New Technology for Surgical Coronary Revascularization

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In the past decade, the face of surgical coronary revascularization has been changed by a number of advances, most notably the development of minimally invasive techniques, including minimally invasive direct coronary artery bypass (MIDCAB), off-pump coronary artery bypass (OPCAB), and totally endoscopic, robot-assisted coronary artery bypass grafting (TECAB). Initial attempts to perform cardiac operations through small incisions were hindered by the absence of appropriate accessory technology, such as visualization systems, anastomotic devices, stabilizers, and alternative methods of vascular cannulation and cardiopulmonary bypass. With the development of these technologies, surgeons have been increasingly able to perform complex cardiac procedures, including coronary artery bypass grafting (CABG), mitral and aortic valve replacement, and atrial septal defect closure, through smaller-than-traditional incisions. Nonetheless, in many cases, the extent to which incision size has been reduced by these minimally invasive approaches has been matched by a corresponding increase in technical difficulty and operative time—and a potentially decreased safety margin—owing to the constraints imposed by limited or incomplete cardiac exposure.

The emerging field of cell-based therapy represents an attractive alternative to surgical bypass. Spurred on by rapid advances in our understanding of vascular biology and positive results from studies of small- and large-animal models, a number of clinical trials have been conducted exploring the use of multiple cell types, either as sole or adjunctive therapy at the time of open heart surgery. Although significant myogenesis remains elusive, substantial progress with angiogenic cell therapy warrants discussion in the context of surgical revascularization. It is likely that the future will bring a convergence of several new technologies, as the way that we treat coronary vascular occlusive disease continues to evolve.

Surgical Revascularization Procedures

Robotic Surgical System

Computer (robotic) enhancement has emerged as a potential facilitator of minimally invasive surgical procedures. Initially, this technology was utilized to maximize visualization of intracardiac structures by providing enhanced (including voice-activated) endoscopic camera control.[1] More recently, robotic surgical systems have permitted the manipulation of surgical instruments through limited thoracic incisions.[2] The Da Vinci Surgical System (Intuitive Surgical, Inc, Mountain View, Calif) consists of 2 primary components: the surgeon's viewing and control console and the surgical arm unit that positions and maneuvers detachable surgical EndoWrist instruments (Figure 1). These pencil-size instruments, which possess small, mechanical joints with 7 degrees of motion, are designed to provide the dexterity of the surgeon's forearm and wrist at the operative site through entry ports <1 cm. One port allows access for the endoscope, and the other 2 ports provide access for surgical instruments. The wrists of the surgical instruments mimic the motions made by the operating surgeon, who sits at a console away from the operating table. The surgeon peers through an eyepiece that provides high-definition, full-color, magnified, 3-dimensional images of the surgical site provided by the endoscope.

IMA Harvest and TECAB

Shortly after its clinical introduction in 1998, the Da Vinci system was first used for endoscopic internal mammary artery (IMA) harvesting. Robotic IMA harvest was associated with a manageable learning curve and gained widespread application in centers utilizing robotic technology for cardiac surgery.[3] In brief, patients are placed in a supine position with the left chest slightly elevated by a roll. The left arm is lowered beyond the level of the posterior axillary line. Double-lumen intubation with selective right-lung ventilation is used, and a 12-mm Sealing-Port (Ethicon, Cincinnati, Ohio) is inserted into the fourth intercostal space (ICS) in the anterior axillary line. Two instrument ports are inserted into the third and sixth ICSs above the anterior axillary line, and the Da Vinci system is placed on the patient's right side. The dissection is performed laterally to the phrenic nerve and medially up to the first rib by low-energy cautery. Distally, dissection is performed up to the sixth ICS. After IMA dissection is complete, the Da Vinci system is withdrawn. Several large series have been published,[4,5] with harvest times <30 minutes being reported by experienced surgeons.

Early success with endoscopic IMA harvest paved the way for the development of a TECAB operation. Loulmet and colleagues[6] reported the first successful TECAB in 1998, and others soon followed.[7] In brief, the left IMA is harvested as described earlier, ligated distally, and clipped. The pericardium is incised at the mediastinal attachment, the incision is

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Figure 1. Example of the Da Vinci EndoWrist instrument.

enlarged laterally, and the left anterior descending coronary artery (LAD) and its collateral branches are identified. After systemic heparinization, the left IMA (LIMA) is skeletonized and clipped distally. The LIMA is divided, spatulated, and prepared. Next, the femoral artery is cannulated with an endoaortic balloon cannula system (Figure 2), and the balloon is positioned in the ascending aorta under transesophageal echocardiographic guidance. The femoral vein is cannulated with a long venous cannula that is directed into the right atrium. At this point, the endoaortic balloon system is deployed to cross-clamp the aorta and to deliver antegrade cardioplegia. Once cardiac arrest is confirmed, the robotic system is used to perform the coronary arteriotomy and the LIMA-to-LAD anastomosis. The endoaortic balloon clamp is removed, with external defibrillation if necessary. The robotic system is removed, and the patient is weaned from cardiopulmonary bypass.

