

Therapeutic Ultrasound for CTO Recanalization

A behind-the-scenes look at catheter-delivered therapeutic ultrasound for CTO crossing using the Crosser® Catheter.

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Therapeutic ultrasound has been used in a variety of medical applications such as lithotripsy and dentistry for several decades. Ultrasound in the frequency range from 20 to 45 kHz is often used in medical applications due to its unique feature of selective disruption of inelastic rigid materials. Since the 1960s, there have been several studies exploring the use of therapeutic ultrasound for vascular intervention. In 1965, Anschuetz and Bernard conducted an in vitro study on the effect of therapeutic ultrasound on atherosclerotic arteries and suggested its use for atherosclerotic plaque ablation.¹ That same year, Lane and Minot demonstrated that ultrasonic energy could defragment calcified plaque in cadaveric coronary arteries.² This work was the beginning of 4 decades of studies and development of therapeutic ultrasound for vascular interventions.

In 1974, Sobbe et al conducted the first published animal study using a wire transmission member to deliver ultrasonic energy to the lesion for vascular plaque disruption.³ Starting in the 1980s, several studies focused on the development of a catheter prototype for initial clinical testing. In 1989, Siegel et al performed the first clinical study on patients with peripheral vascular disease using percutaneous catheter-delivered ultrasound for arterial recanalization.⁴ The results from the initial pilot clinical study were very positive, with three of four chronic total occlusions (CTOs) recanalized and no evidence of arterial emboli, dissection, spasm, or perforation. A num-

ber of clinical studies were conducted in the 1990s and demonstrated promising results for CTO recanalization using catheter-delivered therapeutic ultrasound.⁵⁻⁹

In 1991, Demer et al performed an in vitro study on atherosclerotic cadaver arteries and found that the arterial distensibility was increased after 2 minutes of exposure to a therapeutic ultrasound catheter.⁶ In 2001, Gunn et al published the results of a clinical study on 40 patients with single-vessel stenosed (not occluded) coronary arteries using catheter-delivered therapeutic ultrasound and standard percutaneous transluminal coronary angioplasty (PTCA) treatment. The results showed a 40% lower mean lesion yield pressure in the PTCA treatment in the group with ultrasound, suggesting improved distensibility in atherosclerotic plaque with therapeutic ultrasound treatment.¹⁰

THE CROSSER® RECANALIZATION SYSTEM

Despite the initial success of using therapeutic ultrasound in arterial lesions and CTOs, the lack of trackability, large catheter profile, and insufficient CTO crossing efficacy limited the applicability of this technology. In the early 2000s, the Crosser® Recanalization System was developed by FlowCardia, Inc. to improve on the first-generation ultrasound device performance and provide a low-profile system with good trackability and an increased CTO recanalization success rate. The device was first evaluated in the coronary arteries. In the FACTOR (FlowCardia's



Figure 1. The Crosser® Recanalization System, including the Crosser® Generator, transducer and foot switch, and Flowmate® Injector.

Approach to Chronic Total Occlusion Recanalization) clinical study, the Crosser® System demonstrated a 60.8% crossing success rate in 125 patients with coronary CTOs.¹¹ With this early success, the device was further modified for use in the peripheral arteries. In the PATRIOT (Peripheral Approach to Recanalization in Occluded Totals) clinical trial, the Crosser® System was used to treat 85 patients with CTOs in peripheral arteries.¹² It successfully crossed 84% of guidewire-resistant CTOs with an average ultrasonic energy activation time of 126 seconds. The Crosser® System received CE Mark in the EU in 2004 and was cleared by the FDA in 2007 for CTO crossing.

The Crosser® System consists of a generator, transducer, foot switch, and catheter, and is used in conjunction with the Flowmate® Injector System, which provides saline irrigation (Figures 1 and 2). The Crosser® System was designed to facilitate crossing of CTOs using catheter-delivered ultrasonic vibrational energy at a frequency of 20 kHz.

The Crosser® Catheter is connected to the generator through a handheld transducer. The Crosser® Generator converts AC power into high-frequency electrical current, which then excites the piezoelectric crystals within the transducer, causing them to expand and contract. The piezoelectric crystals convert high-frequency current from the Crosser® Generator into ultrasonic energy. This energy is amplified, and the ultrasonic wave is propagated down the catheter via a core wire to the tip. Upon activation, the Crosser® Catheter tip advances approximately 20 μ m with each stroke, initiating mechanical impact with the CTO material. In addition, saline is injected through the Crosser® Catheter via the Flowmate® Injector and exits through the small irrigation lumens in the catheter tip for cooling and cavitation.

