H₂ Receptor Antagonists and Right Ventricular Morphology: The MESA Right Ventricle Study

Peter J. Leary¹, R. Graham Barr², David A. Bluemke³, Michael R. Bristow⁴, Richard A. Kronmal⁵, Joao A. Lima⁶, David D. Ralph¹, Corey E. Ventetuolo⁷, and Steven M. Kawut⁸

¹Department of Medicine, University of Washington, Seattle, Washington; ²Departments of Medicine and Epidemiology, Columbia University, New York, New York; ³Radiology and Imaging Sciences, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, Maryland; ⁴Department of Medicine, University of Colorado, Aurora, Colorado; ⁵Department of Biostatistics, University of Washington, Seattle, Washington; ⁶Departments of Medicine and Radiology, Johns Hopkins Hospital, Baltimore, Maryland; ⁷Departments of Medicine and Health Services, Policy, and Practice, Alpert Medical School of Brown University, Providence, Rhode Island; and ⁸Departments of Medicine and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Rationale: H₂ receptor antagonist (H2RA) use is common and may act directly on the heart through myocardial H₂ receptors or indirectly through changes in pulmonary vascular resistance.

Objectives: To determine the relationship between histamine H2RA use and right ventricular (RV) morphology.

Methods: We studied 4,122 participants in the Multi-Ethnic Study of Atherosclerosis without clinical cardiovascular disease who had magnetic resonance imaging assessment of RV morphology and ascertainment of medication use. Multivariable linear regression estimated cross-sectional associations between H2RA use and RV morphology after adjusting for demographics, anthropometrics, smoking status, diabetes mellitus, and hypertension. Further adjustments for co-medication use, left ventricular parameters, lung structure and function, renal function, or inflammatory markers were considered in separate models. Analyses in a subcohort restricted to H2RA or proton pump

inhibitor users accounted for confounding by the indication of gastroesophageal reflux disease.

Measurements and Main Results: H2RA use was associated with lower RV mass (−0.7 g; 95% confidence interval, −1.2 to −0.2 g; $P = 0.004$) and smaller RV end-diastolic volume (−4.2 ml; 95% confidence interval, −7.2 to −1.2 ml; $P = 0.006$). This relationship was unchanged with adjustment for co-medication use, lung structure and function, renal function, and inflammation. The relationship with RV mass was independent of left ventricular mass. Results were similar in the smaller cohort restricted to proton pump inhibitor and H2RA users.

Conclusions: H2RA use was associated with lower RV mass and smaller RV end-diastolic volume. Additional study of histamine and H₂ receptors in cardiopulmonary diseases affecting the RV may have direct clinical relevance.

Keywords: histamine, histamine H₂ receptors, heart ventricles, pulmonary hypertension

(Received in original form July 31, 2014; accepted in final form September 11, 2014)

Supported by the National Institutes of Health (RC1-HL100543, R01-HL086719, K24-103844, R01-HL077612, N01-HC95159 through N01-HC95165, and N01-HC95169). This publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award no. KL2TR000421.

An abstract of preliminary findings was presented at the Grover Conference (biennial conference of the American Thoracic Society's Pulmonary Circulation Assembly) in September 2013.

Author Contributions: All authors participated in the conception and design of the research. D.A.B. and J.A.L. developed the right ventricular MRI metrics. R.A.K. provided statistical support. P.J.L. and S.M.K. analyzed and interpreted the data and drafted the report. All authors reviewed, revised, and approved the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Peter Leary, M.D., M.S., 1959 NE Pacific Street, University of Washington Medical Center, BB-1361, Box 356522, Seattle, WA 98195-6522. E-mail: learyp@uw.edu

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Ann Am Thorac Soc Vol 11, No 9, pp 1379–1386, Nov 2014

Copyright © 2014 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201407-344OC

Internet address: www.atsjournals.org

Gastroesophageal reflux disease (GERD) is commonly treated with histamine H₂ receptor antagonists (H2RAs) (1, 2). H2RA use may have ramifications beyond GERD control (3–5). Histamine is abundant in the myocardium and myocardial H₂ receptors activate stimulatory G-proteins by a mechanism similar to myocardial β -receptors (5, 6). H2RA use prevents heart failure in animal models and is associated with decreased left ventricular (LV) size and improved symptoms in patients with left heart failure (7–9). Mast cell activation and histamine release may also contribute to pulmonary vascular remodeling and lead to increased pulmonary vascular resistance and right ventricular (RV) afterload in pulmonary arterial hypertension (10).

