# First in human experience with direct sodium removal using a zero sodium peritoneal solution: A new candidate therapy for volume overload

*Veena Rao, Jeffrey Turner, Devin Mahoney, Matthew Griffin, Jennifer Asher, Juan Ivey-Miranda, Nicole Gomez, Fredric Finkelstein, Jeffrey Testani*

Jeffrey M. Testani, MD, MTR
Associate Professor of Medicine
Director of Heart Failure Research
Yale University

# Disclosures

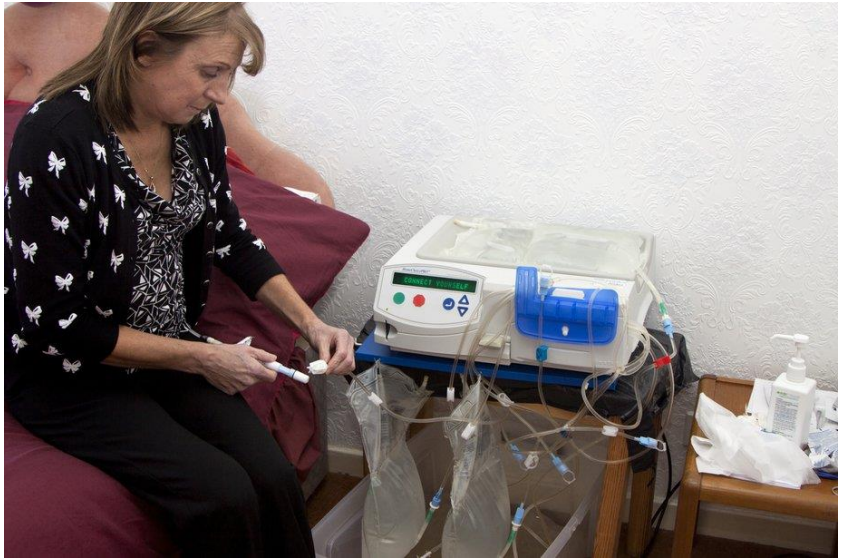
- Related to the presentation: Research funding and consulting fees from Sequana Medical
- Unrelated to the presentation: Grants and consulting fees from BMS, consulting fees from AstraZeneca, consulting fees from Novartis, grants and consulting fees from 3ive Labs, consulting fees from Cardionomic, consulting fees from Bayer, grants and consulting fees from Boehringer Ingelheim, consulting fees from MagentaMed, grants from Otsuka, consulting fees from Reprieve Medical, grants and consulting fees from Sanofi, grants and consulting fees from FIRE1, grants from Abbott, consulting fees from W.L. Gore

# Heart Failure: Can we do better than diuretics?

- On a population level, symptoms and hospitalizations are driven by volume overload
  - Loop diuretics are the mainstay of therapy
  - Well described toxicity
  - Resistance is common
- Long list of failed cardio-renal therapeutics has accumulated over the last decade
  - A new pill that replaces the loop diuretics is not likely soon
- Sodium removal through non-renal routes is an attractive option
  - Veno-Venous ultrafiltration has been explored;
    - » Not an ideal chronic therapy
  - Peritoneal dialysis for chronic volume maintenance has had low levels of interest

# Why is peritoneal dialysis (PD) not used more frequently in heart failure?

- Standard PD has several limitations:
  - Large volumes (~8 to 10 liters) and long dwell times with the patient connected to PD cycler
  - External catheter with infection risks
  - Dialysis stigma
- Only modest fluid and sodium removal with standard PD solutions
  - PD is designed primary to “clean” the blood rather than remove sodium

