Original Article

# Right Ventricular Structure and Function Are Associated With Incident Atrial Fibrillation

## MESA-RV Study (Multi-Ethnic Study of Atherosclerosis–Right Ventricle)

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***Background***—Right ventricular (RV) morphology has been associated with drivers of atrial fibrillation (AF) risk, including left ventricular and pulmonary pathology, systemic inflammation, and neurohormonal activation. The aim of this study was to investigate the association between RV morphology and risk of incident AF.

***Methods and Results***—We interpreted cardiac magnetic resonance imaging in 4204 participants free of clinical cardiovascular disease in the MESA (Multi-Ethnic Study of Atherosclerosis). Incident AF was determined using hospital discharge records, study electrocardiograms, and Medicare claims data. The study sample (n=3819) was 61±10 years old and 47% male with 47.2% current/former smokers. After adjustment for demographics and clinical factors, including incident heart failure, higher RV ejection fraction (hazard ratio, 1.16 per SD; 95% confidence interval, 1.03–1.32; *P*=0.02) and greater RV mass (hazard ratio, 1.25 per SD; 95% confidence interval, 1.08–1.44; *P*=0.002) were significantly associated with incident AF. After additional adjustment for the respective left ventricular parameter, higher RV ejection fraction remained significantly associated with incident AF (hazard ratio, 1.15 per SD; 95% confidence interval, 1.01–1.32; *P*=0.04), whereas the association was attenuated for RV mass (hazard ratio, 1.16 per SD; 95% confidence interval, 0.99–1.35; *P*=0.07). In a subset of patients with available spirometry (n=2540), higher RV ejection fraction and mass remained significantly associated with incident AF after additional adjustment for lung function (*P*=0.02 for both).

***Conclusions***—Higher RV ejection fraction and greater RV mass were associated with an increased risk of AF in a multiethnic population free of clinical cardiovascular disease at baseline. **(*Circ Arrhythm Electrophysiol*. 2017;10:e004738. DOI: 10.1161/CIRCEP.116.004738.)**

**Key Words:** atrial fibrillation ■ heart failure ■ heart ventricles ■ magnetic resonance imaging



Atrial fibrillation (AF) is a major public health burden associated with stroke, heart failure, and mortality.[1,2] Improved diagnostic surveillance and increased survival after diagnosis frame the rising prevalence of AF which is estimated to affect nearly 12 million people in the United States by 2050.[3,4] Improved AF risk prediction, particularly in those without cardiovascular disease, is necessary for timely deployment of therapies and preventative strategies.[5] To this end, standard clinical risk factors (eg, diabetes mellitus, hypertension, obesity, and smoking) account for only half of the risk of AF in contemporary community-based cohorts.[6] These observations suggest that more refined markers of AF risk that directly reflect the underlying pathophysiology of disease development may be useful.

There is an increasing recognition of the prognostic and clinical importance of the right ventricle (RV) in cardiovascular disease.[7–10] RV morphology may reflect pulmonary pathology[11] and subclinical left ventricular (LV) disease[12,13] or may directly contribute to cardiovascular risk.[7] To date, the relationship between cardiovascular structure and incident AF has centered on the left heart,[14–16] whereas the relationship between RV morphology and incident AF remains unknown. RV morphology may serve as a structural indicator of established clinical risk factors (eg, obesity and sleep apnea)[17,18] or biologically relevant pathways (eg, inflammation and neurohormonal activation)[19,20] implicated in the pathogenesis of AF.

To examine the relationship between RV morphology and AF risk, we studied participants in the MESA (Multi-Ethnic Study of Atherosclerosis)—a prospective, multiethnic cohort free of clinical cardiovascular disease at baseline—with detailed cardiac magnetic resonance (CMR) imaging of RV structure and function.

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For the author affiliations, please see the Appendix.

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### WHAT IS KNOWN

- RV structure and function provide prognostic information for patients with established cardiovascular disease.
- RV morphology has been associated with known drivers of AF risk, including systemic inflammation, neurohormonal activation, and pulmonary pathology.
- The relationship between RV morphology and incident AF risk is uncertain.

