Robotic Devices for Minimally Invasive Endovascular Interventions: A New Dawn for Interventional Radiology

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Minimally invasive endovascular interventions have become the cornerstone of medical practice in the treatment of a variety of vascular diseases. Tools developed for these interventions have also opened new avenues for targeted delivery of therapeutics, such as chemotherapy or radiation therapy, using the vessels as highways into remote lesions. A more ambitious move toward an all-endovascular approach to acute or chronic conditions, however, is fundamentally hindered by a variety of challenges, such as the complexity of the vascular anatomy, access to smaller vessels, the fragility of diseased vessels, emergency procedure requirements, prolonged exposure to ionizing X-ray radiation, and patient-specific factors including coagulopathy. These shortcomings necessitate new advances to the current practice. Smart soft-body robots that fit the smallest vessels with high-precision wireless control and autonomous capabilities have the potential to set the future standards of minimally invasive endovascular therapies. Herein, the current state of the small-scale robotics from the viewpoint of endovascular applications is discussed, and their potential advantages to the existing tethered clinical devices are compared. Then, technical challenges and the clinical requirements toward realistic applications of small-scale untethered robots inside the vasculature are discussed.

1. Introduction

Cardiovascular diseases continue to be a major cause of morbidity and mortality worldwide.[1] A variety of vascular conditions, including vascular injury, atherosclerosis, thrombosis, thromboembolic diseases, and aneurysms are responsible for the high rate of mortality. Historically, most of these conditions were addressed using open surgical techniques; however, with the advent of minimally invasive endovascular techniques, nonsurgical approaches are now favored with faster recovery times, lower perioperative mortality rates, a better quality of life, lower hospitalization, and lower intensive care unit stays.[2] In addition, endovascular procedures are typically more cost effective when compared with open vascular surgeries.[3] Using minimally invasive endovascular techniques, interventional radiologists have also enabled unprecedented local treatment strategies including transcatheter chemoembolization, radioembolization, and other ablative techniques, vascular embolization to treat hemorrhage as well as benign conditions such as benign prostatic hyperplasia and uterine fibroids, and mechanical techniques such as thrombectomy.[4]

Despite this recognized popularity, the state-of-the-art endovascular procedures still remain to be improved. Challenges include navigating complex vascular anatomicies resulting from tortuosity or diseased vessels, which may be narrowed or occluded from atherosclerosis or thrombosis. In addition, catheter-directed treatment of small vessel disease is often risky and limited to the delivery of drugs and micro-particles. Some of the recent clinical evaluations suggest that despite the reduced early mortality following minimally invasive endovascular procedures, the long-term survival rates of open surgery and endovascular interventions are comparable.[5] Furthermore, endovascular approaches may require repeated interventions. For example, rebleeding rates or failure following coil embolization of aneurysms can be as high as 47% requiring additional procedures; thrombectomy procedures may need to be staged and include combinatorial approaches that may span several days.[6] Patients that receive vascular stents may become restenosed or occluded, requiring additional procedures that may include angioplasty, additional stents or thrombolysis.[7]

Over the past several decades, there has been incremental innovation in endovascular techniques, largely limited to the development of catheters with minor improvements, more angioplasty balloons, and stents. To address the many limitations of endovascular therapies today, the next generation of minimally invasive interventions will likely involve robotics including small-scale untethered robots. The past decade has seen great interest in the development of robotic systems for healthcare applications. Devices and platforms for robot-assisted surgery, compliant soft robots, assistive devices, and pill-sized capsule endoscopes for gastrointestinal delivery[8] are among the notable examples, that underpin a progressive trend toward minimally invasive, patient-centered, precise, and personalized medical solutions.
Untethered mobile robots, smaller than a few hundred micrometers, may substantially advance the scope and success of minimally invasive endovascular procedures and targeted therapies. They can navigate through hard-to-reach vessels and distal vasculature to perform local and targeted diagnostic and therapeutic interventions with high precision and reproducibility.\(^\text{[9]}\) Advancements to this end have resulted in a number of remotely controlled small-scale mobile robotic designs in recent years (Figure 1).\(^\text{[10]}\) In spite of significant accomplishments of these and other landmark designs in bringing together smart materials and mobility control, common to all of them is that they mostly lack a comprehensive design approach that can realistically address the requirements of their target clinical applications. The design of an endovascular microrobot should be adaptable to the specific requirement of the clinical condition, including entry into the body, real-time tracking capability, antifouling, safety of operation at the targeted site, and device retrieval when required after the procedure.\(^\text{[8]}\) These aspects become even more important because any failure inside the circulatory system could rapidly escalate and result in morbidity and even mortality from nontarget embolization, perforation, vessel wall injuries such as dissection and thrombosis. This is a major potential bottleneck of any remotely controlled devices designed to operate within the vascular system. It is therefore critical to realize that the failure tolerance for devices inside the vasculature is extremely low to nil.

