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Title: First in Human Experience with Alfapump DSR System in Diuretic Resistant Chronic Heart Failure.

Introduction: Given the toxicity of loop diuretics and the high prevalence of resistance to these agents, there is significant interest in developing alternative therapies for sodium and fluid removal in heart failure (HF). We have previously demonstrated that Direct Sodium Removal (DSR) with a sodium-free peritoneal solution is highly effective in extracting large quantities of sodium and water. The alfapump is a fully implantable transcutaneously chargeable pump that can transport fluid from the peritoneum to the bladder facilitating chronic use of DSR therapy (Figure). The objective of this study was to understand the safety, tolerability, and cardio-renal effects of replacing loop diuretics with alfapump DSR therapy for 6 weeks in diuretic resistant HF patients.

Methods: Stable clinically euvolemic HF patients chronically receiving high dose loop diuretics (≥ 80 mg furosemide equivalents) underwent alfapump system implantation (Figure). Approximately 2 weeks post implant, participants were hospitalized, loop diuretics were discontinued, and a controlled sodium diet was instituted (3g/day moderate sodium for the first week and 5g/day high sodium for the second week). DSR therapy (sodium free 10% dextrose) was initiated at 1L three times weekly. Volume, dwell time, and frequency were titrated up or down based on a nomogram to maintain constant body weight. After 2 weeks in-hospital, participants completed an additional 4 weeks of outpatient DSR therapy on their usual Na home diet. After the 6-week DSR intervention, loop diuretics could be resumed and titrated at the discretion of the treating physician. This study was approved by the local ethics committees and registered on clinicaltrials.gov (NCT04116034).

Results: Eight participants were enrolled with 7 completing the 6-week study (sudden cardiac death occurred in one participant on day 3). Disease severity was high with an average baseline NT-proBNP of 4589 ± 2945 pg/ml despite a background of 323 ± 263 mg/day of furosemide equivalents. Overall alfapump DSR therapy was well-tolerated with one patient experiencing device related serious adverse event (catheter blockage). Non-serious device/therapy related adverse events included post implant hematuria (n=1), implant site hematoma (n=1) and mild abdominal discomfort during pumping (n=1). Loop diuretics were successfully withdrawn for the full 6-week study period with a neutral sodium balance during the 2-week controlled diet period (-1.3 grams Na) and stable weight over the 6-week study period (75.6 to 75.5 kg). This was despite the per protocol down titration of DSR therapy to prevent weight loss (average 10% dextrose volume 750 ± 348 ml/treatment). There was a 30% improvement in NT-proBNP and a 22% improvement in estimated glomerular filtration rate ($p < .001$ for both, Figure). After 6 weeks of DSR therapy, diuretic response improved to 259% of baseline ($p < 0.001$, figure). This was durable as at a median of 10 months post study with average loop diuretic dose 21% of baseline and all patients were receiving $\leq 50\%$ of the baseline diuretic dose.

Conclusion: Six weeks of alfapump DSR therapy was overall well tolerated and successfully maintained a neutral sodium balance and stable body weight, despite complete withdraw of loop diuretics. A significant benefit to cardio-renal function was observed with meaningful improvement in NT-proBNP and renal function. Diuretic resistance improved substantially and durably. Additional research is warranted to better understand the cardio-renal benefits of alfapump DSR therapy and the application to HF patients.