### WHAT THE STUDY ADDS

- In 4204 individuals free of cardiovascular disease at baseline, higher RVEF and greater RV mass were associated with incident AF even after accounting for lung function, incident heart failure, and measures of left heart structure and function.
- RV morphology may serve as an integrative barometer of AF risk, independent of left heart function. The clinical use of RV morphology assessment in AF risk prediction and its potential influence on outcomes in AF warrants further investigation.

## Methods

### Study Population

The MESA is a prospective, multicenter cohort study whose methods and objectives have been previously detailed.[21] In brief, 6814 men and women aged 45 to 84 years without clinical cardiovascular disease (including stroke, myocardial infarction, heart failure, AF, or coronary heart disease) were enrolled between 2000 and 2002 in 6 US communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA). A total of 5098 participants underwent CMR imaging, and 5004 had scans interpretable for LV structure and function. The MESA-RV Study was an ancillary study which selected 4634 of the available 5004 scans (without regard to age, sex, or race) and attempted to read 4484 of which 4204 were available and interpretable for RV morphology (Figure 1).[7] For this study, participants were excluded if baseline characteristics including ECG data were missing. Given the established relationship between LV systolic dysfunction and AF, participants with baseline CMR LV ejection fraction (EF) <50% were additionally excluded.

The protocols of MESA were approved by the institutional review boards of each collaborating institution and the National Heart, Lung, and Blood Institute. Participants provided written informed consent.

### CMR Imaging Measures

The CMR protocol and interpretation, including RV assessment, have been previously described in detail.[22,23] In brief, CMR was performed using a 1.5-T system with ECG gating and fast gradient echo cine images with temporal resolution of ≤50 ms. CMR interpretation was performed at a core laboratory as previously described.[7] RV assessment included manual trace of endocardial and epicardial borders of short-axis cine images at end systole and end diastole. Contours were modified at basal slices using the tricuspid valve to exclude the right atrium and thus avoid overestimation of RV volume assessment. RV volumes (end-diastolic volume [EDV] and end-systolic volume) were calculated using the Simpson's rule. RV volumes