While initially restricted to single-vessel, LIMA-LAD revascularization, cases of alternative vessel and multiple bypasses have been reported. Dogan et al[8] performed a successful totally endoscopic LIMA-LAD and right IMA–right coronary artery (RCA) operation in a young diabetic patient, and Farhat et al[9] reported the first off-pump, bilateral IMA bypass using a conventional OPCAB stabilizer and coronary shunts introduced through a subxiphoid port.

Figure 2. Endoaortic balloon cannula used during TECAB.

A number of technical issues related to TECAB have prevented its widespread acceptance and deployment. The learning curve is significant, which has translated into long operating room (OR) and cardiopulmonary bypass times.[10,11] In addition, conversion rates to minimally invasive access or conventional sternotomy remain high and are often related to the difficulty with remote-access perfusion or inadequate intrathoracic working space.[10,12] Nevertheless, given the feasibility demonstrated largely by European centers, a multicenter, US Food and Drug Administration–sanctioned, investigational device exemption trial investigating the safety and efficacy of arrested-heart, single-vessel TECAB was conducted and recently completed by Argenziano and colleagues.[13] Although the trial was restricted to single-vessel, LIMA-LAD anastomosis with the use of cardiopulmonary bypass, the investigators reported a low, 6% conversion rate, with an acceptable freedom from reintervention or angiographic failure.

Innovative efforts to reduce OR times, conversion rates, and technical error continue. Falk and colleagues[14] are developing 3-dimensional imaging algorithms that combine patient-specific registration of anatomic landmarks with conventional imaging techniques, such as coronary angiography and computed tomography scanning to produce virtual models. These models can then be used to guide proper port placement and instrument trajectories and avoid intrathoracic and extrathoracic collisions. Continued refinement of the beating-heart technique has also reduced procedure times in some centers.[15] Finally, the use of anastomotic devices (discussed later in this review) offers another way to greatly reduce OR times.[16]

Minimally Invasive Direct Coronary Artery Bypass

An alternative operation to TECAB for isolated LAD disease is the MIDCAB. The IMA can be harvested either under direct vision[17] or with robotic assistance,[18] as described previously. A small anterior thoracotomy is made in the fourth ICS, and an off-pump, hand-sewn LIMA-LAD anastomosis is performed under direct vision. This eliminates the need for femoral cannulation and cardiopulmonary bypass and greatly reduces procedural times compared with TECAB. In a trial of 220 patients with isolated proximal LAD disease randomized to MIDCAB or stenting, no difference in 6-month survival was observed between the groups.[19] However, a major adverse cardiac event occurred in 31% of stented patients versus 15% of surgically treated patients, driven primarily by the need for target-vessel revascularization (29% in stented patients versus 8% in the MIDCAB group). In addition, freedom from angina at 6 months was 79% in the MIDCAB group versus 62% in the stent group. A more recent retrospective series by Shirai et al,[20] comparing stenting to MIDCAB, reported similar results. Subramanian and colleagues[21] recently reported on a series of 30 consecutive MIDCAB patients who received an average of 2.6 anastomoses and demonstrated that with appropriate selection and fast tracking, 97% of MIDCAB patients were extubated in the OR, and 77% were discharged in 1 to 2 days postoperatively.

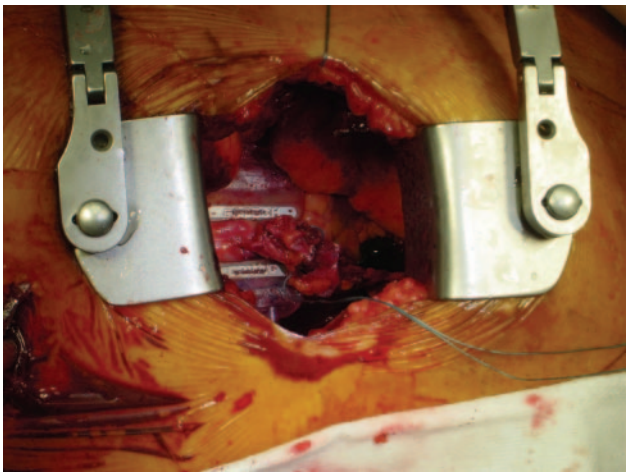


Figure 3. Direct coronary anastomosis performed through a 6-cm anterior minithoracotomy during MIDCAB surgery.

