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RESEARCH ARTICLE

Renal negative pressure treatment as a novel therapy for heart failure-induced renal dysfunction

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Abstract

Congestion is the primary pathophysiological lesion in most heart failure (HF) hospitalizations. Renal congestion increases renal tubular pressure, reducing glomerular filtration rate (GFR) and diuresis. Because each nephron is a fluid-filled column, renal negative pressure therapy (rNPT) applied to the urinary collecting system should reduce tubular pressure, potentially improving kidney function. We evaluated the renal response to rNPT in congestive HF. Ten anesthetized ~80-kg pigs underwent instrumentation with bilateral renal pelvic JuxtaFlow catheters. GFR was determined by iothalamate clearance (mGFR) and renal plasma flow (RPF) by para-aminohippurate clearance. Each animal served as its own control with randomization of left versus right kidney to −30 mmHg rNPT or no rNPT. mGFR and RPF were measured simultaneously from the rNPT and no rNPT kidney. Congestive HF was induced via cardiac tamponade maintaining central venous pressure at 20–22.5 mmHg throughout the experiment. Before HF induction, rNPT increased natriuresis, diuresis, and mGFR compared with the control kidney ($P < 0.001$ for all). Natriuresis, diuresis, and mGFR decreased following HF ($P < 0.001$ for all) but were higher in rNPT kidney versus control ($P < 0.001$ for all). RPF decreased during HF ($P < 0.001$) without significant differences between rNPT treatments. During HF, the rNPT kidney had similar diuresis and natriuresis ($P > 0.5$ for both) and higher fractional excretion of sodium ($P = 0.001$) compared with the non-rNPT kidney in the no HF period. In conclusion, rNPT resulted in significantly increased diuresis, natriuresis, and mGFR, with or without experimental HF. rNPT improved key renal parameters of the congested cardiorenal phenotype.

cardiorenal syndrome; diuretic; heart failure; renal negative pressure

INTRODUCTION

Affecting over 1 million Americans annually, acute decompensated heart failure (ADHF) is the most common hospital discharge diagnosis among Medicare beneficiaries and accounts for more than half of all heart failure (HF)-related expenditures (1–3). On a population level, ADHF is primarily a disease of congestion rather than low cardiac output (4–7). In addition to causing classic HF symptoms, congestion can lead to organ dysfunction with notable adverse effects on the kidneys. In experiments dating back to the 1860s, it was shown that partial occlusion of the renal vein led to a prompt decline in renal blood flow, glomerular filtration rate (GFR), and sodium excretion, with resolution of these abnormalities after relief of the congestion (8, 9). Since the kidneys are encapsulated and thus can only minimally expand, congestion increases intrarenal and tubular pressures with an associated worsening of GFR and sodium avidity (10–15). Renal venous congestion also diminishes diuretic response, creating a vicious cycle where congestion impedes treatment response and intensifies renal sodium avidity (13, 14, 16). Unfortunately, loop diuretic therapy also exacerbates aberrations in intratubular pressure, potentially intensifying this process (17). Therefore, strategies to reduce intratubular pressure and arrest this positive-feedback cycle warrant investigation. Because each nephron is a fluid-filled column connecting the urinary collecting system to the glomerulus, negative pressure applied to the urine collection system might reduce intratubular pressure throughout the nephron. We sought to investigate the effects of renal negative

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pressure therapy (rNPT) on natriuresis and kidney function during experimental heart failure.

METHODS

The animal study was conducted in accordance with approval by the Yale University Institutional Animal Care and Use Committee.

Animal Experiments

Ten Yorkshire farm female pigs 18–20 wk of age (~80 kg) were used to investigate the effects of rNPT from the JuxtaFlow catheter system (3ive Labs, Roswell, GA). The JuxtaFlow catheter is a memory polymer catheter that expands into a three-dimensional helix when deployed in the renal pelvis allowing application of negative pressure (−30 mmHg) without causing collapse (Supplemental Figure; see https://doi.org/10.6084/m9.figshare.14503062.v1).