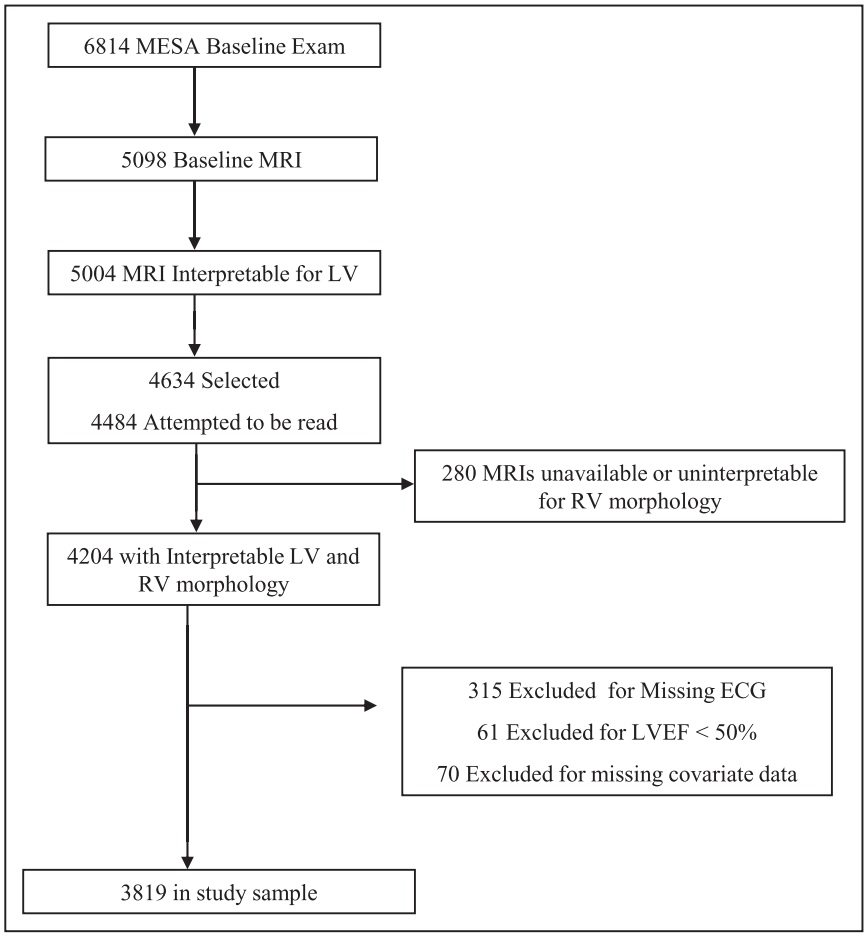


**Figure 1.** Study sample. EF indicates ejection fraction; LV, left ventricle; MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging; and RV, right ventricle.

included the outflow tract, papillary muscles, and trabeculae. RV mass was determined at end diastole as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the myocardium (1.05 g/mL).[23] The septum, papillary muscles, and trabeculae were not included in the measurement of RV mass as previously described.[7,23] The original MESA CMR protocol did not measure left atrium (LA) size; however, LA volume was measured in a subset of participants with AF and interpretable CMR images along with a 1:1 matched (age, sex, and race) population as previously reported.[14]

Intra- and inter-reader intraclass correlation coefficients for RV mass, volume, and function have been previously reported in MESA-RV using blinded rereads of CMR scans.[7] Intrareader correlation coefficients were 0.94 for RV mass, 0.99 for RVEDV, and 0.89 for RVEF. Inter-reader correlation coefficients were 0.89 for RV mass, 0.96 for RVEDV, and 0.80 for RVEF.

## Covariates

Race/ethnicity was self-reported using 2000 US Census criteria for race (Caucasian, African-American, and Chinese) and ethnicity (Hispanic or non-Hispanic). Participants self-identifying as Hispanic were categorized as Hispanic. Body mass index, self-reported intentional exercise, education level, hypertension, smoking status (never, former, or current), smoking pack-years, diabetes mellitus, and medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, and antiarrhythmic medications) were assessed using standardized methods.[24] Spirometry was performed in a subset of participants in the MESA Lung ancillary study, as previously described.[12]

## End Point Ascertainment

AF was determined using MESA-ascertained hospital-discharge International Classification of Disease codes, MESA study ECG, or Medicare inpatient claims data.[14] Per study protocol, participants were contacted by study coordinators at intervals of 9 to 12 months to solicit updated hospitalizations, outpatient diagnoses and procedures, and deaths.[7,21] Trained personnel abstracted all relevant hospital records, including ECGs, clinical history, and procedures, and transmitted these data to the coordinating center. Medicare claims data were used to identify AF diagnoses for inpatient encounters for participants ≥65 years enrolled in fee-for-service Medicare. International Classification of Disease-9 codes for AF (427.31) and atrial flutter (427.32) were used. Incident AF was ascertained through December 31, 2011. For patients who did not have incident AF, time was set to (1) date of death (if patient died), (2) date of last MESA follow-up if before December 31, 2011, or (3) the end of the ascertainment window if follow-up was after 2011.

