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Ventriculocoronary Artery Bypass (VCAB), a Novel Approach to Myocardial Revascularization

Dr. Tweden

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ABSTRACT

Background: The long-term patency rate of saphenous vein grafts for myocardial revascularization is poor (50% at 10 years). Half of the patent grafts develop severe atherosclerosis. In this paper, we report on an implantation technique and an in vivo evaluation of a device that creates a ventriculocoronary artery bypass (VCAB™)*, a permanent transmyocardial channel between the left ventricle and a coronary artery.

Methods: An L-shaped titanium tube with an exterior polyester cuff was implanted from the base of the left ventricle to the proximal left anterior descending coronary artery in 11 juvenile domestic pigs using a beating heart approach. Flow rates were measured at implantation. Patency was assessed when explanted at two weeks.

Results: The flow rate through the device after implantation was 76% of baseline. Forward flow occurred during systole. The patency rate was 91% at two weeks. Histologic analysis showed the formation of an organizing tissue at the coronary interface.

Conclusions: These preliminary studies show the promise of perfusing ischemic myocardium with systolic flow. Patency of the transmyocardial titanium conduit was excellent at two weeks and warrants longer duration studies.

INTRODUCTION

Coronary artery bypass grafting frequently relies on the use of saphenous vein grafts (SVGs) for revascularizing arteries other than the left anterior descending coronary artery (LAD). SVGs have been shown to have occlusion rates up to 15% in the first month [Paz 1993], 25% in the first year [Campos 1993], and 50% at 10 years with half of the patent grafts developing severe atherosclerosis at 10 years [Campos 1993]. These occlusion rates clearly remain a significant problem.

Conduit options for revascularizing the heart with native vessels other than the SVG and internal mammary artery (e.g., radial artery, gastroepiploic artery) are limited primarily because of potential damage at the donor site [Schroeyers 1997, Nunoo-Mensah 1998]. Non-autologous conduit options have also had limited clinical success. High late mortality rates have been reported with cryopreserved allographs [Tice 1976]. Synthetic conduits, such as expanded polytetrafluoroethylene (ePTFE), have been shown to have lower patency rates than SVGs [Hehrlein 1984]. In addition, phase II clinical trials of administering growth factors (specifically vascular endothelial growth factor) to improve cardiac circulation have been disappointing [Henry 1999].

Perfusing ischemic myocardium directly by creating channels in the myocardium with a laser has been studied more recently by Horvath and colleagues [Horvath 1997]. However, these transmyocardial channels have been shown to occlude almost immediately [Fisher 1997]. Despite the observed occlusion, the quality of life of patients undergoing this procedure improved as measured by transitions within the New York Heart Association classification of angina [Horvath 1997]. The exact cause for the improvement is not definitely known. Fisher and associates have hypothesized that the clinical subjective improvement is due to a combination of denervation of the heart at the surgical site and the stimulation of the formation of collateral vessels [Fisher 1997]. Importantly, no increased survival was observed when this procedure was compared with medical management alone [Schofield 1999].

Myocardial revascularization, direct from the cavity of the left ventricle, was investigated by Munro and Allen in

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1969 [Munro 1969]. The experimental model consisted of inserting a long polymeric tube into the left ventricle and then looping the tube through an arc, external to the heart, to a coronary artery. Reporting an average flow rate of only 30% of the observed baseline flow rate, Munro concluded that "operations designed to revascularize the myocardium direct from the cavity of the left ventricle make the myocardium ischemic and are unlikely to succeed" [Munro 1969].

The transmyocardial device and the ventriculocoronary artery bypass (VCAB) procedure developed by our group circumvents the problems of native vessels. The device maintains a high flow rate by directly connecting the left ventricular chamber with the lumen of an overlying coronary artery and maintains the channel with a nonporous, biocompatible conduit.

We report here the early preclinical results of a revolutionary, permanently implanted, transmyocardial coronary device for the revascularization of ischemic cardiac tissue.

MATERIALS AND METHODS

Device design

The device design consisted of an L-shaped hollow tube with a gradual 90 degree bend. The dimensions of the device for animal trials were: outer diameter (OD), 2.5 mm; myocardial arm length, 25 mm; and vascular arm length, 7 mm. Unalloyed, grade 2 titanium (ASTM B-338-95; Tico Titanium, Inc., Farmington Hills, MI) was chosen as the substrate for the tube based on its long history of use in the cardiovascular environment, specifically in heart valve and artificial heart applications. A portion of the outer surface of the device was wrapped in polyethylene terephthalate (polyester velour, style 6108; C.R. Bard, Inc., Billerica, MA) fabric to encourage integration of the device within the myocardium. The device was steam sterilized using standard techniques before use. Tools used in the implantation, which are described below, were either steam or ethylene oxide sterilized using standard techniques.

