Efficacy of Veno-Venous Ultrafiltration in Diuretic Resistant Patients Admitted with Decompensated Systolic Heart Failure: A Pilot Study

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A. Study Purpose and Rationale

Congestive Heart Failure (CHF) prevalence:

CHF affects nearly 2% of the population, with almost 1 million hospital admissions for acute decompensated CHF in the U.S. annually. Eighty percent of the admissions in patients with chronic systolic heart failure result from volume overload and 90% of these patients are treated with intravenous diuretics. It is estimated that 25 to 30% of these patients are diuretic resistant with 50% of patients losing less than 5 lbs from admission weight and 20% actually gaining weight during the hospitalization (5). Nearly 2% of all hospital admissions in the United States are for decompensated CHF, and heart failure is the most frequent cause of hospitalization in patients over the age of 65. Patients admitted for acute decompensated heart failure have a high 6 month readmission rate for acute CHF, ranging from 23% to 40% in different studies (1-4).

Diuretic Resistance In Congestive Heart Failure:

Many of the symptoms of CHF result from retention of sodium and fluid. Although diuretics have not been shown to improve survival in patients with CHF, they effectively alleviate symptoms of congestion. Diuretics have been part of standard CHF therapy in all recent survival trials of β-blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers (6). Loop diuretics have been shown to be the most effective diuretics as single agents in moderate to severe heart failure (7). However, loop diuretics may be associated with increased morbidity and mortality attributable to deleterious effects on neurohormonal activation, electrolyte balance, and cardiac and renal function (17-20).

Removal of excessive fluid in patients with CHF is usually achieved by a combination of salt restriction and loop diuretics, but in some cases volume overload persists despite adequate dosing of diuretic therapy. The majority of patients presenting with acute symptoms of fluid overload are responsive to diuretic drugs, at least initially. However, after chronic exposure to loop diuretics, some patients will require increasing doses. This early resistance to diuretics progresses to a failure to decrease the extracellular fluid volume despite high dose diuretics and reasonable restriction of salt intake. Attempts have been made to quantify this resistance. In clinical settings, diuretic resistance in edematous patients has been defined as a clinical state in which sodium intake and excretion are equalized before adequate elimination of excess extracellular volume occurs (8). More technically, diuretic resistance has been expressed as a fractional sodium excretion (FENa+) of <0.2%. (FENa+) represents the amount of sodium excreted (mmol/time) as a percentage of filtered load (9). Finally, Epstein et al. (10) defined diuretic resistance as a failure to excrete at least 90 mmol of sodium within 72 hours of a 160-mg oral furosemide dose given twice daily.

The prevalence of diuretic resistance in the heart failure population is unknown. In a recent retrospective analysis of 1153 patients with advanced CHF, 402 patients (35%) had diuretic resistance (defined in this study as requirement of furosemide >80 mg or bumetanide >2 mg daily). Diuretic resistance was independently associated with total mortality, sudden death, and pump failure death (10).

The mechanism of diuretic resistance is thought to be secondary to various factors including, delayed absorption of the diuretic, reduced secretion of the diuretic into the tubular lumen of the

nephron, compensatory retention of sodium after the effective period of the diuretic, and hypertrophy and hyperplasia of epithelial cells of the distal convoluted tubule leading to an increased reabsorption of sodium in this segment, thereby blunting the natriuretic effect (14-15). Indirect data obtained from a human study are consistent with the data obtained from rats (16).

Approaches to overcoming diuretic resistance include higher doses and/or more frequent administration, use of intravenous agents to bypass the gastrointestinal tract and overcome delayed absorption from bowel edema and use of combination of diuretics that target both the proximal and distal renal tubules. A newer approach is the use of aquapheresis.

Unlike diuretics, ultrafiltration with aquapheresis does not decrease sodium presentation to the macula densa and thus avoids neurohormonally mediated sodium and water reabsorption (19). This isotonic fluid removal may restore renal medullary concentration gradients of electrolytes and enhance the future effectiveness of diuretics while causing less neuroendocrine activation. Improved outcomes following ultrafiltration could also be due to reduced exposure to diuretics (26). In the recently published UNLOAD study (21), discharge oral diuretic doses were reduced in the ultrafiltration group and increased in the standard-care group. These observations suggest that a strategy of early ultrafiltration and "diuretic holiday" may improve responsiveness to diuretics (27). Restoration of diuretic responsiveness may help to decrease the rate of hospital readmissions for CHF.

The primary objective is to define the prevalence of diuretic resistance in patients admitted with decompensated systolic heart failure and the efficacy of aquapheresis in this population. Within 24 hours of admission, using both clinical and objective criteria, patients will be identified as diuretic resistant. Patients found to be diuretic resistant will be randomized to standard care versus aquapheresis. The effect of aquapheresis on weight loss, fluid removal, length of hospitalization, restoration of diuretic responsiveness and 6 month re-hospitalization rate will be assessed.

