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NEW RESEARCH PAPER

Pulsed Cavitational Ultrasound Softening

A New Noninvasive Therapeutic Approach for Calcified Bioprosthetic Valve Stenosis

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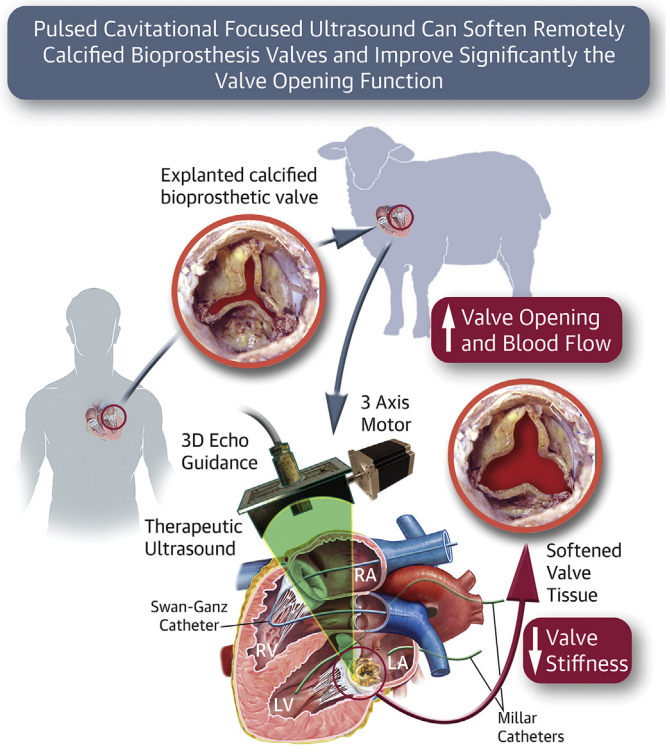
VISUAL ABSTRACT



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HIGHLIGHTS

- **Bioprosthetic heart valves have limited durability, with a progressive deterioration of the bioprosthesis after 12 to 15 years, mainly due to intravalvular calcifications.**
- **In this proof-of-concept study, we demonstrated in vivo using an ovine model and in vitro that pulsed cavitational focused ultrasound can be used to remotely soften human degenerative calcified bioprosthetic valves and significantly improve the valve opening function.**
- **This new noninvasive approach has the potential to improve the outcome of patients with severe bioprosthesis stenosis.**

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ABBREVIATIONS AND ACRONYMS

CPB = cardiopulmonary bypass

PCU = pulsed cavitational ultrasound

PHT = pressure half time

SUMMARY

The authors propose a novel noninvasive therapeutic approach for degenerative calcified bioprosthetic heart valves based on pulsed cavitational ultrasound (PCU) to improve the valvular function by remotely softening calcified stiff cusps. This study aims to demonstrate both in vivo, using an ovine model with implanted human calcified bioprosthesis, and in vitro that PCU can significantly improve the bioprosthesis function. A 50% decrease of the transvalvular gradient was found, demonstrating a strong improvement of the valve opening function. This new noninvasive approach has the potential to improve the outcomes of patients with severe bioprosthesis stenosis. (J Am Coll Cardiol Basic Trans Science 2017;■:■–■)

Bioprosthetic valves are becoming increasingly common in patients with valvular heart diseases. They are often favored over mechanical valves because of a lower risk of thrombotic or bleeding events, as well as the desire to avoid lifetime anticoagulation medications (1). However, bioprosthetic valves have limited durability, with a progressive deterioration of the bioprosthesis after 12 to 15 years, mainly due to intravalvular calcifications (2). The need for a redo surgery due to the incidence of structural valve deterioration is expected to increase (3). Nevertheless, redo valve surgery is associated with significant morbidity and mortality (4). Transcatheter valve-in-valve implantation has emerged as a promising, less invasive alternative to redo surgery; however, it still comes with its own various set of complications (5).

In parallel, for about 30 years, other therapeutic strategies (6,7) have been investigated to treat calcified valves (native or bioprosthetic). One promising approach was ultrasound-based (8), but it remained limited at the time by the need for open surgery with cardiopulmonary bypass (CPB). Nevertheless, this limitation must be challenged again with the recent improvement of technologies and concepts of pulsed cavitational focused ultrasound (PCU) or histotripsy. Histotripsy is a noninvasive, cavitation-based therapy (mechanical effect) based on very short, high-pressure ultrasound pulses focused in tissues to generate a dense, energetic, lesion-producing bubble cloud. Although histotripsy can be used to produce sharp lesions in soft tissues (9,10), recent studies have suggested that cavitation activity can also soften biological tissues (11).

The objective of our study was to evaluate the efficacy of PCU to significantly improve valve opening of severe degenerative calcified bioprosthetic valves. First, we demonstrated in vitro the efficacy of PCU on a human explanted calcified bioprosthesis mounted on an artificial heart pump and quantified the improvement of the valvular function. Then, we demonstrated its feasibility and efficacy in vivo in the beating heart of an ovine model with implanted calcified bioprosthesis.

METHODS

MODEL OF HEART CALCIFIED VALVE. We used Carpentier-Edwards Perimount Magna (stented bovine pericardial bioprosthesis, Edwards Lifesciences, Irvine, California), explanted on a human, as a model of heart calcified valve stenosis. For all patients, the indication of explant was a severe stenosis with calcification. Each valve was fixed in glutaraldehyde 0.6% immediately after explant. Before each experiment, the valve was immersed for 5 min in saline serum (0.9% NaCl) 3 consecutive times. This protocol was in agreement with institutional guidelines (national reference number of the 143 study: 02255.02).

ULTRASOUND GENERATION AND PCU ACOUSTIC PARAMETERS. A 1.25-MHz focused single-element transducer (Imasonic, Besançon, France), called a therapy transducer, was used to generate PCU. This transductor had a 100-mm focal length (f-number = 1) and was driven by a high-voltage amplifier (GA-2500A, RITEC, Warwick, Rhode Island). We produced PCU using 10-cycle pulses, each 8 μs long, delivered at a pulse repetition frequency of 100 Hz. We estimated the pressure peak amplitudes at the focal spot to be 70 and −19 MPa, respectively, for the positive and negative peak pressure.

ULTRASOUND CAVITATIONAL TREATMENT GUIDANCE AND MONITORING. Three-dimensional echocardiography was used to guide and monitor the treatment. An IE33 scanner and X5-1 probe (xMATRIX array, 3 MHz, 3,040 elements with microbeam-forming) (Philips Healthcare, Bothell, Washington) were used. The imaging probe was fixed through a hole in the center of the therapy transducer (**Figure 1**). The focal