Surgical technique

All animals were treated according to the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication 85-23, revised 1985). The device was implanted in 11 domestic Yorkshire-cross pigs weighing 65–75 kg. The pigs were treated with aspirin (325 mg q.d., p.o.) and clopidogrel (75 mg, q.d., p.o.) beginning 3 days prior to the procedure and continuing until sacrifice. Diltiazem (60 mg, p.o.) was administered one day prior to and on the morning of surgery. Anesthesia was induced with a combination of Telazol (tiletamine and zolazepam, 5 mg/kg; A. H. Robbins Co., Richmond, VA) and xylazine (5 mg/kg). After intubation, subsequent anesthesia was maintained with 1–2% isofluorane. A bolus of lidocaine (2 mg/kg) was given intravenously at the start of the surgery and a lidocaine drip (1 mg/kg) was maintained throughout the surgery. Cardiopulmonary bypass was not used (beating heart approach). A left thoracotomy and pericardial cradle were performed to expose the left anterior wall of the heart. A fluid-filled line was advanced into the left ventricle from the left atrial appendage to monitor left ventricular pressure. The pig was given an initial 5000-unit intravenous bolus of heparin.

One centimeter of the LAD was dissected free from the surrounding tissue 15 to 25 mm below the origin of the left main coronary artery bifurcation. The proximal end of the dissected segment was looped with a 2-0 polypropylene or polyester suture. Another 1-cm length of LAD was dissected free from the surrounding tissue 2 to 3 cm distal to the first segment. Lidocaine was applied topically to the segments of LAD to relieve contact vasospasm. The outside diameter of the LAD at the targeted implant site was then measured using a set of fixed-width calipers. A 2.0- to 3.0-mm ultrasonic flowprobe (Transonics model 2.5 or 3.0SB; Ithaca, NY) was placed around the distal LAD segment. Baseline electrocardiogram (ECG), left ventricle (LV) pressure, and LAD blood flow data were recorded for approximately 4 minutes (Gould 6600 Smart Case; Gould Instrument Systems, Inc., Valley View, OH). The heart was preconditioned by occluding the LAD for 15 seconds.

The pig was given a further 250-unit/kg intravenous bolus of heparin. The device was seated into the LV using the method described next. A polymeric inverted model of the device (needle guide) was superimposed on the epicardium adjacent to the proximal LAD segment to determine the proper implant angle of the device. A single-port 16 G x 3½" cone ventricular needle connected to a pressure monitor via a fluid-filled catheter was inserted through the lumen of the model and advanced through the LV free wall into the ventricular chamber (Figure 1A,). Penetration into the LV chamber was confirmed by observing the pressure tracing on the monitor. The ventricular needle was withdrawn until the distal port just penetrated the LV chamber. The model was then advanced down the needle until it rested against the epicardium. A guide wire was advanced through the lumen of the needle into the LV chamber and the needle and model were removed. LV wall thickness was obtained by measuring the distance on the needle between the model and the port at the distal end of the needle.

The vascular end of the device was temporarily sealed using silicone tubing with a 3-way stopcock on its end. The device was then primed with heparinized saline (2 units/ml heparin). A modified needle holder clamped to the coronary arm of the device was used to manipulate the device.

A 12 F cone-shaped introducing sheath with dilator was advanced over the wire and through the LV wall (Figure 1B,). The wire and dilator were then removed and the ventricular arm of the device was place in the sheath (Figure 1C,). The sheath was removed and the proximal LAD was ligated to simulate a totally occluded artery. The device was then introduced into the coronary artery as described next. A longitudinal incision was made in the LAD distal to the ligation at the mid-coronary arm level of the device. An introducer, made of low density polyethyl-

