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The history of proximal carotid protection and flow reversal to prevent stent angioplasty embolization

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Abstract

Innovation in medicine is often driven by the observations of imaginative physicians who are blessed with insatiable curiosity, coupled with the inability to accept technical boundaries, the status quo of patient care, or the acceptance of procedural morbidity. Few examples illustrate this truism better than the physician-originated clinical research that transformed the safety of carotid stent angioplasty over the last 2 decades. Initial clinical application of carotid stenting suggested that proximal protection may be a better approach to prevent embolic stroke during the angioplasty procedure. The history of how this innovation was developed is particularly relevant as vascular surgeons adopt new endovascular therapies. It has been more than 15 years since Dr Juan Parodi put together a multidisciplinary team of scientists and clinicians to test the “proximal protection” hypothesis. The goal of this overview was to provide Dr Parodi team’s perspective on the development of the proximal protection and flow reversal concept to minimize plaque embolization during carotid stent angioplasty procedures.

1. Introduction

In the early 1990s, vascular surgeons were keenly aware that soft, friable atherosclerotic plaque encountered during carotid endarterectomy (CEA) procedure would pose a limitation for endovascular catheter procedures from the groin due to risk of embolization. Dr Jacques Theron set out to overcome this obstacle by inventing a “triaxial” system with a distal balloon occlusion catheter centered inside the wire lumen of a balloon-dilating catheter that could be delivered through a guide or sheath system [1]. Theron’s idea was later iterated and

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commercialized as the “PercuSurge” device by Medtronic (Minneapolis, MN). The PercuSurge system included a balloon on the distal end of a 0.014” hypotube that could be inflated by a removable deflator, such that the hypotube could substitute for a guide wire, allowing delivery of therapeutic devices while the carotid remained occluded (Fig. 1). Aspiration of stagnant embolic debris-laden blood in the proximal internal carotid artery (ICA) cul-de-sac was then performed with a monorail aspiration catheter. Subsequently, Drs. Parodi and Schönholz collaborated with Dr Patrick Whitlow from the Cleveland Clinic to initiate the first PercuSurge trials and coauthored the initial publications describing this technique [2].

During the PercuSurge carotid angioplasty procedure, Dr Parodi utilized transcranial Doppler (TCD) monitoring of middle cerebral artery flow to assess collateral flow during ICA balloon inflation and to detect distal embolization. From his experience with TCD monitoring during CEA, the team recognized that TCD monitoring could detect high-intensity signals (HITS) representative of emboli and identify the need for a shunt in patients with an incomplete Circle of Willis and poor collateral flow. It was Dr Parodi’s initial intent to assess adequacy of contralateral flow during distal balloon occlusion with TCD, but he was surprised to learn that HITS persisted during distal occlusion (Fig. 2). He postulated this phenomenon was related to paradoxical embolization from reflux into the external carotid artery and particle escape into the ipsilateral hemisphere via macrocollaterals. In addition, a small number of patients experienced intolerance to balloon occlusion of the ICA, resulting in the need for rapid export of debris to complete a given stage of the procedure. Performing the procedure in stages during intolerance usually allowed completion of early distal occlusion cases, but the associated “fire drill” was unpleasant for patients and the interventional team.

The limitations of PercuSurge led other physicians to develop ICA filters. Dr Jay Yadav developed one of the first distal filters and, once again, Dr Parodi was involved with the early cases and trials using the AngioGuard device along with other clinicians (Fig. 3). Dr Parodi observed that crossing the carotid lesion with the AngioGuard filter induced showers of HIT particles migrating to the brain, based on TCD monitoring. The TCD-detected emboli observed during distal filter protection clinical trials led Dr Parodi to reflect on his experience with CEA, which had fewer TCD-detected HITS, and explore other procedural alternatives for carotid artery stenting (CAS). Years before, he had observed flow reversal in the middle cerebral artery while inserting a shunt into the distal internal carotid during a CEA procedure, and noted this hemodynamic change was well tolerated in the awake patient (Fig. 4). This transient flow reversal observed in the operating room led to the hypothesis that flow reversal could potentially be induced via transcatheter proximal occlusion, be tolerated by the awake patient, and, during the period of flow reversal, embolic particles from the carotid plaque would not reach the brain. Dr Parodi then performed the first operation that induced flow reversal during CAS in 1998. A short incision was made at the base of the neck in a patient with a high-grade stenosis of the ICA exposing the common carotid artery (Fig. 5). To ensure an adequate landing zone for the sheath and delivery system, Dr Parodi’s team marked the carotid bifurcation on the skin using ultrasound imaging before access. After systemic heparinization, an 8Fr sheath was introduced in the common carotid artery guided by a guide wire inserted in the external carotid artery (ECA).

A PercuSurge balloon was advanced through the sheath to occlude the ECA. The proximal carotid artery was then clamped and flow reversal was established during CAS using passive flow reversal by opening the side port and active flow reversal by pulling suction with a syringe from the side port of the sheath. This index case and subsequent cases were all done using continuous TCD monitoring of middle cerebral artery flow and were performed with or without pre-dilatation of the stenotic ICA lesion, depending on its severity. From the beginning, an 8-mm Wallstent (Boston Scientific, Marlborough, MA) of varied lengths based on plaque anatomy was deployed. Dr Parodi was pleased to find that no HITS were detected and this was the first evidence that the “proximal protection” hypothesis was correct.

