pathway genetic variants (1). However, as illustrated by the families reported here, even with the combination of telomere length measurement and genetic testing, assignment of disease risk to individual RVs may be difficult. As the spectrum of genetic risk for familial and sporadic IPF is expanded, we anticipate that enhanced understanding of the complex genetic influences underlying this disease will improve our ability to use genetic information in the care of these patients. ■

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Cardiac Morphometry on Computed Tomography and Exacerbation Reduction with β-Blocker Therapy in Chronic Obstructive Pulmonary Disease

To the Editor:

Chronic obstructive pulmonary disease (COPD) is associated with cardiovascular disease (1), and a subset of COPD exacerbations may be the result of overt or subclinical cardiovascular disease (1). We, and others, have shown that the use of cardiac function modulating β-blockers is associated with substantially lower rates of exacerbations (2). COPD is associated with functional and structural

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Table 1. Cardiac Morphometry by GOLD Stage

	Overall (*N = 3,436*)	GOLD 2 (*N = 1,819*)	GOLD 3 (*N = 1,080*)	GOLD 4 (*N = 537*)
Age, yr	63.4 (8.5)	62.3 (8.8)	64.3 (8.3)*	64.1 (7.5)*
African American race, n (%)†	750 (21.8%)	437 (24.0%)	217 (20.1%)	96 (17.9%)
Female sex, n (%)†	1530 (44.5%)	852 (46.8%)	456 (42.2%)	222 (41.3%)
Body mass index, kg/m^2	28.1 (6.3)	28.9 (6.2)	28.1 (6.3)*	25.5 (5.6)*
Pack-years of smoking	53.2 (27.5)	50.9 (26.9)	55.4 (27.8)*	56.4 (28.6)*
Diabetes mellitus, n (%)†	434 (12.6%)	229 (12.6%)	157 (14.5%)	48 (8.9%)
Hypertension, n (%)†	1744 (50.8%)	935 (51.4%)	588 (54.4%)	221 (41.2%)
Coronary artery disease, n (%)	563 (16.4%)	279 (15.3%)	200 (18.5%)	84 (15.6%)
Congestive heart failure, n (%)†	178 (5.2%)	69 (3.8%)	72 (6.7%)	37 (6.9%)
FEV_1, L	1.45 (0.63)	1.87 (0.51)	1.14 (0.30)*	0.64 (0.19)*
Emphysema on CT, %	12.9 (12.6)	7.1 (7.7)	16.1 (12.3)*	26.9 (13.8)*
Long-acting respiratory medications, n (%)†	1487 (43%)	528 (30.3%)	587 (56.6%)	372 (72.0%)
Log CAC	4.8 (1.7)	4.8 (1.7)	4.9 (1.8)	4.9 (1.6)
β-blocker use, n (%)†	471 (13.7%)	291 (16.0%)	142 (13.1%)	38 (7.1%)
RV volume Index	53.24 (17.13)	53.78 (16.38)	52.75 (18.32)	52.40 (17.09)
LV volume Index	102.03 (27.14)	104.79 (26.73)	100.39 (28.22)*	95.99 (25.05)*
RV/LV ratio	0.52 (0.11)	0.52 (0.10)	0.53 0.11)*	0.55 (0.11)*
RV sphericity	0.34 (0.06)	0.33 (0.06)	0.34 (0.07)*	0.36 (0.07)*
LV sphericity	0.45 (0.07)	0.45 (0.07)	0.45 (0.07)	0.48 (0.08)*

Definition of abbreviations: CAC = coronary artery calcium score; CT = computed tomography; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LV = left ventricle; RV = right ventricle.
All values expressed as mean (standard deviation) unless specified otherwise.
*$P < 0.05$ in comparison with GOLD 2.
†$P < 0.05$ for differences between categorical groups.

cardiac abnormalities (1), and it is plausible that patients with varied ventricular characteristics respond differentially to β-blockers.

We recently derived estimates of right (RV) and left ventricular (LV) morphometry from non-cardiac gated, noncontrast computed tomography (CT) scans that are highly correlated with structural and functional data obtained from echocardiography and magnetic resonance imaging (3). Using prospectively collected data, we hypothesized that variations in ventricular size and geometry determined on CT scans can phenotype participants most likely to respond to β-blockers with reduction in exacerbation frequency.