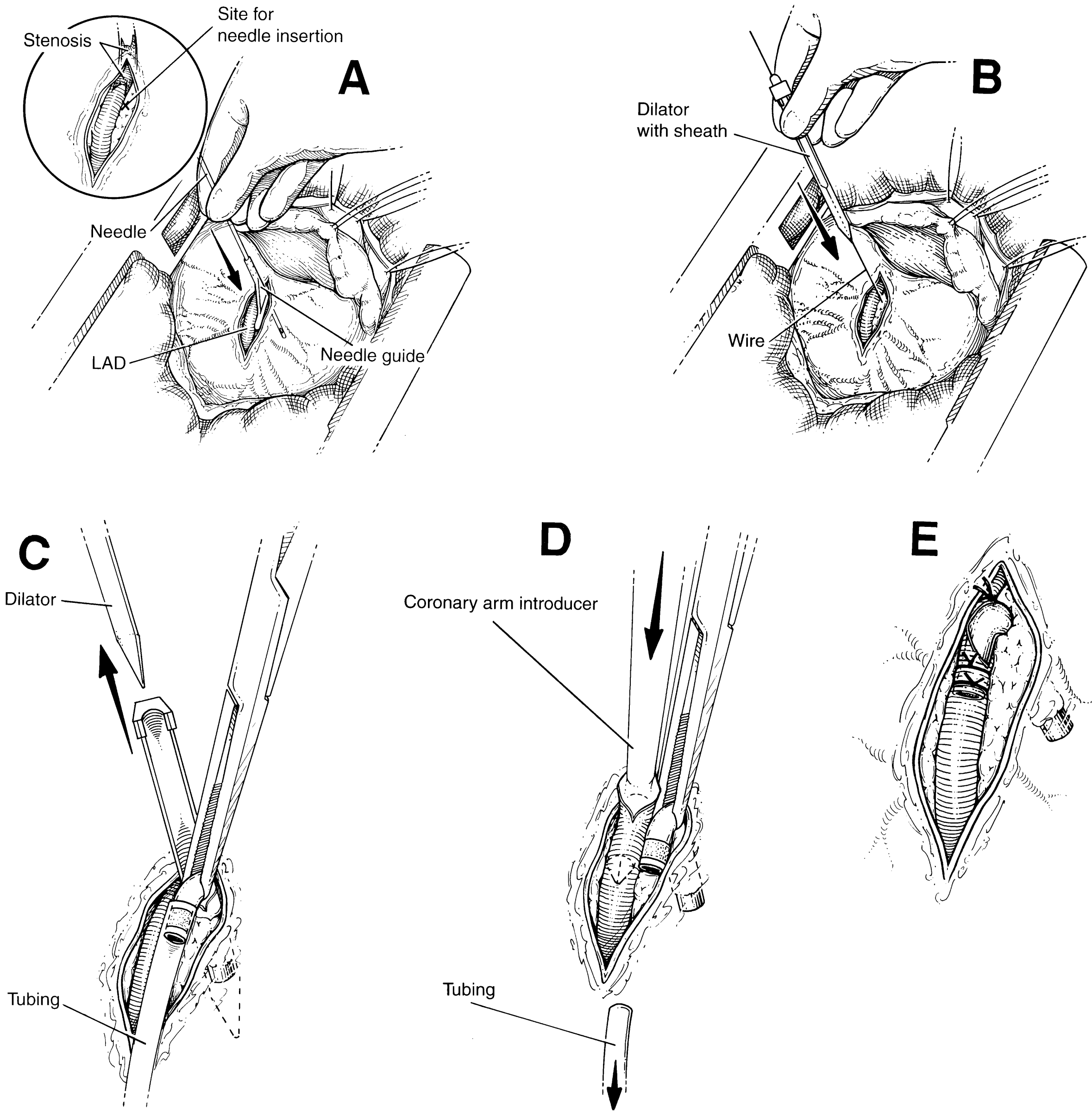

Figure 1. Illustration of implantation of the device into the LAD. A) Creation of left ventricle access tract, B) cone-shaped introducing sheath with dilator, C) seating of device in ventricle, D) introduction of device into coronary artery, and E) implanted device.

ene, was placed in the distal lumen of the LAD (Figure 1D, ◉). The tubing was then removed and the device was inserted through the introducer. The introducer was removed and the device was secured in the LAD and anchored to the myocardium using 2-0 polyester stitches (Figure 1E, ◉). The duration of ischemia was recorded.

The flowprobe was replaced around the LAD distal to the device. ECG, arterial pressure, and LAD blood flow data were measured as described above within 10 minutes after the device was implanted. Finally, the pericardial sac was approximated, the thoracotomy was closed, and the animals were recovered. The animals survived for two weeks.

Tissue preparation

All pigs were sacrificed two weeks after implantation using Buthanasia™ (Schering-Plough, Kenilworth, NJ). Fifteen minutes before sacrifice, the animals were given 250 units/kg of heparin. The heart was quickly exposed using a right thoracotomy and excised. The LAD was perfusion rinsed at 100 to 120 mm Hg with lactated Ringer's solution until the artery ran clear. McDowell-Trumps fixative was introduced next and infused at 100 mm Hg for 15 minutes. The heart was then placed in one liter of fresh fixative and fixed for at least 24 hours before handling.

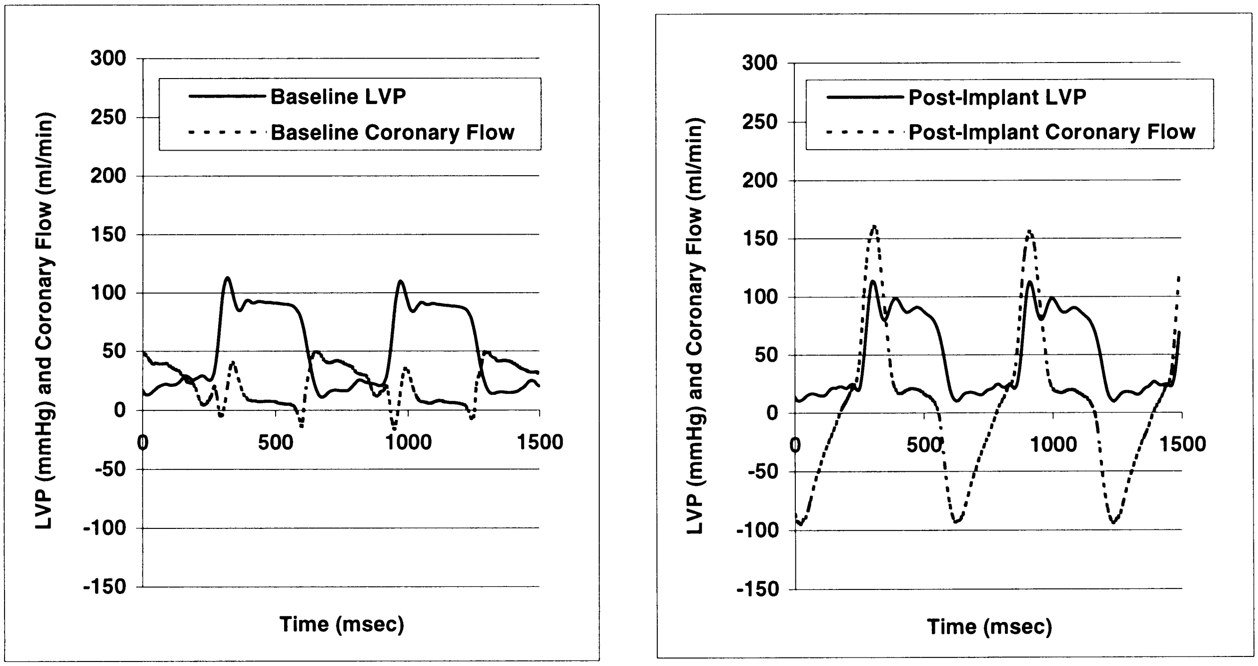

Figure 2. Flow and left ventricular pressure waveforms for A) native LAD and B) distal to the device immediately after implantation.

