Noninvasive Renal Denervation for Resistant Hypertension Using High-Intensity Focused Ultrasound

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To the Editor:
Renal denervation (RDN) has emerged as a promising therapy for patients with resistant hypertension and other diseases related to sympathetic overactivation. High-intensity focused ultrasound (HIFU) has been demonstrated to be a novel strategy for effective noninvasive deep tissue ablation in clinical practice. The exploration of HIFU has expanded to cardiovascular research, such as noninvasive septal and electrophysiological ablations. We previously reported that efficient RDN can be achieved using the HIFU procedure with an excellent safety profile in a canine model. Thus, the clinical use of HIFU-based RDN to treat resistant hypertension should be investigated.

Methods
This clinical study was approved by the Institutional Ethical Review Committee at The Second Affiliated Hospital of Chongqing Medical University and was registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR-ONC-13003231). The primary efficacy objective was the change in average 24-hour ambulatory systolic blood pressure at 6 months. The primary safety objective was all adverse events during the study. Eligible patients were treated with HIFU-based RDN from August 2013 to May 2014 with 6 months of follow-up. Written informed consent was obtained from all of the enrolled patients.

The enrollment criteria included adult patients with resistant hypertension or patients who could not tolerate antihypertensive medications. The participating patients received stable antihypertensive drug regimen for at least 4 weeks before enrollment and were evaluated by ambulatory blood pressure monitoring to exclude the white coat hypertension and pseudohypertension. A complete listing of the key inclusion and exclusion criteria is shown in Table 1.

Baseline data collection included the medical history, physical examination, review of medications, ambulatory blood pressure monitoring, office blood pressure (BP), Holter monitoring (including heart rate variability [HRV] analysis), renal artery computed tomography angiography, echocardiography, plasma noradrenaline level, and blood chemistries test (including serum creatinine, blood urea nitrogen, and electrolyte levels). Ambulatory blood pressure monitoring was measured using an Ambulatory Blood Pressure System (SunTech Medical Inc, Morrisville, NC) every 20 minutes during the day and every hour at night. The office BP was collected according to the Standard Joint National Committee VII Guidelines with an Automatic BP Monitor (Omron Healthcare, Tokyo, Japan). The average values of triplicate measures were used. Holter monitoring was used for 24 hours to measure the HRV and was analyzed by a CardioScan Premier 11 Holter System (DM Software Inc, CA). The cardiac conditions were evaluated by echocardiography with an iE33 xMATRIX Echocardiography System (Royal Philips, Amsterdam, The Netherlands).

The time-domain HRV parameters included the SD of all normal RR intervals (SDNN), the SD of the averaged normal RR intervals for all 5-minute segments (SDANN), mean of the SD of all normal RR intervals for all 5-minute segments (SDNN index), the root mean square of differences between adjacent R–R intervals (rMSSD), and the percentage of adjacent R–R intervals that varied by >50 ms (pNN50).

The echocardiographic parameters included the following: the left atrial diameter, the left ventricular end-diastolic dimension, the interventricular septum thickness, the left ventricular posterior wall thickness, fractional shortening, the left ventricular ejection fraction, and the ratio of E and A peak velocity of mitral valve flow (E/A ratio).

Model-JC HIFU tumor therapeutic system (Chongqing Haifu Technology Co., Ltd., Chongqing, China) was used in this study. Rigorous bowel preparation and skin cleaning were performed before treatment. The patients were placed on the treatment bed in a posterior oblique position (at an angle of 30°–45°) with their lower backs immersed in the degassed water of the therapeutic chamber. Preoperative computed tomography angiography and intraoperative Color Doppler flow imaging (CDFI) were used to guide the target plan. By changing of the CDFI views, 5 to 6 discrete targets (based on the length of the targeted artery) were set longitudinally and spirally covering 4 quadrants of the renal arterial CDFI with a longitudinal interval of 5 mm (Figure 1). The targets were distributed in the middle and distal segments of the renal artery, with the exception of the proximal segment because it was close to the centrum and far away from the transducer. A relatively low therapeutic power of 200 to 300 W×2 s was used for a single acoustic energy emission. The emissions were repeated 50× for each target sequentially. The time interval between emissions was 2 s. The ablation procedure was performed on the bilateral renal arteries in all of the treated patients. The patients were freely conscious during the procedure.

Patients were followed up at 1, 3, and 6 months. Physical examination, a review of medications, ambulatory blood pressure monitoring, and monitoring for adverse events were conducted at all follow-up time points. Holter monitoring, blood chemistry tests, and renal artery imaging examination (CDFI or computed tomography angiography) were conducted at 1- and 6-month follow-up time points. The echocardiography and plasma noradrenaline level were conducted only at the 6-month follow-up time point.

For statistics, all of the continuous values are presented as the mean and SD. All of the categorical parameters are summarized...
Results

A total of 10 patients completed the baseline evaluation, underwent the noninvasive HIFU-based RDN, and finished the follow-up visits. Baseline demographic characteristics, clinical conditions, and medication data for the enrolled patients are shown in Table 2. The procedure time (from the beginning to the completion of acoustic energy delivery) was 61.2±5.8 minutes. The HIFU ablation time was 19.0±0.9 minutes, and the acoustic energy was 293.8±43.2 kJ.

The baseline values of 24-hour ambulatory and office BP were 159.1±8.9/90.7±11.2 and 169.0±5.8/91.0±11.0 mm Hg, respectively. The mean reductions in the 24-hour ambulatory BP from baseline to 1, 3, and 6 months were −13.1/−7.6 (SD 9.5/8.5), −14.9/−9.0 (8.7/7.0), and −11.4/−4.8 (4.8/4.8) mm Hg, respectively (Figure 2).

