VOL. 8, NO. 4, 2023
ISSN 2452-302X

FOCUS ISSUE: TECHNOLOGY AND HEART FAILURE THERAPEUTICS 2023 SHARK TANK

RESEARCH LETTER

Prolonged Low-Intensity Ultrasound Delivery as Potential Kidneys Treatment for Acutely Decompensated Heart Failure Patients

Patients hospitalized with acutely decompensated heart failure (HF) may exhibit inadequate response to diuretics and experience worsened renal function, prolonged hospitalization, and poor outcome. A primary treatment goal for such patients is to clear excessive fluid and sodium while preserving or improving renal function. Some of the patients require dialysis, which is invasive and might be associated with known complications.

The innovative concept being evaluated includes delivery of prolonged low-intensity ultrasound energy to the kidneys to potentially affect its membranes by microvibrations, thus hypothetically affecting the kidney's function. This novel first-in-human feasibility study evaluated the delivery of such prolonged low-intensity ultrasound to the kidneys as a potential noninvasive treatment option for such patients. The study was approved by the Brandenburg (Germany) Ethical Committee. The primary endpoint of the study is safety of the use of prolonged low-intensity ultrasound energy applied to the kidneys, defined as the incidence and severity of unanticipated ultrasound application-related adverse events, and serious adverse events related to the ultrasound application. The prespecified exploratory endpoint was defined as improvement in one of a set of measurements, including mean and relative change between "off" and "on" phases in urine output rate, excess urine output rate, sodium (Na) excretion rate, calculated glomerular filtration rate (GFR) and other blood and urine analytes.

Exposure of tissue to ultrasonic vibration may potentially improve fluid and compound flow through membranes.[1,2] Ultrasound may be delivered noninvasively through coupling of transducers to the skin; thus, ultrasonic microvibrations would propagate through the body.

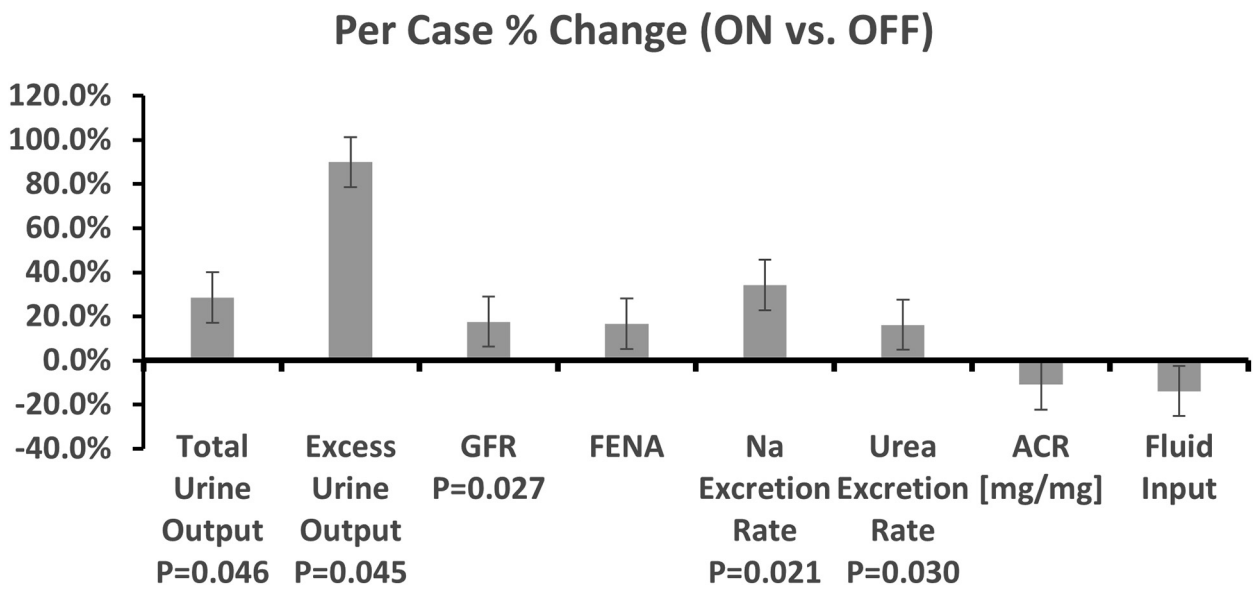
The ultrasonic microvibrations may interact with the membranes at the target area, affecting the filtering or transport of solute and fluids. Unlike therapeutic ultrasound devices that use high intensity to heat tissue or high pressure to generate cavitation and therefore are limited in duration of treatment, the design of the ultrasound delivery used herein is intended to offer a potentially prolonged treatment option. Accordingly, to minimize tissue damage, low intensity is used by design and no ultrasonic contrast media (eg, microbubbles) is used.