Dr Parodi then set out to develop a percutaneous flow reversal system inserted from a femoral artery approach. The project began by developing a long 9Fr sheath with a soft elastomeric balloon tip, called the ArterioA device (Fig. 6). We insisted on special attention to balloon shape and design, such that the final pear shape allowed for a “funnel-like” entry into the sheath to prevent particle collection on the outer edges of the balloon. A long hypotube with a distal shapeable guide wire and soft occlusion balloon 3 cm from the tip was developed to access and occlude the ECA. The ECA occlusion system had a two-way stopcock to keep the balloon inflated.

During the femoral access design phase, Drs. Bates and Ohki were enlisted to assist with the animal studies. At that time, Dr Bates was working on a distal filter system that was separate from the wire, but was concerned about clinical observations reported in the 1960s that suggested radioisotope-labeled spheres $>25\text{ }\mu\text{m}$ injected into the carotid artery would not traverse into the venous phase and, thus, must be occlusive to the brain arteriolar system [3]. Unfortunately, his initial filter prototypes with sub- $50\text{-}\mu\text{m}$ pores obstructed flow and caused a windsock-like driven distal filter migration during animal studies. Thus, he became intrigued by Dr Parodi’s flow reversal concept, especially because the team at Wake Forest had documented that a decrease in cognitive function after cardiopulmonary bypass surgery was likely due to particles that were $<60\text{ }\mu\text{m}$ [4].

The first flow reversal studies in animal were done at the Charleston Area Medical Center Research Institute in Charleston, WV, utilizing a swine model. The first three swine were done on a Saturday afternoon in late 1998 and the objective was to troubleshoot the prototype balloon-tipped sheaths (at the time known as the Parodi Sheath) and the external balloon occlusion wire, affectionately called “the PEB” (Parodi External Balloon). Dr Bates and his team found the system worked beautifully and initially he was able to show radiopaque lead and platinum particles could be released in the mid carotid and retrieved with flow reversal. Before starting the third animal, Dr Bates reported the exciting positive findings from the Parodi device and the early experimental success to Dr Parodi in Argentina. He also raised concerns about blood loss during passive flow reversal and discussed how this was improved by adding an empty intravenous bag to the sheath port. However, during the break while waiting for the third case, it occurred to Dr Bates that it might be possible to take advantage of the natural gradient and attach the Parodi guide catheter to a venous sheath. One of the technicians went to the hospital perfusion team and obtained a male-to-male adapter that allowed this simple connection to be made. Later that

night, Dr Bates added a filter because lead particles could be found in the lungs after flow reversal testing with the arteriovenous shunt and there would always be the inherent risk of paradoxical embolization if a PFO were present. The next set of animals done by Dr Bates included additional testing of flow patterns with a Doppler flow wire in the pig carotid [5]. At the same time Dr Bates was doing additional animal studies with the final design, Dr Takao Ohki was doing elegant well-controlled canine studies [6]. Of note is that Dr David Chang, who was a founder of Silk Road Medical (Sunnyvale, CA), was a vascular fellow at Montefiore Medical Center at this time, and assisted Dr Ohki in performing these Parodi protection canine studies, perhaps leading to his enthusiasm about the concept. In addition, Dr Ohki had already redefined how protection device assessment would be conducted with the invention of an ex vitro model that utilized carotid plaques obtained during CEA [7]. His model showed that CAS performed in clinically significant plaques generated numerous emboli and also confirmed Drs Parodi's and Bates' concerns about microemboli that were smaller than current filter pores.

The final device was then ready for clinical trials. Dr Claudio Schönholz was instrumental in starting the clinical program, and Dr Parodi did the first-in-human transcatheter flow reversal case in mid-1999. Later that same year, now almost 1 year after the first cervical case, Dr Schönholz did the second transfemoral case with Dr Parodi. Dr Bates, along with the engineer-led catheter design team, was present in Argentina for this landmark case. Angiogram images recorded before and during the carotid stent procedure with flow reversal in the first patient are shown in Figure 7. The patient was completely asymptomatic and talking throughout the entire procedure. The device worked well in this case and in all subsequent cases, but in response to concerns about access in some Type 3 aortic arches, Dr Parodi modified his 1998 cervical access procedure to involve flow reversal in late 1999.

In the year 2000, the first article describing cerebral protection during CAS using three different devices—the Percusurge balloon, the AngioGuard distal ICA filter, and the newly developed flow reversal system—was published [8]. Dr Parodi reported the first series of flow reversal cases in 2005 and 2007, including some of his experience outside Argentina [9]. A flow reversal case performed with Dr Parodi by Dr Doblas in Toledo, Spain may have contributed to his interest, along with Dr Enrique Criado, to develop the Enroute Transcarotid Neuroprotection system. Silk Road Medical manufactures this cervical access flow reversal system and, as noted, was founded by Tony Chou and Michi Garrison based on work done by David Chang (Dr Ohki's previous fellow). The device used an 8Fr carotid sheath placed in the common carotid artery through a small incision at the base of the neck, which was connected to the common femoral sheath with an interposing filter.