Here, we provide a critical perspective on next-generation endovascular devices based on emerging robotic technologies, which have increasingly become smaller, untethered, and mobile. Smart soft-body designs that can navigate within the smallest vessels with high-precision steerability represent a major engineering achievement where tethered catheters often fail. To some extent, microrobots with autonomous functional capabilities can achieve a new standard of medical practice in future minimally invasive endovascular procedures.

2. State of the Art in Tethered Endovascular Devices

Endovascular interventions are typically performed using a catheter, which is a long, thin, and flexible tube visible under fluoroscopy. Historically, catheters were first used in an endovascular intervention for the dilation of a stenosis using inflatable balloons, a procedure known as angioplasty, which was pioneered by Dr. Dotter, an interventional radiologist in 1964.\(^\text{[11]}\) Conventional catheters have a limited range of motion and flexibility and heavily rely on the skill and experience of their operators to maneuver the catheter tip to reach and interact with the target site in a stable manner. In fact, in early catheter designs, a bunsen burner was used at point-of-care to heat portions of the catheter to achieve a bend so that arteries could be better catheterized; today, catheters with fixed shapes such as a Cobra catheter are used with a one-size-fits-all approach. As a result, the shortcomings of these tethered devices are the difficulties in the operation in terms of dexterity, safety, and stability at complex anatomies and the lack of force sensing. Such factors are eventually responsible for the failures and complications of the intervention.

Two-dimensional live fluoroscopy continues to be the primary imaging strategy in endovascular interventions. Consequently, the invaluable information of the 3D anatomy of the vasculature is lost to the operator.\(^\text{[12]}\) In addition to visualization, force

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**Figure 1.** Small-scale robotic designs for potential endovascular applications. a) Soft polymer screw microswimmers that rotate around the major helical axis for propulsion. Reproduced with permission.\(^\text{[41]}\) Copyright 2015, John Wiley and Sons. b) Tethered ferromagnetic soft robot with magnetic steering and navigation capabilities. Reproduced with permission.\(^\text{[33]}\) Copyright 2019, AAAS.
sensing and haptic feedback are of paramount importance for interventionalists. New trainees especially can have difficulties until they learn how to collect and respond to these tactile cues. Handling the catheters/guidewires can become quite complicated because of the length of the catheter. For example, when the operator rotates a 150 cm long catheter, the distal tip should also rotate accordingly despite being looped around the body. As such, taking angles may not be achievable when the vector force is in a different direction from the desired direction of movement. Also, the shape and the stiffness of the tip contribute to this entanglement. While the ability of stiff catheters to be bent or turned is less, the catheters with soft tips are more difficult to advance through the vasculature due to the loss of pushability. If the origin of the targeted vessel is too small or located at an acute angle, with the consideration of the simultaneous blood flow, the catheterization process may take significant time and numerous catheters/guidewires adding to healthcare costs. Not only can this result in vessel injury, but also increases the use of contrast agents and prolongs radiation exposure to the patient and the operator. For these reasons, teleoperated robotic navigation systems have been developed. The aim of these systems includes increased dexterity and precision, reduced vessel wall contact, elimination of radiation exposure, as well as comfortable working position for the operator.[13] A setback of these teleoperated robotic navigation systems is the lack of haptic or force feedback during wire, catheter, or device manipulation, i.e., stent deployment, inflation of angioplasty balloons, or the use of thrombectomy devices. Such feedback is vital to avoid complications; to-date, they are either non-existent or in early stages of development. For example, promising work on haptic sensation combined with teleoperated robotic-assisted systems are often validated in vitro. For clinical adoption, comprehensive in vivo testing in animal models followed by patient-based studies are required.[14]