Methods

We included 3,436 participants with moderate to severe COPD from the multicenter COPDGene cohort (details published previously; ClinicalTrials.gov NCT00608764) (4). Medication data were recorded at enrollment, and we contacted participants prospectively every 3 to 6 months to ascertain exacerbation frequency (2). As previously described, cardiac segmentation and measurement of ventricular volume and sphericity were performed using a statistical model based on nonaffine deformations of cardiac structure to model anatomic variability, with segmentation performed by manual initialization followed by automated, iterative deformation of the model to fit the surface of the heart (3). LV and RV volume were estimated on the basis of the epicardial surface fit and included both the wall and chamber volume. LV and RV sphericity were defined by the ratio of surface area of a sphere the same volume as the cavity divided by the actual surface area of the cavity (3). We also measured the ratio of the diameter of the main pulmonary artery (PA) at the level of its bifurcation to the diameter of the ascending aorta at the same level, using standard DICOM software (OsiriX DICOM Viewer, version 4.0; Bernex, Switzerland) (5).

Using negative binomial regression, we compared the adjusted rates of total number of exacerbations and severe exacerbations on follow-up between those receiving and those not receiving β-blockers. To adjust for the lower propensity to prescribe β-blockers in COPD, and higher propensity in coronary artery disease and congestive heart failure, we created a logistic regression model with β-blocker use as the dependent variable, and age, sex, race, body mass index, coronary artery disease and congestive heart failure, and COPD severity by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (2–4) as independent variables. The predicted probability of β-blocker therapy (propensity score) was used to adjust for prescription propensity. As there was a significant interaction between β-blocker use and LV volume and sphericity, as well as RV/LV ratio (all $P < 0.001$), we categorized participants by median values for LV and RV epicardial volume indices and RV/LV ratio and repeated these analyses in these dichotomous groups. Similar analyses were repeated after categorizing participants by PA/aorta (A) ratio as ⩽1.0 and >1.0.

Results

Demographics and cardiac size metrics are shown in Table 1. With increasing airflow limitation, there was a progressive reduction in LV volume, no change in RV volume, and an increase in RV/LV ratio. Both RV and LV sphericity increased with progressive disease severity.

We had follow-up data on 2,902 participants (median follow-up, 2.1 years; interquartile range, 1.4–2.8 years). On multivariable analyses, the use of β-blockers was associated with a lower adjusted incidence rate ratio (IRR) of total number of exacerbations (IRR, 0.70; 95% confidence interval [CI], 0.57–0.86; $P < 0.0001$), as well as severe exacerbations (IRR, 0.58; 95% CI, 0.41–0.82; $P = 0.002$).

Figure 1 shows that in those with RV epicardial volume index higher than median (50.7 ml^3), β-blocker use was associated with lower total (IRR, 0.74; 95% CI, 0.55–0.99; $P = 0.040$) and severe (IRR, 0.49; 95% CI, 0.30–0.81; $P = 0.005$) exacerbations. In those with RV epicardial volume index at median or below, β-blocker use was associated with lower total exacerbations (IRR, 0.67; 95% CI, 0.50–0.91;