Right heart failure is an important cause of morbidity and mortality, and increased RV mass is an independent risk factor for heart failure and cardiovascular death in community-dwelling adults without clinical cardiovascular disease (11, 12). H2RA use could contribute to changes in RV structure and function through impacts on the pulmonary vasculature, myocardium, or both; however, relationships between H₂ receptor antagonism and the RV have not been previously evaluated.

We examined the association between H2RA use and magnetic resonance imaging (MRI) measures of RV structure and function in a multiethnic cohort of adults free of clinical cardiovascular disease. We hypothesized that H2RA use would be independently associated with lower RV mass and smaller RV end-diastolic volume (RVEDV). Some of the results of these studies have been previously reported in the form of an abstract (13).

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study designed to investigate subclinical cardiovascular disease in white, African-American, Hispanic, and Chinese individuals (14). In 2000–2002, MESA recruited men and women aged 45–84 years from six U.S. communities. Exclusion criteria included clinical cardiovascular disease (physician-diagnosed heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight greater than 136 kg (300 lb), pregnancy, or

impediment to long-term participation. The MESA-RV Study was an ancillary study funded to interpret 4,204 cardiac MRIs at baseline (examination 1) for RV structure and function. The institutional review boards of participating institutions and the National Heart, Lung, and Blood Institute (National Institutes of Health, Bethesda, MD) approved the protocols of MESA and all studies described herein. All participants provided informed consent.

Cardiac MRI Measures

The cardiac MRI protocol has been previously described (15). Methods for interpretation of LV and RV parameters in MESA have been previously reported (16, 17). Briefly, endocardial and epicardial borders of the RV were traced on MRI short-axis cine images at end-systole and end-diastole. The outflow tract was included in RV volume. Papillary muscles and trabeculae were included in RV volumes and excluded from RV mass, as is commonly done for LV mass (18, 19). RV end-systolic volume and RVEDV were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. The difference between epicardial and endocardial volumes of the RV free wall at end-diastole multiplied by the specific gravity of the heart (1.05 g/ml) was used to estimate RV mass. RV stroke

volume was calculated by subtracting RV end-systolic volume from the RVEDV. RV ejection fraction (RVEF) was calculated by dividing RV stroke volume by RVEDV.

Medication Use

A validated medication inventory was used to assess medication use (20). Participants were asked to bring all medications used during the 2 weeks before a study visit. Study staff transcribed current medications and the use or nonuse of medications. Participants were considered H2RA users if they used either prescription or over-the-counter H2RAs. Participants were considered proton pump inhibitor (PPI) users if they used PPIs. Participants who used both H2RAs and PPIs were considered H2RA users reflecting their exposure to the medication of interest. Participants who used H2RAs, PPIs, or both were considered likely to have shared the indication of GERD. Other medications considered as confounders included angiotensin-converting enzyme inhibitors ($\pm$ diuretic), angiotensin II receptor blockers ($\pm$ diuretic), β -blockers ($\pm$ diuretic), oral steroids, nonsteroidal antiinflammatories (including aspirin, cyclooxygenase-2 inhibitors, and other nonsteroidal antiinflammatory medications), and leukotriene antagonists.

Figure 1. Study sample. H2RA = histamine H₂ receptor antagonist; MESA = Multi-Ethnic Study of Atherosclerosis Study; MRI = magnetic resonance imaging; PPI = proton pump inhibitor; RV = right ventricular.

Covariables

Covariables in the limited and fully adjusted models included age, sex, race/ethnicity, height, weight, education, presence of hypertension or diabetes mellitus, impaired glucose tolerance, cholesterol, time spent performing intentional exercise, smoking status, and pack-years of smoking as assessed at the initial MESA examination (21). Co-medication use and LV parameters, markers of lung structure (percent emphysema from chest CT) and function (FEV₁ and FVC), renal function (estimated glomerular filtration rate), markers of inflammation (C-reactive protein and IL-6), and heart rate were measured as previously described and added to fully adjusted models (22–24). Body mass index category was considered an effect modifier in four categories including normal weight and grade 1–3 overweight.