To improve the capabilities of the catheters, steerable endovascular catheters were introduced. They provide better control and remote manipulation by an operator on demand. The deflection of the distal tip of the steerable catheter is more controllable with the possibility of remote control. Therefore, they have improved accessibility to difficult anatomy and provided better catheter stability in operation. The remotely steerable catheters further enable the possibility of intervening with the patient at a distance (in another room or even many miles away), resulting in lower exposure to X-ray irradiation for the physician. Main actuation mechanisms that are used by the most common steerable catheters include pull-wire (tendon drives), smart material-actuated, magnetic, and hydraulic drives.[12,15] A number of minimally invasive clinical applications have greatly benefited from steerable catheters, including ablation procedures for the treatment of cardiac arrhythmia and the targeting of the peripheral vasculature.[15] Nevertheless, tethered device-related complications include perioperative bleeding, thrombosis, perforation, rupture, dissection, restenosis, and endovascular leaks.[16]

Food and Drug Administration has approved the use of several robotic navigation platforms in the field of interventional medicine. The Sensei X and Magellan (Hansen Medical, Mountain View, CA, USA) are among the robotic catheterization systems that have been employed in clinical practice. The Sensei robotic system has an outer sheath controlled by tendon drives in which catheters are used for various purposes such as ablation or mapping. Tendon drives can be controlled by the operator with a joystick or navigation buttons. This robotic system has been utilized for cardiac electrophysiological applications[17] and endovascular aneurysm repair.[18] The Magellan Robotic System, which has been re-engineered from The Sensei robotic system, uses a smaller outer guide catheter to navigate inside the vasculature under 2D fluoroscopy. One of the drawbacks of this system is the lack of the implementation of haptic feedback. Its application areas include a diverse range of endovascular procedures[19], including diagnostic cerebral angiography.[20] Due to its limited ability to bend around sharp corners, this system might not possess the right qualities for neurovascular interventions. In this sense, magnetic catheters can present more viable options in the cerebral vascular bed as the lower stiffness of these catheters may provide improved navigation at acute angles. In addition, catheter injury-related complications can be reduced when the catheters are less stiff. The ideal catheter system should also address size limitations to be deployed in the cerebral vasculature.

Another commercial system is the Niobe robotic magnetic navigation system (Stereotaxis, St. Louis, MO, USA), where two permanent magnets produce the magnetic field to control the tip of the magnetic catheters/guidewires. This system has also been used in cardiac electrophysiological studies and coronary and peripheral arterial disease treatments.[21] Similarly, the Amigo system (Catheter Precision) is a mechanically driven system developed to perform mapping and ablation for cardiac electrophysiology procedures. Standard electrophysiology catheters can be steered in three degrees-of-freedom (insertion/withdrawal, rotation, and tip deflection) by the remote control of this robotic system.[22]

CorPath GRX robotic-assisted platform, which is the next-generation successor of CorPath 200, includes more controlled and precise device manipulation especially after reaching the target site.[23] However, a physician is still needed for vascular access, for initial catheter guidance, for any device deployments and additional personnel are required for the procedure. The advantages that these robotic systems can bring should be considered and further efforts should be made to enhance especially the duration of their set-up, compatibility with current devices and reduce the cost to healthcare. In their evaluation of this platform toward elective diagnostic cerebral angiography and carotid artery stenting in ten patients, Sajja et al.[23] drew attention to the fact that relying on the robotics system to manage or treat medical emergencies such as stroke would be detrimental until advanced systems are available for timely use. Finally, we acknowledge that such robotic systems hold a great potential provided that breakthrough advances take place in these devices.

