JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2018 PUBLISHED BY ELSEVIER ON BEHALF OF THE
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 72, NO. 10, 2018

Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction

Jasper Tromp, MD,[a,b,c] B. Daan Westenbrink, MD, PhD,[a] Wouter Ouwerkerk, PhD,[d] Dirk J. van Veldhuisen, MD, PhD,[a] Nilesh J. Samani, MD,[e] Piotr Ponikowski, MD,[f] Marco Metra, MD,[g] Stefan D. Anker, MD, PhD,[h] John G. Cleland, MD,[i] Kenneth Dickstein, MD, PhD,[j] Gerasimos Filippatos, MD,[k] Pim van der Harst, MD, PhD,[a] Chim C. Lang, MD,[l] Leong L. Ng, MD,[e] Faiez Zannad, MD, PhD,[m] Aelko H. Zwinderman, PhD,[d] Hans L. Hillege, MD, PhD,[a] Peter van der Meer, MD, PhD,[a] Adriaan A. Voors, MD, PhD[a]

ABSTRACT

BACKGROUND Information on the pathophysiological differences between heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved ejection fraction (HFpEF) is needed

OBJECTIVES The purpose of this study was to establish biological pathways specifically related to HFrEF and HFpEF.

METHODS The authors performed a network analysis to identify unique biomarker correlations in HFrEF and HFpEF using 92 biomarkers from different pathophysiological domains in a cohort of 1,544 heart failure (HF) patients. Data were independently validated in 804 patients with HF. Networks were enriched with existing knowledge on protein–protein interactions and translated into biological pathways uniquely related to HFrEF, HF with a midrange ejection fraction, and HFpEF.

RESULTS In the index cohort (mean age 74 years; 34% female), 718 (47%) patients had HFrEF (left ventricular ejection fraction [LVEF] <40%) and 431 (27%) patients had HFpEF (LVEF ≥50%). A total of 8 (12%) correlations were unique for HFrEF and 6 (9%) were unique to HFpEF. Central proteins in HFrEF were N-terminal B-type natriuretic peptide, growth differentiation factor-15, interleukin-1 receptor type 1, and activating transcription factor 2, while central proteins in HFpEF were integrin subunit beta-2 and catenin beta-1. Biological pathways in HFrEF were related to DNA binding transcription factor activity, cellular protein metabolism, and regulation of nitric oxide biosynthesis. Unique pathways in patients with HFpEF were related to cytokine response, extracellular matrix organization, and inflammation. Biological pathways of patients with HF with a midrange ejection fraction were in between HFrEF and HFpEF.

CONCLUSIONS Network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas biomarker profiles specific for HFpEF are related to inflammation and extracellular matrix reorganization. (The BIOlogy Study to TAilored Treatment in Chronic Heart Failure [BIOSTAT-CHF]; EudraCT 2010-020808-29) (J Am Coll Cardiol 2018;72:1081–90) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Cardiology, University of Groningen, Groningen, the Netherlands; [b]National Heart Centre Singapore, Singapore; [c]Duke-NUS Medical School, Singapore, Singapore; [d]Department of Epidemiology, Biostatistics & Bioinformatics, Academic Medical Center, Amsterdam, the Netherlands; [e]Department of Cardiovascular Sciences, University of Leicester, and NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom; [f]Department of Heart Diseases, Wroclaw Medical University, and Cardiology Department, Military Hospital, Wroclaw, Poland; [g]Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [h]Division of Cardiology and Metabolism-Heart Failure, Cachexia & Sarcopenia, Department of Cardiology (CVK), and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), at Charité University Medicine, Berlin, Germany; [i]Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow Royal Infirmary, Glasgow, United Kingdom; [j]University of Bergen, Stavanger University Hospital, Stavanger, Norway; [k]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, Athens, Greece; [l]Division of Molecular & Clinical Medicine, University of Dundee, Dundee, United Kingdom; and [m]Inserm CIC 1433, Université de Lorrain, CHU de Nancy, Nancy, France. BIOSTAT-CHF was funded by the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29).

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.06.050

ABBREVIATIONS AND ACRONYMS

GDF = growth differentiation factor

HFmrEF = heart failure with a mid-range ejection fraction

HFpEF = heart failure with a preserved ejection fraction

HFrEF = heart failure with a reduced ejection fraction

IL1RL1 = interleukin-1 receptor-like type 1

ITGB2 = integrin subunit beta 2

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

Heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) were originally considered to be 2 extremes of the same disease. However, where angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists are associated with improved clinical outcome in patients with HFrEF (1–3), no such benefit was seen in patients with HFpEF (4–6). The underlying pathophysiology is currently considered to be different between HFrEF and HFpEF (7–11).

