ELSEVIER

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

Elevated pulmonary arterial and systemic plasma aldosterone levels associate with impaired cardiac reserve capacity during exercise in left ventricular systolic heart failure patients: A pilot study

Bradley A. Maron, MD,[a,b] Thomas E. Stephens, BA,[a] Laurie A. Farrell, RN,[c] William M. Oldham, MD, PhD,[d] Joseph Loscalzo, MD, PhD,[a] Jane A. Leopold, MD,[a] and Gregory D. Lewis, MD[c]

From the [a]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [b]Department of Cardiology, Veterans Affairs Boston Healthcare System, West Roxbury, Massachusetts; [c]Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the [d]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

KEYWORDS:
aldosterone;
exercise;
heart failure;
cardiac reserve;
reduced ejection fraction

BACKGROUND: Elevated levels of aldosterone are a modifiable contributor to clinical worsening in heart failure with reduced ejection fraction (HFrEF). Endothelin-1 (ET-1), which is increased in HFrEF, induces pulmonary endothelial aldosterone synthesis in vitro. However, whether transpulmonary aldosterone release occurs in humans or aldosterone relates to functional capacity in HFrEF is not known. Therefore, we aimed to characterize ET-1 and transpulmonary aldosterone levels in HFrEF and determine if aldosterone levels relate to peak volume of oxygen uptake (pVO_2).

METHODS: Data from 42 consecutive HFrEF patients and 18 controls referred for invasive cardiopulmonary exercise testing were analyzed retrospectively.

RESULTS: Radial ET-1 levels (median [interquartile range]) were higher in HFrEF patients compared with controls (17.5 [11.5–31.4] vs 11.5 [4.4–19.0] pg/ml, $p = 0.04$). A significant ET-1 transpulmonary gradient (pulmonary arterial [PA] – radial arterial levels) was present in HFrEF ($p < 0.001$) but not in controls ($p = 0.24$). Compared with controls, aldosterone levels (median [interquartile range]) were increased in HFrEF patients in the PA (364 [250–489] vs 581 [400–914] ng/dl, $p < 0.01$) and radial compartments (366 [273–466] vs 702 [443–1223] ng/dl, $p < 0.001$). Akin to ET-1, a transpulmonary increase (median [interquartile range]) in aldosterone concentration was also observed between controls and HFrEF patients at rest (7.5 [–54 to 40] vs 61.6 [–13.6 to 165] ng/dl, $p = 0.01$) and peak exercise (–20.7 [–39.6 to 79.1] vs 25.8 [–29.2 to 109.3] ng/dl, $p = 0.02$). The adjusted pVO_2 correlated inversely with aldosterone levels at peak activity in the PA ($r = –0.31$, $p = 0.01$) and radial artery ($r = –0.32$, $p = 0.01$).

CONCLUSIONS: These data provide preliminary evidence in support of increased transpulmonary aldosterone levels in HFrEF and suggest an inverse relationship between circulating aldosterone and

Reprint requests: Gregory D. Lewis, MD, Heart Failure and Cardiac Transplantation Unit, Massachusetts General Hospital, Bigelow, 800 Fruit Street, Boston, MA 02114. Telephone: 617-726-9554. Fax: 617-525-4830.
E-mail address: glewis@partners.orrg

1053-2498/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.healun.2015.10.019

pVO_2. Future prospective studies are needed to characterize the functional effects of transpulmonary and circulating aldosterone on cardiac reserve capacity in HFrEF.
J Heart Lung Transplant 2016;35:342–351
Published by Elsevier Inc.

Elevated circulating levels of the mineralocorticoid hormone aldosterone are observed in left ventricular (LV) systolic dysfunction and contribute to the heart failure with reduced ejection fraction (HFrEF) syndrome, partly by promoting myocardial fibrosis and a hypertrophic vasculopathy in systemic blood vessels that impairs vascular compliance.[1–3] Pharmacologic inhibition of the mineralocorticoid receptor, in turn, abrogates the adverse effects of aldosterone on pulmonary and systemic vascular function and improves cardiac output in experimental models of HF, suggesting that hyperaldosteronism may promote impaired exercise tolerance.[4–6] However, the ramifications of maladaptive changes to cardiovascular function mediated by increased aldosterone on the clinical profile of HFrEF patients, including exercise reserve capacity (peak volume of oxygen consumption [pVO_2]), are not well established.

