ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Impact of insulin resistance on ventricular function in pulmonary arterial hypertension

Nathan W. Brunner, MD,[a,b] Mehdi Skhiri, MD,[a] Olga Fortenko, MD,[a,b] Andrew Hsi,[a] Francois Haddad, MD,[a,c] Nayer Khazeni, MD, MS,[b,d] and Roham T. Zamanian, MD[a,b]

From the [a]Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford, California; the [b]Division of Pulmonary & Critical Care Medicine, Stanford University School of Medicine, Stanford, California; the [c]Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California; and the [d]Center for Health Policy/Center for Primary Care and Outcomes Research, Stanford, California.

KEYWORDS:
insulin resistance;
pulmonary arterial hypertension;
right ventricle;
myocardial function;
diastolic dysfunction

BACKGROUND: Insulin resistance (IR) is an independent prognostic marker in pulmonary arterial hypertension (PAH), although the mechanism by which it engenders risk is unknown. We prospectively investigated the clinical, laboratory, hemodynamic, and echocardiographic characteristics of insulin-sensitive (IS) and IR patients with PAH.

METHODS: This was a prospective cohort study including well-phenotyped patients with PAH proven at cardiac catheterization. Patients were classified as IS or IR on the basis of the well-validated triglyceride/high-density lipoprotein-cholesterol ratio. Clinical, laboratory, and hemodynamic characteristics were compared between cohorts. Distance walked on the 6-minute walk test (6MWT) and echocardiograms were compared between IS and IR for the sub-set of patients that had these tests within 1 month of cardiac catheterization.

RESULTS: Of the 111 PAH patients enrolled, 59 were IS, 25 were IR, and 27 were classified as indeterminate. Mean age was 45.8 ± 15.0 years. IR was associated with worse New York Heart Association class ($p = 0.02$). There were no differences in hemodynamics, biomarkers, 6MWT distance, or parameters of right ventricular function (i.e., tricuspid annular plane systolic excursion, myocardial performance index, and fractional area change) between groups. Despite similar systemic vascular resistance, parameters of left ventricular diastolic function were more favorable for IS vs IR, including mitral inflow E wave velocity (82 ± 17 vs 64 ± 19 msec, $p = 0.02$), E/A ratio (1.2 ± 0.4 vs 0.8 ± 0.2, $p = 0.01$), and lateral mitral valve E' velocity (13.9 ± 3.5 vs 10.4 ± 2.2 msec, $p = 0.01$).

CONCLUSIONS: IR is associated with worse functional class and diastology compared with IS in PAH, although other prognostic parameters are similar.

J Heart Lung Transplant ■■■■;■:■■■–■■■

Pulmonary arterial hypertension (PAH) is a complex disease leading to progressive loss of pulmonary arterioles, increased resistance to flow in the pulmonary circulation, right ventricular failure, and death.[1] Although numerous triggers for PAH have been identified, the pathophysiology is complex and poorly understood.

Insulin resistance (IR) is an inflammatory condition associated with obesity, dyslipidemia, and increased cardiovascular risk.[2–4] Recently, PAH has been associated with a higher prevalence of IR and glucose intolerance compared with the general population.[5,6] In our previous retrospective analysis, we showed that IR, as defined by the triglyceride (TG)–to–high-density lipoprotein cholesterol (HDL-C) ratio, is a marker of short-term event-free survival to a much

Reprint requests: Roham T. Zamanian, MD, Division of Pulmonary & Critical Care Medicine, 300 Pasteur Dr, Rm H3143, Stanford, CA 94305. Telephone: 650-725-5495. Fax: 650- 725-5489.
E-mail address: zamanian@stanford.edu

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2014.02.016

greater extent than is seen in general populations.[5] The mechanism(s) by which IR worsens prognosis in PAH remains unknown. Other studies have attempted to explore this association but have been small and have relied on non-standard markers of IR.[6,7]

Determining how IR leads to worse outcomes in PAH is imperative for our understanding of this complex disease process. That right ventricular (RV) function is a major determinant of outcomes in PAH has been well established. IR has been linked with heart failure and left ventricular (LV) cardiomyopathy, conditions that share similar pathophysiologic profiles to PAH with RV failure.[8–10] Thus, we hypothesized that IR may be associated with RV myocardial dysfunction. We performed a prospective cohort study comparing clinical, biomarker, hemodynamic, and echocardiographic parameters associated with RV function in PAH patients with and without IR.

Methods

This study was approved by the Stanford University Institutional Review Board.