Dr Parodi's enthusiasm was infectious, as he began doing cases with pioneering physicians around the world, including the team in Modena, Italy. Nine months after Dr Parodi filed his first carotid proximal protection patent (March 13, 1998), Dr Giacchino Coppi in Modena, Italy filed a patent on a single-unit proximal protection occlusion system (December 3, 1998) known as the MO.MA system. The MO.MA system has also reported excellent results and is now manufactured and sold by Medtronic [10].

We formed a company with Dr Gerald Dorros called ArteriA in 1999, which was later acquired by W.L. Gore and Associates (Flagstaff, AZ), naming it the Gore Flow Reversal system. Gore proved the efficacy of the system with the EMPiRE trial [11]. Rate of intolerance to flow reversal was only 2.4%, much lower than with the PercuSurge. We speculated that this was due to recruitment of pial collaterals. However, Dr Enrique Criado did a study suggesting the enhanced tolerance of flow reversal with the Silk Road Medical system was related to enhancing collateral flow from the contralateral hemisphere. In any event, for the occasional patient with intolerance to flow reversal, we described the “seat belt and air bag technique,” which combines the use of flow reversal and a filter in 2002 [12]. Flow reversal was used when crossing the lesion with a filter and then the rest of the procedure was done under filter protection. Claudio Schönholz and his group from the Medical University of South Carolina compared TCD findings in patients undergoing CAS with flow reversal to filter-protected stenting showing significant reduction of HITS with flow reversal [13]. Paradoxically, as data began to surface showing reduced stroke rates, decreased HITS with TCD, and reduced post-stent abnormalities on diffusion-weighted magnetic resonance imaging, W.L. Gore made a business decision to discontinue sales of the Gore Flow Reversal system due to discouraging CAS market forecasts and contracting sales prices.

2. Conclusions

Results of the application of ICA flow reversal in clinical trials suggest better outcomes than expected with filters, and many authorities in the field now consider it the most effective protection device for CAS. During the 2015 Society of Vascular Surgery meeting (Chicago, IL), Dr Christopher Kwolek presented the ROADSTER (Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure) study using the Enroute Transcarotid Neuroprotection system (Silk Road Medical). Kwolek reported a zero incidence of stroke in symptomatic patients, as well as patients older than 75 years of age (one of the most exciting findings to date). During the last 1½ decades, each of the authors has continued to work on innovations in this domain, resulting in many publications as well as the acquisition of the Bates patents related to a filter that can be placed after the wire is already across the lesion. However, throughout that time, the entire flow reversal team has continued to believe in the initial theory and vision of Dr Parodi. More importantly, each of us looks back and cherishes the friendships that were forged during the discovery phase of this project under Dr Parodi’s direction. The CREST 2 (Carotid Revascularization for Primary Prevention of Stroke) trial will include flow reversal in the endovascular arm and will hopefully provide level I evidence confirming Dr Parodi’s initial hypothesis. Further insight into the thinking that led to flow reversal is provided in the editorial entitled “Chance Favors the Prepared Mind” [14].

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Fig. 1 –.

Schematic and angiographic images of the PercuSurge balloon occlusion embolic protection device used during carotid stent angioplasty. (A) The balloon is partially inflated in the distal internal carotid artery (ICA). (B) The balloon is completely inflated and no contrast is seen in the ICA, indicating cessation of flow.

Fig. 2 –.

Transcranial Doppler waveform recorded from the middle cerebral artery showing a shower of high-intensity signals (HITS) during a carotid artery stenting (CAS) procedure. The embolic HITS were observed during distal protection CAS procedure using the PercuSurge device or with deployment of a filter device in the internal carotid artery.

Fig. 3 –.
Schematic of the Angioguard filter device deployed in the distal internal carotid artery (ICA) to capture embolic debris during stent angioplasty of the proximal ICA stenosis.

Fig. 4 –.
Schematic of shunt insertion in the internal carotid artery during a carotid endarterectomy procedure with transcranial Doppler waveforms recorded from the middle cerebral artery (MCA) before (top waveform) showing normal antegrade flow and flow reversal during shunt insertion (bottom waveform). The patient, who was awake, exhibited no neurologic signs during or after the flow reversal episode.

Fig. 5 –.
Operative photo of the first procedure to produce flow reversal during a carotid stent procedure. A small incision was made at the base of the neck and common carotid artery and jugular vein were dissected. Introducer catheters were placed in both vessels and then connected with a tube containing a filter.

Fig. 6 –.

Left: Photo of the ArteriA device composed of a 9Fr, 90-cm sheath with a balloon at the end and a hypotube with a balloon to occlude the external carotid artery. Right: Schematic of device inserted in the carotid bifurcation with balloon in the external carotid artery.

Fig. 7 –.
Angiogram images of the first patient treated with internal carotid artery flow reversal. Left: Before stent placement. Right: After stent placement.