The peripheral Crosser® Catheter portfolio includes rapid-exchange (RX) and over-the-wire (OTW) systems, along with a lower-profile system that does not use a guidewire for delivery. Each Crosser® Catheter includes a hub with irrigation port, hydrophilic-coated outer body over a transmission wire, irrigation outlets, and metal tip. The Crosser® Catheter 14S and 14P have a 1.1-mm tip and are compatible with 0.014-inch guidewires utilized for both above- and below-the-knee CTO crossing applications. The Crosser® Catheter S6 is a smaller-profile system that is not delivered over a guidewire with a 0.6-mm tip used in highly calcified lesions above and below the knee. The small tip focuses vibrational energy providing twice the efficiency of the Crosser® Catheter 14S, as shown in a bench occlusion model.^{13†} Compared to first-generation ultrasonic CTO crossing devices, the Crosser® Catheters offer small catheter profile and improved trackability in the peripheral anatomy and are considered major improvements over the early catheter designs.



Figure 2. The Crosser® Catheter 14S RX.

MECHANISM OF CROSSER® SYSTEM RECANALIZATION

The CTO crossing mechanism of the Crosser® Catheter is a combination of mechanical vibration and cavitation. Mechanical fragmentation is caused by the high-frequency vibration of the Crosser® Catheter tip impacting the calcified plaque. As shown in the high-speed video snapshots in Figure 3, the tip of the Crosser® Catheter vibrates a distance of approximately 20 μ m at 20,000 cycles per second. This type of low-amplitude and high-frequency mechanical vibration enables the catheter tip to act like a vibrational “jackhammer” and ablate the calcified plaque into particles that are carried away by the bloodstream.

Cavitation is a key component of CTO recanalization using the Crosser® System. High-frequency vibration of the Crosser® Catheter creates strong negative and positive pressure cycles in the surrounding fluid. Cavitation bubbles are formed from the dissolved gas on the negative side of the pressure cycle when the catheter tip is retracting.^{14,15} The bubbles quickly collapse on the positive side of the pressure cycle (Figure 3). The collapse of cavitation bubbles generates strong mechanical shock waves that erode the calcified plaque. In addition, microstreaming occurs as a secondary effect caused by the collapse of cavitation bubbles. When cavitation bubbles collapse, a jet-like ejection occurs, resulting in high-velocity fluid streaming, which also helps ablate the calcified lesion.¹⁶ Cavitation-induced shock waves and microstreaming together create a localized region with intense shear stresses and break the internal fibrin structure of calcified plaque for mechanical penetration. Figure 4 shows the microscopic pictures of a Class 4 super-hard plaster stone (Bego USA) before and after

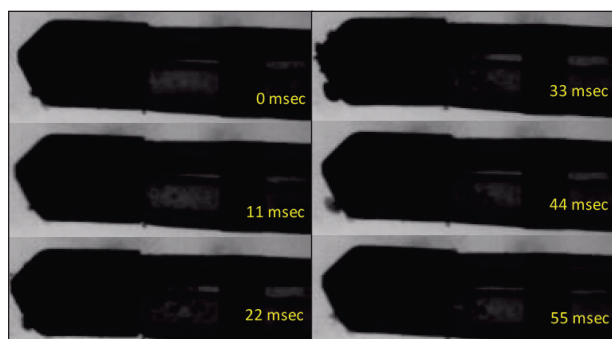


Figure 3. High-speed video snapshots of a Crosser® Catheter 14P tip vibrating in water with approximately 20 μm displacement. The catheter tip starts to move forward at 0 msec. Then it retracts around 22 msec, entering the negative side of the pressure cycle. Cavitation bubbles are generated from the dissolved gas. The cavitation bubbles collapse around 44 msec when the catheter tip starts to move forward again.

Crosser® Catheter activation.¹³ The tip of the Crosser® Catheter was placed close but not in physical contact with the stone surface during activation. The strong erosion on the stone surface after activation demonstrates the effect of cavitation and microstreaming of the Crosser® Catheter.[†]

BIOEFFECT OF THERAPEUTIC ULTRASOUND-BASED CTO RECANALIZATION

The most distinctive feature of therapeutic ultrasound-based CTO recanalization is plaque ablation selectivity. Specifically, tissues with high collagen and elastin content are extremely resistant to ultrasonic disruption; however, tissues lacking these components can be very susceptible to disruption.^{5,15} In 1965, Anschuetz and Bernard concluded that normal and atherosclerotic arterial tissue were more resistant to damage than other tissue types. Other early researchers observed that ultrasound destroys atherosclerotic plaque but leaves the adjacent vascular wall relatively unaffected.^{1,18} Ernst investigated this theory further to determine whether high-intensity ultrasound could discriminate between fibrous or calcified plaque and normal arterial wall. The results of the study showed that ultrasonic disruption is inversely related to tissue elasticity—the time to perforate cadaveric arterial wall sites was significantly longer than the fibrous or calcified plaque sites.¹⁸