B. Study Design and Statistical Analysis:

This is a prospective randomized cohort study to be completed over 12 months. Patients with evidence of volume overload admitted with decompensation from chronic systolic heart failure and meeting inclusion criteria as listed below will be enrolled within 24 hours of admission and undergo an objective assessment for diuretic resistance. Patient who are defined as diuretic resistant will then undergo stratified randomization based on NYHA class (II, III, IV) for a total of 6 strata, 3 strata (NYHA II, NYHA III, NYHA IV) in each arm. These patients will be randomized to standard of care versus aquapheresis.

The primary outcome for this study will be weight loss at 4 weeks after randomization. Secondary endpoints that will be followed will be: total fluid removal, renal function, rate of restoration of diuretic responsiveness, neurohormonal levels, BNP, Quality of Life: NYHA class, Minnesota Living With Heart Failure Questionnaire (MLWHFQ), complication rates from aquapheresis, duration of hospitalization, and hospital re-admission rate 6 months after trial completion, death.

Patients will also be characterized on basis of age, gender, race, body mass index (BMI), etiology of heart failure, NYHA class, duration of heart failure, co-morbid conditions like diabetes, COPD, history of malignancy, baseline renal function, outpatient medications, and echo characteristics like ejection fraction, right sided heart failure, valvular abnormalities and any baseline arrhythmias.

An unpaired t-test will be used to analyze the primary outcome. Using the equation as follows: $N = 1 + 16 (\text{std dev/effect})^2$, a sample size of 6 in each strata is sufficient for 80% power testing at a p value of 0.05 to assess a significant difference in weight at the 4 week endpoint between diuretic resistant patients treated with and without aquapheresis assuming a standard deviation of 5 lbs and a weight difference of 10 lbs. Assuming dropouts, we would aim for a sample size of 40. All patient outcomes will be analyzed using the intention-to-treat principle.

Event rates (complications associated with aquapharesis, readmission for heart failure causes, readmission for all causes, death) will be analyzed by the chi-square test. Time to an event (readmission, transplant, death) will be analyzed by Kaplan Meir analysis. Continuous variables (renal function, urinary response to re-introduction of oral diuretic, quality of Life: NYHA class, MLWHFQ) will be tested for normal distribution. If normally distributed, they will be analyzed by t-test. If not normally distributed, they will be analyzed by nonparametric tests. Multiple regression analysis will be performed for all primary outcome measures; independent variables will include demographic and physiologic variables including age, gender, sex etc.

C. Study Procedures:

Weight, complete blood count, blood chemistry, brain natriuretic peptide, prothrombin time and partial thromboplastin time, aldosterone, renin, urine sodium, creatinine and osmolality will be obtained at baseline. Patients will complete the Minnesota Living With Heart Failure Questionnaire (MLWHFQ). Transthoracic echocardiography (if not documented in the past three months) will be obtained.

Assessment of diuretic resistance will include escalating doses of intravenous loop diuretic in combination with an intravenous distal tubule diuretic agent. For patients already on loop diuretic therapy, the initial loop diuretic dose will be the intravenous equivalent of the chronic oral dose administered as intravenous bumex. The conversion from furosemide to bumetanide will be 40:1 and from torsemide to bumetanide will be 20:1. For patients on no preceding diuretic therapy intravenous bumetanide will be initiated. If the urine output over 1 hour is less than 200 ml, then double the prior intravenous diuretic dose will be administered. The hourly urine output will be monitored and if again the urine output is less than 200 cc, the diuretic dose will be increased to a maximum dose of 10 mg bumetanide with 500 mg chlorothiazide. Patients will be considered diuretic resistant if after 12 hours the urine output is less than 2 liters.

40 patients with diuretic resistance will then be randomized to two arms, namely aquapheresis versus standard care. In the aquapheresis group, diuretics will be discontinued and volume removal will be performed with the Aquadex system as described above. Daily weight, urine volume, oral intake will be measured in all patients. Drug therapy will be recorded. Those patients randomized to aquapheresis will receive 2 days of treatment with up to 5 liters of fluid

removed daily depending on clinical parameters. Patients not randomized will continue to receive standard intravenous diuretic therapy. On day 3 after randomization, all patients are rechallenged with the above IV diuretic dose titration to determine whether aquapheresis has restored diuretic responsiveness.

All patients will receive daily 2 g sodium and 1500 ml fluid intake restriction. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers will be continued throughout the study, as tolerated, in all patients.

Follow-up:
All patients who participate in the study will have their weight checked daily during hospitalization and then again at 4 weeks after randomization. They will also be contacted monthly after hospital discharge for 6 months via telephone to assess their status, daily diuretic dose, need for emergency room visits or hospital re admission.

Study Drugs:
Standard inpatient therapy for decompensated CHF will be provided for all patients. Patients not randomized to Aquadex therapy will continue to receive intravenous diuretic therapy as intermittent boluses or as continuous infusion according to the discretion of their primary physician. Use of intravenous ionotropic agents will be permitted in both groups and again will be at the discretion of the primary physician.