Statistical Analysis

We used linear regression to characterize relationships between H2RA use and RV parameters. All models were adjusted for height and weight to account for differences in body size. Additional covariables were chosen *a priori* on the basis of known associations with ventricular size, heart disease, and comorbidities. In limited models, we adjusted for age, sex, race/ethnicity, height, and weight. In fully adjusted models, we also included MESA field center, education, and cardiovascular risk factors including intentional exercise, smoking status, pack-years of smoking, hypertension, diabetes mellitus, cholesterol, and impaired glucose tolerance. In prespecified models, we further adjusted the full model for co-medication use, LV parameters, markers of lung structure and function, renal function, or markers of inflammation in separate models to evaluate independence from these factors. In an attempt to further account for confounding by indication (in which the underlying disease of GERD, rather than treatment, could be linked to RV morphology), analyses were repeated in a cohort restricted to participants who used either H2RAs or PPIs such that all participants likely had the same indication for treatment (GERD or peptic ulcer disease).

Primary analyses examined cross-sectional relationships between RV parameters and H2RA use at the baseline MESA examination. Exploratory models evaluated whether age, sex, body mass index category, or β -blocker use modified the

association between H2RA use and RV parameters. An additional exploratory model further adjusted the full model for heart rate. Analyses were performed with STATA 12.0 (StataCorp, College Station, TX).

Results

Of 6,814 participants enrolled in MESA, 5,098 underwent cardiac MRI and 4,634 participants were selected for the MESA-RV ancillary study. MRI reads were attempted in 4,484 participants before achieving the study goal of 4,204 participants (94% of attempted reads). H2RA use was ascertained in 4,198 of these participants. Seventy-six

participants were excluded for missing covariables, leaving 4,122 in the study sample (Figure 1). The mean age of the study sample was 63.2 years, 52.6% were women, 39.3% were white, 26.3% were African-American, 21.9% were Hispanic, and 12.5% were Chinese. Mean RV mass in the study sample was 21.0 ± 4.5 g, mean RVEDV was 124.1 ± 30.9 ml, and mean RVEF was $70.5 \pm 6.5\%$. One hundred and ninety-two participants (4.7%) used H2RAs; 10 of these participants used both H2RAs and PPIs.

Table 1 shows the characteristics of participants who used H2RAs, PPIs, or who did not report use of medications for acid suppression. Participants who did not use acid suppression were younger with a lower

Table 1. Characteristics of study sample

	No Acid Suppression (n = 3,705)	H2RA Users (n = 192)	PPI Users (n = 225)
Age, yr	61.2 $\pm$ 10.1	64.2 $\pm$ 9.7	63.8 $\pm$ 9.9
Female, %	51.8	53.7	64.4
Race, %			
White	38.6	44.3	47.6
African-American	26.4	20.8	27.6
Hispanic	21.8	26.6	20.0
Chinese	13.2	8.3	4.9
Height, cm	166.5 $\pm$ 10.0	165.4 $\pm$ 9.6	165.1 $\pm$ 9.7
Weight, kg	77.1 $\pm$ 16.3	78.6 $\pm$ 15.3	80.1 $\pm$ 15.4
Body mass index, kg/m ²	27.7 $\pm$ 4.9	28.7 $\pm$ 5.2	29.4 $\pm$ 5.0
Educational attainment, %			
No high school degree	16.1	19.3	16.4
High school degree	17.9	21.4	24.9
Some college	16.1	15.1	18.2
Bachelor's degree	18.3	20.8	12.9
Higher than bachelor's degree	18.9	15.1	18.7
Intentional exercise, MET-hr/wk	27.1 $\pm$ 40.4	19.3 $\pm$ 28.2	26.1 $\pm$ 40.0
Cigarette smoking status, %			
Never	52.2	54.2	51.6
Former	34.9	36.5	41.3
Current	13.0	9.4	7.1
Pack-years of cigarette smoking	10.7 $\pm$ 22.8	13.3 $\pm$ 24.4	11.0 $\pm$ 20.5
Hypertension, %	42.0	47.4	55.1
Systolic blood pressure, mm Hg	125.3 $\pm$ 21.2	127.2 $\pm$ 19.3	127.3 $\pm$ 18.0
Diabetes mellitus, %	12.6	14.1	12.0
Cholesterol, mg/dl	194.4 $\pm$ 35.3	197.2 $\pm$ 34.5	190.9 $\pm$ 31.8
Glucose, mg/dl	96.4 $\pm$ 29.4	95.8 $\pm$ 25.3	93.2 $\pm$ 17.8
ACE inhibitor or ARB use $\pm$ diuretic, %	16.4	21.4	23.1
β -Blocker use $\pm$ diuretic, %	8.6	14.6	17.3
Antiinflammatory use, %	41.2	54.7	56.9
FEV ₁ , L	2.4 $\pm$ 0.7	2.4 $\pm$ 0.7	2.2 $\pm$ 0.7
Estimated glomerular filtration rate, ml/min	81.5 $\pm$ 17.2	78.1 $\pm$ 18.4	77.1 $\pm$ 17.3
C-reactive protein, mg/L	3.4 $\pm$ 5.5	4.3 $\pm$ 5.6	4.6 $\pm$ 5.9
IL-6, pg/ml	1.5 $\pm$ 1.2	1.6 $\pm$ 1.2	1.5 $\pm$ 1.1

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; H2RA = H₂ receptor antagonist; MET-hr/wk = metabolic hours per week; PPI = proton pump inhibitor.