## Statistical Analysis

Continuous data are presented as mean±SD. Categorical data are presented as frequency. Univariable and multivariable Cox proportional hazards models were used to examine the associations between RV morphological measures and time to AF. The proportional hazards assumption was tested for all models using Schoenfeld residuals. We estimated univariate associations for RV end-diastolic mass (RVEDM), RV volumes (RV end-systolic volume and RVEDV), and RV function (RVEF) per SD increase in each measure. We then adjusted for age, sex, race/ethnicity, body mass index, hypertension, diabetes mellitus, medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, and antiarrhythmic), smoking (status and pack-years), and education level. In a subset with available spirometry, adjustment was additionally performed for forced expiratory volume in 1 s ($FEV_1$). Anthropometrics, diabetes mellitus status, hypertension, smoking status, and medication use were assessed as time-varying covariates. Given the established association between CMR-derived left ventricular hypertrophy (LVH) and incident AF in MESA,[14] models for RV volumes (RV end-systolic volume and RVEDV) and RV function (RVEF) were also initially adjusted for CMR-LVH (LV mass >95th percentile of healthy MESA population, as defined previously).[14] Next, given the established relationship between RV morphology and incident heart failure,[7] and the association of heart failure and AF,[25] we further adjusted multivariable models for

**Table 1. Baseline Characteristics of the Study Population**

| Baseline Characteristic | Study Sample, N=3819 |
|---|---|
| Demographic and clinical variables | |
| Age, y | 61±10 |
| Male sex, n (%) | 1774 (47) |
| Race/ethnicity, n (%) | |
| Caucasian | 1485 (39) |
| African-American | 976 (26) |
| Hispanic | 859 (23) |
| Chinese | 499 (13) |
| Education level, n (%) | |
| Less than high school | 636 (16) |
| High school/GED | 690 (18) |
| Less than college (more than high school) | 1100 (29) |
| Bachelor degree | 685 (18) |
| Graduate degree | 708 (19) |
| Body mass index, kg/m$^2$ | 27.9±5.0 |
| Smoking status, n (%) | |
| Never | 2017 (53) |
| Former | 1343 (35) |
| Current | 459 (12) |
| Smoking pack-years | 10.7±23.0 |
| Forced expiratory volume in 1 s, mL* | 2413±732 |
| Diabetes mellitus, n (%) | 432 (11) |
| Hypertension, n (%) | 1616 (42) |
| Medications, n (%) | |
| RAAS inhibitor | 632 (17) |
| β-Blocker | 352 (9) |
| Antiarrhythmic | 21 (<1) |
| Cardiac structure and function | |
| Right ventricle | |
| End-diastolic mass, g | 21±5 |
| End-diastolic volume, mL | 124±31 |
| End-systolic volume, mL | 37±14 |
| Ejection fraction, % | 71±6 |
| Left ventricle | |
| End-diastolic mass, g | 144±38 |
| End-diastolic volume, mL | 126±31 |
| End-systolic volume, mL | 39±15 |
| Ejection fraction, % | 70±7 |

GED indicates general education development test; and RAAS, renin–angiotensin–aldosterone system.

*Assessed in a subset of the study population (n=2540).

incident heart failure before or concurrent with AF (heart failure ascertainment in MESA previously described in detail).[26] To more closely assess the relationship between the RV morphology and AF risk, we finally adjusted models for the respective LV parameter (eg, for RVEDM, adjustment for LVEDM). Finally, in a nested case:control subpopulation of MESA-RV participants with LA volume measures (138 pairs matched on age, sex, and ethnicity), we examined the association between RV measures and incident AF. We then used a conditional shared frailty Cox proportional hazards model with incident AF as the outcome and RV measures as the independent variable. Multivariable adjustment includes matching factors, to account for residual confounding, as well as anthropomorphic measures, medication use, clinical characteristics (smoking, diabetes mellitus, and incident HF), and CMR-defined LVH as specified above, followed by the addition of LA volume. Freedom from AF stratified by the median value of significant RV measures (ie, RVEDM and RVEF) was estimated using Cox proportional hazards models with multivariable adjustment as specified above. SAS (version 9.3; SAS Institute, Cary, NC) and R (version 3.2.1; R Project of Statistical Computing) were used for all analyses. Values of $P<0.05$ were considered statistically significant.