After fixation, the device/artery interface was exposed by carefully cutting longitudinally starting 2 cm distal to the device and ending 5 mm proximal to the myocardial insertion site of the device. The interface was photographed macroscopically (Nikon SMZ-U; Nikon, Inc., Melville, NY). The heart was assessed grossly for changes to the artery, epicardium, myocardium, and endocardium by the study pathologist (J.D.C.). Serial sections were taken from the LAD proximal to the device and approximately 1, 3, and 5 cm distal to the device to assess arterial changes and to look for embolization. The device was removed by cutting the polyester cuff longitudinally along the myocardial arm of the device. The remaining block of tissue was divided into a coronary artery block and a myocardial cuff block along the device tract. The device/artery interface block was cut longitudinally to assess arterial reaction and the myocardial block was cut transversely to assess integration of the fabric. The myocardium was sectioned at two locations distal to the device and at the septum to assess perfusion histologically. All blocks, except the cuff block, were paraffin embedded, sectioned, and stained with hematoxylin and eosin (H&E) and Elastic van Gieson (EVG) for elastic structures. The cuff block was plastic embedded and stained with H&E only. The titanium portion of the device was removed from the heart, sectioned in half with a low-speed diamond saw (Isomet 1000; Buehler, Inc., Lake Bluff, IL), dehydrated through a series of ethanols, critical point dried with CO_2 (Autosamdri-814; Tousimis, Inc., Rockville, MD), coated with 200 Å of carbon (DV-502A Vacuum Evaporator; Denton Vacuum, Moorestown, NJ) and analyzed by scanning electron microscopy (Hitachi S-450; Hitachi, Inc., Mountain View, CA) for biological deposits.

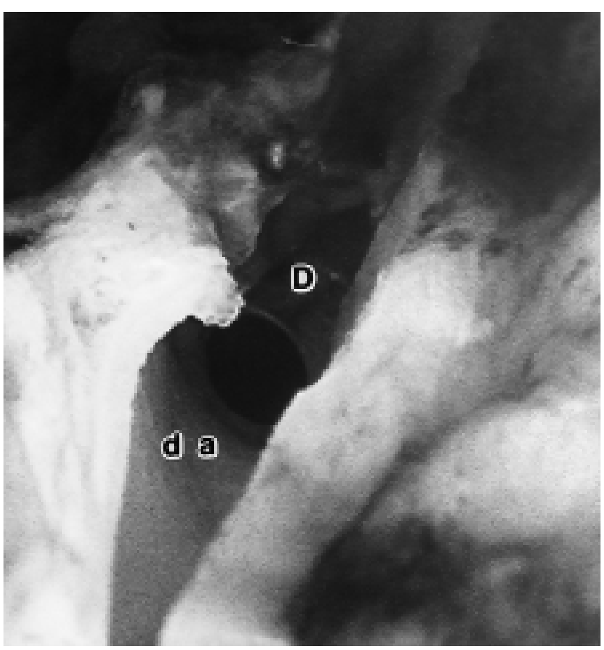

Figure 3. Gross photograph of device/artery interface 2 weeks after implantation. LAD opened longitudinally. da, distal artery; D, device.

RESULTS

The flow pattern seen with this device is one of forward flow during systole and retrograde flow during diastole (Figure 2,). No areas of stasis occurred during any part of

