

SIS ALMANAC ONLINE:

CRYOTHERAPY

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INTRODUCTION:

Percutaneous coronary interventions (PCI) such as angioplasty and stenting are common methods of coronary revascularization in the United States. Despite advances in PCI, restenosis remains a major problem.¹⁻² Restenosis occurs in 20-50% of patients after balloon angioplasty and in 10-30% of patients receiving a stent.² Angioplasty is associated with scarring, subsequent vessel recoil, neointimal proliferation, negative remodeling, vascular endothelial cell erosion (denudation) of the intimal lining and early thrombus formation.²⁻³ Drug-eluting stents, brachytherapy (intracoronary radiation) and antiplatelet medications have reduced these events significantly, but have not eliminated the problem. Novel antirestenosis technologies, such as cryotherapy (the endovascular application of low temperature), have emerged as alternative options.

Tissue response to freezing injury is dependent upon several factors. These include the duration of freezing, freezing and thawing rates, tissue type, and vascular reaction to freezing temperatures. If tissues are exposed to a freezing temperature range of 0°C to -10°C within a short time span, the injury produces an inflammatory response with minimal cell death. Tissues exposed to that temperature range are associated with little or no ice crystal formation⁴. Freezing temperatures in the range of -40°C to -50°C ultimately ends in cell destruction. Tissues react and heal differently depending on the tissue type. Blood vessel structure and function are usually preserved after freezing and thawing.

Scientists and clinicians have experimented on the potential therapeutic applications of cold temperatures. With regards to restenosis therapy, the goal of cryotherapy is to inhibit smooth muscle proliferation rather than promote muscle destruction. Previous studies have demonstrated that apoptosis occurs when tissues are subjected to milder freezing temperatures (-5°C to -15°C). Apoptosis in smooth muscle cells does not produce inflammatory consequences that result in cell proliferation and vessel restenosis.⁵⁻⁶ As tissues thaw, a benign healing process begins that results in a smooth intimal layer with reduced elastic recoil and decreased propensity for dissection. This result promotes improved laminar flow and normal re-endothelialization of blood vessel lumen.⁷

A technique known as cryoplasty (see Figure 1) combines simultaneous vessel dilation and freezing of the artery. It is similar to conventional balloon angioplasty. The balloon is inflated with a cryogen such as pressurized liquid nitrous oxide instead of saline. As the balloon expands within the stenosed vessel lumen, the cryogen cools the vessel and surrounding tissue to -10°C . This treatment is proposed to be gentler on the artery wall, minimizing trauma and may result in improved clinical outcomes. Studies have shown significant reduction in restenosis rates. These effects have been seen six to nine months post-treatment.⁶



Fig.1: Cryoplasty technique. Pressurized liquid nitrous oxide expands the balloon within a stenosed vessel.

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Aside from the potential for antirestenosis treatment, cryotherapy has applications in the treatment of myocardial ischemia and tachyarrhythmias as well as the detection of vulnerable plaque.

ANGIOGENESIS

Cryogenic injury in tissue is associated with angiogenesis. After freezing injures tissues, new blood vessels develop at the periphery of the uninjured areas. Thereafter, the new vessels penetrate into the injured sites to stimulate repair. This principle has been used in experiments of cryogenic angiogenesis in myocardial ischemia. A thin cryogenic probe is used to make puncture wounds in the myocardium, freezing the muscle tissue to produce an injury that would stimulate angiogenesis.^{5,8} New blood vessels promote the healing process by supplying additional oxygen and nutrients to the ischemic heart.

ABLATION

Cryoablation is a technique used in the treatment of atrial fibrillation and other tachyarrhythmias due to accessory pathway conduction. Before beginning the ablation process, one needs to know the exact source of the abnormal rhythm or the location of the accessory nerves. This is commonly done by diagnostic electrophysiology. Cryogenic mapping or ice mapping is a technique that can also be utilized for this purpose. An initial assessment is made to determine an area of tissue as the source of the arrhythmia. An Argon-powered cold probe is cooled to -30°C or -40°C and applied to the suspected tissue. The freezing temperature temporarily stops the conduction of nerve impulses. The tissue is then allowed to thaw slowly. If abnormal rhythm returns from the site, a confirmation is made. The treatment then proceeds with the further cooling of the probe to -70°C to -80°C , whereby the target tissue is ablated for 2-3 minutes.^{5, 9-10} The procedure can be repeated in various areas until the desired results are achieved.

Several cryoablative techniques have been developed to treat the tachyarrhythmias. Recurrent supraventricular tachycardia is treated by cryoablation of the atrioventricular node followed by a cardiac pacemaker implant.¹⁰⁻¹¹ Cryoablation of the coronary sinus combined with atrial incisions (the Cox MAZE procedure) interrupts conduction across the posterior-inferior wall of the left atrium.¹²⁻¹⁵ A linear cryoablation of the atrial tissue surrounding the pulmonary veins and the mitral valve annulus is sometimes required.¹⁶

VULNERABLE PLAQUE

Vulnerable plaque is composed of a thin fibrous cap covering a core of lipid deposits, inflammatory and smooth muscle cells, and cellular debris. This cap may erode or rupture due to both internal and external factors, thereby exposing the clot-promoting contents of the plaque to blood. Plaque contents may activate the coagulation cascade and give rise to thrombus formation. This in turn may lead to life-threatening conditions such as stroke or sudden cardiac death.¹⁷ A dual balloon cryotherapy catheter device was designed to provide a temperature sensing mechanism for thermographic detection of vulnerable plaque. Sensors attached to the second balloon monitor a temperature gradient between the vessel lumen and the plaque.¹⁸ When the vulnerable plaque core is cooled to a freezing range of 10°C to -10°C , the lipid-rich liquid state turns into a crystalline solid or gel condition. This cooling stabilizes the plaque and helps maintain patency of the vessel lumen. Exposing the plaque and its surrounding tissue to freezing temperatures inhibits necrosis, inflammation, and further deterioration and eventual rupture of the cap.¹⁸

CONCLUSION

Novel therapeutic modalities such as cryotherapy represent a viable and cost-effective arsenal against cardiovascular disease. When cold thermal energy is applied during angioplasty, the freezing temperatures minimize trauma on the vessel wall. This insures a smooth intimal wall during the repair process and decreases the likelihood of restenosis.¹⁹ Cryotherapy can also be used as treatment of myocardial ischemia by promoting angiogenesis. Several techniques have been developed using the principles of cryotherapy for the ablation of abnormal nerve tissue in atrial fibrillation. Cryotherapy has also found applications in the detection and treatment of vulnerable plaque. Basic and clinical research in cryobiology proceeds with brisk pace. New discoveries together with improved product development may yield further breakthroughs in this emerging technology.

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