PVP-Guided Decongestive Therapy in HF 2 (PERIPHERAL-HF2)

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Study Title: ***Peripheral Venous Pressure-Guided Decongestive Therapy in Heart Failure*** **2**

Short title: ***PERIPHERAL-HF2***

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I. BACKGROUND AND SIGNIFICANCE

Precise assessment of volume status is essential in diagnosis and management of diuretic therapy in patients hospitalized for heart failure (HF). Unfortunately, no clear guidelines are present for in-hospital management of congestion. Consequently, nearly half of the patients hospitalized for congestive HF are discharged with persistent congestion. This contributes to high rates of readmission and mortality.

Recently, it has been shown that a simple assessment of peripheral venous pressure (PVP) demonstrates a high correlation with central venous pressure (CVP), indicating that PVP may be useful in the standard bedside clinical assessment of volume status in HF patients to help guiding decongestive therapy.

II. THE HYPOTHESIS

We hypothesize that a simple assessment of peripheral venous pressure (PVP) will better predict the diuretic need and long-term outcomes (all-cause mortality, all cause rehospitalization, emergency department visits) compared to standard evaluation.

III. METHODS

1. Application for Institutional Review Board (IRB)/Ethics board approval

The study will be at participating centers. An IRB/Ethics board approval has been obtained from Marmara University, Pendik Training and Research Hospital local ethics board.

2. Study population

Patients 18-99 years old who were admitted with a de novo or decompensated chronic HF and accept to participate in the study will be enrolled. Patients will be included regardless of ejection fraction or etiology of HF, but these will be noted as baseline variables. All patients or legal surrogate decision makers will be requested to provide a written informed consent prior to enrollment. Patients who withdraw their consent, those with upper extremity venous pathology, those with a baseline creatinine level equal to or above 3.5 mg/dL, those with severe stenotic valvular disease and hypertrophic cardiomyopathy will be excluded.

3. Centers and Personnel

The study will be undertaken at Health Sciences University, Başakşehir Pine and Sakura City Hospital, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, and other participating centers. The complete list is as follows:

1, Ankara Etlik City Hospital, Principal investigator: Belma Kalaycı, Çağatay Tunca

2, Antalya Atatürk State Hospital, Principal investigator: Özgür Çağaç

3, Akdeniz University, Faculty of Medicine, Principal investigator: Nagehan Küçükler

4, Bağcılar Training and Research Hospital, Principal investigator: Esra Dönmez, Researcher: Sevgi Özcan

5, Bakırçay University, Faculty of Medicine, Çiğli Training and Research Hospital, Principal investigator: Saadet Aydın

6, Başakşehir Pine and Sakura City Hospital, Principal investigator: Emre Aslanger, Researchers: Ahmet İlker Tekkeşin, Funda Özlem Pamuk, Yelda Saltan

7, Çanakkale Onsekiz Mart University, Faculty of Medicine, Principal investigator: Hakkı Kaya

8, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Principal investigator: Özlem Yıldırımtürk

9, Eskişehir City Hospital, Principal investigator: Ezgi Çamlı Babyiğit

10, Erzurum Training and Research Hospital, Principal investigator: Oğuzhan Birdal

11, İdil State Hospital, Principal investigator: Barış Güven

12, Kafkas University Health Research and Application Hospital, Principal investigator: Doğan İliş

13, Kartal Koşuyolu High Specialization Education and Research Hospital, Principal investigator: Süleyman Çağan Efe

14, Kütahya Health Sciences University, Faculty of Medicine, Principal investigator: Taner Şen, Mevlüt Demir

15, Mehmet Akif Ersoy Training and Research Hospital, Principal investigator: Ali Kemal Kalkan

16, Pazarcık State Hospital, Principal investigator: Orhan Karaca

17, Tokat Gaziosmanpaşa University, Faculty of Medicine, Principal investigator: Çağrı Zorlu

18, Trakya University, Faculty of Medicine, Principal investigator: Cihan Öztürk

4. Data Collection

The study will start at participating centers on July 15, 2024.

Baseline variables

Baseline variables will be collected via chart review and entered to the electronic study form (see below).

Procedures

A peripheral intravenous (IV) access, using an 18 to 22-gauge IV line, will be placed preferably to an upper extremity vein before enrollment. This line will be used to draw blood samples first. After blood samples were collected the subjects will be randomized to standard or PVP guided therapy groups. Randomization will be done using a computer-generated random allocation list. The details of demographic characteristics, symptoms, physical examination findings and drug list will be noted to a standard electronic study form (see below). A routine electrocardiogram and echocardiogram will be performed at the earliest convenience.