**Table 2. Proportional Hazards Models for Right Ventricular Structure and Function and Incident Atrial Fibrillation**

| | HR (95% CI) | *P* Value |
|---|---|---|
| RVEF | | |
| Unadjusted | 1.21 (1.08–1.35) | 0.001 |
| Model 1* | 1.16 (1.03–1.32) | 0.02 |
| Model 2† | 1.16 (1.03–1.32) | 0.02 |
| Model 2+LVEF | 1.15 (1.01–1.32) | 0.04 |
| RVEDM | | |
| Unadjusted | 0.93 (0.83–1.05) | 0.23 |
| Model 1‡ | 1.25 (1.09–1.44) | 0.002 |
| Model 2† | 1.25 (1.08–1.44) | 0.002 |
| Model 2+LVEDM | 1.16 (0.99–1.35) | 0.07 |
| RVEDV | | |
| Unadjusted | 0.92 (0.82–1.03) | 0.15 |
| Model 1* | 1.10 (0.94–1.28) | 0.23 |
| Model 2† | 1.11 (0.95–1.29) | 0.18 |
| Model 2+LVEDV | 1.00 (0.82–1.21) | 0.97 |
| RVESV | | |
| Unadjusted | 0.84 (0.75–0.94) | 0.004 |
| Model 1* | 0.91 (0.79–1.06) | 0.24 |
| Model 2† | 0.92 (0.79–1.07) | 0.28 |
| Model 2+LVESV | 0.89 (0.76–1.05) | 0.17 |

Hazard ratios are per SD increase in parameter (SD RVEF: 6.3%; RVEDM: 4.5 g; RVEDV: 31.0 mL; and RVESV: 15.0 mL). CI indicates confidence interval; EDM, end-diastolic mass; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, hazard ratio; LV, left ventricle; and RV, right ventricle.

*Model 1 includes adjustment for age, sex, race, body mass index, hypertension, diabetes mellitus, medication use (renin–angiotensin–aldosterone system, β-blocker, and antiarrhythmic), smoking (status and pack-years), education level, and left ventricular hypertrophy.

†Model 2 includes adjustment for prevalent or concurrent heart failure at time of atrial fibrillation diagnosis in addition to Model 1 covariates.

‡Model 1 for RVEDM does not include adjustment for left ventricular hypertrophy; adjustment for LV mass (LVEDM) is performed subsequently.

# Results

## Baseline Characteristics

The total number of MESA participants with CMR assessment, LVEF ≥50%, and complete baseline covariate and ECG assessment was 3819 (Figure 1). The mean age of the study sample was 61±10 years, and 47% were male (Table 1). The mean body mass index was 27.9±5 kg/m$^2$, and 47% were former/current smokers. The prevalence of hypertension was 42%, and 11% of participants had diabetes mellitus. Baseline CMR-derived biventricular structure and function measures are shown in Table 1. Spirometry was assessed in a subset of the study population under another ancillary study (n=2540), and the mean $FEV_1$ was 2413±732 mL. Compared with patients excluded, study participants were slightly younger and less likely to have hypertension or diabetes mellitus (Table I in the Data Supplement).

## RV Morphology and Incident AF

During the study period, there were 308 incident AF events during a median follow-up of 10.2 years (interquartile range, 9.6–10.7). In unadjusted analysis, greater RVEF and lower RV end-systolic volume were associated with incident AF ($P<0.004$ for both; Table 2). In multivariable models with time-varying adjustment of clinical and lifestyle measures, both higher RVEF (hazard ratio [HR], 1.21 per SD; 95% confidence interval [CI], 1.08–1.35; $P=0.02$) and greater RV mass (HR, 1.21 per SD; 95% CI, 1.04–1.40; $P=0.002$) were significantly associated with incident AF. In the subset of participants with baseline spirometry, there were significant associations between higher RVEF, RVEDM, and RVEDV and incident AF after additional adjustment for $FEV_1$ ($P<0.02$ for all; Table II in the Data Supplement).