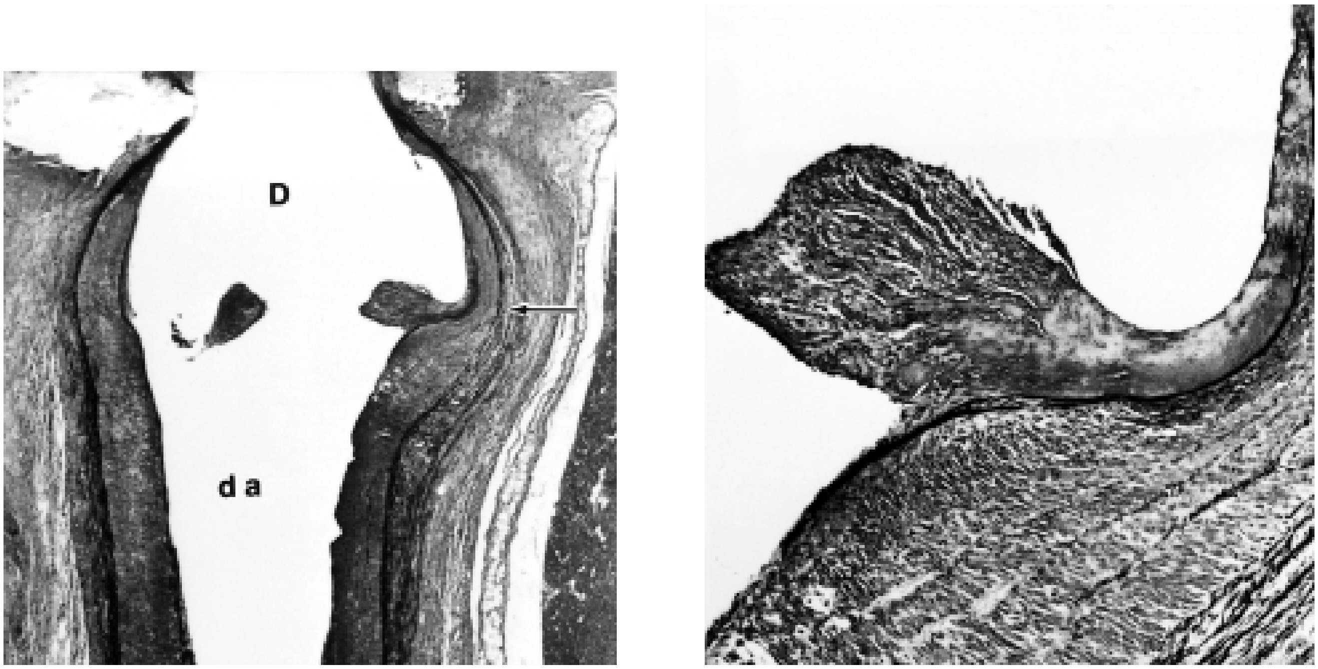

Figure 4. Photomicrograph of reaction at device/artery interface shown in Figure 3, device is removed. A) Hematoxylin and eosin stain, original magnification 40x, B) Elastic van Gieson stain, original magnification 100x. da, distal artery; D, space occupied by the device; arrow points to device/arterial interface.

the cycle. Flow rate through the device immediately after implantation was an average of 76 ± 25% that of the baseline flow rate. Average peak forward flow measured 166 + 52 ml/min and average peak retrograde flow measured –83 ± 33 ml/min through the device compared to 54 ± 17 ml/min average peak forward and –29 ± 16 ml/min average peak retrograde in the native coronary artery. The average ischemic time period during implantation of the device was 90 ± 12 seconds.

Two weeks after implantation, 10 out of 11 devices were patent. The remaining device thrombosed. This thrombosis was believed to be due to entrapment of the myocardial inflow arm in the mitral valve chordae tendinae. Echocardiography at the time of implant would prevent the occurrence of this event. All other devices flushed at sacrifice and were widely patent upon gross examination.

The gross analysis of the device/artery interface of the 10 patent devices showed a thin tissue lining between the artery and device located at the interface (Figure 3, ◎). Histological analysis of this tissue showed fibroblast infiltration with a lining of cuboidal cells covering the tissue (Figure 4A, ◎). The EVG stain showed the internal elastic lamina was intact (Figure 4B, ◎). The titanium appeared to have no adverse effects on the adjacent tissues (Figures 3 and 4, ◎). The device was clearly adequately immobilized at the arterial and endocardial interfaces (Figures 4 and 5, ◎). In addition, no gross deposits were observed on the aspect of the device that protrudes into the left ventricle (Figure 5, ◎). Tissue ingrowth into the cuff, shown in Figure 6 (◎), is characterized by fibroblast infiltration with a mild to moderate chronic inflammatory cell response. Scanning electron microscopic analysis of the inside of the device showed little deposition of thrombotic material (Figure 7A, ◎). Occasionally, individual platelets or small platelet aggregations that were less than 10 microns in diameter were observed (Figure 7B, ◎). A photomicrograph of myocardium from the distal anterior wall of the heart, shown in Figure 8 (◎), demonstrates minimal changes due to the initial ischemic event of implanting the transmyocardial device. No evidence of progressive ischemia was observed.

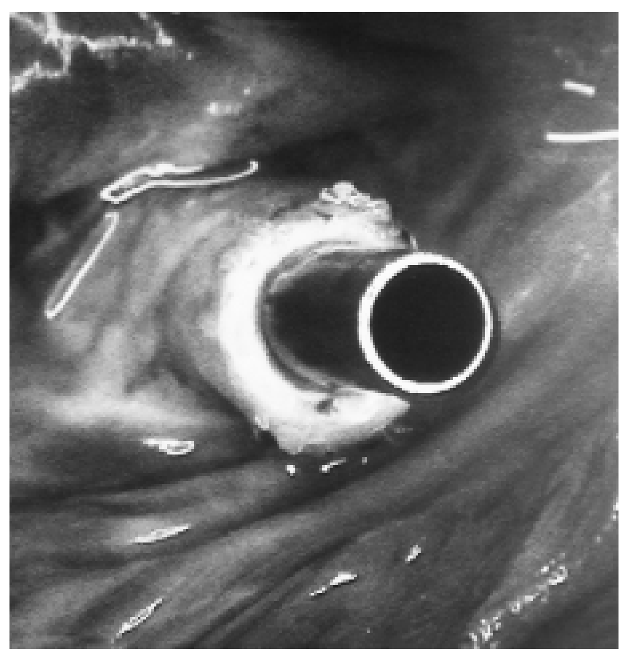

Figure 5. Gross photograph of endocardial/device interface at two weeks.