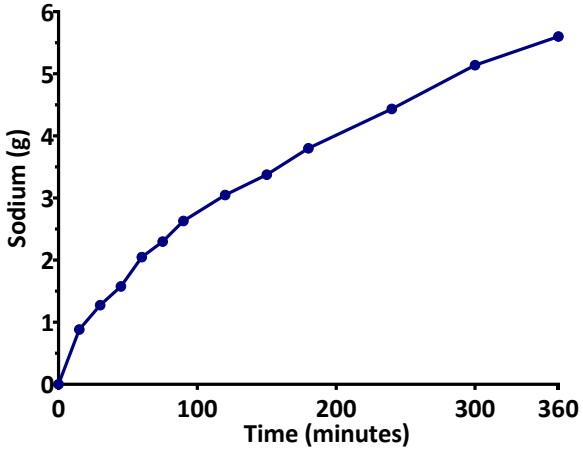


# Can we use the peritoneal membrane more efficiently to directly remove sodium in HF patients?

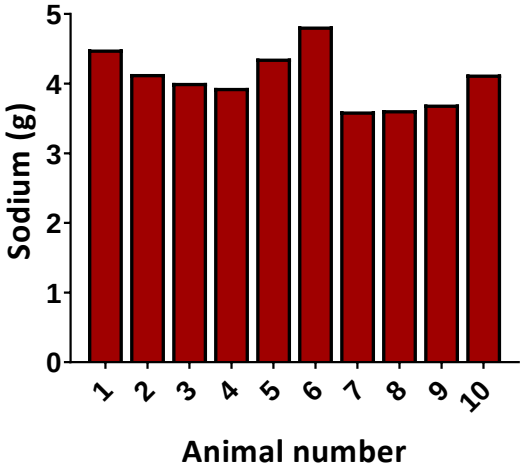
- Most HF patients have acceptably functioning kidneys
  - No need to “clean” the blood
- Standard PD solutions have ~7.5 grams of salt per liter
  - Nearly isotonic to plasma (~132 mmol/L)
  - Very small gradient for sodium to diffuse
- By using a zero sodium osmotic solution should achieve much more efficient sodium removal
  - Standard peritoneal ultrafiltration
  - We can also capitalize on diffusion down a huge concentration gradient (~140 mmol/L to 0 mmol/L)
- More efficient sodium removal allows for smaller volume of fluid and shorter dwell times
  - Less invasive methods for filling and removal of solution from the peritoneum

# Pre-clinical data: Results in normal swine

- 1 Liter of sodium free 10% dextrose in water as the Direct Sodium Removal (DSR) solution
- 6 hour dwell: (n=4)
  - 5.5 grams of sodium
  - 1.5L of ultrafiltrate




- 2 hour dwell (N=10):
  - 3.9 grams of sodium
  - 800 cc of ultrafiltrate

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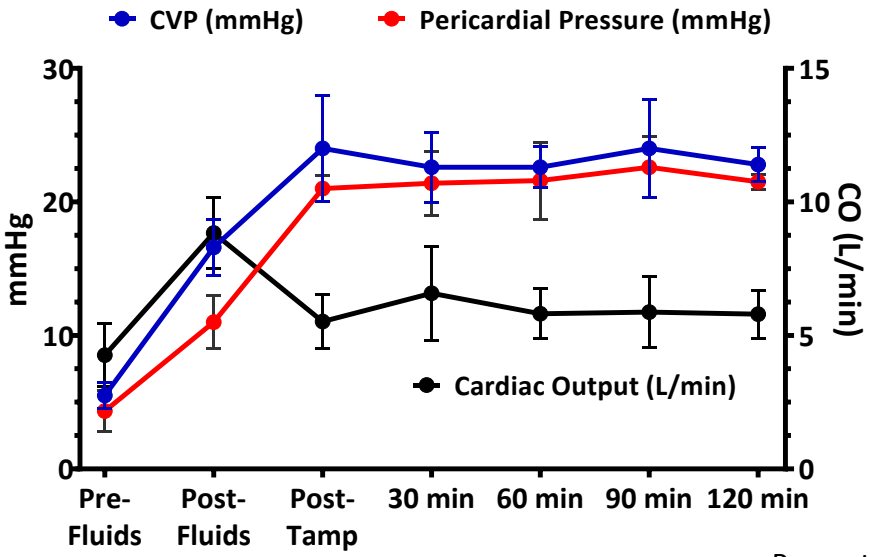
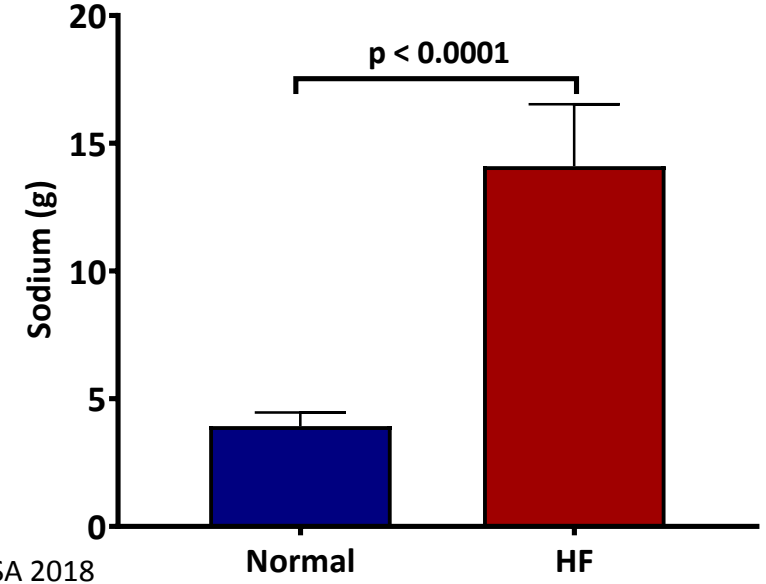
# Pre-clinical data: Heart Failure vs. normal pigs

