Prognostic Value of Glomerular Filtration Changes Versus Natriuretic Response in Decompensated Heart Failure With Reduced Ejection

FREDERIK HENDRIK VERBRUGGE, MD,[1,2] PETRA NIJST, MD,[1,2] MATTHIAS DUPONT, MD,[1] CARMEN REYNDERS, MSc,[3] JORIS PENDERS, MD, PhD,[3,4] W.H. WILSON TANG, MD,[5] AND WILFRIED MULLENS, MD, PhD[1,4]

Genk and Diepenbeek, Belgium; and Cleveland, Ohio

ABSTRACT

Background: Glomerular filtration rate (GFR) and natriuretic response to diuretics represent important treatment targets in acute decompensated heart failure (ADHF).

Methods and Results: Consecutive ADHF patients (n = 50) with ejection fraction ≤45% and clinical signs of volume overload received protocol-driven decongestive therapy. Serum creatinine (Cr), cystatin C (CysC), and β-trace protein (βTP) were measured on admission and three subsequent days of treatment. Worsening renal function (WRF) was defined as a ≥0.3 increase in absolute biomarker levels or ≥20% decrease in estimated GFR. Consecutive 24-hour urinary collections were simultaneously performed to measure Cr clearance and natriuresis. Serum Cr, CysC, and βTP were strongly correlated at admission (ρ = 0.788−0.909) and during decongestive treatment (ρ = 0.884−888). Moreover, derived GFR estimates correlated well with Cr clearance (ρ = 0.820−0.908). Nevertheless, WRF incidence differed markedly according to Cr- (26%−30%), CysC- (46%−54%), or βTP-based definitions (31%−48%). WRF by any definition was not associated with all-cause mortality or ADHF readmission, in contrast to stronger natriuresis per loop diuretic dose [hazard ratio 0.20 (95% confidence interval 0.06−0.64); P = .007].

Conclusions: Serial measurements of CysC/βTP, compared with serum Cr, more frequently indicate WRF during decongestive treatment in ADHF. However, adverse clinical outcome in such patients might be better predicted by the natriuretic response to diuretic therapy. (*J Cardiac Fail 2014;20:817−824*)

Key Words: Glomerular filtration rate, congestive heart failure, natriuresis.

Renal function has traditionally been appraised by the ability of the kidneys to achieve glomerular filtration. Glomerular filtration rate (GFR) is a strong predictor of all-cause mortality in both chronic and acute decompensated heart failure (ADHF), outperforming left ventricular ejection fraction and New York Heart Association functional class in this respect.[1,2] Despite some well known limitations, such as analytic assay variability, secretion by the proximal tubules, and dependency on muscle mass, diet, and physical activity, widespread availability allows serum creatinine (Cr) to serve as the major biomarker to estimate GFR.[3−6] Recently, serum cystatin C (CysC) and β-trace protein (βTP) have been proposed as alternatives with potentially fewer shortcomings. At the population level in ADHF, admission values of CysC or βTP portend stronger prognostic value compared with serum Cr.[7] Therefore,

From the [1]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; [3]Department of Laboratory Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium; [4]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium and [5]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio.

Manuscript received June 13, 2014; revised manuscript received July 28, 2014; revised manuscript accepted August 7, 2014.

Reprint requests: Wilfried Mullens, MD, PhD, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. Tel: +32 89 32 70 87; Fax: +32 89 32 79 18. E-mail: wilfried.mullens@zol.be

Funding: Frederik Verbrugge is supported by a PhD fellowship from the Research Foundation−Flanders (FWO, 11L8214N). Frederik Verbrugge, Petra Nijst, and Wilfried Mullens are researchers for the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the Limburg Sterk Merk foundation, Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital.

See page 823 for disclosure information.

1071-9164/$ - see front matter

© *2014 Elsevier Inc. All rights reserved.*

http://dx.doi.org/10.1016/j.cardfail.2014.08.002

these novel GFR biomarkers have been suggested to provide better detection of renal impairment associated with ADHF, even though underlying mechanisms of this phenomenon are insufficiently elucidated. Because the kidneys are pivotal organs to relieve congestion, changes in GFR have always been assumed to result in concordant alterations of the ability to achieve natriuresis and diuresis. Yet, there has been a growing recognition that thorough decongestion, even if achieved at the cost of a decrease in GFR, is associated with better survival.[8,9] This raises the possibility that during ADHF treatment, a favorable response to diuretics—to achieve adequate decongestion—may be more important than determination of GFR itself, even with improved estimations via novel renal biomarkers. In this respect, we prospectively investigated the comparative prognostic value of novel GFR biomarker changes (ie, CysC and βTP) versus the natriuretic response to diuretic therapy in contemporary ADHF patients with reduced ejection fraction.

