Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 21, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.050

PRE-CLINICAL RESEARCH

Noninvasive Renal Sympathetic Denervation by Extracorporeal High-Intensity Focused Ultrasound in a Pre-Clinical Canine Model

Qifeng Wang, MM,* Rui Guo, MD, PHD,† Shunkang Rong, MD,*‡ Gang Yang, MD, PHD,* Que Zhu, MD, PHD,* Yonghong Jiang, MD,* Changming Deng, MD,* Dichuan Liu, MD,* Qi Zhou, MD, PHD,* Qi Wu, MD, PHD,* Shunhe Wang, MD,§ Jun Qian, MM,* Qi Wang, MS,‡ Han Lei, MD,† Tong-Chuan He, MD, PHD,‖ Zhibiao Wang, MD, PHD,‡ Jing Huang, MD*‡
Chongqing, China; and Chicago, Illinois

Objectives This study investigated the feasibility of noninvasive renal sympathetic denervation (RSD) by using the novel approach of extracorporeal high-intensity focused ultrasound (HIFU).

Background Catheter-based RSD has achieved promising clinical outcomes.

Methods Under the guidance of Doppler flow imaging, therapeutic ablations (250 W × 2 s) were performed by using extracorporeal HIFU on the bilateral renal nerves (36.3 ± 2.8 HIFU emissions in each animal) in a mean 27.4-min procedure in 18 healthy canines of the ablation group. Similar procedures without acoustic energy treatment were conducted in 5 canines of the sham group. The animals were killed on day 6 or 28. Blood pressure (BP), plasma noradrenaline (NA) level, and renal function were determined on days 0, 6, and 28. Pathological examinations were performed on all retrieved samples.

Results All of the animals survived the treatment. After ablation, BP and NA significantly decreased compared with the baseline values (BP changed −15.9/−13.6 mmHg, NA changed −55.4% [$p < 0.001$] 28 days after ablation]) and compared with the sham group on days 6 and 28. Ablation lesions around the renal artery adventitia were observed on day 6. A histological examination revealed the disruption of nerve fibers, necrosis of Schwann cells and neurons, and apparent denervation on day 28. No procedure-related complications were observed.

Conclusions Effective RSD was successfully achieved by using the extracorporeal HIFU method in canines. Thus, noninvasive HIFU may be further explored as an important and novel strategy for RSD. (J Am Coll Cardiol 2013;61: 2185–92) © 2013 by the American College of Cardiology Foundation

It is estimated that 1 billion individuals worldwide suffer from hypertension, and hypertension-related complications are recognized as the major cause of morbidity and mortality (1). Recently, a catheter-based strategy for renal sympathetic denervation (RSD) was developed for the management of drug-resistant hypertension, and it has achieved encouraging clinical outcomes (2). The therapeutic benefits of RSD have also been shown for those diseases associated with sympathetic overactivity, such as insulin resistance, arrhythmia, and heart failure (3,4). However, intervention-related complications can occasionally occur. In addition, vascular wall injury has been observed in a pre-clinical model (5), and hemodynamic stenosis has been found in clinical case reports, possibly due to related complications (6). Many new devices are currently under investigation, such as chemical renal denervation using a drug delivery approach with a sidehole balloon catheter, which may help to reduce the potential damage to the artery wall (7).

High-intensity focused ultrasound (HIFU) has been used to noninvasively ablate tissue by extracorporeally delivering focused acoustic energy. This technique is considered the

From *The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; †The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; ‡State Key Laboratory of Ultrasound Engineering in Medicine Co-Founded by Chongqing and the Ministry of Science and Technology, and National Engineering Research Center of Ultrasound Medicine, Chongqing, China; §Chongqing Medical University, Chongqing, China; and the ‖Molecular Oncology Laboratory, Department of Surgery, The University of Chicago Medical Center, Chicago, Illinois.
This study was supported in part by research grants from the National Natural Science Foundation of China (30527001, 30830040, and 81201173), the National Key Basic Research Program (973 Program; 2011CB707902), and the Foundation for Key Scientific and Technical Research of Chongqing, China (CSTC2005AA5008-5 and CSTC2009AB5003). Dr. Z. Wang is a shareholder of Chongqing Haifu and the professor of the Department of Biomedical Engineering of Chongqing Medical University, Chongqing, China. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first 3 authors contributed equally and are joint first authors to this article.

Manuscript received December 12, 2012; revised manuscript received February 11, 2013, accepted February 14, 2013.

JACC Vol. 61, No. 21, 2013
May 28, 2013:2185–92

Abbreviations and Acronyms

BP = blood pressure
BUN = blood urea nitrogen
CDFI = color Doppler flow imaging
HIFU = high-intensity focused ultrasound
NA = noradrenaline
Na^+ = sodium
RSD = renal sympathetic denervation
sCr = serum creatinine

ideal source of energy, especially for the ablation of deep solid tissue (8). It has also been clinically used to treat uterus, kidney, and liver tumors (9,10). In addition, the application of HIFU has been expanded significantly in recent years (11,12).

To the best of our knowledge, few studies have reported the use of noninvasive HIFU for RSD. The current study was designed to explore the possible use of this new technique for RSD in a canine model by investigating the feasibility and safety associated with this procedure.