To evaluate whether the association between RV measures and incident AF was mediated by intercurrent heart failure, multivariable models were further adjusted for prevalent heart failure at the time of AF diagnosis. Greater RVEF and RV mass remained associated with incident AF in heart failure–adjusted models ($P\leq0.02$ for both; Table 2). To further isolate the relationship between RV morphology and incident AF, associations were further adjusted for the respective LV parameter. After adjusting for LVEF, higher RVEF remained significantly associated with incident AF (HR, 1.15 per SD; 95% CI, 1.01–1.32; $P=0.04$), whereas the association between greater RV mass and incident AF was slightly weakened after adjustment for LV mass (HR, 1.16 per SD; 95% CI, 0.99–1.35; $P=0.07$). In participants with baseline spirometry, both greater RVEF (adjusted HR, 1.23 per SD; 95% CI, 1.03–1.46; $P=0.02$) and RV mass (adjusted HR, 1.26 per SD; 95% CI, 1.04–1.54; $P=0.02$) remained associated with incident AF after adjustment for demographic and clinical factors, $FEV_1$, and respective LV parameter (Table II in the Data Supplement). Finally, in a nested case:control subpopulation of 276 patients (138 with incident AF, and 138 controls matched on age, sex, and ethnicity) with LA volume measurement, increasing RVEF was significantly associated with incident AF in multivariable-adjusted models (HR, 1.38 per SD; 95% CI, 1.14–1.66; $P<0.001$) and remained significantly associated after additional adjustment for LA volume