Note: Antiinflammatory use included the following: oral steroids, nonsteroidal antiinflammatory use, and leukotriene antagonist use.

prevalence of comorbidity and less medication use. The prevalence of diabetes mellitus was slightly higher among H2RA users than among participants in either of the other groups. The prevalence of β -blocker use, angiotensin-converting enzyme inhibitor use, and mean C-reactive protein (which may be indicators of subclinical cardiovascular disease) among H2RA users was intermediate between participants who used PPIs and those who did not use acid suppression.

H2RA use was associated with lower RV mass (0.7 g less with H2RA use; 95% confidence interval [95% CI], -1.2 to -0.3 g; $P = 0.002$) (Table 2). This relationship was not different after adjustment for cardiovascular risk factors in the fully adjusted model or when further accounting for co-medication use (accounting for all co-medication use in one model or in models separated by drug class) (Table 2; and see Table E1 in the online supplement). The relationship between H2RA use and RV mass was only slightly changed after adjustment for LV mass (-0.6 g with H2RA use; 95% CI, -1.0 to -0.1 g; $P = 0.009$). Restricting analyses to the 417 participants who used either PPIs or H2RAs (suggesting that all had GERD or peptic ulcer disease) showed that H2RA use was still associated with a decrease in RV mass relative to PPI use (0.7 g less with H2RA use; 95% CI, -1.4 to 0.0 g; $P = 0.04$) (Table 3).

H2RA use was associated with a smaller RVEDV (-4.7 ml with H2RA use; 95% CI, -7.9 to -1.6 ml; $P = 0.003$) (Table 2). This relationship was not different after adjustment for cardiovascular risk factors in the fully adjusted model or when further accounting for co-medication use (Table 2 and Table E1). The relationship between H2RA use and RVEDV was not present after adjustment for LVEDV (-0.7 ml with H2RA use; 95% CI, -3.0 to 1.5 ml; $P = 0.53$). Restricting analyses to the 417 participants who used PPIs or H2RAs showed relationships with RVEDV that were qualitatively similar to those in the main analyses, but were not statistically significant, likely because of smaller sample size (Table 3).

H2RA use was not associated with RVEF. Consideration of confounding by cardiovascular risk factors, co-medication use, or LV ejection fraction did not change this result. Additional control for confounding in analyses restricted only to users of H2RAs or PPIs also did not suggest a relationship between H2RA use and RVEF.

Table 2. Multivariable linear regression estimating associations between H₂ receptor antagonist use and right ventricular structure and function in the full study sample (n = 4,122)

Model	H2RA Use Relative to Nonuse		
	Difference	95% CI	P Value
RV mass, g			
Limited model*	-0.7	-1.2, -0.3	0.002
Full Model [†]	-0.7	-1.2, -0.2	0.004
Full Model [†] + Co-medication use	-0.7	-1.2, -0.2	0.005
Full Model [†] + LV mass	-0.6	-1.0, -0.1	0.009
RVEDV, mL			
Limited model	-4.7	-7.9, -1.6	0.003
Full Model	-4.2	-7.2, -1.2	0.006
Full Model + Co-medication use	-4.2	-7.3, -1.1	0.007
Full Model + LVEDV	-0.7	-3.0, 1.5	0.53
RVEF, %			
Limited model	0.0	-0.9, 0.8	0.92
Full Model	-0.1	-1.0, 0.8	0.85
Full Model + Co-medication use	-0.1	-1.0, 0.8	0.76
Full Model + LVEF	-0.3	-1.1, 0.5	0.52

Definition of abbreviations: CI = confidence interval; EDV = end-diastolic volume; EF = ejection fraction; H2RA = H₂ receptor antagonist; LV = left ventricular; RV = right ventricular.

