JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 68, NO. 4, 2016

ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2016.05.047

Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

Christian F. Opitz, MD,[a,b] Marius M. Hoeper, MD,[c] J. Simon R. Gibbs, MD,[d] Harald Kaemmerer, MD, VMD,[e] Joanna Pepke-Zaba, MD,[f] J. Gerry Coghlan, MD,[g] Laura Scelsi, MD,[h] Michele D'Alto, MD,[i] Karen M. Olsson, MD,[c] Silvia Ulrich, MD,[j] Werner Scholtz, MD,[k] Uwe Schulz, MD,[l] Ekkehard Grünig, MD,[m] Carmine D. Vizza, MD,[n] Gerd Staehler, MD,[o] Leonhard Bruch, MD,[p] Doerte Huscher, MSc, PhD,[q,r] David Pittrow, MD,[s] Stephan Rosenkranz, MD[t,u]

ABSTRACT

BACKGROUND Pulmonary hypertension (PH) is hemodynamically classified as pre-capillary (as seen in idiopathic pulmonary arterial hypertension [IPAH]) or post-capillary (as seen in heart failure with preserved ejection fraction [HFpEF]). Overlaps between these conditions exist. Some patients present with risk factors for left heart disease but pre-capillary PH, whereas patients with HFpEF may have combined pre- and post-capillary PH.

OBJECTIVES This study sought to further characterize similarities and differences among patient populations with either PH-HFpEF or IPAH.

METHODS We used registry data to analyze clinical characteristics, hemodynamics, and treatment responses in patients with typical IPAH (<3 risk factors for left heart disease; n = 421), atypical IPAH (≥3 risk factors for left heart disease; n = 139), and PH-HFpEF (n = 226) receiving PH-targeted therapy.

RESULTS Compared with typical IPAH, patients with atypical IPAH and PH-HFpEF were older, had a higher body mass index, had more comorbidities, and had a lower 6-min walking distance, whereas mean pulmonary artery pressure (46.9 ± 13.3 mm Hg vs. 43.9 ± 10.7 mm Hg vs. 45.7 ± 9.4 mm Hg, respectively) and cardiac index (2.3 ± 0.8 l/min/m^2 vs. 2.2 ± 0.8 l/min/m^2 vs. 2.2 ± 0.7 l/min/m^2, respectively) were comparable among groups. After initiation of targeted PH therapies, all groups showed improvement in exercise capacity, functional class, and natriuretic peptides from baseline to 12 months, but treatment effects were less pronounced in patients with PH-HFpEF than typical IPAH; with atypical IPAH in between. Survival rates at 1, 3, and 5 years were almost identical for the 3 groups.

CONCLUSIONS Patients with atypical IPAH share features of both typical IPAH and PH-HFpEF, suggesting that there may be a continuum between these conditions. (J Am Coll Cardiol 2016;68:368–78) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, DRK Kliniken Berlin, Berlin, Germany; [b]Department of Cardiology, Medical University of Greifswald, Greifswald, Germany; [c]Department of Respiratory Medicine and German Center of Lung Research (DZL), Hannover Medical School, Hannover, Germany; [d]Department of Cardiology, National Heart & Lung Institute, Imperial College London, London, United Kingdom; [e]Department of Pediatric Cardiology and Congenital Heart Disease, German Heart Center, München, Technical University Munich, Munich, Germany; [f]Pulmonary Vascular Diseases Unit, Papworth Hospital, Cambridge, United Kingdom; [g]Cardiology Department, Royal Free Hospital, London, United Kingdom; [h]Division of Cardiology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [i]Department of Cardiology, Second University of Naples-Monaldi Hospital, Naples, Italy; [j]Clinic of Pulmonology, University Hospital Zurich, Zurich, Switzerland; [k]Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany; [l]Clinic for Thoracic and Cardiovascular Surgery, Heart and Diabetes Center NRW, Ruhr University Bochum, Bad Oeynhausen, Germany; [m]Centre for Pulmonary Hypertension, University Hospital, Heidelberg, Germany; [n]Pulmonary Hypertension Unit Department of Cardiovascular and Respiratory Disease, University of Rome 'La Sapienza,' Rome, Italy; [o]Medical Clinic I, Pneumology, Loewenstein Clinic, Loewenstein, Germany; [p]Department of Internal Medicine, Unfallkrankenhaus Berlin, Berlin, Germany; [q]Epidemiology Unit, German Rheumatism Research Centre, Berlin; [r]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany; [s]Institute for Clinical Pharmacology, Medical Faculty, Technical University Carl Gustav Carus, Dresden, Germany; [t]Clinic III for Internal Medicine (Cardiology), and Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany; and the [u]Cologne Cardiovascular Research Center (CCRC), University of Cologne, Cologne, Germany. COMPERA is currently supported by

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

Heart failure with preserved ejection fraction (HFpEF) is frequently accompanied by pulmonary hypertension (PH), which is associated with a poor outcome. Recent studies have suggested that PH is found in 36% to 83% of patients with HFpEF (1–3) and that both elevated pulmonary artery pressure and right ventricular (RV) dysfunction are independent predictors of death in patients with HFpEF (1,4–6).