After an overnight fast, pigs were anesthetized with a combination of intramuscular ketamine and tiletamine-zolazepam (Telazol), intubated, and maintained on inhaled isoflurane. An intrapericardial catheter was placed via a left lateral thoracotomy, a Swan-Ganz catheter was placed via a right internal jugular vein cutdown, and an arterial line for continuous hemodynamic monitoring was placed in the carotid or femoral artery by either the Seldinger technique or an arterial cutdown. Large bore central venous access was similarly placed in either the contralateral jugular or a femoral vein for fluid and tracer infusions. To catheterize the ureters, the bladder was retracted caudally through a small suprapubic incision and each ureter was isolated and directly cannulated through a small incision. The JuxtaFlow catheters were advanced into the renal pelvis under fluoroscopic guidance. They were either drained passively at atmospheric pressure or attached to a vacuum assisted negative pressure pump (−30 mmHg).

Since loop diuretics are used almost universally in patients during the treatment of decompensated heart failure, experiments were undertaken during ongoing furosemide infusion. The effects of rNPT were studied during maximal furosemide diuresis in the absence of HF and in a state of HF characterized by venous congestion and preserved cardiac output. During the two phases, each animal served as its own control with randomization of either the left or right kidney to rNPT versus no rNPT. The animal received intravenous bolus and continuous infusion of iothalamate (IOT, 120 mg bolus with 0.3 mg/min infusion, Guerbet), para-aminohippurate (PAH 800 mg bolus with 8.4 mg/min infusion, Millipore Sigma, St. Louis, MO), and furosemide (400 mg bolus with infusion at 80 mg/h) that were maintained for 2.5 h. A 4-L intravenous infusion of normal saline was administered at baseline, followed by a maintenance intravenous infusion matched 1:1 to urine output. The 4-L infusion was utilized *1*) to increase urine output facilitating the timed urine collection and *2*) because during the development of this model of acute heart failure, this amount of fluid led to relative stability in filling pressures over time (18). Blinding of rNPT was not feasible during these experiments given that a specific device was used to perform renal negative pressure. We did not specify inclusion and exclusion criteria for animal models either before or after the study, as the experiments were designed for healthy animals.

Experimental Periods

After equilibration of tracers (~2.5 h), the right and left kidneys were randomized to −30 mmHg rNPT or to drainage at atmospheric pressure. Measurements of RPF and mGFR were taken simultaneously from the rNPT kidney and the control contralateral kidney (no rNPT). To ensure that the pretamponade (no HF) and tamponade (HF) experimental periods had similar background fluid status, a rapid large volume normal saline infusion of 20%–25% body weight occurred at this point. After a 10-min equilibration, the animals underwent two 15-min "postfluid" clearance periods. Next, cardiac tamponade was induced by pericardial instillation of ~200 mL of 6% hydroxyethyl starch (18). Pericardial hydroxyethyl starch and additional intravenous normal saline infusion were titrated to maintain a hemodynamic profile relative to baseline prefluid readings, with preservation of cardiac output and mean arterial pressure and goal central venous pressure at 20–22.5 mmHg throughout the experiment. After stabilization and a 10-min equilibration, two 15-min study periods were repeated.

Assays and Calculations

A Randox Imola automated clinical chemistry analyzer was used to measure urine or serum chemistry parameters (Randox Laboratories, Crumlin, UK). Creatinine measurements were standardized to IDMS traceable National Institute of Standards and Technology reference material (SRM 967). Urine and plasma iothalamate were measured on an Agilent 6490 QTOF equipped with Agilent 1290 UHPLC. Briefly, a stock solution of iothalamate was serially diluted in 0.1% formic acid containing deuterated iothalamate to create the calibration curve (1–2,000 ng/mL). Plasma samples (100 μL) were deproteinized by adding 300 μL of 100% methanol containing deuterated iothalamate (1,000 ng/mL; Cambridge Isotope Laboratories, Inc., Tewksbury, MA), vortexed, and centrifuged at 12,000 rpm for 10 min. Then, 200 μL of the supernatant were transferred to glass vials, and 10 μL of the sample were injected to UHPLC–MS/MS system. Urine samples were diluted 10-fold with 0.1% formic acid containing the internal standard, and 10 μL of the sample were injected. Separation was achieved using Agilent Zorbax Eclipse plus RP 2.1 × 50-mm 1.8-μm column with a constant flow rate of 400 μL/min and an instrument-controlled gradient. Also, 0.1% formic acid and 100% methanol were used as Buffer A and B, respectively. Quantitation was achieved using the Agilent MassHunter Quantitative analysis software. Urine and plasma PAH were measured using PAH colorimetric assay kits from Abcam (Cambridge, UK). Urine neutrophil gelatinase-associated lipocalin (NGAL) was measured with a porcine NGAL kit from Alpco (Alpco, Salem, NH). Urine cGMP concentrations were measured by competitive enzyme-linked immunosorbent assay according to the manufacturer's guidelines (Parameter cGMP Assay, R&D Systems Inc, Minneapolis, MN).