Endocrine or paracrine functionality of the lung-pulmonary vascular axis is recognized increasingly as a potential contributor to the pathophysiology of HF. For example, pulmonary arterial levels of the vasoactive peptide endothelin-1 (ET-1) correlate positively with pulmonary artery pressure (PAP) in patients with HFrEF and are thought to increase pulmonary vascular resistance,[7] whereas transpulmonary differences in the vasodilator molecule cyclic guanosine monophosphate (cGMP) identify a high-risk HFrEF pathophenotype.[8] Despite these findings highlighting the prognostic and functional significance of pulmonary vasoactive small molecules in HF, our understanding of transpulmonary biochemical profiles and their functional significance in HF remains limited.

We recently demonstrated that ET-1 induces pulmonary endothelial synthesis of functionally relevant aldosterone in vitro at levels akin to those observed in HF,[4] raising the possibility that extra-adrenal aldosterone synthesis may occur in human HFrEF. Thus, in the current study, we investigated the hypothesis that transpulmonary aldosterone release occurs in the setting of increased pulmonary arterial ET-1 and is related to impaired cardiac reserve capacity in HFrEF.

Methods

This study was approved by the Partners Human Research Committee (Number 20100P1704) and complied with the Declaration of Helsinki.

Patient population

Written informed consent for study participation was obtained from all subjects who participated in this study. We analyzed data from 42 consecutive HF patients and 18 controls evaluated at the Massachusetts General Hospital for HFrEF or unexplained dyspnea, respectively, during a 6-year period. All HFrEF patients had an LV ejection fraction (LVEF) of $\leq$ 40% and chronic New York Heart Association Functional Class II to IV symptoms. Control patients were characterized by exertional dyspnea despite normal LVEF or an evident pulmonary mechanical, cardiovascular, or metabolic limit to exercise. None of the patients investigated had cardiac angina or electrocardiogram-based evidence of active myocardial ischemia during exercise.

Cardiopulmonary exercise testing

All patients underwent invasive cardiopulmonary exercise testing (iCPET) according to methods reported previously.[9] Briefly, patients were instructed to fast for at least 6 hours before testing, which generally occurred between 9 A.M. and 12 P.M. Pulmonary and systemic arterial catheters were inserted via the internal jugular vein and radial artery, respectively. A uniform approach to standardizing the "zero pressure line" was adopted whereby the axilla was used to estimate the level of the midright atrium on all study participants. Resting first-pass radionuclide ventriculography was used to confirm appropriate catheter positioning at the midright atrium. In addition, right ventricle EF (RVEF) and LVEF was assessed by first-pass radionuclide ventriculography immediately before cycle ergometry testing and during the final minute of incremental exercise.[10]

Study participants underwent maximum incremental upright cycle ergometry iCPET (5–15 W/min continuous ramp after an initial 3-minute period of unloaded exercise; MedGraphics, St. Paul, MN) with simultaneous hemodynamic monitoring (Witt Biomedical Inc, Melbourne, FL), as previously described.[10,11] End-expiratory hemodynamic measurements were obtained with the patient upright and seated on the cycle at rest and at 1-minute intervals during exercise for right atrial pressure (RAP), PAP, PA wedge pressure (PAWP), and mean systemic arterial pressure (MAP). Direct Fick cardiac outputs (COs) were determined using standard methods,[10] and pVO_2 was defined as the average maximum O_2 measured over 30 seconds during the final minute of symptom-limited exercise, as previously reported.[10,11] All patients exceeded their anaerobic threshold as determined by the V-slope method.

Sample processing

All patients underwent elective cardiac catheterization immediately before testing and thus had confirmed no oral intake dietary status (with the exception of adherence to baseline oral medication use) for $\geq$ 6 hours before sample collection. Whole-blood samples from the PA and radial compartments were collected with the patient upright at rest and during peak exercise (i.e., final minute of symptom-limited exercise) via the PA catheter or radial artery catheter, respectively. After acquisition, samples were centrifuged immediately at 1200 rpm for 10 minutes at 4°C. The plasma was collected and immediately stored at –80°C, as reported previously.[12]

Aldosterone levels were analyzed by immunoassay (Cayman; detection limit, 21 pg/ml; mean intraassay variation, 10.7%;