The current paradigm on the underlying pathophysiology of HFpEF suggests that a proinflammatory state is responsible for stiffening of the heart muscle and increased filling pressures (7). Indeed, Paulus et al. (7) suggested that the plethora of comorbidities that usually affect patients with HFpEF cause low-level inflammation, which affects the coronary vascular endothelium and reduces nitric oxide bioavailability. Their hypothesis suggests that this directly affects the cardiomyocytes and causes cellular hypertrophy as well as cardiac stiffening (7,12).

SEE PAGE 1091

Network analysis is a tool to gain novel insights in disease pathways and pathophysiology by studying protein-protein (biomarker-biomarker) correlations (9,10,13). By enriching experimentally found protein biomarker networks with knowledge-based protein-protein interactions, empirically found correlations can be placed in the context of known pathways (14,15). We therefore performed a network analysis enriched by knowledge-based interactions to uncover biological mechanisms that are unique for patients with HFrEF and HFpEF.

METHODS

PATIENT POPULATION. We studied patients from the BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure) project, which is described elsewhere (16–20). In brief, BIOSTAT-CHF includes 2 cohorts of patients with heart failure (HF) included in Scotland and Europe. The aim of the BIOSTAT-CHF study was to characterize biological pathways related to response/no-response to guideline-recommended pharmacological therapy for HF. Therefore, patients had to be suboptimally treated at inclusion. We used the Scottish cohort of the BIOSTAT-CHF study as our primary study cohort and the European cohort of the BIOSTAT-CHF study as our validation cohort because this was a less-selected population. The Scottish cohort consisted of 1,738 patients from 6 centers in Scotland, United Kingdom. Patients were required to be ≥18 years of age, diagnosed with HF, and previously admitted with HF requiring diuretic treatment. Biomarkers were measured in 1,707 of the total of 1,738 patients. From these patients, echocardiography was available in 1,544 patients. We validated our findings in the European cohort of the BIOSTAT-CHF study, which originally consisted of 2,516 patients with HF from 69 centers in 11 European countries. Inclusion criteria for the European cohort include: >18 years of age and having symptoms of new-onset or worsening HF confirmed either by a LVEF of ≤40% or B-type natriuretic peptide and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels >400 or >2,000 ng/l, respectively. Because of this difference in inclusion criteria for patients with LVEF >40%, we excluded all patients with HFrEF and an NT-proBNP

Support was also provided by the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON2014-11 RECONNECT. Dr. Westenbrink has received consulting and speaker fees from Boehringer Ingelheim and Bayer; and has received a travel grant from Novartis. Dr. van Veldhuisen has received board membership fees or travel expenses from Novartis, Johnson & Johnson, and Vifor. Dr. Metra has received consulting honoraria from Amgen, AstraZeneca, Bayer, Novartis, Relypsa, Servier, Stealth Therapeutics, and Trevena; and speaker fees from Abbott Vascular, Novartis, and Servier. Dr. Anker has received grants from Vifor and Abbott Vascular; and fees for consultancy or speaking from Vifor, V-Wave, Impulse Dynamics, Bayer, Boehringer Ingelheim, Brahms, Janssen, Novartis, Servier, Stealth Peptides, and ASTRA. Dr. Cleland has served on the advisory board for Amgen, Novartis, and Medtronic; and has received research grants from Amgen, Medtronic, Novartis, Philips, Stealth Biotherapeutics, and Bristol-Myers Squibb. Dr. Filippatos has received committee fees and/or research grants from Novartis, Bayer, Medtronic, Vifor, and Servier; has received a research grant from the European Union; and is a member of the steering committee of trials sponsored by Novartis and Servier. Dr. Lang has received consultancy fees and/or research grants from Amgen, AstraZeneca, Merck Sharp & Dohme, Novartis, and Servier. Dr. Voors has received consultancy fees and/or research grants from Alere, Amgen, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, GlaxoSmithKline, Merck/Merck Sharp & Dohme, Novartis, Servier, Stealth Peptides, Singulex, Sphingotec, Trevena, Vifor, and ZS Pharma. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 3, 2018; revised manuscript received June 15, 2018, accepted June 18, 2018.