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Creatinine clearance was calculated as urine creatinine × volume of urine per minute/plasma creatinine. Measured GFR was calculated as urine iothalamate × volume of urine per minute/plasma iothalamate. Renal plasma flow was calculated as (urine PAH × volume of urine per minute/plasma PAH)/0.9; 0.9 is the adjustment for the 90% extraction of PAH. Filtration fraction was calculated as GFR/renal plasma flow (19, 20). Fractional excretion of sodium (FENa) was calculated as $(Na_{urine}/Na_{serum}) \times (Cr_{serum}/Cr_{urine}) \times 100\%$.

Statistical Analysis

Continuous data are shown as means ± standard deviation or median (quartile 1–quartile 3) according to observed distribution. Categorical data are shown as frequency (percentage). Variables with skewed distribution were log transformed to approximate normal distribution. Changes in systolic blood pressure, mean arterial pressure, cardiac output, central venous pressure, pulmonary capillary wedge pressure, heart rate, NGAL, and cGMP from baseline to postfluid (no HF) or to HF model of venous congestion were analyzed using linear mixed models accounting for correlations within animals; time was included as a main factor with three levels, and comparisons were undertaken for each pair of time points. Likewise, changes in urine output, urine sodium output, FENa, renal plasma flow, iothalamate clearance, and filtration fraction during the experiments were analyzed by linear mixed models accounting for correlations within animals. rNPT and HF model of venous congestion were included as main factors (binary variables) in a full factorial model. Then, comparisons were undertaken for each pair, i.e., "no rNPT" versus "rNPT" in each HF period ("no HF period" and "HF period"). In addition, the effect of the HF model of venous congestion was analyzed by comparing the "no HF" measurements versus the "HF" measurements. Statistical significance was defined as two-tailed $P < 0.05$. Statistical analysis was performed with IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY) and Stata SE version 16.0 (StataCorp, College Station, TX).

RESULTS

Induction of cardiac tamponade was successful in producing a "warm and wet" HF phenotype with preserved cardiac output and blood pressure but severely elevated right-sided filling pressures (Fig. 1). A cardiorenal phenotype also emerged, as evidenced by substantial decreases in urine output (37%), renal sodium excretion (40%), measured GFR (27%), and renal plasma flow (50%) ($P < 0.001$ for all), leading to an increase in filtration fraction (42 ± 18% vs. 56 ± 21%, $P = 0.001$). Furthermore, urine cGMP decreased substantially ($P < 0.001$, Fig. 1) and NGAL (a marker of tubular injury) tended to increase with induction of HF, but this did not reach significance ($P = 0.14$; Fig. 1).

During furosemide diuresis, the rNPT kidney substantially increased natriuresis (2.4 ± 0.6 mmol/min vs. 1.5 ± 0.5 mmol/min; $P < 0.001$) and diuresis (19.7 ± 4.5 mL/min vs. 11.8 ± 3.7 mL/min; $P < 0.001$) compared with the control kidney (Fig. 2). rNPT increased iothalamate clearance (79 ± 28 mL/min vs. 62 ± 23 mL/min; $P < 0.001$, Fig. 2) and creatinine clearance (105 ± 38 mL/min vs. 85 ± 30 mL/min, $P = 0.001$). Renal