The mean reductions in office BP were −25.6/−10.2 (SD 9.5/8.2), −29.9/−12.2 (5.7/9.2), and −29.2/−11.2 (6.8/9.7) mm Hg at the 1-, 3-, and 6-month time points, respectively (Figure 2).

The HRV analysis results showed that the SDNN (138.7±34.4 and 141.7±41.2 versus 122.0±31.6, \(P=0.027\)) and SDANN (126.0±32.9 and 137.1±41.0 versus 111.0±31.1, \(P=0.047\)) were increased significantly at the 1- and 6-month visits compared with that at baseline. However, the other parameters, SDNN index, rMSSD, and pNN50, showed no statistically significant difference compared with the baseline values.

The echocardiographic results showed that the fractional shortening (37.0±4.8% versus 41.1±5.1%, \(P=0.026\)) and left ventricular ejection fraction (65.5±6.6% versus 71.8±6.0%, \(P=0.019\)) were increased significantly, whereas the left atrial diameter, left ventricular end-diastolic dimension, interventricular septum thickness, left ventricular posterior wall thickness values, and the E/A ratio were not statistically significantly different at 6 months compared with baseline. In addition, the noradrenaline values were not significantly different from baseline levels at 6 months (160.19±29.70 versus 156.54±7.87 pg/mL; \(P=0.747\)).

No serious complications were observed during the study. No myalgias, back pain, and hematuria were observed. Two patients encountered transient edema at the skin along the HIFU beam path. Vasovagal response was observed in 2 patients during ablation. One patient had a skin allergy during the baseline Holter monitoring and was unrelated to the HIFU procedure. Renal artery imaging evaluation showed that no patient developed a new hemodynamically significant renal artery stenosis. At the 1- and 6-month follow-up time points, the serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate (using the modified diet in renal disease formula) were not significantly different compared with the baseline values.

Discussion

Based on the acceptable targeting controllability of the HIFU technique in clinical practice, the HIFU foci could be conveniently set spirally to cover 4 quadrants at each renal artery by CDFI guidance and then the acoustic energy could be delivered with planned parameters. The repeated emissions strategy has been shown to be beneficial for lesion generation adjacent to major vessels in clinical tumor
treatment.9 With 50× repeated emissions, enough energy should be deposited periarterially for RDN. An ultrasound-mediated nerve conduction block can be achieved with lower acoustic energy dose, suggesting that the nerve fibers may be highly sensitive to HIFU energy.10 Therefore, the HIFU may offer benefit to RDN by an efficient and direct heating generation at the target nerves. Our results showed a significant reduction in the 24-hour ambulatory and office BP after ablation, suggesting efficient denervation of the noninvasive HIFU procedure. Although only 10 patients were enrolled in this study, younger individuals, rigorous enroll procedure and with stable drug regimen for at least 4 weeks, might contribute to the positive findings. Moreover, the extracorporeal HIFU procedure may achieve more efficient RDN, because the energy delivery of this procedure was without limit of the distance between the intima and nerves and the heating was generated directly at the adventitia and around fatty.

A reduced HRV generally indicates a vagal-sympathetic imbalance favoring sympathetic activity in resistant hypertensive patients.11 SDNN is an estimate of the overall HRV, and SDANN is an estimate of the long-term components of HRV. The 2 parameters mainly reflect a sympathetic tone.12 Our results showed that these 2 parameters increased significantly after RDN, suggesting that the sympathetic tone may be at least partially reduced by HIFU ablation. In addition, the increase in fractional shortening and left ventricular ejection fraction suggests an improvement of the heart systolic function, which may be attributed to the lowered cardiac afterload following the BP reduction post RDN.

The HIFU-based procedure presented an excellent safe profile in animal experiments with intact renal arteries after ablation, as demonstrated by the pathological results.5 It was important to the safety of HIFU-based RDN that the procedure was conducted without any catheter blocking the renal artery. When the HIFU energy was targeted at the artery wall and adventitia, the intima and wall of the renal artery could be well protected by the cooling effect of the fast blood flowing. In this study, the results of the blood chemistry tests and imaging examination showed no significant injuries to the renal functions or renal artery injuries, consistently presenting a good safety profile of the HIFU-based RDN procedure.

In conclusion, noninvasive RDN by extracorporal HIFU appeared to have a BP lowering effect that was sustained for 6 months with a good safety in resistant hypertensive patients. This first-in-man study has provided the scientific basis for future randomized controlled trials.

Sources of Funding
This study was supported in part by the Medical Scientific Project of Chongqing Municipal Health Bureau, China (2012-2-510),

### Table 2. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable at Baseline</th>
<th>n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.8±9.7</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0±2.2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Diabetes mellitus type II</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>98.9±19.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±6.4</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>159.1±8.9</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>90.7±11.2</td>
</tr>
<tr>
<td>Day SBP, mm Hg</td>
<td>160.8±7.2</td>
</tr>
<tr>
<td>Day DBP, mm Hg</td>
<td>92.1±10.5</td>
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<tr>
<td>Night SBP, mm Hg</td>
<td>154.3±14.3</td>
</tr>
<tr>
<td>Night DBP, mm Hg</td>
<td>86.8±14.0</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>169.0±5.8</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>91.0±11.0</td>
</tr>
<tr>
<td>Number of antihypertensive drugs</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>8 (80%)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean (SD) or number (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and SBP, systolic blood pressure.

Figure 2. The blood pressure measurements for the enrolled patients at baseline and follow-up time points are shown. A significant reduction from baseline to 6 months in both the 24-hour ambulatory and office blood pressure was observed. DBP indicates diastolic blood pressure; and SBP systolic blood pressure.
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Disclosures
Dr Wang is a shareholder in Chongqing Haifu, Chongqing and a professor of The Chongqing Medical University, China. The other authors report no conflicts.

References
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