Materials and Methods

Study Design

The first and last authors designed the study, which was carried out as a prospective cohort study in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium). The investigation conformed to the principles outlined in the Declaration of Helsinki. The Institutional Committee on Human Research approved the study protocol, and written informed consent was obtained from every patient. All authors had full access to the data and contributed to the writing of the manuscript. Together, they take responsibility for the integrity of the data and agreed to the report as written.

Study Population

Consecutive patients, admitted with a primary diagnosis of ADHF from January 2012 to September 2013, were screened. Patients were eligible for the study if they were ≥18 years of age and able to give informed consent. Additionally, all of the following criteria had to be fulfilled: (1) presence of ≥3 signs of volume overload (edema, ascites, jugular venous distension, pulmonary vascular congestion); (2) plasma N-terminal pro−B-type natriuretic peptide (NT-proBNP) levels >1,000 ng/L; and (3) left ventricular ejection fraction ≤45% as assessed by echocardiography; for which a treatment strategy with intravenous loop diuretics was planned. Exclusion criteria were: (1) treatment with intravenous loop diuretics during the index hospitalization before study inclusion; (2) mechanical ventilation; (3) inotropic or vasopressor support; (4) concurrent diagnosis of an acute coronary syndrome; and (5) renal replacement therapy.

Glomerular Filtration Measurements and Calculations

A baseline venous blood sample was obtained at the time of admission, before initiation of diuretic therapy, with repeated samples acquired in the morning of the next 3 days. Urine was collected during 3 consecutive 24-hour intervals; the first collection started together with the first administration of intravenous loop diuretics. Serum Cr levels were measured on all samples with the use of the O'Leary-modified Jaffé reaction on a Modular P unit (Roche Diagnostics, Indianapolis, Indiana, USA). Serum CysC levels were simultaneously assessed by a particle-enhanced immunoturbidimetric assay (Tina-quant a Cystatin C; Roche Diagnostics). In addition, βTP levels were determined by means of the N Latex βTP test kit (Siemens Healthcare Diagnostics Products, Marburg, Germany). The GFR was estimated according to 7 different contemporary formulas based on serum Cr, CysC, and/or βTP levels: the Cockroft-Gault formula; the Modification of Diet in Renal Disease (MDRD) formula; the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for serum Cr, CysC, and both biomarkers; and the βTP-based equations proposed by Pöge et al with and without inclusion of serum Cr (Supplemental Table 1).[10−14] Finally, Cr clearance was calculated as the product of urinary Cr concentration (mg/dL) and total diuretic volume (mL) over serum Cr concentration (mg/dL) per unit of collection time (min), and subsequently normalized for 1.73 m^2 of body surface area.

Decongestive Treatment and Natriuresis Measurement

During the 72-hour study period, loop diuretics were administered through a standard protocol as intravenous boluses of bumetanide. The initial dose administered at baseline was equal to twice the patient's daily dose of oral loop diuretics, with 1 mg of bumetanide considered to be equivalent to 40 mg of furosemide. In loop diuretic−naïve patients, a dose of 1 mg was used. The nursing staff was instructed to make sure adherence to a low-salt diet (2−3 g/d) was met. On morning rounds, patients were independently evaluated by 2 dedicated heart failure specialists involved in the study (M.D. and W.M.). Based on bedside information, they decided together whether the patient was still volume overloaded. Patients who had reached a euvolemic state were switched to oral therapy. Natriuresis (mmol) was measured for each 24-hour urinary collection as the product of urine output (L) and urinary sodium concentration (mmol/L). To assess the natriuretic response to diuretic therapy in an individual patient, we calculated the ratio of total natriuresis [mmol] during the 72-hour study period over the loop diuretic dose administered (mg bumetanide equivalents) during the same time frame.

Study End Points

We assessed the incidence of worsening renal function (WRF) according to contemporary definitions: a ≥0.3 mg/dL rise in serum Cr, a ≥0.3 mg/L rise in serum CysC, a ≥0.3 mg/L rise in serum βTP, or a ≥20% decrease in estimated GFR during the 72-hour study period. Subsequently, we compared the impact of changes in serum Cr, CysC, βTP, and derived GFR estimates with the natriuretic response to diuretic therapy to predict all-cause mortality or hospital readmissions for ADHF. Mortality and readmission data were prospectively collected by chart review, with patients lost to follow-up contacted by telephone to assess their vital status. ADHF readmissions were prespecified as hospital admissions because of signs and/or symptoms of congestion and/or low cardiac output, during which intravenous diuretics, inotropes and/or vasodilators were administered.

Statistical Analysis

Continuous variables were expressed as mean ± SD if normally distributed or otherwise as median (interquartile range) and compared with the use of the Student *t*-test or Mann-Whitney *U* test, as appropriate. Normality was assessed with the use of the Shapiro-Wilk statistic. Categoric data were expressed as

Download English Version:

https://daneshyari.com/en/article/5983774

Download Persian Version:

https://daneshyari.com/article/5983774

Daneshyari.com