Hemodynamically, pre-capillary PH—characterized by a mean pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg—is distinguished from post-capillary PH, as indicated by a PAWP >15 mm Hg (7–11). The classic example of a disease characterized by pre-capillary PH is idiopathic pulmonary arterial hypertension (IPAH), which is caused by an obliterative pulmonary vasculopathy affecting predominantly small pulmonary arterioles. In contrast, left heart disease, such as HFpEF, causes post-capillary PH due to backward transmission of elevated left-sided filling pressures into the pulmonary circulation. The latter group may present with isolated post-capillary PH or combined post-capillary PH with a pre-capillary component, as indicated by an elevated diastolic pressure gradient and/or an increased pulmonary vascular resistance (PVR) (8,11,12).

Despite these seemingly clear definitions, a growing number of patients with PH are identified in whom criteria from multiple PH categories exist simultaneously. For example, several registries have documented a change of phenotype in patients diagnosed with IPAH, associated with increasing age (13,14). A significant number of these patients have a comorbidity profile typically found in patients with HFpEF, such as arterial hypertension, obesity, diabetes, and atrial fibrillation (15). Recently, the terms typical and atypical PAH have been proposed to distinguish between these populations (16). The AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial excluded patients with 3 or more of these risk factors from the primary analysis set (17).

SEE PAGE 379

Although targeted therapies, including phosphodiesterase type 5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), and prostacyclin analogues (PCA), are available for IPAH, evidence-based recommendations for the management of PH-HFpEF are lacking and current guidelines do not support the use of targeted PAH therapies in patients with PH-HFpEF (8,10,12). Additionally, patients with atypical IPAH have been underrepresented or excluded in clinical trials.

To further determine similarities and differences in demographics, comorbidities, hemodynamics,

ABBREVIATIONS AND ACRONYMS

ERA = endothelin receptor antagonist

HFpEF = heart failure with preserved ejection fraction

IPAH = idiopathic pulmonary arterial hypertension

PAPm = mean pulmonary artery pressure

PAWP = pulmonary arterial wedge pressure

PCA = prostacyclin analogue

PDE5i = phosphodiesterase type 5 inhibitor

PVR = pulmonary vascular resistance

TPG = mean transpulmonary pressure gradient

unrestricted educational grants from Actelion, Bayer, and GlaxoSmithKline (in the past it was also supported by Lilly, Novartis, Encysive, AOP Orphan, and Pfizer). Dr. Opitz's institution has received speaker fees and honoraria for consultations from Actelion, Bayer, GlaxoSmithKline, Novartis, and Pfizer. Dr. Hoeper has received speaker fees and honoraria for consultations from Actelion, Bayer, Gilead, GlaxoSmithKline, Lilly, Novartis and Pfizer. Dr. Gibbs has received speaker fees and honoraria for consultations from Actelion, Bayer, Gilead, GlaxoSmithKline, Lilly, Novartis, and Pfizer; has received speaker fees from AOP Orphan; and has served on the Speakers Bureau for Actelion, Bayer, and GlaxoSmithKline. Dr. Kaemmerer has received speaker fees and honoraria from Actelion and Pfizer. Dr. Pepke-Zaba has received speaker fees and honoraria for consultations from Actelion, Bayer, GlaxoSmithKline; and her institution has received educational and research grants from Actelion, Bayer, and GlaxoSmithKline. Dr. Coghlan has received honoraria and consultancy fees from Actelion, GlaxoSmithKline, Bayer, United Therapeutics, and Endotronix; and has received grants from Actelion and GlaxoSmithKline. Dr. Olsson has received speaker fees from Actelion, Bayer, GlaxoSmithKline, Pfizer, and United Therapeutics. Dr. Ulrich has received honoraria for lectures and/or consultancy from Actelion and Bayer; has received grant money from the Swiss National Science Foundation and Zurich Lung League; and her institution has received research grants from Actelion, Bayer, and United Therapeutics. Dr. Schulz has received an unrestricted educational grant and speaker honoraria from Actelion; and has received a research grant from Bayer. Dr. Grünig has received honorariums for consultations and/or speaking at conferences from Actelion, Bayer, Gilead, GlaxoSmithKline, Lilly, Milteney, Novartis, Pfizer, United Therapeutics, AOP Orphan, and Rotex Medica; has served as an advisory board member of GlaxoSmithKline, Actelion, Bayer, United Therapeutics, and AOP Orphan; and has received funding for clinical trials by Actelion, Bayer, GlaxoSmithKline, Encysive, Lilly, and Pfizer. Dr. Vizza has received fees for serving as a speaker, consultant, and advisory board member from Actelion, Bayer, Dompè, GlaxoSmithKline, Italfarmaco, Lilly, Pfizer, UTEL, and United Therapeutics; and his institution has received research grants from Actelion, Bayer, GlaxoSmithKline, Lilly, Pfizer, and United Therapeutics. Dr. Staehler has received honoraria for lectures and/or consultancy for Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis, and Pfizer. Dr. Bruch has received speaker honoraria from Actelion and Bayer. Dr. Huscher has received consultancy fees from Actelion. Dr. Pittrow has received speaker fees or honoraria for consultations from Actelion, Bayer, Genzyme, Boehringer Ingelheim, Novartis, and Pfizer. Dr. Rosenkranz has received honoraria for lectures and/or consultancy from Actelion, Bayer, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics; and his institution has received research grants from Actelion, Bayer, Novartis, Pfizer, and United Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 24, 2015; revised manuscript received April 28, 2016, accepted May 3, 2016.