At our institution, we have performed >40 MIDCAB procedures utilizing the Da Vinci system for endoscopic LIMA harvest and a 6-cm anterior thoracotomy for direct coronary anastomosis (Figure 3). We have also developed a novel suction stabilizer that is deployed through one of the robotic trochar sites and greatly facilitates sewing of the anastomosis (Figure 4). When compared with all single-vessel OPCAB procedures performed during this same period, our MIDCAB patients had a shorter hospital length of stay (4.6±1.9 versus 6.4±3.5 days, $P<0.01$) and more frequently returned to work within 6 weeks (82% versus 39%, $P=0.018$). MIDCAB procedures have also been employed successfully for reoperations,[22,23] obviating the need for a redo sternotomy and reducing operative morbidity in these high-risk patients.

Hybrid Revascularization

For patients with complex lesion sets not amenable to any of the aforementioned approaches, another newly emerging alternative is hybrid revascularization. Under this paradigm, both percutaneous coronary intervention and minimally invasive CABG surgery are performed during the same procedure. Typically, the LIMA is anastomosed to the LAD, whereas the right and circumflex systems are stented. Kiaii et al[24] reported the first case involving a 64-year-old diabetic patient with a history of diabetes and renal insufficiency status after liver transplantation who was admitted with chest pain and diagnosed with proximal LAD and RCA lesions. Using an enhanced OR suite (Figure 5) employing both a digital C-arm and the Da Vinci system, the investigators performed a robot-assisted MIDCAB followed by stenting of the RCA without complication. Although there are several logistical hurdles involved with combining percutaneous and surgical revascularization in a single procedure,[25] approaches such as these combine the long-term patency of LIMA-LAD grafts[26] with equivalent stenting outcomes in other vessels[27] to produce functionally complete revascularization with minimal trauma and acceptable outcomes.

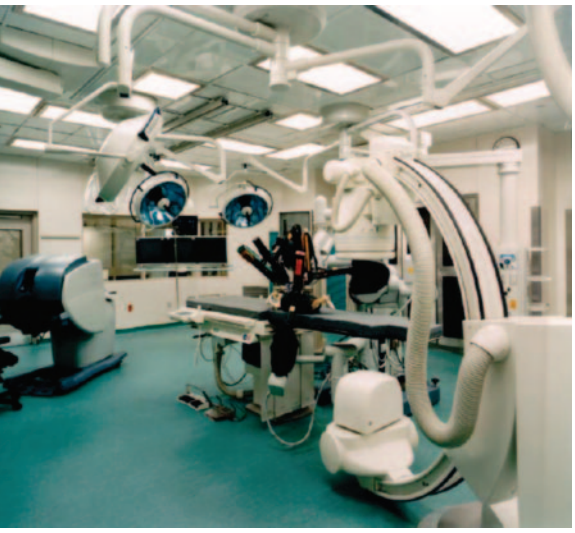
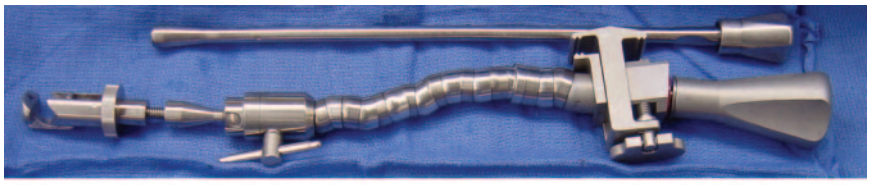


Figure 5. A hybrid OR that utilizes both robotic and percutaneous technology. Reprinted with permission from *Chest*.[24] Copyright 2005.

It is important to note that although minimally invasive techniques for surgical revascularization have been in clinical



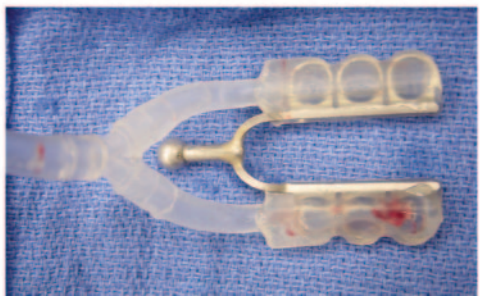


Figure 4. Port-deployed MIDCAB suction stabilizer.