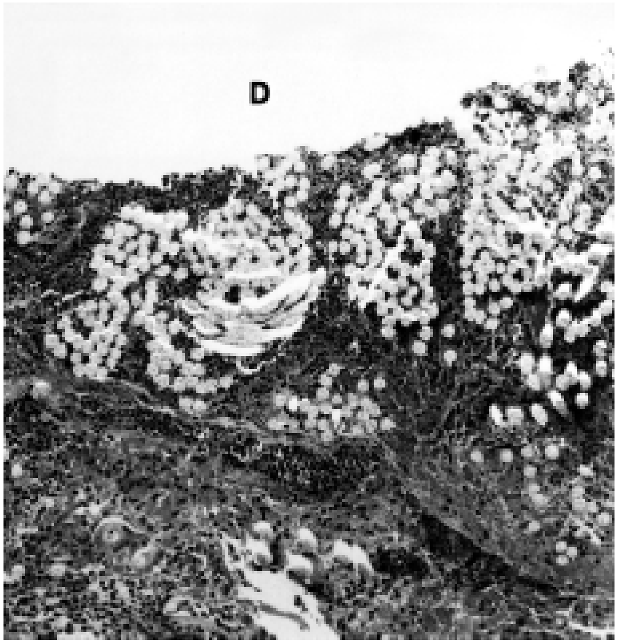

Figure 6. Photomicrograph of polyester cuff two weeks after implantation. D, space occupied by the device. Hematoxylin and eosin stain, original magnification 100x.

COMMENT

Researchers have been working on a synthetic vascular graft for use in coronary artery bypass procedures for over 30 years with limited success. At best, synthetic grafts such as the Perma-Flow® graft (Possis, Inc., Minneapolis, MN) have been available only recently for use in humans who have inadequate autologous conduits to permit full revascularization [Emery 1996]. With the poor long-term prognosis of SVGs [Campos 1993, Paz 1993] and the heavy dependence on those grafts for complete or primary revascularization, the need for a reliable, readily available revascularization device is clear.

Munro and Allen's conclusion [Munro 1969] that myocardial revascularization, direct from the LV, is likely to be a functional failure due to ischemia is not supported by our data. Specifically, we obtained flow rates of 76% of baseline that were able to sustain the growth of a juvenile model with insignificant changes to the myocardium.

From a critical analysis of Munro and Allen's study [Munro 1969], it is unclear from their description of the LV-coronary conduit and implant technique as to how entry into the artery was performed and if any effort was made to optimize alignment of the LV-coronary conduit within the artery. Further, Munro and Allen do not suggest whether the artery was occluded proximal to the LV-coronary conduit. Also, their study provides insufficient information to determine whether the LV-coronary conduit was sufficiently rigid to avoid constriction during systole. It has been our experience that these are critical components to the success of the device and procedure. We observed a maximum flow rate of 110% of baseline in the reported set of experiments compared with a maximum of 48% in the Munro and Allen study.

Our data indicate that a juvenile pig heart can be sustained with systolic LAD flow. The model used in this work, the domestic Yorkshire-cross pig, has a growth rate of 3 kg/week. This rapid growth limits the length of time that this model can be used because the ventricular myocardium will outgrow the device. Even so, we have