Note: Co-medication use included the following: angiotensin-converting enzyme inhibitor use ($\pm$ diuretic), angiotensin II receptor blocker use ($\pm$ diuretic), β -blocker use ($\pm$ diuretic), oral steroid use, nonsteroidal antiinflammatory use (including aspirin, cyclooxygenase-2 inhibitors, and other nonsteroidal antiinflammatory medications), or leukotriene antagonist use.

*Limited model: Age, sex, race/ethnicity, height, and weight.

[†]Full model: Limited + MESA field center, education, intentional exercise, smoking status, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance.

Further adjustment for lung structure and function, renal function (as estimated by the glomerular filtration rate), or markers of inflammation did not change the relationship between H2RA use and any RV parameter (Figure 2). In exploratory models, there was no significant effect modification by age, sex, body mass index, or β -blocker use for any RV parameter (see Table E2). Additional adjustment for heart rate attenuated the relationship between H2RA use and RVEDV (-2.8 ml with H2RA use; 95% CI, -5.8 to 0.1 ml; $P = 0.06$), but did not change the relationship with RV mass (-0.5 g with H2RA use; 95% CI, -1.0 to -0.1 g; $P = 0.02$). An exploratory analysis of additional medications in the co-medication model (including calcium channel blockers, potassium-sparing diuretics, and vasodilators, such as hydralazine and clonidine) did not change the results (data not shown).

Discussion

We have shown that H2RA use is associated with lower RV mass and a smaller RVEDV

in a multiethnic cohort of adults without clinical cardiovascular disease. MESA participants who used H2RAs had 0.7 g (3.3%) less RV mass and a 4.7 ml (3.8%) smaller RVEDV. Differences in RV mass are an independent risk factor for heart failure and cardiovascular death in individuals without cardiovascular disease, which may support the clinical relevance of our findings (12). A similar magnitude of difference in LV mass has been seen in other notable modifiers of heart disease, such as the presence of diabetes mellitus or use of β -adrenergic blockade (25, 26).

This is the first report to suggest that H2RA use may have implications for right heart morphology, but not the first to suggest that H2RA use may impact the heart. Chronotropic effects of H₂ receptor antagonism were in the initial description of H2RAs (27). Later studies confirmed that stimulation of H₂ receptors increased heart rate and suggested positive inotropy with H₂ receptor stimulation (28).

H2RA use may benefit the heart. H2RA use can prevent left heart failure and renal

Table 3. Multivariable linear regression estimating associations between H₂ receptor antagonist use and right ventricular morphology among participants with a likely diagnosis of gastroesophageal reflux or peptic ulcer disease (n = 417)

Model	H2RA Use Relative to PPI Use		
	Difference	95% CI	P Value
RV mass, g			
Limited model*	−0.7	−1.4, 0.0	0.04
Full Model†	−0.7	−1.4, 0.0	0.05
Full Model† + Co-medication use	−0.7	−1.4, 0.0	0.06
Full Model† + LV mass	−0.7	−1.3, −0.1	0.03
RVEDV, mL			
Limited model	−4.4	−8.6, −0.2	0.04
Full Model	−3.1	−7.4, 1.1	0.15
Full Model + Co-medication use	−2.9	−7.4, 1.6	0.21
Full Model + LVEDV	−1.9	−5.0, 1.1	0.21
RVEF, %			
Limited model	0.5	−0.7, 1.7	0.39
Full Model	0.0	−1.2, 1.2	0.98
Full Model + Co-medication use	−0.1	−1.3, 1.1	0.85
Full Model + LVEF	−0.1	−1.2, 1.0	0.82

Definition of abbreviations: CI = confidence interval; EDV = end-diastolic volume; EF = ejection fraction; H2RA = H₂ receptor antagonist; LV = left ventricular; PPI = proton pump inhibitor; RV = right ventricular.

Note: Co-medication use included the following: angiotensin-converting enzyme inhibitor use ($\pm$ diuretic), angiotensin II receptor blocker use ($\pm$ diuretic), β -blocker use ($\pm$ diuretic), oral steroid use, nonsteroidal antiinflammatory use (including aspirin, cyclooxygenase-2 inhibitors, and other nonsteroidal antiinflammatory medications), or leukotriene antagonist use.

*Limited model: Age, sex, race/ethnicity, height, and weight.

†Full model: Limited + MESA field center, education, intentional exercise, smoking status, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance.

damage in rabbit models of anthracycline toxicity and in dogs with tachycardia-induced heart failure (8, 9, 29). In Japanese men and women with LV failure, H2RA use is associated with improved heart failure symptoms and smaller LV end-diastolic volume (7). Mechanisms to explain these associations are speculative, but could include histamine-related remodeling in the myocardium, alteration of renal blood flow, or altered systemic blood pressure (5, 30–32).