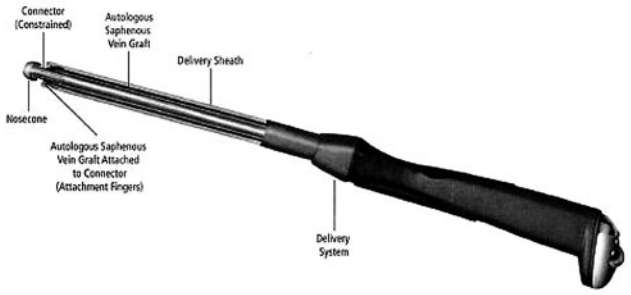


Figure 6. The Symmetry proximal anastomotic connector. Reprinted from *Journal of Thoracic and Cardiovascular Surgery*[35] with permission from the American Association for Thoracic Surgery. Copyright 2005.

use for almost a decade, their adoption by the surgical community has been variable. Reasons include the initial cost of the robotic system ($1.53 million for the latest version), a relatively steep learning curve, and significantly longer OR times. Nevertheless, Intuitive Surgical has installed ≈300 Da Vinci systems in the United States for cardiac surgical applications.

Anastomotic Devices

With the increase in off-pump, minimally invasive, and totally endoscopic CABG procedures being performed, another area of technological innovation has been the development of anastomotic devices. The goal that all of these devices share is to create a reproducible, geometrically optimal anastomosis with minimal blood-exposed surface and little or no endothelial damage. A myriad of experimental designs exist, from which some of the most common are discussed. Although a number of the early devices have failed in clinical trials and have been removed from the market, technological advances and continued refinement continue to bring potential designs into the clinical arena.

St. Jude Symmetry Aortic Connector

The St. Jude Medical Anastomotic Technology Group has developed devices for both proximal and distal saphenous vein graft (SVG) anastomoses. The proximal device, otherwise known as the Symmetry proximal anastomotic connector (St. Jude Medical, Inc, St. Paul, Minn), was the first to market and was designed to eliminate aortic manipulation and reduce postoperative cerebrovascular events in patients with extensive aortic calcification. The Symmetry system consists of a nitinol connector, a delivery system, and an atraumatic rotatable blade to create a precisely sized, round hole without the need for an aortic partial-occlusion clamp.[28] Once the aortotomy is created, the aortic connector system with loaded SVG is inserted into the neo-ostium, and the aortic connector is deployed by pushing a button on the top of the handle (Figure 6). Simply pulling back the handle perpendicular to the anastomosis deploys the external struts and completes the anastomosis in a matter of seconds.

Several large series have been published evaluating the Symmetry device, with somewhat conflicting results. Kitamura et al[29] followed up a cohort of 31 patients in whom at least 1 proximal anastomosis was made with the Symmetry device,

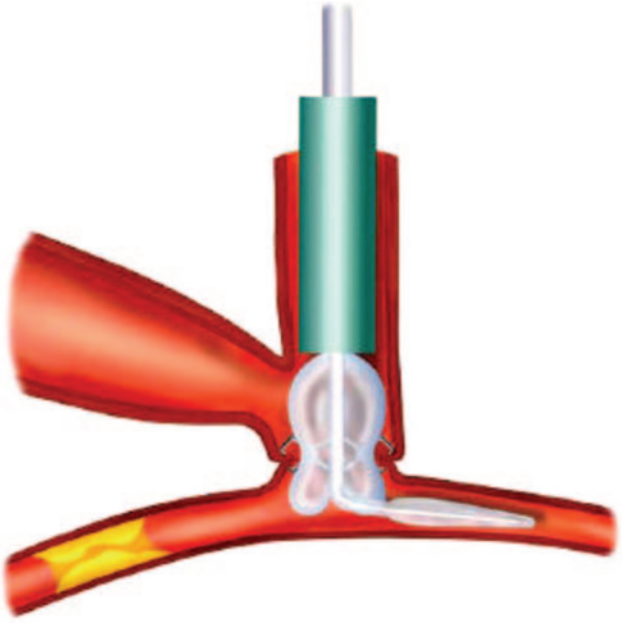


Figure 7. St. Jude distal anastomotic device. Reprinted from *Journal of Thoracic and Cardiovascular Surgery*[28] with permission from the American Association for Thoracic Surgery. Copyright 2002.

