactory results. Comparative trials may be required to assess the true value of robotic laparoscopic surgery compared with conventional laparoscopic and open aortic surgery to be able to quantify the advantage of the robotic system and help to justify the cost of each system. With the advent of endovascular surgical techniques, it is likely that the need for laparoscopic surgical techniques will fall. However, robotic laparoscopic vascular procedures may provide an alternative minimally-invasive surgical option in cases where anatomical factors preclude current endovascular treatments and may be used as adjuncts to currently evolving innovative treatment methods for complex aortic disease such as hybrid open/endovascular repair of thoraco-abdominal aneurysms.

The application of robotic steerable catheter systems in endovascular procedures has shown promising results within preclinical studies. However, further clinical research assessing the role of the endovascular robot is required.

AUTHOR CONTRIBUTIONS

Conception and design: GA, CB

Analysis and interpretation: GA, CR, EM, NC, CB

Data collection: GA, CR, EM

Writing the article: GA

Critical revision of the article: GA, CR, EM, NC, CB

Final approval of the article: GA, CR, EM, NC, CB

Statistical analysis: GA

Obtained funding: GA, CR, EM, NC, CB

Overall responsibility: CB

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Submitted Mar 16, 2010; accepted Jun 15, 2010.