After the blood samples were collected, line will be flushed carefully. PVP will be obtained by transducing a peripheral intravenous line after zeroing at the phlebostatic axis. The phlebostatic axis will be accepted as the midpoint between the anterior and posterior surfaces of the chest at the level of the fourth intercostal space meets with sternum, which is assumed to be correlated with the mid-level of the right atrium. The patient's arm will be placed parallel to the patient such that the position of the peripheral IV to be at the phlebostatic axis. Continuity of the peripheral IV line with the central venous system will be confirmed by demonstrating augmentation of the venous pressure waveform using manual or tourniquet circumferential occlusion of the extremity proximal to the catheter. If the pressure waveform failed to augment appropriately, data will not be collected, and the patient will be documented for study purposes as a technique failure. Daily fluid intake and output, weight, and biochemistry measurements, as required, will be done.

The patients in whom the first and the predischarge PVP cannot be measured due to technical issues (unable to provide upper extremity IV access, unable to confirm augmentation or Valsalva test) will be excluded from the study. Also, the patients requiring in-hospital intubation, high-dose inotrope or vasopressor infusion ($\geq$10 mcg.kg^{-1}.min^{-1} dopamine, dobutamine or equivalent), intraaortic balloon support, dialysis or veno-venous ultrafiltration will be excluded from the study (but these patients will be included in the in-hospital analyses).

In hospital diuretic treatment will be guided by ESC guidelines (see below for algorithm). In the standard therapy arm, the treatment and the decision of discharge will be left to physicians' discretion. In the PVP-guided arm, a PVP < 9 mmHg will be targeted before discharge.

Outcomes

The primary outcome of the study is the composite endpoint of all-cause mortality, all-cause hospitalization and all-cause emergency department visits. The secondary outcomes will include cardiovascular mortality, HF-related hospitalization, HF-related emergency department visits. This information on these outcomes will be obtained from the national electronic database. The follow-up duration is planned to be limited to one year.

Summary of patient enrollment criteria

Inclusion criteria

- Hospitalization for heart failure (de novo or decompensated chronic heart failure) irrespective of left ventricular ejection fraction
- Age 18-99
- Accept to participate

Exclusion criteria

- A prior history of upper extremity venous disease
- Serum creatinine ≥ 3.5 mg/dL
- Severe stenotic valvular disease
- Hypertrophic obstructive cardiomyopathy
- Withdrawal of consent

Exclusion from long term follow-up after randomization

- Unable to obtain first and pre-discharge PVP due to technical issues (unable to access an upper extremity vein, negative augmentation test)
- In-hospital intubation
- Need for high-dose vasopressor or inotrope medications (≥10 $mcg.kg.^{-1}.min^{-1}$ dopamine, dobutamine or equivalent)
- Need for intra-aortic balloon pump support
- In-hospital need for dialysis or veno-venous ultrafiltration

Predefined secondary analyses

There will be subanalyses from the same cohort, as defined below:

- The correlation between predischarge PVP and long-term outcomes. A multivariable analysis will also be executed for predicting the primary end point.
- The correlation between the change in PVP during hospital stay and long-term outcomes. A multivariable analysis will also be executed for predicting the primary end point.
- The correlation between the change in PVP during hospital stay and worsening renal function, renal injury, need for dialysis or veno-venous ultrafiltration.

- The comparison of the two arms in terms of worsening renal function, need for dialysis or veno-venous ultrafiltration.
- The comparison of the two arms in terms of EVEREST congestion score.
- The comparison of the two arms in terms of the days in hospital.
- The comparison of the two arms in terms of the number of repeat hospitalizations.
- Usual patterns of diuretic use
- The derivation and validation of an algorithm regarding the use of diuretic dose and peripheric venous pressure will also be aimed. It will be derived and validated in the first and second half of the study, respectively.

Estimated number of subjects to be submitted:

We estimated that the enrollment of 586 participants would provide the study with a statistical power of 95% to detect a relative excess rate of 10% in primary outcome (peripheral pressure guided group 20% versus standard approach 30%) with the use of a two-sided test at the 0.05 level. Accordingly, we expect to enroll at least 600 patients in a one-year enrollment period.

