

# Right Ventricular Failure Following Chronic Pressure Overload Is Associated With Reduction in Left Ventricular Mass

## Evidence for Atrophic Remodeling

Maxim Hardziyenka, MD, PhD,\*§ Maria E. Campian, MD,\* Herre J. Reesink, MD, PhD,† Sulaiman Surie, MD,† Berto J. Bouma, MD, PhD,‡ Maarten Groenink, MD, PhD,‡ Christine A. Klemens, BSc,\*§ Leander Beekman, BSc,\* Carol A. Remme, MD, PhD,\* Paul Bresser, MD, PhD,† Hanno L. Tan, MD, PhD\*‡

*Amsterdam and Utrecht, the Netherlands*

- Objectives** We sought to study whether patients with right ventricular failure (RVF) secondary to chronic thromboembolic pulmonary hypertension (CTEPH) have reduced left ventricular (LV) mass, and whether LV mass reduction is caused by atrophy.
- Background** The LV in patients with CTEPH is underfilled (unloaded). LV unloading may cause atrophic remodeling that is associated with diastolic and systolic dysfunction.
- Methods** We studied LV mass using cardiac magnetic resonance imaging (MRI) in 36 consecutive CTEPH patients (before/after pulmonary endarterectomy [PEA]) and 11 healthy volunteers selected to match age and sex of patients. We studied whether LV atrophy is present in monocrotaline (MCT)-injected rats with RVF or controls by measuring myocyte dimensions and performing in situ hybridization.
- Results** At baseline, CTEPH patients with RVF had significantly lower LV free wall mass indexes than patients without RVF ( $35 \pm 6$  g/m<sup>2</sup> vs.  $44 \pm 7$  g/m<sup>2</sup>,  $p = 0.007$ ) or volunteers ( $42 \pm 6$  g/m<sup>2</sup>,  $p = 0.006$ ). After PEA, LV free wall mass index increased (from  $38 \pm 6$  g/m<sup>2</sup> to  $44 \pm 9$  g/m<sup>2</sup>,  $p = 0.001$ ), as right ventricular (RV) ejection fraction improved (from  $31 \pm 8\%$  to  $56 \pm 12\%$ ,  $p < 0.001$ ). Compared with controls, rats with RVF had reduced LV free wall mass and smaller LV free wall myocytes. Expression of atrial natriuretic peptide was higher, whereas that of  $\alpha$ -myosin heavy chain and sarcoplasmic reticulum calcium ATPase-2 were lower in RVF than in controls, both in RV and LV.
- Conclusions** RVF in patients with CTEPH is associated with reversible reduction in LV free wall mass. In a rat model of RVF, myocyte shrinkage due to atrophic remodeling contributed to reduction in LV free wall mass. (J Am Coll Cardiol 2011;57:921–8) © 2011 by the American College of Cardiology Foundation

Right ventricular failure (RVF) secondary to chronic pressure overload determines survival in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and other forms of pulmonary arterial hypertension (PAH) (1). The mechanisms underlying the development of heart

failure in these patients are not fully understood. Both right ventricular (RV) and left ventricular (LV) dysfunction occur in patients with CTEPH (2–4) and other forms of chronic PAH (5–8). This may be based on the fact that RV and LV function are closely interdependent (9). In particular, because diastolic LV peak filling rate relates directly to RV ejection fraction (7), LV diastolic filling is diminished in patients with CTEPH (3,10) and other forms of chronic PAH (6–8). This may cause LV unloading and atrophy. As

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From the \*Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; †Department of Pulmonology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ‡Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam the Netherlands; and the §Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands. Dr. Tan was supported by the Netherlands Organization for Scientific Research (NWO, grant ZonMW Vici 918.86.616). All authors have reported that they have no relationships to disclose.

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the diastolic and systolic function of fully (11) or partially (12,13) unloaded LV is impaired due to atrophic remodel-

**Abbreviations and Acronyms**

- CTEPH** = chronic thromboembolic pulmonary hypertension
- IVS** = interventricular septum
- LV** = left ventricle/ventricular
- MCT** = monocrotaline
- MRI** = magnetic resonance imaging
- PAH** = pulmonary arterial hypertension
- PEA** = pulmonary endarterectomy
- RV** = right ventricle/ventricular
- RVF** = right ventricular failure

ing (14–16), we hypothesized that LV atrophy occurs in pressure overload-associated RVF, and that it contributes to heart failure pathophysiology. The aim of the present study was to provide evidence for reduction in LV mass in CTEPH patients with RVF with the use of cardiac magnetic resonance imaging (MRI). Moreover, we sought to establish whether reduction in LV mass is caused by atrophic remodeling by studying rats in which RVF secondary to pulmonary hypertension was induced by monocrotaline (MCT) injection (17). This model is suitable to study LV remodeling, because we recently found that underfilled LV of these rats exhibits electrophysiologic changes (18) that resemble those reported in atrophic LV (19).