In some clinical conditions, a desired prolonged kidney treatment may last hours, a whole day, and up to multiple days. In the present study, the ultrasonic vibrations are generated noninvasively near the skin, and may be aimed to a desired direction. Low-intensity ultrasound allows prolonged exposure periods which are in line with safety recommendations.[3] Low peak pressure is used to reduce undesired mechanical effects such as cavitations. Thus, the prolonged ultrasound energy is delivered with a low thermal index and low mechanical index.[4]

This single-center, single-arm, open-label, feasibility study was performed in Immanuel Hospital Bernau, Heart Centre Brandenburg Bernau, Brandenburg Medical School (MHB), Germany, on a cohort of 8 decompensated HF patients after at least 24 hours following admission with signs of inadequate response to stable continuous intravenous diuretics. Oral diuretics were not administered during the test. Patients had a mean age of 78.8 $\pm$ 6.9 (SD) [range: 68 to 87] years, 5 were male, estimated GFR averaged 40.9 $\pm$ 11.5 (range: 24 to 52) mL/min/1.73m^2, and left ventricular ejection fraction averaged 30.0% $\pm$ 7.6% (range: 20% to 40%). The evaluation was performed during a 10-hour period, with every case serving as its own control with "off-on-off" phases of device activation, repeated in 2 test cycles. The duration of each "off" or "on" phase was 1.5 hours. Washout periods were applied at the start of each phase and were excluded from analysis. During "on" phases, noninvasive low-intensity ultrasound energy was delivered to both kidneys. Evaluations included blood and urine samples and measurement of urine output every 30 minutes.

Patient characteristics at baseline, defined as mean values averaged per test cycle per subject

FIGURE 1 Mean Percent Change ("On" vs "Off" Phases)



Mean percent change per case per activation cycle, compared between "on" phase to the preceding and subsequent "off" phases in the measured values. ACR = albumin to creatinine ratio; FENA = fractional excretion of sodium; GFR = glomerular filtration rate; Na = sodium.

during both "off" phases, include urine output of 1.92 ± 1.18 (SD) mL/min, excess fluid clearance of 0.97 ± 0.85 mL/min, GFR of 44.5 ± 15.9 mL/min, and Na excretion 145.6 ± 131.3 μmol/min. Mean relative percent change per test cycle per subject comparing each parameter between the subject's "on" to the "off" phases shows statistically and clinically significant improvements (28.6% ± 13.1% SE) in urine output (P = 0.046), 89.9 ± 41.1% in excess fluid clearance (P = 0.045), 17.6 ± 7.2% in GFR (P = 0.027), 34.2% ± 13.2% in rate of Na excretion (P = 0.021) (Figure 1). Fluid intake did not differ during "on" vs "off" phases (−13.9% ± 9.4%; P = NS); thus, the observed improvements do not result from increased fluid input. Mean urine output, extrapolated to 24 hours, showed a trend of 2.8 ± 0.4 L/day vs 3.7 ± 0.7 L/day when comparing "off" vs "on" phases, respectively. There was no adverse event reported, no urine protein elevation, no side effects reported, and no elevation in mean albumin to creatinine ratio (trend of reduction: −10.9% ± 8.2%, P = NS).

In this first-in-human feasibility study in a small cohort of HF patients, the use of prolonged low-intensity ultrasound energy delivered to the kidneys was safe and showed statistically and clinically significant improvements in all measured renal function parameters, including increased removal of fluids and solutes. This technology may have the potential as a novel noninvasive device-based treatment option for improving renal function in HF patients. Further research is warranted.

*Benny Rousso, PhD
Naama Winetraub, MA
Boaz Rippin, MSc
Marvin Albrecht, MD
Christian Butter, MD

*Renal Innovation Ltd
1 Hamada Street
Rehovot 7670301, Israel
E-mail: rousso.benny@gmail.com

https://doi.org/10.1016/j.jacbts.2023.03.008

This study was sponsored by Renal Innovation Ltd. Dr Benny Rousso, Naama Winetraub, and Boaz Rippin are employees/officers of Renal Innovation Ltd. All other authors are affiliated with the Department of Cardiology, Heart Centre Brandenburg Bernau, Brandenburg Medical School (MHB) Theodor Fontane Faculty of Health Sciences Brandenbeurg, Bernau, Germany, and have reported that they have no relationships relevant to the contents of this paper to disclose and have no conflicting interest.

This work was presented at the 2023 CRF THT Shark Tank; March 20-22, 2023; Boston, Massachusetts.

Editor's Note: To view the authors' full presentation at TCTMD Shark Tank, please visit https://www.jacc.org/journal/basic-translational/tht-2023-shark-tank

The 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 Author Center.

REFERENCES

1. Izadifar Z, Babyn P, Chapman D. Mechanical and Biological effects of ultrasound: a review of present knowledge. *Ultrasound Med Biol*. 2017;43(6):1085–1104.

2. Rawool NM, Goldberg BB, Forsberg F, Winder AA, Hume E. Power Doppler assessment of vascular changes during fracture treatment with low-intensity ultrasound. *J Ultrasound Med*. 2003;22(2):145–153.

3. Safety Group of the British Medical Ultrasound Society. Guidelines for the safe use of diagnostic ultrasound equipment. *Ultrasound*. 2010;18(2):52–59.

4. Kollman C, ter Haar G, Dolezal L, Hennerici M, Salvesen KA, Valentin L. Ultrasound output: thermal (TI) and mechanical (MI) indices. *Ultraschall in der Medizin*. 2013;34(5):422–434.