with discharge and 1-year patency rates of 100% and 92.6%, respectively, by angiography. They noted 2 vein graft occlusions at 1 year, both of which occurred in patients with low graft flow at the time of operation. However, in a series of 38 anastomoses performed during OPCAB, Toyama and colleagues[30] documented early SVG events in 24% of patients, with 8 complete occlusions and 1 case of stenosis, although multivariate analysis failed to identify any significant predictors. In a larger series of 166 patients in whom at least 1 proximal anastomosis was performed with the Symmetry proximal anastomotic connector, Dewey et al[31] found a higher incidence of early major adverse cardiac events driven by a need for target-vessel revascularization, primarily in diabetics. Finally, Skjelland et al[32] employed continuous multifrequency transcranial Doppler scanning during OPCAB and documented no increase in solid emboli but a significant increase in gaseous emboli associated with the Symmetry device compared with standard suturing techniques with partial aortic occlusion. Ongoing concerns over early and mid-term postoperative graft compromise have hindered widespread adoption of this technology and will need to be addressed by future trials or device design modifications.

The St. Jude Medical Anastomotic Technology Group has also developed a device for distal vein graft–to–coronary artery anastomoses. This device uses a delivery system that is inserted through one end of the vein graft (Figure 7). A side hole is made in the SVG through which the delivery device is inserted into the lumen of the target coronary vessel. A balloon on the nosecone is then inflated to deliver the anastomotic clip. The balloon is then deflated, and the device is removed through the end of the SVG. The first clinical use was reported in 2002,[33] and initial follow-up was promising.[34] However, more recent randomized, controlled studies[35] have again demonstrated significantly higher rates of occlusion

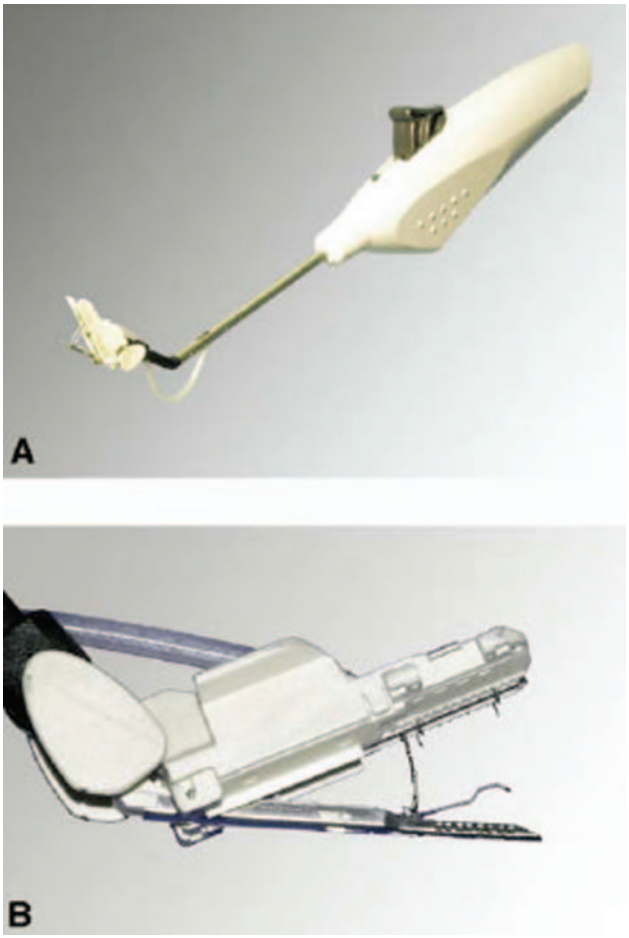


Figure 8. The Cardica C-Port System. Reprinted from *Journal of Thoracic and Cardiovascular Surgery*[36] with permission from the American Association for Thoracic Surgery. Copyright 2005.

(26% at 190 days) compared with hand-sewn anastomoses. As a result, this device was pulled from the market.

The Cardica C-Port Anastomotic System

The Cardica C-Port (Cardica, Inc, Redwood City, Calif) and PAS-Port Anastomotic Systems were recently introduced to facilitate SVG-to–coronary artery distal and proximal anastomoses. The C-Port system (Figure 8) utilizes 8 stainless steel anastomotic clips, each of which has 4 tines that provide a total of 32 points for tissue approximation. A vein graft is loaded onto the device, and a small nick is made in the target vessel to allow insertion of the device's anvil. Once inserted, depressing the device trigger results in clip deployment. A small blade located within the anvil completes the arteriotomy and then releases the device. Hemostatic sutures are then applied as necessary to the anvil hole, toe, and heel of the anastomosis. In a recent series of 133 patients, 130 distal anastomoses were attempted with use of the C-Port system.[36] Of these, 14 were converted to a hand-sewn anastomosis secondary to incomplete anastomoses or inadequate distal flow. Freedom from stenosis on angiography was 96.2% at discharge and 92.1% at 6 months, which represent significant improvements over conventional vein graft patency rates reported in the recent literature.[37] Randomized, controlled trials will need to confirm these initial results before widespread adoption is seen.