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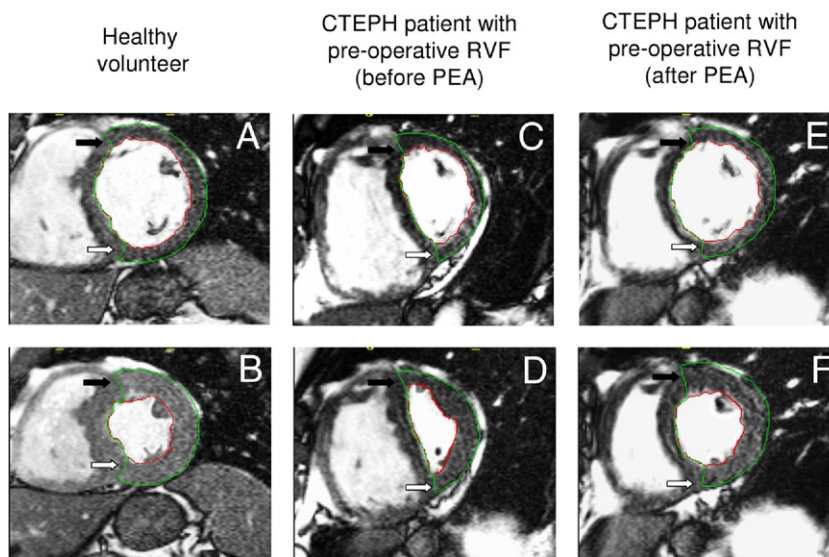
**Methods**

*Clinical Study*

**Patients.** We retrospectively studied 36 consecutive CTEPH patients who were referred for pulmonary endarterectomy (PEA), and who underwent cardiac MRI at

preoperative assessment. CTEPH was diagnosed as reported previously (20). PEA was performed using standardized surgical techniques (21). Preoperatively, all patients underwent pulmonary angiography and RV catheterization. Coronary angiography was routinely performed in all patients older than 50 years of age, and in patients older than 40 years of age if they had a history of smoking. Plasma brain natriuretic peptide levels were measured in all patients, and 6-min walking distance (22) was determined in 26 patients. All patients who survived PEA were reassessed by cardiac MRI at 3 to 18 months post-PEA (median, 8 months). Eleven healthy volunteers served as controls for the RV and LV volumes and mass. Particular care was taken to match control subjects for age and sex (mean age  $52 \pm 10$  years, 5 males). All subjects included gave written informed consent. Investigations were approved by the local institutional review board.

**Determination of cardiac volumes and mass by MRI.** RVF was defined as MRI-derived RV ejection fraction <45% (23). Masses of LV free wall and interventricular septum (IVS) were assessed from the stack of parallel short-axis images by manual detection of endocardial and epicardial borders on each slice; the papillary muscles were excluded from analysis of masses of LV and free wall (24) (Fig. 1). The LV free wall extends from the RV-LV junction in the anterior wall to the RV-LV junction in the inferior wall, as shown in Figure 1. Cardiac volume and mass were normalized to body surface area. Additionally, the following parameters were calculated: RV and LV end-diastolic volume indexes



**Figure 1** Short-Axis MRI Images at the Level of Papillary Muscles

Images from a healthy volunteer at end-diastole (A) and end-systole (B); image from a chronic thromboembolic pulmonary hypertension (CTEPH) patient with right ventricular failure (RVF) at end-diastole (C) and end-systole (D) before pulmonary endarterectomy (PEA); images of a CTEPH patient with pre-operative RVF at end-diastole (E) and end-systole (F) after PEA. Left ventricular (LV) free wall is measured as the area encountered between manually bordered endocardial (red) and epicardial (green) curves and right ventricular (RV)-LV junction in the anterior wall (indicated with black arrows) to the RV-LV junction in the inferior wall (indicated with white arrows).

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