Our data suggest that H2RA use may have cardiac implications in men and women without clinically apparent cardiovascular disease and is the first to suggest a relationship with the RV. In pulmonary arterial hypertension, a smaller RV with less mass is a good prognostic sign and suggests adequate response to therapy (33). We observed this pattern with H2RA use and this may suggest H2RA use benefits the RV; however, others have shown that decreased RV mass may be linked to pathology (34). Further study would be needed before extrapolating

H2RA use to diseases of right heart failure (34).

Several possible mechanisms may explain our results. Histamine H₂ receptors are the predominant myocardial histamine receptor subtype, and histamine is abundant in the myocardium (6). As has been suggested for the LV, H2RAs may act directly on the myocardium to influence RV growth, adaptation, and development (7, 8). Alternatively, a smaller RV with less mass may suggest lower pulmonary vascular resistance in H2RA users. GERD has been implicated in lung damage, which could lead to increased pulmonary vascular resistance; however, associations with the RV were specific to H2RA use (35). PPI use was not related to RV metrics and adjustment for lung structure and function did not affect our results, arguing against any explanation based on GERD or lung damage. Acute H₂ receptor agonism, particularly with hypoxia, may lead to pulmonary vasodilation (36); however, chronic histamine release, the effect of which

would be abrogated by H2RA use, may lead to pulmonary vascular remodeling. This would increase pulmonary vascular resistance independent of lung damage or GERD (10, 37). Less pulmonary vascular remodeling with H2RA use could theoretically contribute to our findings.

We found that associations between H2RA use and the RV were independent of cardiovascular risk factors, such as diabetes, hypertension, or obesity. The relationship between H2RA use and RV mass was independent of differences in LV mass, suggesting that the relationship with mass was either specific or more pronounced in the RV. The relationship between H2RA use and RVEDV was not independent of LVEDV. This suggests H2RA use is associated with biventricular decreases in end-diastolic volume. H2RA use may impact renal blood flow, which could have implications for fluid balance and biventricular loading, but exploratory analyses did not suggest our results depended on differences in renal function (29). The relationship between RV mass and RVEDV was slightly attenuated by adjustment for heart rate. Chronotropic actions of H2RAs could contribute to differences in the RV or may represent an unrelated coefficient of H2RA use.

This study has limitations. Confounding by indication is a significant concern; however, the consistency of results using multiple approaches is reassuring. Limiting the population to participants using medication for acid suppression (H2RA or PPI) makes it less likely our results are explained by factors leading to H2RA use (e.g., access to care or a diagnosis of GERD) and more likely that H2RA use itself is relevant. Residual or unmeasured confounding in this observational study is still possible. The low prevalence of H2RA use may suggest unreported H2RA use in those we classified as nonusers, but is similar to the prevalence of H2RA use reported in contemporary studies (2). If present, such misclassification would be anticipated to be nondifferential with respect to RV morphology and the true relationship between H2RA use and RV differences may, if anything, be stronger than we report. Additional information on duration and dose of H2RA and other medications, which may have informed an understanding of dose response, was not available and information about use of H₁

Figure 2. Relationship of histamine receptor antagonist use with (A) right ventricular (RV) mass, (B) RV end-diastolic volume (RVEDV), and (C) RV ejection fraction (RVEF) after accounting for potential confounding arising from differences in lung structure and function ($n = 2,700$), renal function ($n = 4,122$), and inflammation ($n = 4,012$).

receptor antagonists was not collected. Type 1 errors (“false positives”) are possible; however, the magnitude of statistical significance and consistency of our results argue against a chance

relationship even when considering the multiple comparisons in this study. Our understanding of the potential mechanism would have been enhanced through measurement of invasive pulmonary

hemodynamics and evaluation of myocardial tissue, neither of which was feasible in this large study of community-dwelling adults without clinical cardiovascular disease.