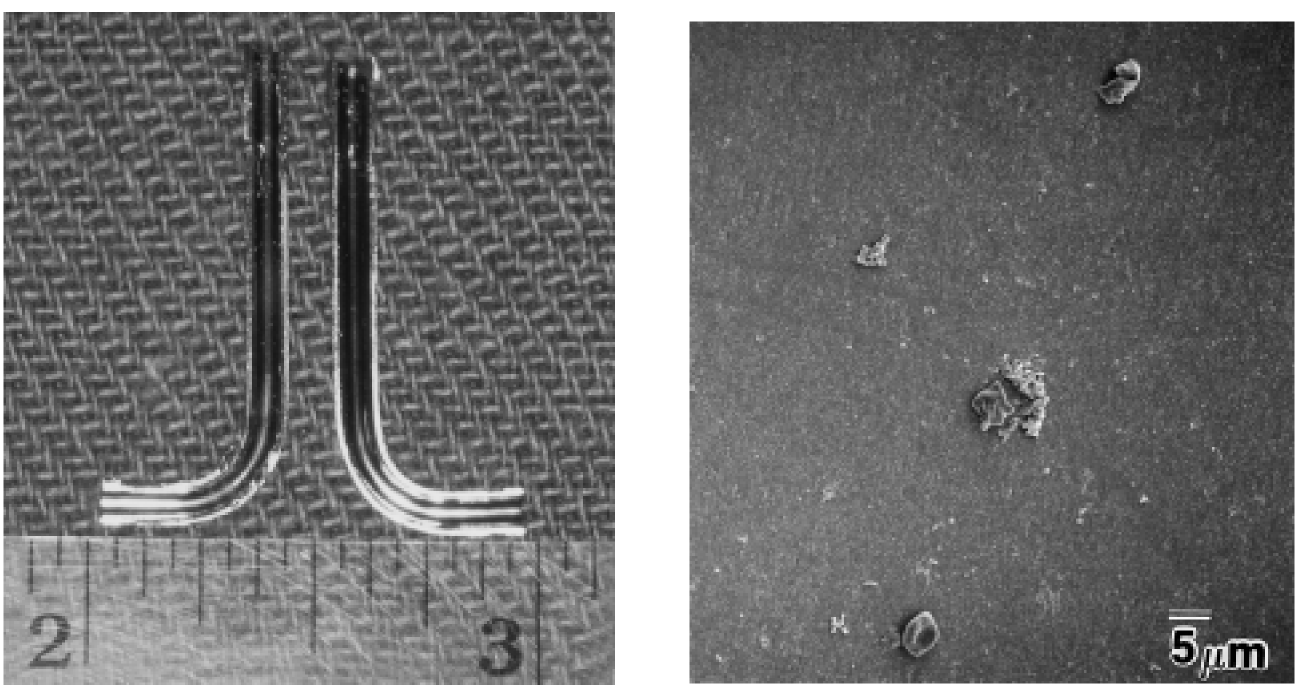

Figure 7. Gross photograph (A) and scanning electron micrograph (B) of two week explant. Original magnification 1000x.

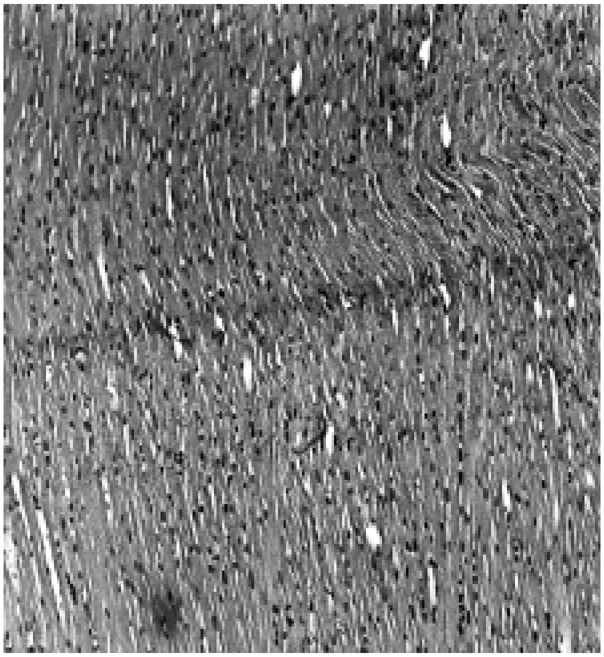

Figure 8. Photomicrograph of endocardial wall. Hematoxylin and eosin stain, original magnification 100x.

sustained this model for up to 12 weeks with this device (data not shown). The surgical implantation method clearly preserves the arterial and myocardial structures. Following an initial procedure-associated ischemic assault of the myocardium, no progressive changes were seen. The device design is such that the vascular arm does occasionally occlude branches of the LAD and therefore can cause ischemia to the tissue fed by those branches. No evidence of emboli was identified in this study.

Advantages of the transmyocardial device reported are many-fold. It can be implanted under both beating heart and cardiopulmonary bypass conditions allowing the use of the device in a wide range of surgical situations. Implantation of the device is relatively straightforward with no traditional anastomoses required. Ischemic time periods for the trained surgeon are less than two minutes. The device is small, lending itself to minimal access incisions. Finally, availability of an SVG is subject to patient health, previous surgery, or preexisting disease, and the painful leg incisions required for SVG harvest are avoided. The titanium transmyocardial device is not subject to these conditions.

Titanium has a long history of successful use in the cardiovascular environment as the housing of prosthetic heart valves [Bain 1991]. Polyester fabric has been used since the early models of prosthetic heart valves to encourage myocardial tissue integration to secure the device in place [Bain 1991]. The transmyocardial device reported was designed such that no areas of stasis occur during any period of the cycle and flow remains laminar during the cycle. The peak flow rates (twice as high as baseline flow rate) and the forward and retrograde flow directions aid in maintaining the patency of this device. The combination of the device design, hemodynamics, and materials contribute to minimal thrombotic deposition.

In conclusion, the combination of the novel transmyocardial device and VCAB procedure reported has the following characteristics: 1) creates a permanent channel between the left ventricle and coronary artery, 2) perfuses the heart with systolic flow, 3) has a net forward flow rate at implant of 76% of baseline coronary flow rate, 4) has excellent patency (91%) two weeks after implantation and 5) causes minimal damage to the myocardium and arterial wall. Results of this study suggest that this device and surgical technique offer a promising alternative to the saphenous vein graft for coronary artery bypass surgery and warrant longer duration studies.

Acknowledgments

Sincere thanks are extended to the people at HeartStent Corp. who assisted in surgery, data collection and analysis, and specifically to Dale Groth, Kris Hagen, Tom Odland, Sue Perron, and Guy Vanney. Joanna Wild illustrated the implant technique. The surgeries were performed at River Valley Farms (Osceola, WI) with Kate Hauer and staff.

Disclosure

Katherine S. Tweden, PhD and Eric E. Solien, BS, are employees of the HeartStent Corporation. Frazier Eales, MD, J. Douglas Cameron, MD, Jerry C. Griffin, MD, and Mark B. Knudson, PhD are consultants for the HeartStent Corporation. All of the authors have a financial interest in the HeartStent device.