Ventrica Magnetic Vascular Port System

The Ventrica Magnetic Vascular Port (MVP) system was designed specifically for use in reduced exposure (MIDCAB and TECAB) CABG. The MVP Series 6000 Distal Anastomosis System consists of 2 sets of clips, an elliptical intravascular magnet, and 2 extravascular magnetic clips preloaded on a delivery instrument (Figure 9). One set of clips forms the anastomotic port in the graft vessel, and the other set forms an identical anastomotic port in the target coronary artery. Instantaneous coupling occurs by bringing the 2 ports within close proximity to each other, forming a self-sealing end-to-side or side-to-side anastomosis. The device has been used for MIDCAB IMA,[38] SVG,[39] and radial artery[39] grafting, with good short-term results in small series.[40] At least 1 case of anastomotic compromise has been reported in a patient noncompliant with antiplatelet therapy.[41] More detailed midterm and long-term follow-up will be needed to assess the patency and obstruction rates associated with this device.

Several other anastomotic devices are in preclinical testing or have seen very limited clinical use. These include the CorLink Automated Anastomotic Device for proximal SVG-aortic anastomoses,[42] the Novare Enclose device,[43] and the Heartstring Aortic Occluder[44] from Guidant (St Paul, Minn). Evolution of these devices, particularly in the minimally invasive and endoscopic arena, will continue. However,

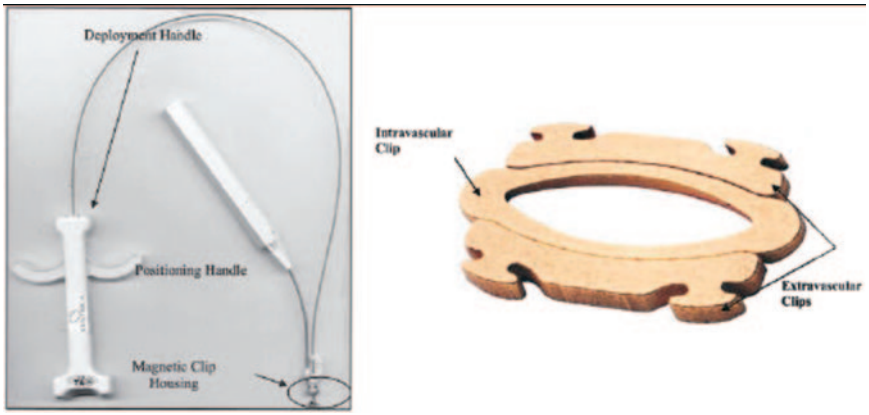


Figure 9. The MVP Series 6000 Distal Anastomosis System. Reprinted from *Circulation*[38] with permission from the American Heart Association. Copyright 2004.

multicenter, randomized demonstration of long-term patency at least equivalent to hand-sewn results must follow before widespread penetrance of these technologies is realized. As minimally invasive and endoscopic techniques undergo continued refinement, the need for a simple, reliable anastomotic device will become more pronounced.

Off-Pump Coronary Artery Bypass

Although OPCAB has been in practice for >10 years, it is sometimes discussed in the context of minimally invasive CABG and will be briefly mentioned here. Initial enthusiasm centered around the ability to perform CABG without the deleterious effects of extracorporeal circulation. Two recent randomized trials[45,46] comparing OPCAB with conventional CABG demonstrated reduced hospital length of stay and decreased transfusion requirements in the OPCAB group. However, other large, randomized trials have shown no difference in length of stay[47] and have called into question the long-term patency of OPCAB grafts.[48] Because of the continued release of both positive and negative study findings, the role of OPCAB in coronary revascularization remains controversial.

Cell-Based Approaches to Surgical Revascularization

During the past decade, explosive growth in the fields of vascular and developmental biology has led to the characterization of multiple cell types with the potential for supporting angiogenesis, myogenesis, or both. The cells can be loosely classified into 3 groups: somatic, bone marrow derived, and embryonic. Virtually every cell type examined has shown some degree of efficacy in animal models, although the exact mechanisms of functional recovery often remain unknown. Nevertheless, results from small- and large-animal studies have been used to justify early clinical trials involving both surgical and catheter-based delivery in the acute and chronic setting. For the purposes of this discussion, an overview of the basic science behind the various cell types will be provided, clinical trial results will be summarized, and some of the issues relevant to surgical delivery of cell-based therapy will be highlighted.