Conclusions

H2RA use is associated with lower RV mass and a smaller RVEDV in adults of several ethnicities without clinical cardiovascular disease. This is the first report to implicate H2RA use with RV morphology and the first to implicate H2RA use with differences in

cardiac morphology in men and women without overt heart disease. Future study of H₂ receptors in cardiopulmonary diseases affecting the RV may have direct clinical relevance. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: This manuscript was reviewed by the MESA Investigators for

scientific content and consistency of data interpretation with previous MESA publications, and significant comments were incorporated before submission for publication. The authors thank the other investigators, staff, and participants of the MESA and MESA-Lung Studies for valuable contributions. A full list of participating MESA Investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

References

- 1 Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H₂-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* [serial on the Internet]. 2013 [accessed October 2014];5:CD002095. Available from: <http://summaries.cochrane.org/>
- 2 Jacobson BC, Ferris TG, Shea TL, Mahlis EM, Lee TH, Wang TC. Who is using chronic acid suppression therapy and why? *Am J Gastroenterol* 2003;98:51–58.
- 3 Laheij RJ, Sturkenboom MC, Hassing R, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955–1960.
- 4 Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B₁₂ deficiency. *JAMA* 2013;310:2435–2442.
- 5 Bristow MR, Ginsburg R, Harrison DC. Histamine and the human heart: the other receptor system. *Am J Cardiol* 1982;49:249–251.
- 6 Matsuda N, Jesmin S, Takahashi Y, Hata E, Kobayashi M, Matsuyama K, Kawakami N, Sakuma I, Gando S, Fukui H, et al. Histamine H₁ and H₂ receptor gene and protein levels are differentially expressed in the hearts of rodents and humans. *J Pharmacol Exp Ther* 2004;309:786–795.
- 7 Kim J, Ogai A, Nakatani S, Hashimura K, Kanzaki H, Komamura K, Asakura M, Asanuma H, Kitamura S, Tomoike H, et al. Impact of blockade of histamine H₂ receptors on chronic heart failure revealed by retrospective and prospective randomized studies. *J Am Coll Cardiol* 2006;48:1378–1384.
- 8 Takahama H, Asanuma H, Sanada S, Fujita M, Sasaki H, Wakeno M, Kim J, Asakura M, Takashima S, Minamino T, et al. A histamine H₂ receptor blocker ameliorates development of heart failure in dogs independently of β -adrenergic receptor blockade. *Basic Res Cardiol* 2010;105:787–794.
- 9 Bristow MR, Kantrowitz NE, Harrison WD, Minobe WA, Sageman WS, Billingham ME. Mediation of subacute anthracycline cardiotoxicity in rabbits by cardiac histamine release. *J Cardiovasc Pharmacol* 1983;5:913–919.
- 10 Farha S, Sharp J, Asosingh K, Park M, Comhair SAA, Tang WH, Thomas J, Farver C, Hsieh F, Loyd JE, et al. Mast cell number, phenotype, and function in human pulmonary arterial hypertension. *Pulm Circ* 2012;2:220–228.
- 11 Ghio SS, Gavazzi AA, Campana CC, Inerra CC, Klersy CC, Sebastiani RR, Arbustini EE, Recusani FF, Tavazzi LL. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001;37:183–188.
- 12 Kawut SM, Barr RG, Lima JA, Praetgaard A, Johnson WC, Chahal H, Ogunyankin KO, Bristow MR, Kizer JR, Tandri H, et al. Right ventricular structure is associated with the risk of heart failure and cardiovascular death: the MESA–Right Ventricle Study. *Circulation* 2012;126:1681–1688.
- 13 Leary PJ, Barr RG, Bluemke DA, Hough CL, Kronmal RA, Lima JA, Ventetuo CE, Kawut SM. Histamine H₂-receptor antagonists and the right ventricle: the MESA Right Ventricle Study [abstract]. Presented at the Grover Conference, Sedalia, CO, September 4–8, 2013.
- 14 Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Kronmal R, Liu K, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871–881.
- 15 Natori S. Cardiovascular function in Multi-Ethnic Study of Atherosclerosis: normal values by age, sex, and ethnicity. *AJR Am J Roentgenol* 2006;186:S357–S365.
- 16 Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events. *J Am Coll Cardiol* 2008;52:2148–2155.
- 17 Kawut SM, Lima JA, Barr RG, Chahal H, Jain A, Tandri H, Praetgaard A, Bagiella E, Kizer JR, Johnson WC, et al. Sex and race differences in right ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis–Right Ventricle Study. *Circulation* 2011;123:2542–2551.
- 18 Vogel-Claussen J, Finn JP, Gomes AS, Hundley GW, Jerosch-Herold M, Pearson G, Sinha S, Lima JA, Bluemke DA. Left ventricular papillary muscle mass: relationship to left ventricular mass and volumes by magnetic resonance imaging. *J Comput Assist Tomogr* 2006;30:426–432.
- 19 Winter MM, Bernink FJ, Groenink M, Bouma BJ, van Dijk AP, Helbing WA, Tijssen JG, Mulder BJ. Evaluating the systemic right ventricle by CMR: the importance of consistent and reproducible delineation of the cavity. *J Cardiovasc Magn Reson* 2008;10:40.
- 20 Smith NL, Psaty BM, Heckbert SR, Tracy RP, Corneli ES. The reliability of medication inventory methods compared to serum levels of cardiovascular drugs in the elderly. *J Clin Epidemiol* 1999;52:143–146.
- 21 MESA manual of operations: field center and laboratory procedures. Seattle, WA: University of Washington; 2008. Available from: <http://www.mesa-nhlbi.org/manuals.aspx>
- 22 Harhay MO, Tracy RP, Bagiella E, Barr RG, Pinder D, Hundley WG, Bluemke DA, Kronmal RA, Lima JA, Kawut SM. Relationship of CRP, IL-6, and fibrinogen with right ventricular structure and function: the MESA–Right Ventricle Study. *Int J Cardiol* 2013;168:3818–3824.
- 23 Smith BM, Hoffman EA, Basner RC, Kawut SM, Kalhan R, Barr RG. Not all measures of hyperinflation are created equal: lung structure and clinical correlates of gas trapping and hyperexpansion in COPD: the Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study. *Chest* 2014;145:1305–1315.
- 24 Robinson-Cohen C, Hoofnagle AN, Ix JH, Sachs MC, Tracy RP, Siscovick DS, Kestenbaum BR, de Boer IH. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. *JAMA* 2013;310:179–188.
- 25 Barron AJ, Hughes AD, Sharp A, Baksi AJ, Surendran P, Jabbour RJ, Stanton A, Poulter N, Fitzgerald D, Sever P, et al.; ASCOT Investigators. Long-term antihypertensive treatment fails to improve E/e' despite regression of left ventricular mass: an Anglo-Scandinavian Cardiac Outcomes Trial substudy. *Hypertension* 2014;63:252–258.
- 26 Heckbert SR, Post W, Pearson GDN, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2006;48:2285–2292.