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REVIEW AND COMMENTARY

1. Editorial Board Member LO23 writes:

This is an interesting, well-written novel approach. This is a new technique of the "transmyocardial revascularisation" concept. However, the relative need / risk of primary systolic compared to diastolic coronary flow should be discussed in greater depth.

Author(s)' Response by Katherine S. Tweden, PhD and Mark B. Knudson, PhD:

The reported approach, ventriculocoronary artery bypass (VCAB), is similar to transmyocardial revascularization (TMR) as both procedures traverse the left ventricular myocardium, but this is where similarity between TMR and VCAB ends. The theoretical therapeutic utility of TMR results from a biologic response to channels created in the myocardium. The potential therapeutic utility from VCAB is direct revascularization of a coronary artery with oxygenated blood from the left ventricle distal to an obstructing lesion.

The clinical need for VCAB is a less invasive means to bypass an obstructed coronary artery. For selected patients, this procedure has potential to eliminate the need to harvest autologous vessels and obviates the conventional sewn anastomosis, thus potentially facilitating a new threshold of less invasive cardiothoracic surgery.

The delivery of oxygenated blood to the coronary arteries via systolic flow has several theoretical advantages. Primary among these is that the flow at rest and at slow heart rates (HR) is the worst-case flow scenario for this treatment modality. As heart rate increases, the majority of the decrease in cycle time comes by reductions in the duration of diastole (T-Q interval). This interval is the time during which perfusion pressure falls most dramatically in this experimental model.

The theoretical risks associated with this procedure include global or sub-endocardial ischemia associated with reduced flow or flow mal-distribution due to intramyocardial pressure gradients. We evaluated this by observing coronary adaptation to systolic flow. This adaptation response appears to occur over the first several hours and results in increased coronary blood flow to the affected region as measured by ultrasonic blood flow probes (Unpublished observations). As discussed in this article, we conducted extensive histopathological evaluation of the hearts of treated animals. This evaluation especially focused on a search for signs of progressive subendocardial ischemia. This was not observed to occur. Our group is advancing pre-clinical investigations to address longer-term outcomes of VCAB.

2. Editorial Board Member NM341 writes:

This article is well done, with great drawings. It is nicely designed and carried out.

Integrated flow-time curves show 76% of the pre-ligation flow at rest. It would have been interesting to stress the animals (rapid pacing, catechols, etc.) and assess flow reserve.

Author(s)' Response by Katherine S. Tweden, PhD:

We recognize the need to demonstrate not only coronary flow at rest and at stress, but also the important measure of myocardial perfusion at rest and at stress to assess the level of revascularization supported by VCAB. In addition, stress echocardiography studies are planned to determine left ventricular wall motion following the VCAB procedure.

3. Editorial Board Member TL41 writes:

It is (and only purports to be) a preliminary study of a new and potentially useful approach to the overall problem of myocardial revascularization. The results are somewhat surprising and even counterintuitive, and therefore provocative. The study opens up a promising line for further investigations. The main weakness, however, is it has a very short follow-up period.

Author(s)' Response by Katherine S. Tweden, PhD:

We agree that results from this preliminary study are provocative and warrant further investigations with longer-term follow-up to assess the potential utility of VCAB. The purpose of the current study was to demonstrate that blood flow directed from the left ventricle to a coronary artery could sustain target myocardium.

4. Editorial Board Member NC124writes:

This could represent a new aproach to treat coronary artery disease. New alternatives for the treatment of coronary artery disease, as for example the transmyocardial approaches or the revival of Claude Beck´s, work with retragrade revascularizatión. I believe this is a good alternative. I myself have been working with alternative models.

I believe it would be great if it could be done interventionally. The only thing I do not like is the fact that it can not offer bi-directional flow. It would be better with a T shape.

Author(s)' Response by Katherine S. Tweden, PhD:

We acknowledge and recognize the potential clinical utility of a device offering both distal and proximal flow in a VCAB procedure. This initial study was designed to definitively prove viability of exclusive systolic forward flow without potential bias of diastolic forward flow. These preliminary results suggest that VCAB with bi-directional flow warrant investigation.

5. Editorial Board Member BN345 writes:

a) This is an intriguing report of a novel experimental attempt to improve myocardial blood flow. The follow-up, however, is woefully short. The short follow-up should have tempered the author's enthusiasm for this device, but they give no hint that the device will probably not work in a long-term study.

b) Second, the device appears to occlude the coronary artery necessarily, because of the mode of its insertion, but the authors fail to specify that all flow measurements were only in the distal coronary artery. Since flow from a conventional bypass graft is often supplied proximally as well as distally, this is a major shortcoming of this device. The discussion should mention this problem.

c) Finally, I was unable to correlate the data given for flow measurements with the assertion that the device provided 76% of baseline flow. The net forward flow was 83cc, which is more than twice the net forward flow at baseline.

Author(s)' Response by Katherine S. Tweden, PhD:

a) We readily acknowledge the need for VCAB studies with longer follow-up duration. We are advancing such studies.

b) All flow measurements were taken at the distal coronary artery only as stated in the Surgical technique section of the Materials and Methods. The distal-only flow of this initial device, and our recognized need for proximal and distal flow capability, is discussed above (response to reviewer NC124).

c) The -83 ml/min measured through the device is the average peak retrograde flow, not the average forward flow through the device. The 76% average was arrived at by averaging the percentage of baseline flow through each device, which was as high as 110% of baseline flow.