Medical Device
The Aquadex FlexFlow Fluid Removal System (from CHF Solutions™, Minneapolis, MN) has recently been FDA approved and provides mechanical iso-osmotic fluid removal in volume overloaded CHF patients via veno-venous ultafiltration. This "aquapharesis" is an alternative method of sodium and water removal in patients who have some degree of diuretic resistance. It has been shown to safely improve hemodynamics in CHF patients (21-25).

The Aquadex FlexFlow Fluid Removal System is a dual rotary pump device used with a sterile, single-use UF 500 Blood Circuit Set. Blood withdrawal is usually from a peripheral arm vein (such as the antecubital vein), using a 16 or 18 gauge, 3.5 cm catheter (similar to a standard IV catheter). A similar IV catheter is used for blood return via a second peripheral vein (typically in the forearm). Blood is removed at a rate of 10-40 mL/min with ultrafiltrate fluid removal rate of up to 500 mL/h and total extracorporeal blood volume of 33 ml (25). Software algorithms in fluid removal system adjust the withdrawal and infusion blood flows and pressure. Patient's blood passes against a polysulfone hollow-fiber membrane which filters molecular weights less than 65,000 dalton, rejecting >98% of the serum albumin, at the maximum ultrafiltration rate. Patients need anticoagulation with either heparin, low molecular weight heparin or thrombin inhibitor substances like argatroban to maintain flow through the aquadex system. The Aquadex FlexFlow is equipped with safety monitors to automatically detect air or blood inside the blood circuit. A data key memory device ensures the blood filter/circuit is not reused. The system is also equipped with a weight scale to monitor how much fluid has been extracted from a patient.

Potential complications associated with the procedure include IV infiltration at the venous access site, bleeding complications, problems with tubing and filter clots in the Aquadex system, low flow rates and positional variation in flow rates and, hypovolemia mediated hypotension (28).

Study Questionnaires:
A quality of life questionnaire will be completed by the subject at enrollment and at discharge. The questionnaire to be used is the commonly used, twenty one question, Minnesota Living with Heart Failure Questionnaire which assesses the effect of heart failure on daily living.

Study Subjects
Patients must be 18 years of age or older and meet the following inclusion and exclusion criteria in order to be enrolled:

Inclusion criteria:
Dyspnea at rest due to decompensated CHF that was severe enough to require hospitalization and intravenous therapy. A cardiac etiology for dyspnea will be established by estimated or measured elevation of cardiac filling pressures (PCWP 20 mm Hg in catheterized patients) and at least 2 of the following: (1) jugular venous distention, (2) paroxysmal nocturnal dyspnea or 2-pillow orthopnea within 72 hours before study entry, (3) abdominal discomfort due to mesenteric congestion, or (4) a chest x-ray film consistent with decompensated CHF and/or (5) a BNP level >100 ng/ml. Patients with acute decompensation of chronic heart failure or gradual worsening of chronic heart failure will be eligible for study.

Exclusion criteria:
Patients with decompensated CHF in the setting of acute coronary syndromes, preserved systolic function, renal failure (serum creatinine >3.5 mg/dl or rising at >0.5mg/dl per day), new onset atrial or ventricular arrhythmias other than atrial fibrillation will be excluded based on these conditions alone. Patients with a systolic blood pressure < 90 mm Hg, age<18 years or >80 yrs, volume depletion (as manifested by orthostasis or PCWP<8), contraindication to anticoagulation, and/or need for mechanical ventilation will also be excluded from study.

Recruitment:
Patients diagnosed with acute decompensation of heart failure will be recruited in the Emergency Room or as inpatients in the Milstein Hospital Building. Subjects will be approached and consented by a co-investigator. Written informed consent will be obtained by all patients prior to the study.

Confidentiality of Study Data:
Each investigator has completed HIPAA training. HIPAA guidelines will be explained to and signed by the subject prior to participation in the study. All information associated with the patient will remain confidential. Patient information will be coded and will remain in the investigators' possession.

Potential Conflict of Interest:
There are no conflicts of interests amongst any of the co-investigators.

Location of the Study:
All participants will be recruited from the Columbia University Medical Center Emergency Room and the Milstein Hospital inpatient ward service. All study procedures will be conducted in clinical areas including the telemetry floor and the CCU.

Potential Risks:
The risks associated with aquapheresis include hypotension, bleeding, infection, pain at insertion site. All precautions will be taken to assure that this does not occur as noted. In the UNLOAD trial the incidence of hypotension was comparable to patients to those receiving intravenous therapy.

Potential Benefits:
Aquadex therapy may restore the responsiveness of oral diuretic therapy, shorten the hospital stay, increase fluid removal and decrease future hospitalizations.

Alternatives:
Subjects may refuse to participate and continue to receive standard therapy for heart failure.

Compensation to Subjects:
Transportation vouchers will be provided to patients for the 4 week visit.

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