As an illustration, the bench demonstration in Figure 5 further shows the plaque ablation selectivity of the Crosser® Catheter. In this bench demonstration, the Crosser® Catheter successfully drills through a guidewire-resistant stone but does not penetrate a thin elastic membrane

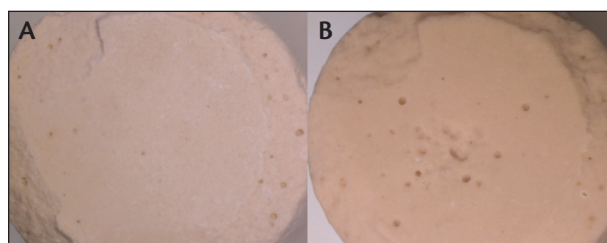


Figure 4. Microscopic pictures of a Bego stone surface before (A) and after (B) Crosser® Catheter activation. The tip of the Crosser® Catheter is placed close to the Bego stone surface but not in any physical contact during activation. The Bego stone is fabricated from a class 4 super-hard plaster with strong resistance to abrasion (Bego USA).¹⁶

layer of latex after crossing. The demonstration shows the effectiveness of the Crosser® Catheter on inelastic materials and also indicates that the elastic materials can absorb the impact of the ultrasonic vibration from the tip of the Crosser® Catheter.[†]

In addition to tissue ablation selectivity, researchers have also investigated the potential risk of peripheral embolization due to ultrasonic ablation of calcific lesions related to the size of resultant particles. Many of the studies on other therapeutic ultrasound devices show that more than 90% of debris particles after ultrasonic ablation are < 20 μm in size.^{5,8,18} Microscopic analysis also reveals that a majority of them are cholesterol monohydrate crystals.⁵ The small size of the resultant debris potentially reduces the risk of peripheral embolization when using therapeutic ultrasound for CTO recanalization. In a clinical study using a catheter-delivered therapeutic ultrasound device for coronary arterial obstruction, no evidence of arterial emboli, heart block, arterial perforation, dissection, or vasospasm was observed.⁸

In the previously discussed FACTOR (coronary) and PATRIOT (peripheral) clinical trials with the Crosser® Catheter, adverse events were tracked 30 days post-procedure, and rates were consistent with other published data on similar devices. In both trials, no Crosser® Catheter-related clinical perforations were found.¹²

SUMMARY

Therapeutic ultrasound for CTO recanalization has evolved from the 1965 in vitro study to today's standard clinical use status. Clinical studies in the past 50 years have demonstrated that this technique provides an effective treatment solution for plaque ablation. The use of therapeutic ultrasound by the Crosser® System provides the device tissue ablation selectivity and differentiates it from other competitive CTO devices. As ultrasound technology continues to evolve, physicians will be