Having acknowledged the novelty and potential that these robotic systems can provide in terms of dexterity and precision during interventional procedures, major limitations remain. Timely access to care is critical in medical emergencies, and these systems may require time to set up and significantly extend the procedure time. In one study, for example, set up of the equipment and sterile draping added up to 70 min; this time is significantly shorter with conventional methods.[24] In clinical practice, therefore, it will be difficult to implement a robotic system for acute procedures, especially in the treatment of
hemorrhage, stroke, and myocardial infarction where speed and success of the intervention determine clinical outcome. More importantly, these systems require a substantial amount of additional operator and staff training to use; the high cost of these systems to purchase, maintain, and operate compared with conventional approaches is also a significant barrier to access. Of note, haptic feedback during these tethered robotic interventions are also lacking,[25] which can lead to poor physician experience.

3. Small-Scale Untethered Mobile Robots for Endovascular Interventions

The opportunities that vascular and interventional radiology can offer, such as better outcomes, faster procedure times, and cost savings, have been recognized in many medical centers around the globe. However, tether-based endovascular interventions harbor many challenges that need addressing via developing advanced devices and techniques. One particular approach to this situation can be the utilization of small-scale untethered mobile robots for endovascular interventions. Thus, the next-generation endovascular devices based on the latest robotic systems should mitigate and tackle the many drawbacks physicians experience today.

In many patients, vascular interventionists have to address various technical and anatomical difficulties.[26] For currently available tethered devices and techniques, navigating them inside complex vascular anatomies with dexterity and precision is one of the most critical elements influencing the results of vascular interventions. Unless endovascular interventions are performed with dexterity and precision, they may potentially result in serious complications. Hence, success in current endovascular interventions mainly depends on the dexterity of the professionals who perform these procedures. With untethered small-scale robots, one major challenge will therefore be to ensure optimum dexterity; direct human interaction with the microrobots is not possible. Scaling the force feedback teleoperation is a viable approach to this end to assist the interventionist engaged inside the vasculature.[27]

To gain access to vascular beds, various sites of deployment can be considered. For instance, in endovascular arterial procedures, the common femoral artery is generally the preferred access site to deploy conventional tethered devices, and several conditions such as iliac tortuosity, inadequate iliopelvic diameter, or aortoiliac vascular disease can limit safe and successful access to the abdominal or thoracic vasculature.[28,16a] In particular, arterial occlusive diseases that have been worsened by calcification may necessitate advanced techniques and devices to navigate through.[29] In addition, vasospasm and injury in the endoluminal surface of the arteries during the manipulation of endovascular devices can result in thrombosis.[30] Furthermore, accessing and reaching the cerebral vascular bed, which is extremely delicate and intricate, can be exceedingly tricky. Any mishap in the cerebral vasculature with a catheter/guidewire may result in significant morbidity as well as fatal complications.

To date, several robotic designs have been engineered; however, due to miniaturization challenges, they remain unfit for vascular interventions until recently.[12,31] Ferromagnetic soft robots, which are a new class of magnetically actuated soft robots, have been reported[32] and tested in a tortuous cerebral vasculature phantom with multiple aneurysms. Kim et al.[33] has shown that this self-lubricating and submillimeter-scale ferromagnetic robot has omnidirectional steering capacity and can navigate through complex environments. To reduce the friction and possibly the risk of complications, they engineered a hydrogel skin for the robot, a thin layer of hydrated and crosslinked polymers. Also, loading these robotic devices with various therapeutic agents and then releasing them in diseased areas can expand the theranostic arsenal of interventional radiology. These robotic designs have significant potential that may enable interventions, until now considered almost unattainable, especially in neurovascular applications. Management of stroke either due to an intravascular hemorrhage or acute thromboembolic event might evolve into a state where minimally invasive radiological interventions are performed using such robots that can very quickly navigate to the region of interest without injury. In another design, helical robots have been used to agitate blood clots in vitro using magnetic actuation and ultrasound visualization to investigate a potential thrombolytic application.[34]

