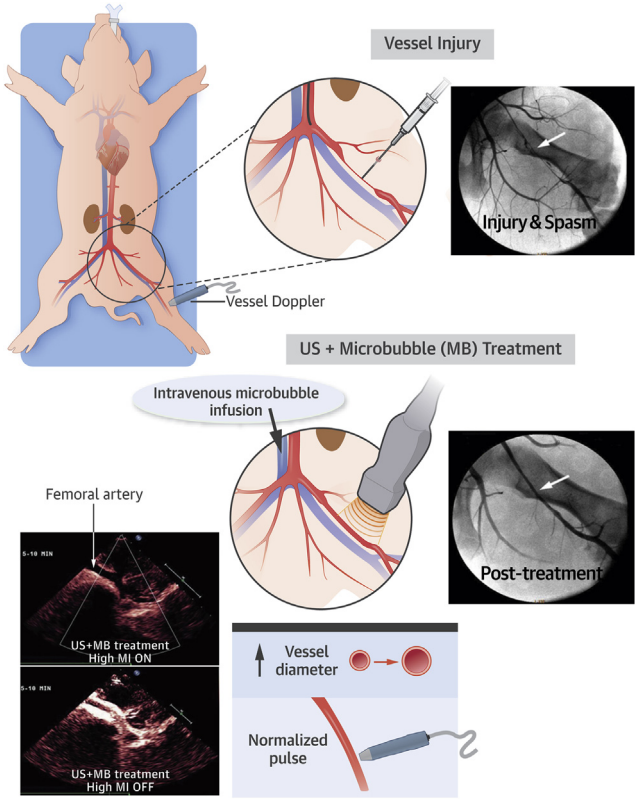
JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 2, NO. 6, 2017
ISSN 2452-302X
https://doi.org/10.1016/j.jacbts.2017.07.011

PRECLINICAL RESEARCH

Ultrasound-Induced Microbubble Cavitation for the Treatment of Catheterization-Induced Vasospasm

Shelby Kutty, MD, PhD, MHCM,[a] Na Liu, MD, PhD,[a,b] Jia Zhou, MD, PhD,[a,c] Yunbin Xiao, MD, PhD,[a] Juefei Wu, MD, PhD,[d] David A. Danford, MD,[a] John Lof, MS,[d] Feng Xie, MD,[d] Thomas R. Porter, MD[d]

VISUAL ABSTRACT



Kutty, S. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(6):748-56.

HIGHLIGHTS

- **In a porcine model, we investigated the therapeutic effectiveness of microbubble enhanced sonothrombolysis for treatment of catheter-induced vasospasm and vascular injury, a common complication after femoral arterial catheterization, particularly in children.**
- **Our results show that microbubble cavitation mediated by brief application of diagnostic high mechanical index impulses is an effective noninvasive method for relieving catheter-induced vasospasm.**
- **This approach could have potential as an effective treatment for reversal of pulse loss after peripheral arterial injury and vasospasm.**

From the [a]Division of Pediatric Cardiology, University of Nebraska College of Medicine/Children's Hospital & Medical Center/Creighton University, Omaha, Nebraska; [b]Department of Cardiology and Cardiac Catheterization Lab, Second Xiangya Hospital, Central South University, Changsha, China; [c]Department of Ultrasonography, the First Affiliated Hospital of University of South China, Hengyang, China; and the [d]Department of Internal Medicine, Section of Cardiology, University of Nebraska Medical Center, Omaha, Nebraska. Dr. Kutty is supported by the American Heart Association and the National Institute of Child Health and Development. Dr. Porter is supported by the Theodore F Hubbard Foundation. Funding sources were not involved in data collection, data analysis, or manuscript drafting. All other authors have reported that they have no relationships relevant to the

SUMMARY

Inertial cavitation inducing ultrasound-mediated microbubble treatments can produce resolution of vasospasm and restoration of distal arterial flow after peripheral artery injury. Resolution of catheter-induced vasospasm is likely to be nitric oxide- mediated because improvements in stenosis diameter and downstream blood flow were blunted following pretreatment with L-NAME. The potential for clinical applicability of this therapy is significant because: 1) microbubbles can be delivered systemically into the site of injury enabling relatively high local concentration; 2) targeted transcutaneous ultrasound delivery is achievable due to the proximity of vessels; and 3) microbubbles and diagnostic ultrasound system used are commercially available. (J Am Coll Cardiol Basic Trans Science 2017;2:748–56) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

CIV = catheter-induced vasospasm

CC = cardiac catheterization

L-NAME = N (ω)-nitro-L-arginine methyl ester

MB = microbubble

MI = mechanical index

NO = nitric oxide

UMC = ultrasound-induced microbubble cavitation

US = ultrasound

Arterial vasospasm is a commonly observed complication of cardiac catheterization (CC). Other sequelae of CC-related vascular injury include thrombus formation and post-thrombotic syndrome with either transient or complete loss of arterial pulses in the femoral and distal arteries. Infants and children with heart disease often undergo multiple CC procedures, and are at higher risk for catheter-induced vasospasm (CIV) and thrombosis. Moreover, infants have an increased incidence of thromboembolism (1). Up to 20% of thrombotic events occur in the femoral vessels (1–4) and are associated with larger arterial access points (5–7) and longer procedure times. These factors may be compounded by small body size, polycythemia, and low cardiac output in sick infants (6,8). CIV and loss of femoral pulse after CC contributes to prolonged hospital stay, increased need for medical and/or surgical interventions, and difficulty with future vascular access. Despite technological improvements such as the use of indwelling arterial sheaths for a shorter duration (9), smaller balloon/catheter profiles (10,11), and systemic heparinization (12), complications of CC-related vascular injury continue to occur.

Ultrasound (US) has been investigated as an adjunct to pharmacologic thrombolysis, as well as an independent treatment for vascular thrombosis (13–16). Guided high mechanical index (MI) impulses from a diagnostic US system during intravenous microbubble (MB) infusion have the potential to dissolve intravascular thrombi (termed sonothrombolysis) without the need for fibrinolytic therapy. We have previously studied the feasibility of treating deeply located acute intravascular thrombi with US and intravenous MBs (17–19). The spasm reversal properties of US + systemic MB therapy have not been previously investigated, but diagnostic US-induced MB cavitation has been shown to enhance endothelial nitric oxide (NO) release (20,21). Our principal hypothesis was that US and MB therapy might have an immediate effect on reversing pulse loss following CIV by promoting NO-mediated resolution of spasm. We sought to investigate the: 1) safety and feasibility; and 2) therapeutic effectiveness of MB-enhanced sonothrombolysis for treatment of CIV. A porcine model was chosen based on our previous work which demonstrated safety of intravenous MB and transcutaneous US in this model.

METHODS

PORCINE MODELS OF CIV. The study was approved by the Institutional Animal Care and Use Committee of the University of Nebraska Medical Center and was in compliance with the standards in the Guide for the Care and Use of Laboratory Animals. Models of CIV were created in pigs: in a unilateral femoral artery, or bilateral femoral arteries separated at 1-week time intervals. Before the procedure, each pig was fasted overnight and pre-anesthetized with an intramuscular mixture of Telazol (4.4 mg/kg; tiletamine HCl and zolazepam HCl, Fort Dodge Animal Health, Fort

contents of this paper to disclose. All institutional and national guidelines for the care and use of laboratory animals were followed and approved by the appropriate institutional committees. Drs. Kutty and Liu contributed equally to this work.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

Manuscript received May 5, 2017; revised manuscript received July 18, 2017, accepted July 20, 2017.