Methods

HIFU system for RSD. The HIFU tumor therapeutic system (Model-JC200, certified by the European Union, Chongqing Haifu Technology Co. Ltd., Chongqing, China) was used. The therapeutic focused ultrasound beam was produced by a 220-mm spherically curved therapeutic transducer with focal length of 132 mm. The physical focal region was ellipsoid and $<2 \times 2 \times 6$ mm^3. The operating frequency was 0.98 MHz (corresponding to 1.58-mm wavelength). The acoustic power of the therapeutic transducer ranged from 33 to 550 W, with an acoustic intensity at focus from 467 to 7,785 W/cm^2 under a degassed water acoustic environment. A diagnostic probe was aligned coaxially to the therapeutic transducer to locate the target tissues. By adjusting the transducer in 3 dimensions, the focus could be moved 1 mm by 1 mm to target the renal artery.

Animal preparation. The experimental protocol was approved by the Institutional Ethics Committee of Chongqing Medical University. The use and care of the animals were in compliance with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals.

Twenty-three healthy mongrel canines (15 to 20 kg, purchased through the Experimental Animal Care Center of Chongqing Medical University) of either sex were distributed randomly into an ablation group (n = 18) and a sham group (n = 5). All of the canines were anesthetized with 3% pentobarbital sodium (30 mg/kg) intraperitoneally. The abdominal fur along the acoustic path was removed, and the skin was degreased with 75% alcohol and suctioned for degassing. The right femoral artery was punctured, and a syringe attached to a pressotransducer (Model YPJ01, Chengdu Instrument Factory, Chengdu, China) temporarily for every invasive blood pressure (BP) measurement. BP was recoded with a RM6240 Physiology Signal Collection Processing System (Chengdu Instrument Factory) before ablation (defined as baseline).

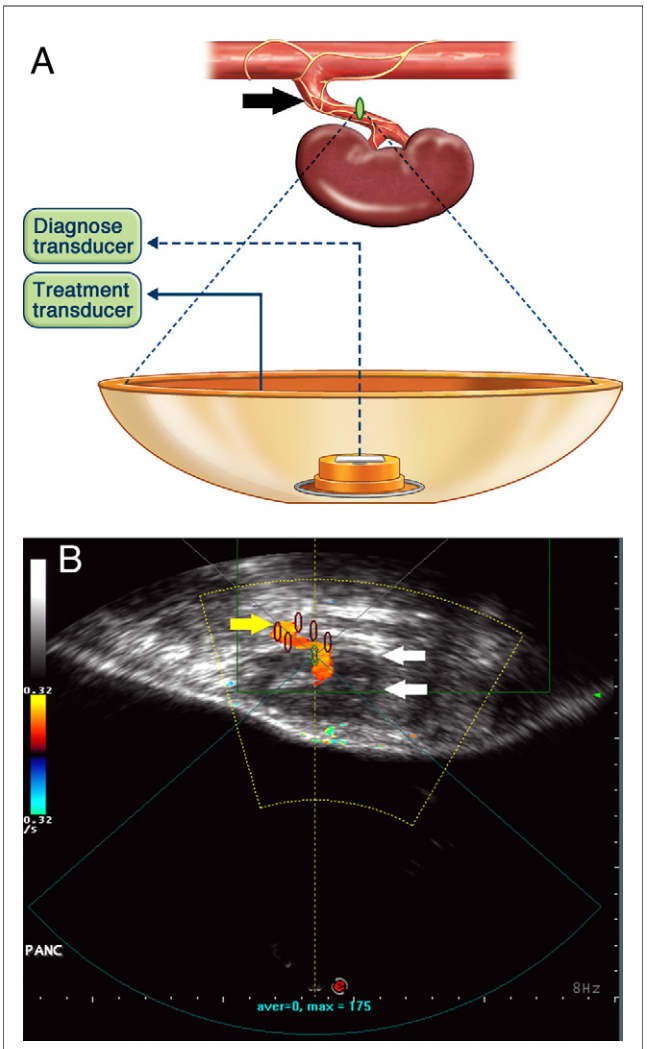

Figure 1 Schematic of RSD With HIFU; Ablation Foci Were Set and Ablated by CDFI Guidance

(A) The focus of high-intensity focused ultrasound (HIFU) energy **(green spot)** was set to cross the wall of the renal artery. **Green spot:** the focal point of the HIFU energy; **black arrow:** renal artery. RSD = renal sympathetic denervation. **(B)** Ablation foci **(green spots)** were targeted by 3-dimensional movement of the transducer guided by color Doppler flow imaging (CDFI). The locations on the renal artery that were ablated appear as **red spots. White arrows** = kidney; **yellow arrow** = renal artery.

At days 6 and 28 post-ablation, the follow-up study used a similar procedure to measure BP, which was recorded 30 min post-anesthesia.

HIFU ablation procedure for RSD. In the ablation group, the left abdominal wall of each canine was immersed in the therapeutic chamber filled with degassed water, which provided acoustic coupling between the transducer and skin (13). Color Doppler flow imaging (CDFI) on the long-axis view of the left renal artery was obtained by adjusting the relative positions of the transducer and animal (Fig. 1A). Using CDFI as a guide, the foci of the extracorporeal HIFU were set on the zygomorphic wall at the proximal, middle, and distal right renal artery, respectively.