# DRUF-CHF: Diuretic Resistance and Ultra Filtration in acute decompensated CHF:

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**A.** ***Study purpose and rationale***

***Design****:* This will be a prospective randomized study designed to assess a number of efficacy and financial endpoints comparing ultra filtration, as performed with the System 100, with IV diuretics (standard medical therapy) in patients hospitalized for CHF and diuretic resistance.

***Rational****:* Many health conditions such as kidney failure, post-surgical overload and metabolic diseases such as glucose intolerance, hyperglycemia and acid maltase can cause fluid-overload, however congestive heart failure (CHF) is the leading cause. CHF remains the leading cause of hospitalization in Medicare beneficiaries. Ninety percent of all hospitalizations for CHF are due to fluid overload. Most of the expense related to the management of heart failure is due to hospital based care, interventions that reduce the amount of time patients spend in the hospital may greatly decrease the cost associated with caring for these patients. The hospital length of stay for patients admitted for adCHF is largely dictated by how quickly the signs and symptoms of congestion can be relieved and whether the ACE inhibitors can be started safely. Diuretics are usually effective in relieving congestion, but achieving adequate diuresis often requires a process of trial and error. Some patients are simply refractory to oral or intravenous diuretics. Diuretics stimulate adverse neurohormonal systems and can cause progressive azotemia. It had been shown that there is a significant increase in renin and aldosterone levels as a response to diuretic treatment rather than as a result of the heart failure itself It has also been shown that loop diuretics diminish glomerular filtration rate in patients with heart failure. In addition, as more diuretics are given, serum electrolyte imbalances often occur, requiring additional monitoring of patients. In the treatment of more advanced stages of heart failure diuretics may fail to control salt and water retention despite the use of appropriate doses. Diuretic resistance may be caused by decreased renal function and reduced and delayed peak concentrations of loop diuretics in the tubular fluid, but it can also be observed in the absence of these pharmacokinetic abnormalities. When the effect of a short acting diuretic has worn off, postdiuretic salt retention will occur during the rest of the day. Chronic treatment with a loop diuretic results in compensatory hypertrophy of epithelial cells downstream from the thick ascending limb and consequently its diuretic effect will be blunted. Conventional strategies to overcome diuretic resistance include restriction of sodium intake, changes in dose, changes in timing, and combination diuretic therapy.

UF has been used as a therapeutic method to remove excessive fluid in patients for over 30 years. UF removes excess water without causing a significant clinical change in the electrolyte composition of the blood or causes adverse effects on the kidneys and neurohormonal system. Studies have shown that UF increases urine output, increases responsiveness to standard oral therapies and decreases readmission rate. While the usefulness of UF in this patient population has great potential, this form of therapy is not usually performed due to need for invasive venous access and increased expense i.e. high flow dialysis machine. CHF Solutions has developed the System 100 that has FDA market clearance for UF. The advantage of the System 100 is its simplicity and the fact that it can be administered by means of peripheral catheters or with a central venous access. Early prospective series and subsequent clinical experience involving adCHF patients have shown that 4 to 8 liters can easily be withdrawn in a short amount of time using the peripheral access approach with the System 100. Volume removal was not associated with disruption of electrolyte balance, worsening of renal distress or impact on blood pressure or heart rate of clinical significance. The System 100 is a predictable, safe and effective way to ensure adequate volume removal that may result in shorter hospital stays, better symptom relief and more

efficient dosing of medications for treatment of adCHF. Pts with diuretic resistance seem to be an ideal group to benefit from ultrafilteration.

**B. Study procedures**

Admitting physician will identify the prospective patient and introduce the study to the patient then notify the study personnel who then discuss the protocol to the patient in detail. Inclusion/exclusion criteria will be reviewed, if the patient meets all the inclusion and none of the exclusion criteria then he/she will sign an informed consent form and be enrolled into the study. Patients will be enrolled in the trial within 24 hours of hospital admission. At study entry, the following will be assessed; Weight, Vital Signs, Physical and cardiovascular exam, Electrolytes, Hematocrit, NYHA class, Renin and Aldosterone, Drugs for CHF, doses and times, BNP and Quality of Life questionnaire. The patient will be randomized to either UF or IV diuretics alone. Patients enrolled in the UF arm can be maintained on the pre-enrollment PO medications including diuretics during their hospital stay. Pts in the IV diuretic arm will receive IV diuretics at the as directed by a CHF specialist. After randomization, an IV access specialist will insert the proper venous catheters. UF therapy will continue at the discretion of the treating CHF specialist. The rate of volume removal is also left to the discretion of the treating physician up to 500 cc/hour. Minimum fluid removal 1L in 8 hours and Maximum fluid removal 4L in 8 hour period. Additional courses of the UF are allowed at the discretion of the treating physician while the patient is hospitalized and if fluid overload is still present. Vasoactive drugs will be discouraged within the first 48 hours after trial entry.