Skeletal Myoblast Transplantation

Skeletal myoblasts, also known as satellite cells, are precursor cells of skeletal muscle. They are normally found under the basal membrane of muscle fibers in a quiescent state but have the potential to reenter the cell cycle, divide, and differentiate into functional skeletal muscle in response to injury. Skeletal myoblasts were the first form of cell therapy to enter the clinical arena in 2000 for several reasons. They have high proliferative potential, yielding >1 billion cells from a single biopsy, yet they are sufficiently lineage restricted to eliminate the threat of tumorigenicity.[49] In addition, they are autologous and therefore do not provoke immune system–mediated rejection and are highly resistant to ischemia.

Several surgical trials have been reported on the implantation of skeletal myoblasts at the time of either CABG[50,51] or left ventricular assist device insertion.[52] In the 2 CABG trials, an improvement in regional contractility was documented by echocardiography in the cell-injected segments, as well as an increase in left ventricular ejection fraction. Menasche et al[50] noted a high incidence of postimplantation ventricular arrhythmias severe enough to require an automated implanted cardioverter/defibrillator in 4 of 10 patients. Dib and colleagues[52] noted similar functional improvements in their study and a lower incidence of ventricular arrhythmias, raising the possibility that the 40% incidence in the study of Menasche et al was an overestimate owing to small sample size. Interestingly, histological assessment of the hearts from left ventricular assist device patients bridged to transplant demonstrated long-term survival and engraftment of injected myoblasts. Because both of these studies combined cell injection with a concomitant surgical procedure and did not include a control group, the relation between myoblast delivery and functional improvement remains unknown. A multicenter, dose-escalation study is currently under way and should shed more light on both the safety and therapeutic potential of skeletal myoblasts.

Bone Marrow–Derived Stem Cells

The discovery of circulating endothelial progenitor cells,[53] their mobilization in response to ischemia,[54] and their origin and isolation from human bone marrow[55] has stimulated intense translational research focused on using bone marrow–derived elements to regenerate ischemic myocardium. The bone marrow compartment can be subdivided into 2 interdependent spaces: the hematopoietic cell compartment and the stroma. The stroma is composed of fibroblasts, adipocytes, nerves, and the bone marrow's vascular system, which consists of a network of fenestrated, thin-walled vessels supported by the surrounding hematopoietic cells. The hematopoietic compartment produces ≈500 billion cells per day, which use the bone marrow vasculature as a conduit to the systemic circulation.[56]

The hematopoietic compartment contains a multitude of cell types in varying stages of differentiation. Cells can be harvested for transplantation either directly by bone marrow aspiration or indirectly through peripheral blood mobilization. The latter method includes granulocyte colony stimulating factor to stimulate mobilization, followed by apheresis to isolate peripheral blood mononuclear cells (PBMNCs) from the circulation. Direct bone marrow aspiration followed by density gradient separation of whole marrow is typically used to isolate bone marrow mononuclear cells (BMMNCs). Either method produces a heterogeneous population of cells containing monocytes, hematopoietic stem cells, endothelial precursors, and assorted other elements. In animal models of acute myocardial ischemia, immunoselected cells from the mononuclear portion of human bone marrow induced angiogenesis in the infarct border zone, reduced myocyte apoptosis, and inhibited left ventricular remodeling and dilation.[55]

Encouraged by preclinical data from PBMNC and BMMNC[57] injection into ischemic myocardium, a number of surgical groups have administered mononuclear cells at the time of CABG or other open heart surgery. Patel et al[58] recently published a prospective, randomized study of BMMNC injection at the time of conventional OPCAB

surgery. Bone marrow was harvested from the iliac crests at the time of surgery, and the mononuclear portion was injected through a 22-guage needle with side holes into viable but dyskinetic segments after completion of OPCAB. Although concurrent revascularization confounds data interpretation, the patients treated with BMMNCs demonstrated a sustained greater improvement in ejection fraction than did the OPCAB-alone group (46% versus 37% at 6 months). A similar Italian trial[59] using BMMNC injections into the border zone during on-pump CABG also demonstrated a small improvement in ejection fraction as well as regional wall-motion score index. Finally, in an uncontrolled trial, Yaoita and colleagues[60] randomized patients to either apheresis or bone marrow aspiration, followed by PBMNC or BMMNC injection at the time of OPCAB. Using single-photon emission computed tomography, the investigators found an equivalent increase in myocardial perfusion in segments receiving either cell type.

