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# Intrarenal Flow Alterations During Transition From Euvolemia to Intravascular Volume Expansion in Heart Failure Patients

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## ABSTRACT

**OBJECTIVES** The goal of this study was to assess: 1) the intrarenal flow in heart failure (HF) patients during the transition from euvolemia to intravascular volume overload; and 2) the relationship between intrarenal flow and diuretic efficiency.

**BACKGROUND** Intrarenal blood flow alterations may help to better understand impaired volume handling in HF.

**METHODS** Resistance index (RI) and venous impedance index (VII) were assessed in 6 healthy subjects, 40 euvolemic HF patients with reduced ejection fraction (HFrEF) and 10 HF patients with preserved ejection fraction (HFpEF). Assessments were performed by using Doppler ultrasonography at baseline, during 3 h of intravascular volume expansion with 1 l of hydroxyethyl starch 6%, and 1 h after the administration of a loop diuretic. Clinical parameters, echocardiography, and biochemistry were assessed. Urine output was collected after 3 and 24 h.

**RESULTS** In response to volume expansion, VII increased significantly in HFrEF patients ($0.4 \pm 0.3$ to $0.7 \pm 0.2$; $p < 0.001$) and in HFpEF patients ($0.4 \pm 0.3$ to $0.7 \pm 0.2$; $p = 0.002$) but not in healthy subjects ($0.2 \pm 0.2$ to $0.3 \pm 0.1$; $p = 0.622$). This outcome was reversed after loop diuretic administration. In contrast, RI did not change significantly after volume expansion. Echocardiographic-estimated filling pressures did not change significantly. VII during volume expansion was significantly correlated with diuretic response in HF patients independent of baseline renal function ($R^2 = 0.35$; $p < 0.001$).

**CONCLUSIONS** In HF patients, intravascular volume expansion resulted in significant blunting of venous flow before a significant increase in cardiac filling pressures could be demonstrated. The observed impaired renal venous flow is correlated with less diuretic efficiency. Intrarenal venous flow patterns may be of interest for evaluating renal congestion. (J Am Coll Cardiol HF 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

Congestive heart failure is characterized by signs and symptoms of volume overload, contributing to a high morbidity and mortality burden. There is increasing recognition that the capacity of the kidneys to compensate for fluid overload relates not only to the underlying intrinsic renal function but also to renal blood flow, in part influenced by increased venous pressure (1). Currently, we have very limited insight at the bedside to distinguish these major factors influencing diuretic efficiency.

Renal vascular ultrasound has been used to assess the degree of severity of renal artery stenosis or to assess vascular and endothelial dysfunction. The intrarenal resistance index (RI) (Figure 1) reflects renal arterial flow and changes in response to

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**ABBREVIATIONS AND ACRONYMS**

**CVP** = central venous pressure

**ECG** = electrocardiogram

**eGFR** = estimated glomerular filtration rate

**HES** = hydroxyethyl starch

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**LVEF** = left ventricular ejection fraction

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**RI** = resistance index

**RVSP** = right ventricular systolic pressure

**VII** = venous impedance index

alterations in arterial resistance and capacitance. A normal RI is approximately 0.60; however, an RI >0.70 is seen in renal artery stenosis, hypotension, renal vein thrombosis, and arterial stiffness (2). In contrast, renal venous flow is normally continuous and the venous impedance index (VII) low. The VII changes in response to alterations in venous compliance, which are determined by central venous pressure and/or renal interstitial pressure (3,4). Interestingly, recent reports have shown that renal flow indices strongly correlate with clinical outcomes in HF independent of estimated glomerular filtration rate (eGFR) and other conventional prognostic factors of HF (5,6). Whether such alterations are directly associated with intravascular volume expansion or removal has not been shown.

Therefore, the objectives of the present study were to: 1) study intrarenal flow in HF patients compared with healthy subjects during the transition from euvolemia to intravascular volume overload; and 2) investigate the relationship between intrarenal flow and the ability to alleviate intravascular volume excess.

## METHODS

This study was conducted in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) between September 2014 and October 2015. The study complies with the principles of the Declaration of Helsinki, and the institutional review board approved the study protocol. Written informed consent was obtained from every subject before any study-specific action was performed.

**STUDY POPULATION.** Subjects were eligible for study inclusion if they were ≥18 years of age and able to give informed consent. Healthy volunteers had the following: 1) no history of cardiac or renal disease except for adequately treated hypertension with guideline-recommended therapy; 2) a normal clinical examination; and 3) a normal transthoracic echocardiography.

Patients with chronic heart failure with reduced ejection fraction (HFrEF) had the following: 1) a clinical diagnosis of heart failure with evidence of impaired left ventricular ejection fraction (LVEF) ≤40% diagnosed at least 6 months before inclusion; and 2) stable doses of medical therapy according to current guideline recommendations during ≥3 months. Exclusion criteria were as follows: 1) renal replacement therapy or severe renal dysfunction with an eGFR ≤15 ml/min/1.73 $m^2$ determined by using the Chronic Kidney Disease Epidemiology Collaboration equation; and 2) any clinical sign or symptom of volume overload (i.e., pulmonary rales, orthopnea, jugular venous distention or ≥1 peripheral edema).

Patients with chronic heart failure with preserved ejection fraction (HFpEF) had a clinical diagnosis of HFpEF diagnosed at least 6 months before inclusion. The diagnosis of HFpEF was based on the presence of clinical signs or symptoms of HF in combination with an LVEF ≥50%, elevated levels of natriuretic peptides, and the presence of left ventricular hypertrophy, left atrial enlargement, or diastolic dysfunction (7). Exclusion criteria were similar to HFrEF patients.

**STUDY DESIGN.** All patients were admitted to the cardiology intensive care unit for research purposes. Each patient took his or her usual dose of medication at 8:00 AM except for the maintenance dose of loop diuretics. Subjects were placed in the semi-supine position, and a venous catheter was placed in the forearm. After a 60-min equilibration period, all subjects were instructed to empty their bladder, and baseline vital parameters (blood pressure, heart rate, and weight), transthoracic echocardiography, intrarenal Doppler ultrasonography, and a venous blood sample were obtained. After baseline measurements, 0.5 l of isotonic hydroxyethyl starch (HES) 6% was infused over 10 min followed by an infusion of 0.5 l over a period of 3 h to maintain a stable intravascular volume expansion of 3 h. Start of infusion was appointed as time point zero, and every hour afterward appointed, for example, as +1 h, +2 h, and so forth. At +3 h, 1 mg of bumetanide was intravenously administered as a bolus infusion in all subjects. Clinical assessment, vital parameters, a venous blood sample, and urine output were collected hourly up to +3 h. Subsequently, urine output was collected until the time point of +24 h. Transthoracic echocardiography and intrarenal Doppler ultrasonography were obtained at baseline, +1 h (during intravascular volume expansion), and +4 h (1 h after administration of the intravenous loop diuretic). Subjects were discharged from the hospital at approximately +5 h. In-hospital intake of oral fluid was 100 ml in all subjects. After hospital discharge, patients were instructed to maintain their usual low-salt diet and maximum intake of 1.5 l over 24 h.

**LABORATORY MEASUREMENTS AND URINE SAMPLING.** Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured by using the