Although such helical or ferromagnetic design concepts seem promising, there are considerable concerns regarding their practical feasibility. The diseases in which the pathophysiology is associated with atherosclerosis or thromboembolic events such as stroke, pulmonary embolism, and myocardial infarction are medical emergencies that have to be managed rapidly. Time to groin puncture is a parameter that is measured and reported in clinical practice.[35] Thus, the utilization of these microrobots and others would not be practical today. Manipulating atherothrombotic plaques can also be dangerous because these structures are neither stable nor degradable by drugs such as tissue plasminogen activator (tPA). Due to their heterogeneous nature, it would be challenging to use these helical and other robots to agitate vascular occlusive diseases and risk distal fragmentation, which can lead to exacerbation of the ischemic disease. In addition, navigation of such bulky devices to the target vasculature, inability to control the diameter of the robotic motion risking vessel wall injury and rupture, and the difficulty in safe retrieval of these devices further increase the risk of these interventions.

Altogether, there are many challenges in developing robotic devices that could be implemented in clinical practice. Broad clinical adoption necessitates significant questions to be answered: How will these “robots” be delivered to the site of the pathology; will it be catheter-based initially? How will these robots be navigated? How will the equipment that allows magnetic-mediated motion and concurrent visualization (via fluoroscopy) engineered? Once these robots reach the region of interest, i.e., thrombus causing stroke, will magnetic motion generate heat and subsequently worsen the situation, if so, what measures will be taken to tackle this? How will the fragmentation and distal nontarget embolization be prevented? Will an embolic protection device be necessary? How will it be determined if the intervention was achieved? Perhaps most importantly, how will these robots be removed? Given that any injury to the intima layer could result in catastrophic complications, how will the motion of the robots stay confined within the vessel wall with magnetic motion?
4. Approach to Robotic Intravascular Procedures

Despite a number of proof-of-concept studies to this end, however, a promising small-scale medical robot targeting a well-defined endovascular problem has not yet been available. This is in part because the development of microrobot designs are challenged by the requirements of their targeted clinical applications. The following sections describe some of the challenges that may need to be addressed in the development of small-scale robots for endovascular applications.

4.1. Patient-Inspired Design Approach

Previously, we advocated for a patient-inspired engineering approach to medical devices to provide engineering solutions to specific problems in medicine. Physicians can provide key insights into clinical problems and disease diagnoses, as well as their challenges in clinical management, clinical progression, and long-term outcomes. Based on this, understanding how a disease impacts the patient can help guide the selection, exploration, development, and translation of potential engineering solutions. While there are many inspirations to the engineering solutions we see today in biology and medicine, we believe that a patient-inspired approach to engineering robotics, would best align the tools developed to the medical needs. A patient-inspired approach that comprehensively focuses on the clinical problem will require closer interactions between scientists, engineers, and physicians. This will increase the translational impact of small-scale robotics in endovascular applications and in all aspects relevant to patients (Figure 2).

4.2. Imaging and Tracking

Tracking of robots moving inside the vasculature is essential for the safety, reliability, and precise application for any given endovascular procedure. Therefore, the design of a small-scale robot should always be compatible with the currently available medical imaging modalities and tracking strategies for specific medical applications. Most of the small-scale robotic studies have demonstrated their operations under optical microscopes or other technologies for nonvascular applications. However, these strategies have not been tested in an in vivo, endovascular setting. A suitable imaging and tracking modality should also be compatible with the actuation method. Physician familiarity with the clinical imaging modalities is also critical for the rapid adaptation to the new techniques. The wide availability and easy access will reduce the cost of adoption, allowing widespread use of robots in clinical practice. The spatial resolution of the instrument, the image acquisition rate, and the penetration depth may be interdependent and can be best optimized for a given medical task. The robotic design parameters such as size, material type, localization accuracy should always be evaluated given the medical requirements and the interdependent parameters of the imaging modalities.