- Right sided HF model with fluid loading and tamponade
- 2 hour DSR dwell

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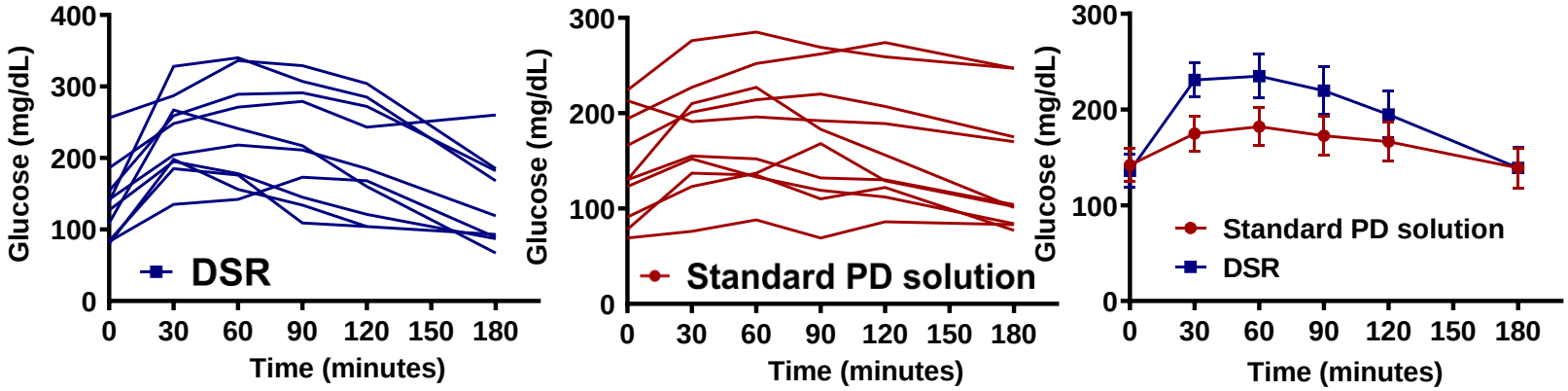
# DSR first in human proof of concept: Design

- **Design:**
  - Randomized open label crossover of DSR vs. standard PD solution
  - Conducted in prevalent PD patients rather than normal subjects due to the risks of PD catheter placement
- **Intervention:**
  - DSR solution: Sodium free 10% dextrose
  - Standard PD solution: 4.25% dextrose standard PD solution (Dianeal, Baxter)
    - Both solutions are approximately 500 mOsm/L
    - 4.25% dextrose PD solution is the “strongest” commercially available product
  - One liter of either solution was infused into the peritoneum and left to dwell for 2 hours
  - Crossover to the alternate solution one week later
- **Endpoints:**
  - Primary: Safety/tolerability defined as completion of the 2-hour dwell without significant discomfort or AE
  - Secondary efficacy endpoint: Difference in sodium removal between DSR solution and standard PD solution