BMMNCs and PBMNCs express a variety of surface markers that can be used to isolate subpopulations of true vascular progenitor cells. One such marker, CD34, was originally used to identify hematopoietic stem cells for the reconstitution of hematopoiesis after myeloablative therapy[61] and is also expressed by endothelial progenitor cells in both the marrow and circulating blood.[53,55] A second marker, AC133, corresponds to an epitope on the transmembrane protein prominin-1 and similarly can be used to isolate hematopoietic and endothelial progenitor cells.[62] Because the CD34+ and AC133+ populations represent a minor fraction of total BMMNCs or PBMNCs, inserting an isolation step increases the homogeneity but decreases the absolute number of cells available for injection. Whether this has an impact on the safety or efficacy of revascularization remains to be seen.

In a phase I study, Stamm et al[63] performed bone marrow aspiration in 12 patients 1 day before CABG surgery. AC133+ cells were isolated with use of a ferrite-conjugated antibody and the CliniMacs Magnetic Cell Separation Device (Miltenyi Biotech, Bergisch Gladbach, Germany) and injected obliquely into the infarct border zone through a standard 1-cm^3 syringe and 20-guage needle at the time of CABG. A significant improvement in left ventricular ejection fraction, decrease in left ventricular end-diastolic dimension, and increase in myocardial perfusion compared with preoperative values was seen at 2 weeks. In the subset of patients with available long-term follow-up data, the authors noted sustained improvements in ventricular function and perfusion. Small studies using CD34+ cells at the time of CABG[64] or AC133+ cells at the time of transmyocardial revascularization[65] have also been reported.

In general, the degree of functional improvement seen with PBMNCs, BMMNCs, or an immunoselected subpopulation thereof is relatively small. This is true of several catheter-based trials as well,[66,67] wherein ejection fraction improvements are typically on the order of 5% to 7%. Although regional differences in contractility and perfusion can be demonstrated, the presence of concomitant revascularization procedures makes data interpretation difficult. However, enough data have been collected to ensure the relative safety of surgical bone marrow–derived mononuclear cell injections. Indeed, the ventricular arrhythmias that plagued some of the early skeletal myoblast trials have not manifested with BMMNC- or PBMNC-derived cells. Larger multicenter, randomized trials will be needed to ascertain their true reparative potential.

Mesenchymal Lineage Cells and Future Directions

Mesenchymal stem cells (MSCs) represent between 0.01% and 0.001% of nucleated cells in adult human bone marrow but can be readily expanded in culture.[68] Unlike endothelial progenitors, which, for the most part, are lineage restricted, MSCs readily form bone, fat, cartilage, and myocytes in vitro.[69] In addition, a growing body of literature suggests that MSCs may be able to evade immune system detection, in part owing to direct inhibition of inflammation, as well as a lack of cell surface costimulatory molecules.[70] These immunomodulatory properties, combined with the ability to rapidly expand MSCs in culture, raise the possibility of developing an off-the-shelf product for myocardial revascularization.

Preclinical data using MSCs in the acute[71] and chronic[72] setting have been promising. Like their hematopoietic and endothelial precursor counterparts, MSCs are capable of stimulating angiogenesis and even arteriogenesis[73] after acute myocardial infarction. However, MSCs may also possess the ability to transdifferentiate into viable myocardium, although the frequency and extent of electromechanical coupling remain unknown.[74] In addition, immunoselection before culture and expansion may allow for selection of a more homogeneous population of mesenchymal progenitor cells.[73] Early clinical experience with MSCs has been limited to small reports of percutaneous delivery in the acute[75] or subacute[76] setting. Nonetheless, a multicenter US trial of intravenous administration is under way, and surgical delivery in a variety of settings is likely to follow.

Regardless of the type of cell studied, a number of issues have come to the forefront of both catheter-based and surgical delivery. Of particular concern are the viability and retention of injected cells. Using an ischemic swine model and radiolabeled PBMNCs, Hou et al[77] compared intracoronary, intramyocardial, and retrograde coronary venous delivery and quantified cell retention 1 hour after delivery. Whereas intramyocardial injection showed the highest level of retention, surprisingly, only 11% of injected cells were recovered from the myocardium, highlighting the need for strategies to improve delivery methods. Possibilities include coinjection of polymerizable scaffolds and modification of current injection systems and needle technology.

Conclusion

The field of surgical revascularization continues to be a fertile ground for innovation and technological progress. Robotic and minimally invasive techniques have paved the way for near-outpatient CABG, and the continuing development of anastomotic devices has held the promise of greatly reducing OR times during these challenging cases. Finally, rapid progress in the cell therapy arena has led to a multifaceted approach that will likely involve surgical as well as biological vascular bypass in the years to come.

Disclosures

None.

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