Study design

Patients of the Stanford Hospital Pulmonary Hypertension clinic undergoing right heart catheterization (RHC) for assessment of PAH at Stanford Hospital from 2007 to 2011 were prospectively screened. Patients were adults aged older than 18 years who had a diagnosis of World Health Organization (WHO) Group I PAH, with mean PA pressure greater than 25 mm Hg and a PA wedge pressure of less than 15 mm Hg. The study excluded patients with WHO Groups II-V pulmonary hypertension, LV systolic dysfunction, valvular heart disease, overt diabetes, or those using anti-hyperglycemic agents.

A complete fasting metabolic profile was drawn for study patients at the time of their cardiac catheterization. This included total cholesterol, low-density lipoprotein (LDL-C), HDL-C, and TG levels, as well as fasting glucose, fasting insulin, and glycosylated hemoglobin (HbA_{1c}). Patients whose fasting glucose and HbA_{1c} levels were consistent with diabetes mellitus[11] were excluded from the subsequent analysis. A TG/HDL-C ratio $<$ 2 was used to identify patients as insulin-sensitive (IS) and a TG/HDL-C ratio $>$ 3 as IR.[5,12] The prospective portion of the study assessed the association between IR status and hemodynamics. As an additional analysis, we reviewed the echocardiograms and 6-minute walk test (6MWT) results obtained on clinical grounds near the date of catheterization to assess differences between the IS and IR populations.

Data collection

Demographic and clinical information was obtained from the Stanford University Vera Moulton Wall Center Pulmonary Hypertension Database. A trained research associate (A.H.) and 3 physicians (M.S., N.W.B., and R.T.Z.) extracted demographic information on all patients participating in the study. The collected variables included age, body mass index, WHO sub-group of PAH, New York Heart Association (NYHA) functional class, and current vasodilator therapy. NYHA functional class was assessed at regularly scheduled clinic visits by pulmonary hypertension specialists who were blinded to IR status. In addition to the metabolic profile described above, levels of serum sodium, serum creatinine, N-terminal prohormone B-type natriuretic peptide (NT-proBNP), fasting glucose, and fasting insulin were obtained at time of cardiac catheterization. Data were collected, stored, and processed in a manner consistent with the Institutional Review Board guidelines.

Cardiac catheterization

RHC was performed by a single operator (R.T.Z.). Swan-Ganz catheters were used for all pressure measurements. Catheterization was performed through the right internal jugular vein or the right femoral vein, at the operator's discretion. All transducers were zeroed at the midaxillary line. Measured pressures included mean right atrial pressure, mean PA pressure (mPAP), RV end-diastolic pressure, and PA wedge pressure. All pressures were measured at end expiration. Hemodynamics were determined using traditional methods and calculations.[13] A vasodilator challenge was carried out when appropriate. Stroke volume was calculated as cardiac output (CO) divided by heart rate at time of catheterization. PA capacitance (PAC) was calculated as the ratio of the stroke volume to the PA pulse pressure. Measures of RV hydraulic power were derived according to the methods of Saouti et al.[14]

Echocardiography

Digitized echocardiograms were analyzed by a single reader (M.S.) who was blinded to IR status. Only echocardiograms performed within 1 month of the RHC were considered. Right and left atrial maximal volumes were measured immediately before mitral and tricuspid valve opening and were indexed for body surface area. Two-dimensional RV fractional area change was measured in the apical 4-chamber view in the manner described by American Society of Echocardiography guidelines.[15] Tricuspid annular plane systolic excursion was measured from an M-mode signal through the lateral tricuspid valve annulus in the apical 4-chamber view.[15] We measured mitral inflow E and A as well as mitral tissue Doppler E' velocities in the apical 4-chamber view.[16] RV myocardial performance index was measured in the manner described by Tei et al.[17]

6MWT assessment

6MWT results, completed within 1 month of cardiac catheterization, were available for a sub-set of our study population. All 6MWTs were performed at Stanford Hospital by the same 2 technicians, who were blinded to IR status. Studies were performed according to the American Thoracic Society recommendations.[18] Heart rate, blood pressure, and oxygen saturation were measured at baseline, at peak exercise, and at 2 minutes into recovery.

Statistical analysis

Key clinical, hemodynamic and echocardiographic parameters for IR and IS patients were compared using the *t*-test or the Mann-Whitney *U*-test for continuous variables and the chi-square test or the Kendall's tau test for categoric variables, as appropriate. Results are expressed as mean $\pm$ standard deviation for continuous variables or as number of patients and percentages for categoric variables. All *p*-values presented are 2-sided, and a value of $p < 0.05$