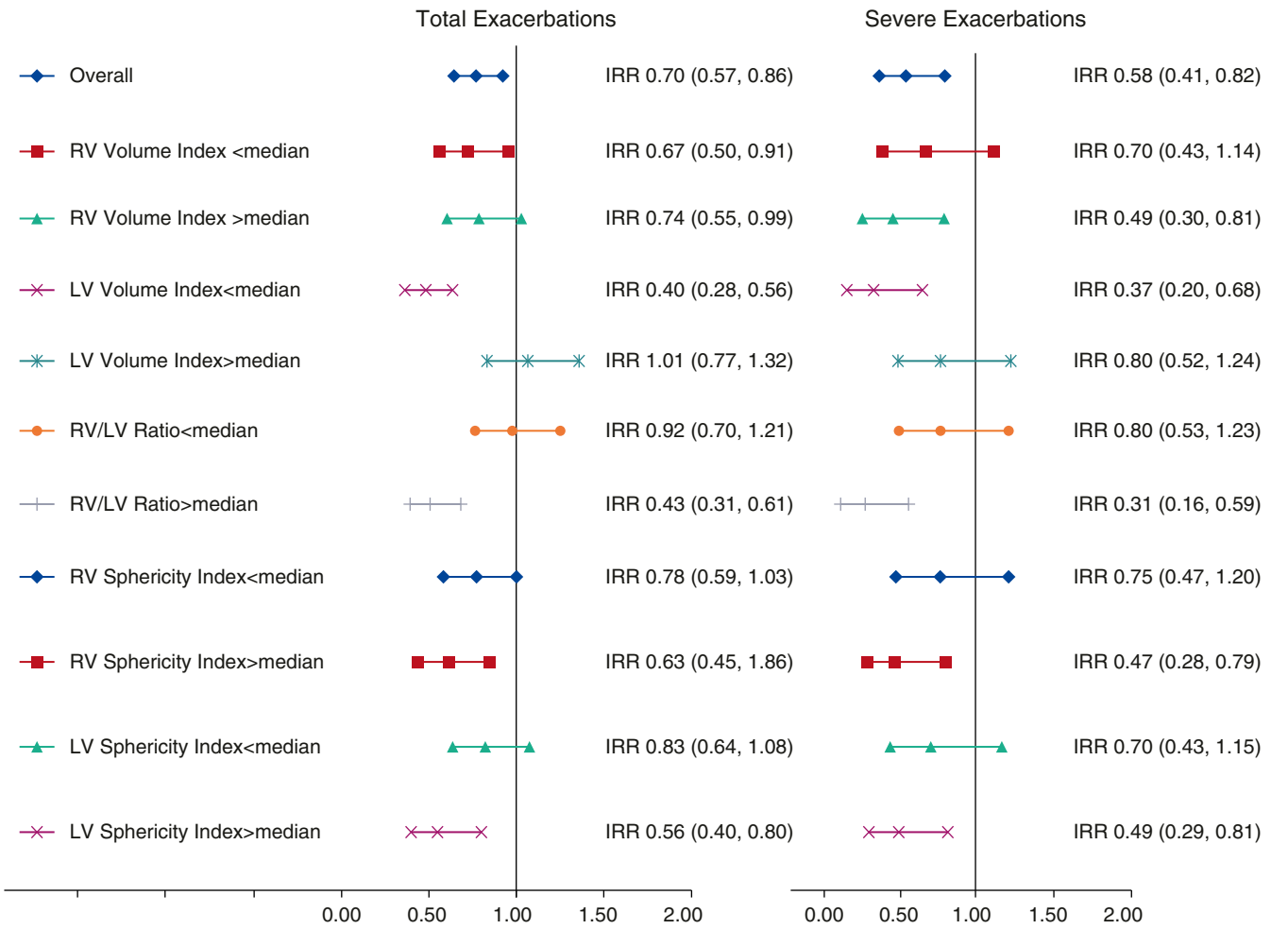

Figure 1. Exacerbation frequency associated with β-blocker use by dichotomized ventricular sizes and dichotomized sphericity indices for right (RV) and left (LV) ventricles. All exacerbation frequencies are expressed as incidence rate ratio (IRR) with 95% confidence intervals. All IRR adjusted for age, sex, race, pack-years of smoking, body mass index, FEV_1, percent emphysema on computed tomography, log-transformed coronary artery calcification, presence of coronary artery disease and congestive heart failure, long-acting respiratory medications (long acting β-agonists/inhaled corticosteroids and long-acting antimuscarinics), and the propensity to prescribe β-blocker therapy.

$P = 0.009$), but not severe exacerbations (IRR, 0.70; 95% CI, 0.43–1.14; $P = 0.151$). In contrast, in those with LV epicardial volume index at or below the median (98.2 ml^3), β-blocker use was associated with lower total (IRR, 0.40; 95% CI, 0.28–0.56; $P < 0.0001$) and severe (IRR, 0.37; 95% CI, 0.20–0.68; $P = 0.001$) exacerbations, but not in those with LV epicardial volume index higher than the median (Figure 1). β-blocker use in those with RV/LV ratio higher than the median (0.52) was associated with lower total (IRR, 0.43; 95% CI, 0.31–0.61; $P < 0.0001$) and severe (IRR, 0.31; 95% CI, 0.16–0.59; $P < 0.0001$) exacerbations, but not in those with RV/LV ratio ⩽0.52. In participants with sphericity of RV or LV above the median, reduction in exacerbation frequency with β-blocker was greater than in those with sphericity indices at median or below (Figure 1).