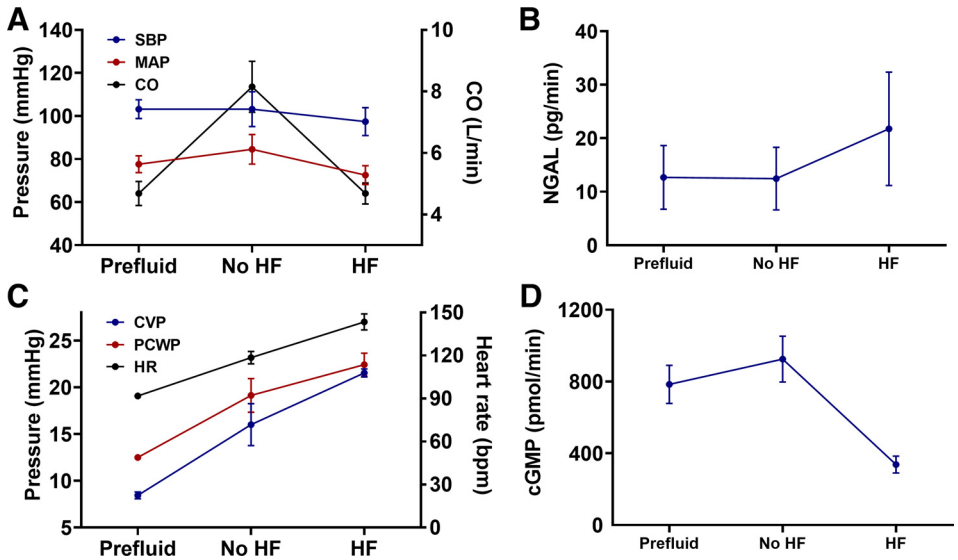

Figure 1. Hemodynamic characteristics of study phases. Hemodynamic variables are presented as means ± SE across the three study periods: *1*) before large volume intravenous fluid administration (prefluid), *2*) after intravenous fluid administration with no heart failure (no HF), and *3*) after induction of an HF model from cardiac tamponade. SBP and MAP (*A*) were not statistically different among the three periods ($P > 0.12$ for each comparison). CO increased from the prefluid to the no HF period ($P < 0.01$) but was not statistically different in the HF model compared with the prefluid period ($P = 0.90$). CVP, PCWP, and HR (*C*) increased significantly from the prefluid to the no HF period and from the no HF period to the HF model ($P < 0.05$ for all comparisons). Neutrophil gelatinase-associated lipocalin (NGAL) did not change from prefluid to no HF but tended to increase from no HF to HF (*B*; $P = 0.14$). cGMP did not change from prefluid to no HF but decreased significantly from no HF to HF (*D*; $P < 0.001$). The experiment was conducted in 10 Yorkshire farm female pigs 18–20 wk of age (~80 kg). Changes in systolic blood pressure, mean arterial pressure, cardiac output, central venous pressure, pulmonary capillary wedge pressure, heart rate, NGAL, and cGMP from baseline to postfluid (no HF) or to HF model of venous congestion were analyzed via linear mixed models accounting for correlations within animals; time was included as a main factor with three levels and comparisons were undertaken for each pair of time points. CO, cardiac output; CVP, central venous pressure; HF, heart failure; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure.