After the UF circuit and tubing is primed and positioned, IV heparin will be administered according to the dosing schedule provided by CHF Solutions. Blood pressure will be assessed every 30 minutes for the first 2 hours after initiation of UF therapy.

At the 8th hour, and 24th hour, the following will be assessed: Urine output, Oral intake, IV fluid intake, Vital Signs, Dypsnea Score, Electrolytes, BNP and Adverse Events. At the 24th hour Weight and Global assessment will also be done.

At Discharge day, all the screening assessments will be done plus Length of hospital stay, Adverse Events, Global Assessment, Dypsnea Score, and 6 minute walk Test.

The patient will be seen as outpatient on the 10th day, 1 month and 3 months. The assessments done at Discharge day will be repeated on these 3 outpatient visits.

The primary endpoint in the study is length of stay and a clinically significant reduction in length of stay would be 2 days. According to recent data from the Advanced Decompensated Heart Failure National Registry length of stay at Columbia Presbyterian Hospital for decompensated heart failure is 6 days (SD=3). No specifc data on length of stay is available for pts with diuretic resistance. Taking a clinically significant absolute difference for LOS between UF and controls to be 2 days a study powered at 80% with an alpha value of 0.05 will require 37 patients in the control group and 37 patients in the Ultra filtration group using the t-test on group of means.

Statistical Analysis The primary and secondary endpoints will be analyzed on an intent-to-treat basis. Patients will therefore be analyzed according to the randomized treatment regardless of the subsequent sequence of events. All clinically relevant baseline variables will be tabulated and compared between the two treatment arms. To detect differences in patient characteristics between the randomized treatment assignment groups, the means of continuous variables will be compared by t tests. Dichotomous variables will be compared by x2 tests.

**C. Study device**

The System 100 consist of

**1)** S100 Console;

**2)** UF 500 blood circuit;

**3)** Extended Length Catheter (ELC) and a catheter extension tubing.

The System 100 console controls the rate at which blood is removed from the patient and extracts ultrafiltrate at a userset maximum rate. System 100 is designed to monitor the extracorporeal blood circuit and to alert the user to abnormal conditions. The device has one user setting that determines the rate of ultrafiltrate removal. Liquid removed during treatment drains into an ultrafiltrate bag. When the bag is full, the UF pump stops and alarms until the user empties the bag; the blood pump continues to operate. Information to assist the user in priming, setup and operation is shown on the System 100 display. The system uses venous vascular access catheters designed for use with the device. The catheters are inserted into veins to withdraw and infuse blood. The catheters are connected to the blood circuit and secured to the skin during treatment. Blood can be withdrawn from a central access line using standard central catheters. However, these catheters must be rated as having flow rates of 59179 ml/mm in order to be used with the System 100. Blood is withdrawn from the vein through the withdrawal catheter. Tubing connects the withdrawal catheter to the blood pump. Blood passes through the withdrawal pressure sensor just before it enters the blood pump tubing loop. Both the withdrawal pressure sensor and the pump loop are mounted on a clipon cartridge. During the operation, the pump loop is compressed be rotating rollers that propel the blood through the tubing. After exiting the blood pump, blood passes through the air detector and enters the hemofilter. The hemofilter is bonded to a clipon cartridge that mounts onto the ultrafiltrate pump raceway on the side of the console. Blood enters the filter through a port on the bottom, exits through the port at the top of the filter and passes through the infusion pressure sensor before returning to the patient. Inside the hemofilter, there is a bundle of hollow fibers. The ultrafiltrate passes through the fiber walls, fills the space between the fibers inside the filter case and exits the filter through a port neat the top of the filter case. After exiting the filter, ultrafiltrate passes through a blood leak detector. Ultrafiltrate then passes through the ultrafiltrate pressure sensor and then to the ultrafiltrate pump. After the pump, the effluent collects in the ultrafiltrate bag that is suspended from the weight scale.