4.3. Hemocompatibility and Biocompatibility

The material composition of a small-scale robot plays the leading role in enabling its prescribed function. Typically, a base material forms the body shape and acts as the carrier matrix for incorporating other subcomponents. The choice of the right base material needs evaluation based on the biocompatibility, mechanical properties, and suitability for manufacturing in the desired shape and composition. The mechanical properties may be important for making a soft robot that relies on shape deformation. A diverse type of information can be encoded by controlling the physical and chemical properties of the robot locally. The interior body shape is vital to create hierarchical and composite designs for encoding magnetic information. Coupled sensing and response capabilities in the material composition can further enable a robot design for achieving dynamic interactions with the environment. This is achievable with materials that are responsive to either remote, e.g., light, temperature, magnetic, and acoustic or local biochemical signals, including pH.

Thrombosis on the robot can impede robotic functionality and may lead to fragmentation to cause distal tissue ischemia and infarction. In the case of soft deformable robots, thrombus can seriously change the mechanical rigidity of the deformable material. In microswimmers, the altered surface chemistry could change the polarity of the microswimmer that would result in impaired motion control. The loss of motion control can further evolve into a scenario where a critical vessel may be permanently occluded.

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The material design of the soft robot will also require it to be immunologically inert. Any complement activation, for example, may render the soft robot immediately nonfunctional. Furthermore, an inflammatory response to these soft robots may have systemic consequences; both short-term and long-term in vivo studies to better understand the systemic responses to these materials will be required. In addition, soft robots that remain intravascular for long periods of time, whether for intended or unintended purposes, their biodegradation, clearance, and toxicity profile will be important.

4.4. Mobility, Steering, and Control

Retrieval of the untethered small-scale robots is a big challenge. Conventional catheters are easy to pull back via their long tether. Small-scale robots lost to control will be carried distally by the blood flow to occlude blood vessels. Particularly, the occlusion of cerebral and pulmonary vessels can result in critical conditions and may prove fatal. Therefore, reliable robotic control, retrieval,
and alternative contingency scenarios are critical features to develop small-scale robots for endovascular applications. A viable strategy to this end may be biodegradable robots that rapidly degrade into biocompatible, nontoxic byproducts in the case of an emergency. Materials that predictably decompose and disappear over time as a result of the resident biological activity have become increasingly important for medical applications. Such degradation could be achieved through enzymatic degradation or solubilization in physiologic fluids.[40] The degradation products should not induce blood clot formation that could create an embolus. Robots not adopting this design aspect may complicate their clinical use due to potential adverse effects in vivo, which may result in severe acute and chronic toxicities and might require additional interventions. Untethered robots can be combined with the delivery catheters, where the catheter is used to deploy and retrieve the robot inside the vasculature.

4.5. Autonomy

Untethered mobile robots may have components designed to deliver visual feedback from within the patient as it moves and functions autonomously in their environment or to be teleoperated by a physician directly using external stimuli or forces.[40] These robots may be coordinated to operate as single entities, teams, or swarms, performing parallel and distributed tasks. The medical operation of an untethered robot inside the vasculature should also include a contingency plan in case the pathological conditions evolve and the robot fails to respond in time. As the level of autonomy and competence of robots increases, the role and responsibility given to the robots may overlap with the physician, which can also trigger new ethical questions in the future. Depending on the medical scenario, fail-safe strategies may be necessary that would contain the situation in case the execution of the given medical task fails or adverse effects are observed.

4.6. Physician Adoption

A critical aspect to consider in the development pipeline of any biomedical device is its adoption by the physician or other relevant healthcare providers, which is often overlooked or simply not considered. A small-scale endovascular robot needs to be intuitive, easy-to-operate, and cost effective and should perform the intervention better than the current standard of medical practice. The learning curve to operate these small-scale robots should be steep.

5. Conclusion

Despite technological achievements, robotic systems thus far face significant challenges when clinically applied. Indeed, more collaboration between clinicians and engineers will help guide existing efforts and improve the outcomes of scientific research. The key to developing a robotic system that would become ubiquitously available in the clinical environment lies in the strong team work, which would enable engineers to better understand the challenges experienced by clinicians and subsequently formulate solutions to these specific challenges. The next-generation tools for image-guided minimally invasive interventions could be based on untethered soft robots; however, much remains to be done before they are deployed within veins and arteries.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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