On comparing exacerbation rates by PA/A categories, β-blocker use was associated with lower exacerbation frequency in those with PA/A ratio as ⩽1.0 (IRR, 0.75 [95% CI, 0.59–0.95; $P = 0.019$] for total number and IRR, 0.53 [95% CI, 0.34–0.83; $P = 0.005$] for severe exacerbations) than in those with PA/A >1.0 in whom there was no reduction in exacerbation frequency (IRR, 0.78 [95% CI, 0.49–1.22; $P = 0.271$] for total number and IRR, 0.85 [95% CI, 0.47–1.52; $P = 0.572$] for severe exacerbations).

Discussion

In patients with moderate to very severe COPD, cardiac geometry as determined on noncontrast CT scans can be used to predict reduction in exacerbation frequency associated with β-blocker use, especially in those with low LV volume index as well as high RV volume index, and a RV/LV ratio of 0.52 can distinguish participants more likely to respond to β-blocker use.

Our results suggest that lower LV size is the main driver of the differential response in participants with RV/LV above the median. The reasons for the greater response are likely multifactorial, including reduction of heightened sympathetic tone, lowering of heart rate and thus better ventricular filling antiarrhythmic effects, and alleviation of diastolic dysfunction (1). Smaller ventricular size is also associated with improved β-adrenergic responsiveness (6). LV size progressively decreases with worsening airflow obstruction and emphysema, likely as a result of reduced

ventricular filling from a combination of distal pulmonary vessel pruning and lung hyperinflation (7, 8). It is also possible that the lower LV size is a result of higher LV mass caused by concentric ventricular remodeling, with a greater mass but lower than normal volume, an adaptive mechanism to overcome myocardial afterload (9). Because we did not have controls, we are unable to distinguish whether the lower LV size is relative or absolute, with the latter implying there might be additional mechanisms involved such as cachexia and apoptosis, with differential response to β-blockers. Ventricular shape is also likely important, and high LV sphericity independently predicts incident heart failure and atrial fibrillation, both conditions likely to benefit from β-blockers (10).

The mechanisms for the beneficial effects of β-blockers in those with elevated RV volume index are less clear. We have previously shown that an elevated PA/A ratio, indicative of pulmonary hypertension, is an independent predictor of exacerbations (5). This finding is associated with right heart structural changes, but not diastolic dysfunction in mild to moderate COPD, and hence is likely independent of LV dysfunction (11). Alternatively, it is possible that the greater RV size is secondary to LV changes, explaining the response to β-blocker therapy. Our finding of a lack of association between β-blocker use and exacerbation reduction in patients with PA/A >1 but a positive response in those with RV/LV above the median suggests the main beneficial effects are driven by the effects of β-blockers on the LV. Recent studies of β-blockers in idiopathic pulmonary hypertension, without LV involvement, suggest they might be harmful (12).

A limitation is that CT scans were nonelectrocardiogram-gated noncontrast scans, and hence we were unable to estimate ventricular mass and end-diastolic or end-systolic volumes separately; however, by providing a global measure of cardiac chamber size that can be easily obtained on clinically available scans, high RV/LV ratio on CT is a potentially useful and easily measurable biomarker for patient selection before administration of β-blockers in patients with COPD. ■

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Benefit of the Shorter Multidrug-Resistant Tuberculosis Treatment Regimen in California and Modified Eligibility Criteria

To the Editor:

As consultants for multidrug-resistant (MDR) tuberculosis (TB) cases in California, we read with interest the correspondence from Varaine and colleagues (1) and Lange and colleagues (2) regarding the new World Health Organization–recommended shorter treatment for MDR TB (3). As Varaine and colleagues noted, the importance for short-course treatment eligibility of resistance to drugs other than injectables and fluoroquinolones remains unclear in the recommendations (1). This has implications for both programs that do and those that do not routinely perform susceptibility testing to all second-line drugs. One specific question is whether or not patients who have *Mycobacterium tuberculosis* organisms that are resistant to ethionamide but have only low-level isoniazid resistance are eligible. Considering these patients eligible makes sense, given the drugs included in the shorter regimen. High-dose isoniazid is likely to be active against organisms with low-level isoniazid resistance, commonly associated with a mutation in the *inhA* gene that also confers resistance to ethionamide (4–6). The efficacy of high-dose isoniazid for organisms with low-level isoniazid resistance is under study (ClinicalTrials.gov identifier: NCT01936831). Ethionamide is more likely to be active against *M. tuberculosis* organisms with high-level resistance to isoniazid, associated with a mutation in *katG*, and that are less commonly resistant to ethionamide (5). The shorter regimen includes both ethionamide and high-dose isoniazid and therefore is likely to be effective against both of these common MDR TB resistance patterns. Lange and colleagues reported that fewer than 8% of patients in Europe with MDR TB would be eligible to be treated with the shorter regimen but did not include information about how many patients' organisms had low-level isoniazid resistance or an *inhA* mutation (2).

We performed an analysis similar to Lange and colleagues (2) of patients with MDR TB during 2009 to 2015 in California with drug susceptibility results available in records for isoniazid, a second-line injectable medication (kanamycin, amikacin, or capreomycin), a fluoroquinolone (moxifloxacin, levofloxacin, or ofloxacin), ethambutol, pyrazinamide, and ethionamide (clofazimine susceptibility testing is not routinely performed; Table 1). Low-level isoniazid resistance was defined as resistance at lower concentrations (i.e., 0.1 μg/ml in broth systems), but susceptibility at a higher concentration (i.e., 0.4 μg/ml in broth systems). Like Lange and colleagues (2), we determined fluoroquinolone and injectable resistance stepwise by the first result available to a drug assessed in the order listed above. Of 180 patients with MDR TB, 171 patients had susceptibility test results for all six drugs/drug classes. Of those, 25 (14.6%) were eligible for the shorter regimen using the definition of Lange and colleagues, which did not consider isoniazid results (2). Consistent with other data (7), of 161 patients with isoniazid results at both concentrations, 30 (19%) had low-level resistance. Among these, an additional 10 patients would be eligible if modified criteria for use of the regimen allowed for ethionamide resistance in patients with low-level isoniazid resistance, for a total of 35 (20.5%) patients eligible.

Although more patients in California would be eligible than in Europe, even more in California would become eligible with these modified criteria. However, even with these modified eligibility criteria, questions remain. The World Health Organization specifically recommends against use of the shorter regimen when there is resistance to one or more of the drugs in the regimen and recommends against alteration of the regimen beyond those drugs used in the observational studies. However, data from those observational studies showed that resistance to drugs in the regimen was common (65–71% for ethambutol

Table 1. Culture-based Drug Resistance Results and Eligibility for the Shorter-Course Multidrug-Resistant Tuberculosis Regimen among Patients with Culture-Positive Multidrug-Resistant Tuberculosis in California, 2009–2015

Total (*N*)	Full DST Done	*Mycobacterium tuberculosis* Drug Resistance from Patients with MDR-TB and Full DST									Eligibility for Shorter Regimen[§]	Alternate Eligibility for Shorter Regimen[‖]
		H (Any)*	H (High)	H (Low)	R	SLID[†]	FQ[‡]	ETO	E	Z		
180	171 (95)	171 (100)	131 (77)	30 (18)	171 (100)	12 (7)	15 (9)	62 (36)	108 (63)	78 (46)	25 (14.6)	35 (20.5)

Definition of abbreviations: DST = drug susceptibility testing; E = ethambutol; ETO = ethionamide; FQ = fluoroquinolone; H = isoniazid; MDR = multidrug resistance, defined as resistance to both isoniazid and rifampin; R = rifampin; SLID = second-line injectable drug; TB = tuberculosis; Z = pyrazinamide. Data are presented as n (%) unless otherwise indicated.

*Includes 10 patients with resistance results available only at the lower concentration.

[†]Resistance to an SLID determined stepwise by the first available result for kanamycin, amikacin, or capreomycin.

[‡]Resistance to a FQ determined stepwise by the first available result for moxifloxacin, levofloxacin, or ofloxacin.

[§]Susceptible to SLID, FQ, ETO, E, and Z.

[‖]Susceptible to SLID, FQ, ETO, E, and Z; *or* if resistant to ETO, susceptible to H at high concentration.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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