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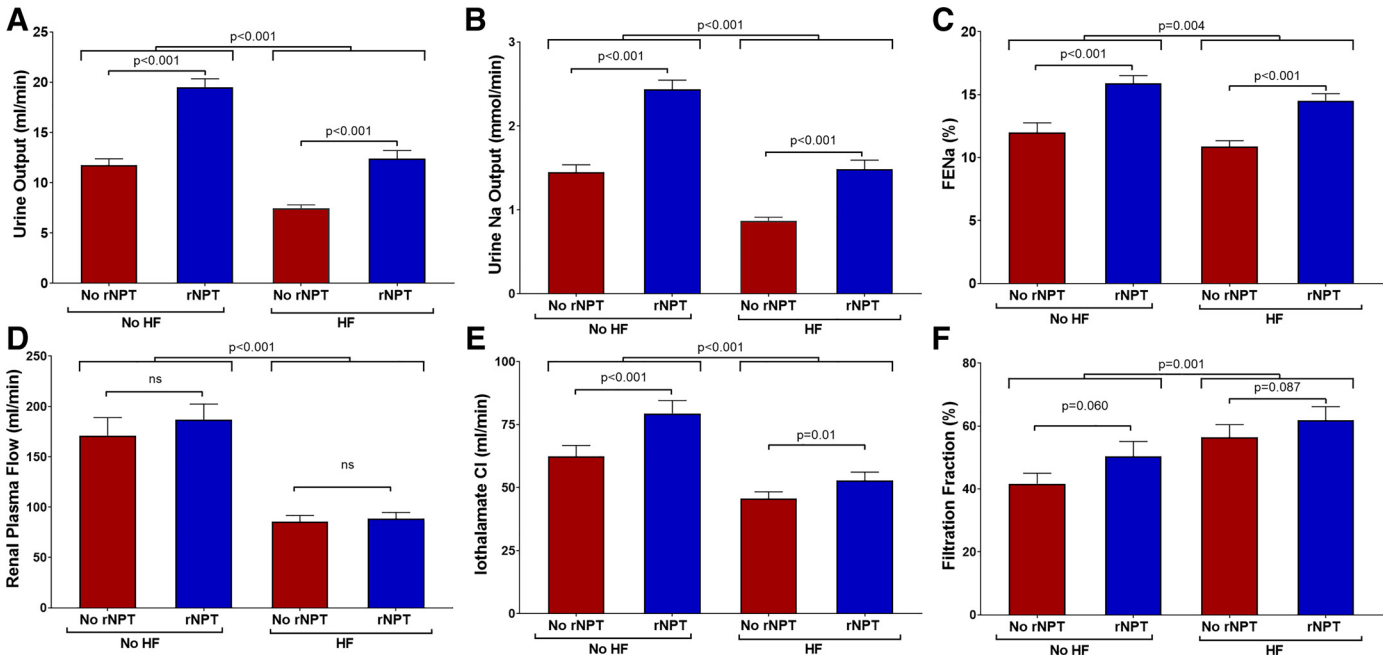

Figure 2. Renal negative pressure treatment's effects on measures of kidney function and diuresis. Urine output (*A*), cumulative urine sodium excretion (*B*), fractional excretion of sodium (*C*), renal plasma flow (*D*), glomerular filtration rate measured by iothalamate (IOT) (*E*), and filtration fraction (*F*) are presented as means ± SE. The experiment was conducted in 10 Yorkshire farm female pigs 18–20 wk of age (~80 kg). Changes in urine output, urine sodium output, FENa, renal plasma flow, iothalamate clearance, and filtration fraction during the experiments were analyzed by linear mixed models accounting for correlations within animals. rNPT and HF model of venous congestion were included as main factors (binary variables) in a full factorial model. Then, comparisons were undertaken for each pair, i.e., "no rNPT" versus "rNPT" in each HF period ("no HF period" and "HF period"). In addition, the effect of the HF model of venous congestion was analyzed by comparing the "no HF" measurements versus the "HF" measurements. Each panel represents a 15-min period. Cl, clearance; FENa, fractional excretion of sodium; HF, heart failure; Na, sodium; rNPT, renal negative pressure treatment.

plasma flow (P = 0.13) did not differ significantly between rNPT and control (Fig. 2). The increased natriuresis with rNPT was not solely driven by increased sodium filtration, as the FENa also was higher with rNPT (15.9 ± 3.3% vs. 12.0 ± 4.2%, $P < 0.001$).

The beneficial effect of rNPT on GFR was similar in the HF and no HF periods (i.e., similar increments in GFR with rNPT; P interaction = 0.23 for a different effect of rNPT in HF and no HF). rNPT did not significantly change renal plasma flow in either the HF or the no HF period (P = 0.47 for the interaction). During HF, rNPT yielded greater urine output (276 ± 113 mL vs. 167 ± 55 mL, $P < 0.001$) and urine sodium excretion (33.0 ± 14.5 mmol vs. 19.5 ± 6.8 mmol; $P < 0.001$) compared with the control kidney (Fig. 2). FENa was also higher with rNPT (14.5 ± 3.0% vs. 10.9 ± 2.7%, $P < 0.001$). Renal plasma flow did not change significantly with rNPT in HF (P = 0.58). Filtration fraction increased during rNPT (55.6 ± 24.8% vs. 49.0 ± 20.8%; P = 0.034) with a similar effect between HF and no HF periods (P = 0.70 for the interaction). Urine NGAL was not influenced by rNPT both during the no HF and HF periods (P = 0.37). Urine cGMP increased significantly with rNPT (P = 0.015), which was similar between the no HF and HF periods (P interaction = 0.25). Importantly, during HF, the rNPT kidney had similar urine output (P = 0.52) and sodium excretion (P = 0.87) yet higher FENa (14.5 ± 3.0% vs. 12.0 ± 4.2%; P = 0.001) compared with the non-rNPT kidney in the no HF period.