Statistical Analysis

Baseline characteristics will be summarized using standard descriptive statistics. Comparisons of relevant parameters between groups will be performed by chi-square, Fisher's exact test, Mann-Whitney U, Kruskal-Wallis H test, one-way ANOVA and student t-test, as appropriate. Patients with missing values will be excluded pairwise from analyses. Kaplan-Meier analysis will be performed to determine the cumulative long-term mortality and composite outcome rates in subgroups. The mortality across groups will be compared using log-rank test. A Cox-regression model will be used to perform a survival analysis according to pre-discharge peripheral venous pressure and composite outcome. Baseline characteristics with a P value of 0.05 or less in the univariate analysis will be included and a step-down procedure will be applied for selection of final covariates. Statistical analyses will be performed with SPSS (version 24.0; SPSS Inc., Chicago, IL) and MedCalc Software (version 18.2.1 [Evaluation version]; MedCalc Software, Ostend, Belgium).

Study form

Protocol no : _____
Age : _____ □ Male □ Female
TR no : _____
Height : _____ **Weight:** _____

Randomization date: ___/___/202__
Censor date: ___/___/202__
□ Excluded (Cause: _____)

□ Standard □ P_{msf} guided (≤10 mmHg)

PRESENTATION □ De novo HF
□ HF exacerbation

ETIOLOGY □ Ischemic
□ Non-ischemic

PRIOR HISTORY

□ Diabetes mellitus (___ years)
□ Hypertension
□ Coronqry artery disease
□ Atrial fibrillation
□ CRT/ICD

□ Chronic kidney disease
□ COPD
□ Others: _____

UNHEALTHY HABITS

Active smoking: □ No □ Yes

DRUGS BEFORE ADMISSON

□ Beta-blocker
□ ACEI/ARB
□ Spironolactone
□ Digoxin
□ Statin
□ Thiazide
□ Loop diuretics
(dose equivalent in oral furosemide): _____mg

□ Others:

BASELINE MEASUREMENTS

ECG

Rhythym: □ Sinus □ AF □ Others **LBBB:** □ Yes □ No

Echocardiogram

EF: % _____ **MR:** □ Mild □ Moderate □ Severe

Biochemistry
BNP: _____, AST: _____ , ALT: _____, CRP: _____, TnT _____, Uric acid: _____.

ADMISSION MEASUREMENTS

Line size □ Green □ Pink □ Blue □ __ G

Dyspnea □ No □ Seldom □ Frq □ Cont
Orthopnea □ No □ Seldom □ Frq □ Cont
Fatigue □ No □ Seldom □ Frq □ Cont

PTE □ No □ Mild □ Mod □ Severe
JVD □ No □ Yes: ____ cm @45°

Lung rales:
□ No □ Basal □ < 1/2 □ >1/2

TA : ____/____ mmHg, HR: ___ /min
Weight: ____ kg

BUN/creatinine: ____ / ____
Sodium/potassium: ____ / ____
Hb/Hct: ____ / ____
Albumin/T.protein: ____ / ____
Pmsf: ____ mmHg
LVDD □ Normal □ I □ II □ III
MR: □ Mild □ Moderate □ Severe
TR: □ Mild □ Moderate □ Severe

DISCHARGE MEASUREMENTS

Line size □ Green □ Pink □ Blue □ __ G

Dyspnea □ No □ Seldom □ Frq □ Cont
Orthopnea □ No □ Seldom □ Frq □ Cont
Fatigue □ No □ Seldom □ Frq □ Cont

PTE □ No □ Mild □ Mod □ Severe
JVD □ No □ Yes: ____ cm @45°

Lung rales:
□ No □ Basal □ < 1/2 □ >1/2

TA : ____/____ mmHg, HR: ___ /min
Weight: ____ kg

BUN/creatinine: ____ / ____
Sodium/potassium: ____ / ____
Hb/Hct: ____ / ____
Albumin/T.protein: ____ / ____
Pmsf: ____ mmHg
LVDD □ Normal □ I □ II □ III
MR: □ Mild □ Moderate □ Severe
TR: □ Mild □ Moderate □ Severe

Total fluid balance: _____

FOLLOW-UP

Mortality □ No □ Yes (__/__/202_)

Hospitalization
All cause
□ No □ Yes (__/__/202_)
CV
□ No □ Yes (__/__/202_)

Emergency department visit
All cause
□ No □ Yes (__/__/202_)
CV
□ No □ Yes (__/__/202_)

DRUGS AT DISCHARGE

□ Beta-blocker
□ ACEI/ARB
□ Spironolactone
□ Digoxin
□ Statin
□ Thiazide
□ Loop diuretics
(dose equivalent in oral furosemide): _____mg

□ Others:
_____
_____
_____
_____
_____
_____