The System 100 is very simple to use and requires minimal supervision and programming. Setup of the System 100 takes less than 10 minutes. Treatment with the System 100 is prescribed by a physician and can be performed by any nurse trained in the use of System 100. Treatment can be performed in the setting of an ICU/CCU or monitored hospital floor. Its size and weight is comparable to a standard IV pump. Operation requires the same nursing skill level and amount of monitoring as blood infusion or standard IV pump.

## D. Study Questionnaire

- Quality of Life The Minnesota Living with Heart Failure Questionnaire
- Dyspnea Assessment
- Global Assessment

## E. Study Subjects

*Inclusion Criteria:*

Patients must be hospitalized with the primary diagnosis of decompensated CHF; Evidence of fluid overload as indicated by the presence of at least 2 of the following:

1) Pitting edema ((2+) of the lower extremities
2) Jugular venous distention
3) Pulmonary edema or pleural effusion on chest xray consistent with adCHF
4) Ascites
5) Paroxysmal nocturia dypsnea or 2pillow orthopnea.

And...

Chronic daily PO Lasix = 80mg po QD or Torsemide = 40mg po QD or Bumetamide = 2mg po QD

And...

Serum Cr >1.5 mg/dl

*Exclusion Criteria:*

1) Acute coronary syndrome
2) Systolic blood pressure <90 mm Hg at time of enrollment
3) Hematocrit >45%
4) Inability to obtain venous access
5) Clinical instability likely to require the addition of pressors or intravenous nitroprusside or anticipated use of IV pressors for any other reason during hospitalization Administration of vasoactive drugs during this hospitalization prior to entry into the trial Use of iodinated radiocontrast material in the last 72 hours or planned IV contrast study during the current hospitalization
6) Severe concomitant disease expected to prolong hospitalization
7) Heparin allergy or contraindication to the use of anticoagulation
8) Patients suffering from sepsis
9) Patients diagnosed with systemic infection
10) Patients who are on dialysis
11) Patients with ARF
12) Patients who have had a cardiac transplant
13) Admitted to the hospital greater than 24 hours prior to randomization.

**F. Recruitment**

Subjects will come to the hospital with decompensated CHF, will be identified by their treating or admitting physician as a good candidate for the study, who will talk to the patient about the protocol. If the subject agrees, the admitting/treating physician then will notify the study personnel who will explain the study in detail, review the patient inclusion/exclusion criteria and if met will consent the patient and enroll into the study.

**G. Confidentiality**

Each patient entered into the trial will be numbered according to the sequence they were entered at the site. All data will be kept confidential. Subjects' anonymity will be maintained and identities will be protected from unauthorized parties. All subject's enrollment log will be maintained by the investigator and kept in a locked file in the office of the Research Coordinators.

**H. Conflict of Interest None**

Location of the Study The primary center for the study will be the New York Presbyterian Hospital - Columbia Campus. The clinical trial at this center will be conducted in the Coronary Care Unit and Heart institute at the Milstein Hospital Building. Additionally there will be multiple sites enrolled at different institutions nationally and internationally.

**I. Risks**

1) Low blood pressure that may cause dizziness and lightheadedness, and irregular heart rate
2) UF can lead to too, much fluid being removed that could potentially damage the kidneys
3) From the use of catheters, risks include bruising and swelling, infection possible clot formation
4) From drawing blood from a vein, risks include discomfort at the site of needle stick, possible bruising and swelling, rarely infection and uncommonly fainting from the *Procedure*
5) Patients treated with OF machine may also experience the additional risk of receiving blood thinner therefore the possibility of bleeding easier, and bruising easier.

**J. Benefits**

There is no guarantee that subject will benefit from participating in this study. However Pts will likely be symptomatically improved earlier then diuretic group.

**K. Alternative**

The alternative to enrolling in this study is to choose not to take part in the study.

**L. Compensation to Subjects**

The patients will not be paid for taking part in this study.

**M. Costs to subjects**

For those randomized to the experimental arm, the System-100 will be provided without any cost. The patient's participation in the study may incur additional costs that will not be covered by the hospital or by the patient's insurance company. Follow-up visits to the patient's local doctor are part of the standard clinical treatment of the patient's cardiac disease, and are the patient's responsibility.