DISCUSSION

The primary observation in this study is that negative pressure applied to the renal pelvis significantly improves a wide range of renal parameters. During high-dose furosemide therapy, rNPT increased GFR, urine output, and sodium output. The increase in cumulative urine sodium excretion could not be ascribed solely to an increase in GFR since the FENa also increased. Importantly, the benefit appeared to be of potential clinical significance since urine output and sodium excretion during experimental HF with rNPT were similar to the non-rNPT kidney during the no HF period.

In ADHF, elevated central venous pressure is transmitted to the renal veins and tubules in the fixed space of the encapsulated kidney (13, 15, 16, 21). Alterations in renal venous blood flow patterns normalize with decongestion, suggesting that interventions to reduce intrarenal pressure may improve diuretic response and thereby ADHF outcomes (15). Indeed, our studies are the first, to our knowledge, to demonstrate that a strategy designed to reduce intrarenal pressure can increase urine output and sodium excretion. These findings are consistent with observations in humans with ADHF; abnormal measurements of renal venous impedance and flow have been associated with higher sodium avidity, diminished diuretic response, and worse HF outcomes independent of central venous pressure (14, 16, 21–23). In patients with ADHF, the inverse relationship between diuretic response

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and elevated renal venous impedance is independent of GFR (16). Similarly, we found that improved natriuresis with renal negative pressure therapy was not driven only by improvement in GFR since FENa improved with rNPT.

Furosemide has been reported to induce several detrimental effects on the kidneys. It reduces GFR by up to 25%, although the mechanism is complex (24, 25). In addition, furosemide causes an abrupt increase in proximal tubular pressure that should reduce the net ultrafiltration pressure and a rise in interstitial pressure that should obstruct capillary blood flow (17). Renal negative pressure treatment improved natriuresis and GFR during high-dose furosemide infusion, even in the absence of HF. This is an interesting finding since increased filtration should activate tubuloglomerular feedback (TGF), thereby reducing filtration and bringing GFR back to baseline. Thus, favorable effects of rNPT on GFR and natriuresis with loop diuretics could prove to be a significant benefit for many patients with worsening renal function and diuretic resistance. Given that rNPT improved natriuresis and GFR in the absence of HF, it is likely that rNPT may be effective in other pathological situations that share the phenotype of venous congestion and/or fluid overload, such as renal or liver disease. However, we note that rNPT did not improve renal plasma flow, a feature that would have been desirable in HF because reduced renal plasma flow is also a characteristic of severely congested kidneys. In addition, the impact of rNPT on congestion could not be measured since congestion was an independent variable in the study, with central venous pressure in the HF condition maintained constant at 20 mmHg by titration of fluids and intrapericardial pressure. Therefore, and by design, hemodynamics were identical during rNPT versus control therapy as each kidney served as its own control. As such, the current study demonstrates the effect of rNPT on renal parameters in the setting of congestive HF, and further studies are needed to assess the effect of rNPT on congestion itself since decongestion is the ultimate goal of diuresis in congestive HF.

The current observations from our congestion predominant HF model shed light on the human literature on kidney dysfunction in human HF. The majority of contemporary human studies have not found a meaningful association between cardiac output and kidney function (14, 26–29). Several human studies have noted an association between central venous pressure (CVP) and renal function (30, 31). In the current experiments, with the severe elevation of CVP induced by cardiac tamponade, we observed a substantial reduction in natriuresis, renal plasma flow, GFR, and urinary cGMP. This was despite a cardiac output and blood pressure that were overall similar to baseline values. These observations reinforce the human observational literature that has found congestion to be a more important driver of cardiorenal interactions than poor forward flow. Therefore, the effect of rNPT in the treatment of hypervolemia in patients with ADHF will be investigated, and a first-in-human study is currently ongoing (NCT04227977). In humans, rNPT will be carried out through ureteral catheters deployed endoscopically to deliver mild controlled negative pressure into the renal pelvis.