# Primary endpoint: Safety and tolerability

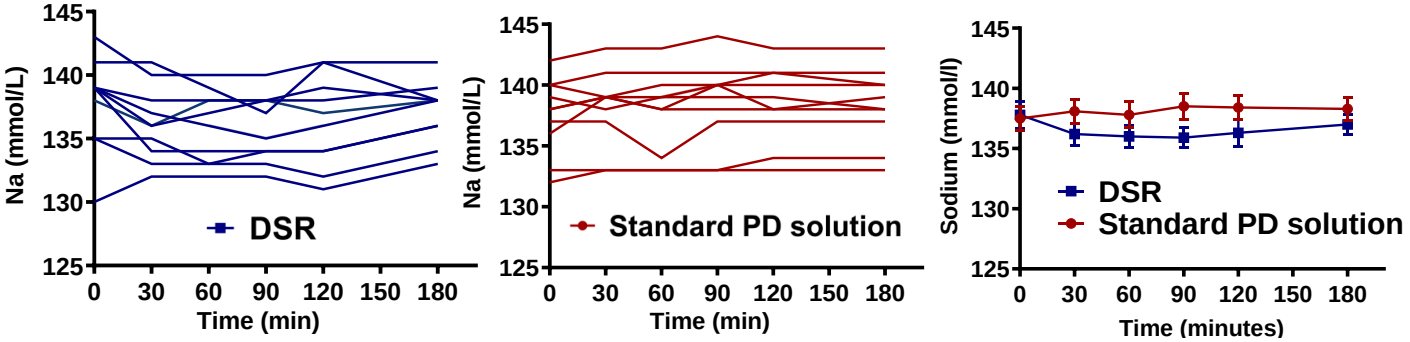
- **Primary endpoint:**
  - All patients completed the 2 hour dwell without adverse event or significant discomfort causing protocol discontinuation
- Mild cramping during fluid instillation lasting <30 minutes occurred in 2 patients
  - One had cramping with DSR solution only
  - One had cramping with both solutions
  - Most patients stated instillation of the DSR solution felt the same as their standard PD solution
- Negligible removal of non-target solutes
  - Potassium (5.7 mmol)
  - Magnesium (1.1 mmol)
  - Phosphorus (2.0 mmol)
  - Calcium (1.7 mmol)