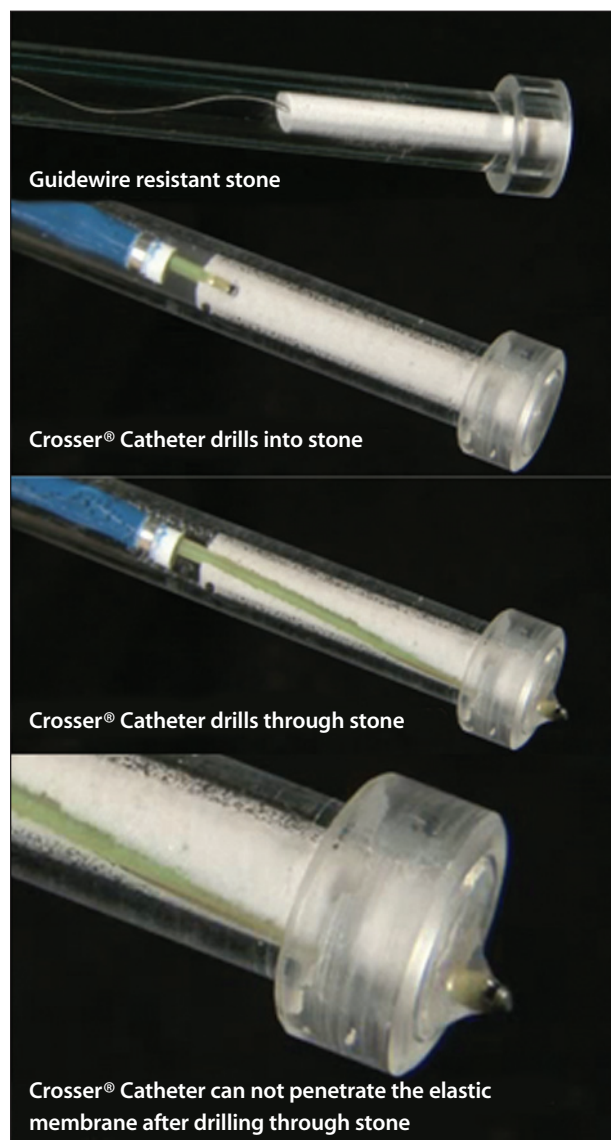


Figure 5. Bench demonstration of the plaque ablation selectivity of Crosser® Catheter. A plaster stone is used in this demo.

able to treat more patients with CTOs, and its use may broaden to other medical applications. ■

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[†]Data on file. Bench test results may not necessarily be indicative of clinical performance. Different tests may yield different results.

1. Anschuetz R, Bernard HR. Ultrasonic irradiation and atherosclerosis. *Surgery*. 1965;57:549-53.
2. Lane WZ, Minot HD. Ultrasonic coronary endarterectomy: a study in feasibility. *The Ann Thorac Surg*. 1965;1:693-696.
3. Sobbe A, Trubenstein G, Stumpf U, et al. Die Ultraschall. Auflösung von Thromben. *Klin Wochenschr*. 1974;52:1117-1121.
4. Siegel R, Myler R, Cumberland D, Donmichael TA. Percutaneous ultrasonic angioplasty: initial clinical experience. *Lancet*. 1989;334:772-774.
5. Rosenschein U, Bernstein JJ, Disegni E, et al. Experimental ultrasound angioplasty: Disruption of atherosclerotic plaques and thrombi in vitro and arterial recanalization in vivo. *J Am Coll Cardiol*. 1990;15:711-777.
6. Demer LL, Ariani M, Siegel RJ. High intensity ultrasound increases distensibility of calcific atherosclerotic arteries. *J Am Coll Cardiol*. 1991;18:1259-1262.
7. Siegel RJ, Gaines P, Crew JR, Cumberland DC. Clinical trial of percutaneous peripheral ultrasound angioplasty. *JACC*. 1993;22:480-488.
8. Siegel RJ, Gunn J, Ahsan A, et al. Use of therapeutic ultrasound in percutaneous coronary angioplasty: Experimental in vitro studies and initial experience. *Circulation* 1994;89:1587-1592.
9. Cannon LA, John J, LaLonde J. Therapeutic ultrasound for chronic total coronary artery occlusions. *Echocardiography*. 2001;18:219-223.
10. Gunn J, Cumberland DC, Siegel RJ. Ultrasound as treatment for coronary artery disease. *Echocardiography*. 2001;18:213-217.
11. Tiroch K, Cannon L, Reisman M, et al. High-frequency vibration for the recanalization of guidewire refractory chronic total coronary occlusions. *Cathet Cardiovasc Interv*. 2008;72:771-780.
12. PATRIOT evaluates FlowCardia's Crosser to mediate CTO recanalization. *Endovasc Today*. 2009. <http://www.evtoday.com/eNews/eNews102909.htm>. Accessed June 23, 2014.
13. Data on file at Bard. (G62123).
14. Nyborg LW. Basic physics of low frequency therapeutic ultrasound. In *Ultrasound Angioplasty*. Pages 1-23, 1996; Boston, Kluwer Academic Publishers.
15. O'Daly B, Morris E, Gavin G, et al. High-power low-frequency ultrasound: a review of tissue dissection and ablation in medicine and surgery. *Journal of Materials Processing Technology*. 2008;200:38-58.
16. Brujan EA. The role of cavitation microjets in the therapeutic applications of ultrasound. *Ultrasound in medicine and biology*. 2004;30:381-387.
17. BegoStone. Instructions for Use. Available at http://begousa.com/media/BegoStone_instructions.pdf. Accessed June 23, 2014.
18. Ernst A. In vitro experiments using ultrasound for plaque ablation. In *Ultrasound Angioplasty*. Pages 93-120, 1996; Boston, Kluwer Academic Publishers.

SAFETY INFORMATION

Prior to use, please see the complete "Instructions for Use" for more information on Indications, Contra-indications, Warnings, Precautions, Adverse Events, and Operator's Instructions. Caution: Federal Law (USA) restricts these devices to sale by or on the order of a physician.