We acknowledge several limitations. First, although the acute cardiac tamponade model provided a stable, predictable, and titratable "warm and wet" HF phenotype, acute tamponade is a rare human HF presentation, and thus, findings may not extrapolate to acute or chronic decompensated human HF. Second, we did not study the effect of rNPT in the absence of diuretics; in addition, even in the setting of HF, our model did not demonstrate poor diuretic response, and thus, we cannot demonstrate that rNPT addresses diuretic resistance. Third, although the presumed mechanism underlying the improved renal function with rNPT is reduction of intratubular and interstitial pressure, this was not directly measured. Fourth, experiments were undertaken in animals anesthetized with isoflurane, which is known to increase renal sympathetic nerve activity and thus could have influenced the observed responses. Fifth, although it is not likely that reducing cardiac output from supranormal to normal values (no HF to HF period) was a driving factor, we cannot negate some potential effect on the observed results. Finally, although utilizing the JuxtaFlow catheter for both negative and atmospheric pressure provided a control for any mechanical effects of instrumenting the renal pelvis, we were unable to measure delivered pressure at the level of the renal pelvis through this single-lumen catheter. Thus, it cannot be determined if the actual delivered pressure deviated from −30 mmHg in the rNPT group and 0 mmHg in the non-rNPT group. As such, these proof-of-concept results should be viewed as hypothesis generating and motivate future studies in patients with HF.

Perspectives and Significance

Initiation of rNPT during high-dose loop diuretic infusion increased diuresis, natriuresis, and mGFR. Importantly, the benefits were of potential clinical significance, as urine output and sodium excretion during HF and rNPT were restored to levels of control kidney. Additional research into the efficacy of the JuxtaFlow system in human decompensated HF is warranted.

SUPPLEMENTAL DATA

Supplemental material: https://doi.org/10.6084/m9.figshare.14503062.v1.

GRANTS

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DISCLOSURES

J. M. Testani reports grants and/or personal fees from 3ive labs, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Astra Zeneca, Novartis, Cardionomic, MagentaMed, Reprieve inc., FIRE1, W.L. Gore, Sanofi, Sequana Medical, Otsuka, Abbott, Merck, Windtree Therapeutics, Lexicon pharmaceuticals, Precardia, Relypsa, Regeneron, BD, Edwards life sciences, and Lilly. In addition, J. M. Testani has a patent Treatment of diuretic resistance issued to Yale and Corvidia Therapeutics Inc, a patent Methods for measuring renalase issued to Yale, and a patent Treatment of diuretic resistance pending with Reprieve inc. Dr. V. S. Rao has a patent Treatment of diuretic resistance US20200079846A1 issued to Yale and Corvidia Therapeutics Inc with royalties paid to Yale University, V. S. Rao, has a patent Methods for measuring renalase

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AUTHOR CONTRIBUTIONS

V.S.R. and J.M. Testani conceived and designed research; V.S.R., J.M. Testani, C.M., and J.L.A. performed experiments; V.S.R., J.M. Testani, J.B.I-M., Z.L.C., J.M-V., D.M., and F.W. analyzed data; V.S.R., C.S.W., J.M. Testani, C.M., J.L.A., J.B.I-M., Z.L.C., J.M-V., D.M., J.M. Turner, and F.W. interpreted results of experiments; V.S.R. prepared figures; V.S.R., J.M. Testani, and J.B.I-M. drafted manuscript; V.S.R., C.S.W., J.M. Testani, C.M., J.L.A., J.B.I-M., Z.L.C., J.M-V., D.M., J.M. Turner, and F.W. edited and revised manuscript; V.S.R., C.S.W., J.M. Testani, C.M., J.L.A., J.B.I-M., Z.L.C., J.M-V., D.M., J.M. Turner, and F.W. approved final version of manuscript.

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