- 27 Black JW, Duncan WA, Durant CJ, Ganellin CR, Parsons EM. Definition and antagonism of histamine H₂-receptors. *Nature* 1972;236:385–390.
- 28 Verma SC, McNeill JH. Cardiac histamine receptors: differences between left and right atria and right ventricle. *J Pharmacol Exp Ther* 1977;200:352–362.
- 29 Bristow MR, Minobe WA, Billingham ME, Marmor JB, Johnson GA, Ishimoto BM, Sageman WS, Daniels JR. Anthracycline-associated cardiac and renal damage in rabbits: evidence for mediation by vasoactive substances. *Lab Invest* 1981;45:157–168.
- 30 Pollock DM, Banks RO, Jacobson ED. Hemodynamic effects of a new histamine H₂ receptor agonist (impromidine) and antagonist (ranitidine). *Pharmacol Res Commun* 1982;14:605–612.
- 31 Ufnal M, Skrzypecki J. Blood borne hormones in a cross-talk between peripheral and brain mechanisms regulating blood pressure: the role of circumventricular organs. *Neuropeptides* 2014;48:65–73.
- 32 Basheer M, Schwalb H, Neshet M, Gilon D, Shefler I, Mekori YA, Shapira OM, Gorodetsky R. Mast cell activation by fibrinogen-related homologous C-terminal peptides (haptides) modulates systemic blood pressure. *J Allergy Clin Immunol* 2010;126:1041–1048.
- 33 McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, Palazzini M, Park MH, Tapson VF, Sitbon O. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D73–D81.
- 34 Grau M, Barr RG, Lima JA, Hoffman EA, Bluemke DA, Carr JJ, Chahal H, Enright PL, Jain A, Prince MR, *et al*. Percent emphysema and right ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis–Lung and Multi-Ethnic Study of Atherosclerosis–Right Ventricle Studies. *Chest* 2013;144:136–144.
- 35 Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G; IPFnet Investigators. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomized controlled trials. *Lancet Respir Med* 2013;1:369–376.
- 36 Russell PC, Wright CE, Barer GR, Howard P. Histamine induced pulmonary vasodilatation in the rat: site of action and changes in chronic hypoxia. *Eur Respir J* 1994;7:1138–1144.
- 37 Bartelds B, van Loon RLE, Mohaupt S, Wijnberg H, Dickinson MG, Boersma B, Takens J, van Albada M, Berger RMF. Mast cell inhibition improves pulmonary vascular remodeling in pulmonary hypertension. *Chest* 2012;141:651–660.