# Change in plasma glucose was modest and transient

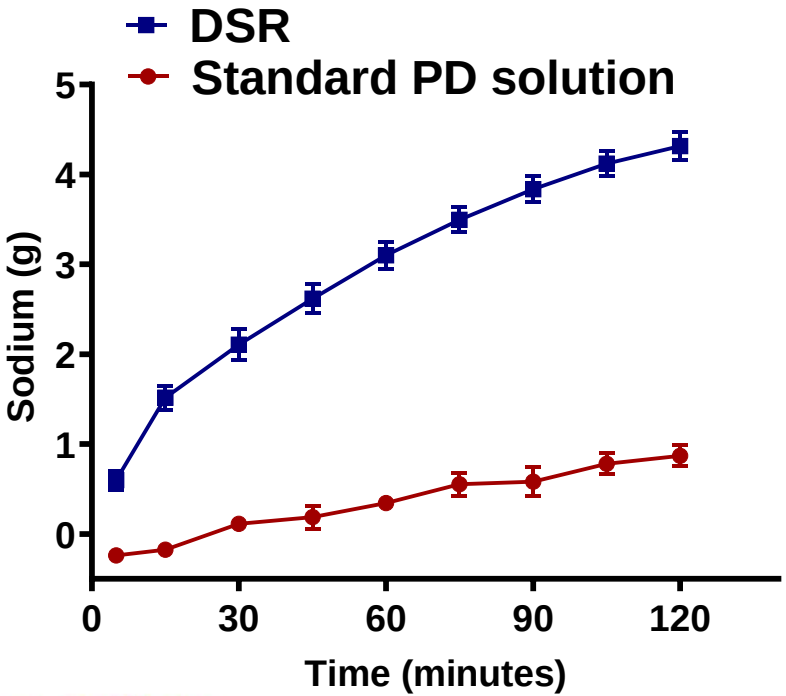


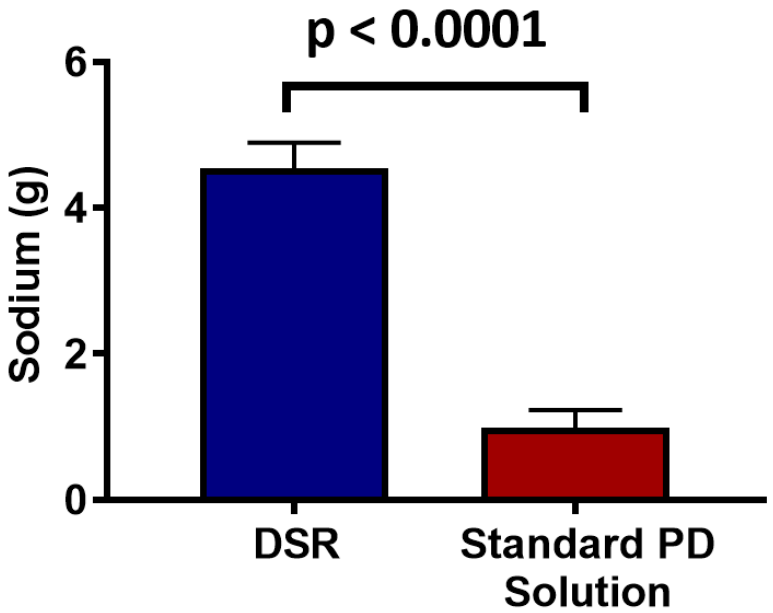
# Changes in serum sodium were small

**Uncorrected serum sodium**



# Secondary efficacy endpoint: Sodium removal was substantially greater with DSR



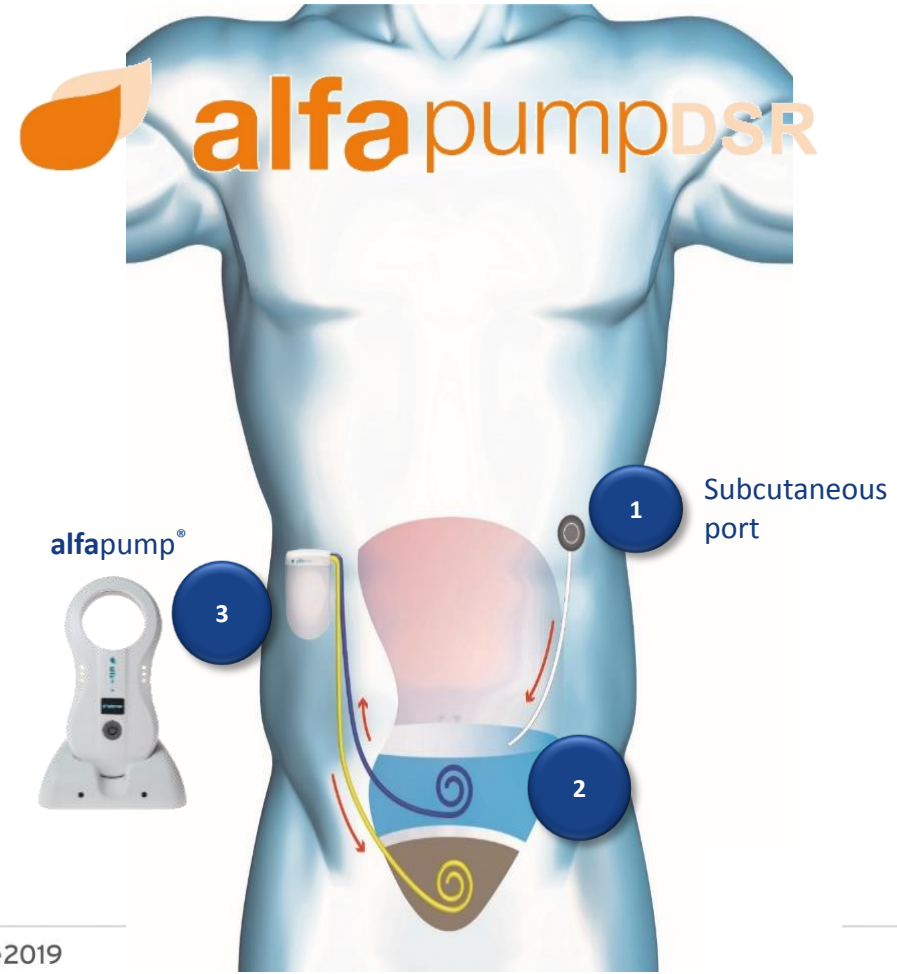



# Conclusion

- These data provide proof of concept that Direct Sodium Removal with a sodium free peritoneal solution is feasible in humans
- **Safety/tolerability:**
  - Well tolerated
  - Minimal off target solute removal
  - Did not result in significant electrolyte disturbances or prolonged or severe hyperglycemia
- **Efficacy:**
  - Substantial sodium removal
    - Nearly 5 grams of sodium with a 2 hour treatment

# Future directions

- Next planned study is a multidose chronic HF study using the alfapump® (Sequana Medical)
  - Fully implanted system
  - Developed for refractory ascites
  - Pump already derisked in this population
    - Over 700 systems implanted and 400 patient years experience to date




1. Administration of DSR solution into peritoneal cavity via subcutaneous port
2. Sodium enters DSR solution via diffusion and ultrafiltration
3. alfapump® clears sodium-rich fluid into the bladder which is eliminated by urination