CROSSER® CTO RECANALIZATION CATHETER

INDICATIONS FOR USE

The Crosser® Recanalization System is indicated to facilitate the intraluminal placement of conventional guidewires beyond peripheral artery chronic total occlusions via atherectomy. The Crosser® Catheter is only intended for use with the Crosser® Generator. Refer to the Crosser® Generator Manual of Operations for proper use.

CONTRAINDICATIONS

The device is contraindicated for use in carotid arteries.

WARNINGS AND PRECAUTIONS

- Never advance or withdraw the Crosser® Catheter without proper fluoroscopic guidance.
- It is not recommended to use the Crosser® Catheter over wires which have polymer-jacketed distal ends.
- When using the Crosser® Catheter 14S or 14P with the MicroSheath® XL Support Catheter Tapered, the Crosser® Catheter can be advanced approximately 15cm from the tip of the support catheter before resistance is encountered due to the taper on the Crosser® Catheter aligning with the taper on the support catheter. A taper lock-up marker (single marker on the Crosser® Catheter shaft) is located 127cm from the distal tip for the 146cm Crosser® Catheter and 87cm from the distal tip for the 106cm Crosser® Catheter. The taper lock-up marker can be used as an indicator that the tapers on the catheters are nearing alignment; advance the Crosser® Catheter slowly. Do not continue to advance the Crosser® Catheter if resistance is encountered.
- When using the Crosser® Catheter in tortuous anatomy, the use of a support catheter is recommended to prevent kinking or prolapse of the Crosser® Catheter tip. Kinking or prolapse of the tip could cause catheter breakage and/or malfunction.

SIDEKICK® AND USHER® SUPPORT CATHETERS

INDICATIONS FOR USE

The Sidekick® and Usher® Support Catheters are single lumen catheters intended to create a pathway for other devices in the peripheral vasculature.

CONTRAINDICATIONS

The Sidekick® and Usher® Catheters are contraindicated for use with cutting/scoring balloons, pediatrics, neonatal and neurovascular patients.

WARNINGS AND PRECAUTIONS

- When the catheter is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Movement of the product without fluoroscopic guidance may result in damage to the product or vasculature or cause vessel perforation.
- Manipulating or torquing a product against resistance may cause damage to the product or vasculature or cause vessel perforation. Never advance, withdraw or torque a catheter which meets resistance.
- Verify compatibility of the product's inner and outer diameters and lengths with other devices before use.

- Refer to package label for tip shape for the Sidekick® and Usher® Catheters. Do not attempt to manipulate or re-shape the tip configurations.

VASCUTRAK® PTA DILATATION CATHETER

INDICATIONS FOR USE

The Vascutrak® PTA Dilatation Catheter is intended to dilate stenoses in the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also recommended for post dilatation of balloon expandable stents, self-expanding stents, and stent grafts in the peripheral vasculature.

CONTRAINDICATIONS

The Vascutrak® PTA Catheter is contraindicated where there is the inability to cross the target lesion with a guidewire and for use in the coronary or neuro vasculature

DORADO® PTA DILATATION CATHETER

INDICATIONS FOR USE

Dorado® Balloon Dilatation Catheters are recommended for Percutaneous Transluminal Angioplasty (PTA) of the renal, iliac, femoral, popliteal, tibial, peroneal, and subclavian arteries and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also recommended for post-dilatation of balloon expandable and self expanding stents in the peripheral vasculature. This catheter is not for use in the coronary arteries.

CONTRAINDICATIONS

None known

LIFESTENT® VASCULAR STENT SYSTEM

INDICATIONS FOR USE

The LifeStent® Vascular Stent System is intended to improve luminal diameter in the treatment of symptomatic de-novo or restenotic lesions up to 240mm in length in the native superficial femoral artery (SFA) and proximal popliteal artery with reference vessel diameters ranging from 4.0-6.5mm.

CONTRAINDICATIONS

The LifeStent® Vascular Stent System is contraindicated for use in:

- Patients with a known hypersensitivity to nitinol (nickel, titanium), and tantalum.
- Patients who cannot receive recommended anti-platelet and/or anti-coagulation therapy.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

ADVERSE EVENTS

As with most percutaneous interventions, potential adverse effects include: Bleeding which may require transfusion or surgical intervention, Hematoma, Perforation, Dissection, Guidewire entrapment and/or fracture, Hypertension / Hypotension, Infection or fever, Allergic reaction, Pseudoaneurysm or fistula Aneurysm, Acute reclosure, Thrombosis, Ischemic events, Distal embolization, Excessive contrast load resulting in renal insufficiency or failure, Excessive exposure to radiation, Stroke/CVA, Restenosis, Repeat catheterization / angioplasty, Peripheral artery bypass, Amputation, Death or other bleeding complications at access site.