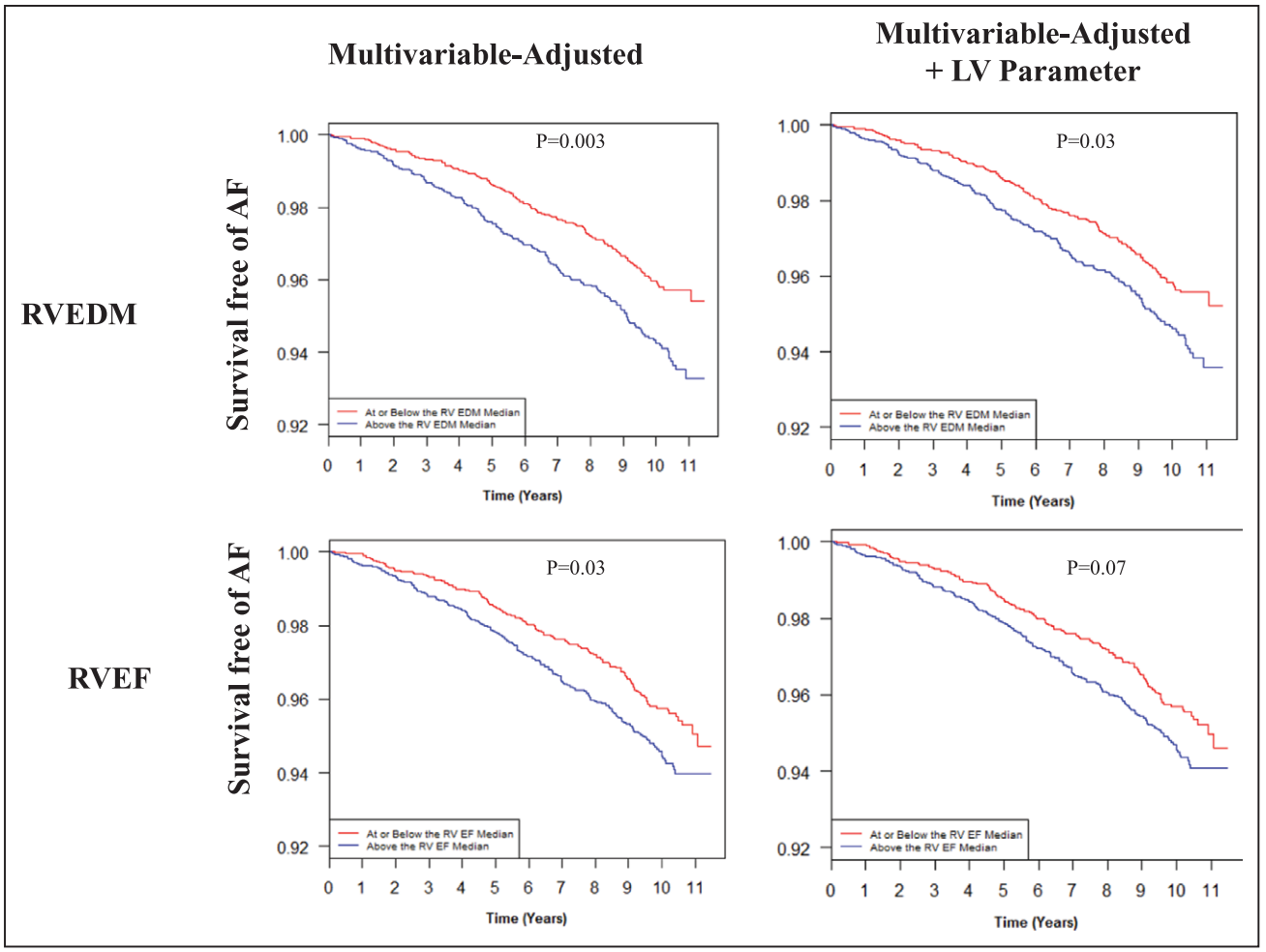


**Figure 2.** Survival free of atrial fibrillation (AF) stratified by median right ventricular (RV) mass and function. Estimated survival free of AF for study participants stratified by median RV end-diastolic mass (EDM; top) and RV ejection fraction (EF; bottom). Multivariable adjustment was for age, sex, race, body mass index, hypertension, diabetes mellitus, medication use (renin–angiotensin–aldosterone system, β-blocker, and antiarrhythmic), smoking (status and pack-years), education level, and left ventricular (LV) hypertrophy. Adjustment was then additionally performed for respective LV parameter (ie, LVEF for RVEF model; LVEDM for RVEDM model). Multivariable model for RVEDM does not include adjustment for LV hypertrophy as adjustment for LV mass (ie, LVEDM) is performed in the LV parameter-adjusted model.

(HR, 1.27 per SD; 95% CI, 1.06–1.53]; *P*=0.011; Table III in the Data Supplement).

When stratified by median value, participants with RVEDM and RVEF above the median had a significantly greater incidence of AF over the study duration even after adjustment for demographic and clinical factors (Figure 2). In the dichotomized assessment of RV morphology, RVEDM above the median remained significantly associated with AF after further adjustment for LVEDM (*P*=0.03), whereas the association between RVEF and AF was attenuated after LVEF adjustment (*P*=0.07; Figure 2).

## Discussion

In this study, we examined the association between RV morphology and risk of incident AF in a multiethnic cohort free of cardiovascular disease at baseline. We demonstrate that higher RVEF and greater RV mass are associated with incident AF even after accounting for baseline lung function, incident heart failure, and parameters of LV structure and function. These data raise the possibility of RV morphology as a structural biomarker of AF risk.

The prognostic role of RV structure and function in cardiopulmonary disease is well established.[7,9,27,28] In patients free of cardiovascular disease at baseline, greater RV mass is associated with an increased risk of heart failure and cardiovascular mortality.[7] In MESA participants, abnormal RV morphology has been linked to subclinical LV dysfunction,[13] conditions associated with abnormal pulmonary vascular function (obesity and emphysema),[17,29] and biomarkers of inflammation and neurohormonal activation.[19,20,30] In turn, each of these features—pulmonary pathology, left heart function, systemic inflammation, and neurohormonal activation—has been implicated in the pathogenesis of AF.[31,32] Nevertheless, there has been no assessment of the relationship between RV morphology and incident AF in patients free of cardiovascular disease at baseline.

In this study, we identified significant associations between greater RVEF and mass with incident AF. There are several possible explanations for these associations. First, RV morphology may serve as a structural surrogate for systemic processes implicated in AF pathogenesis, including inflammation, neurohormonal activation, and sex hormone excess.

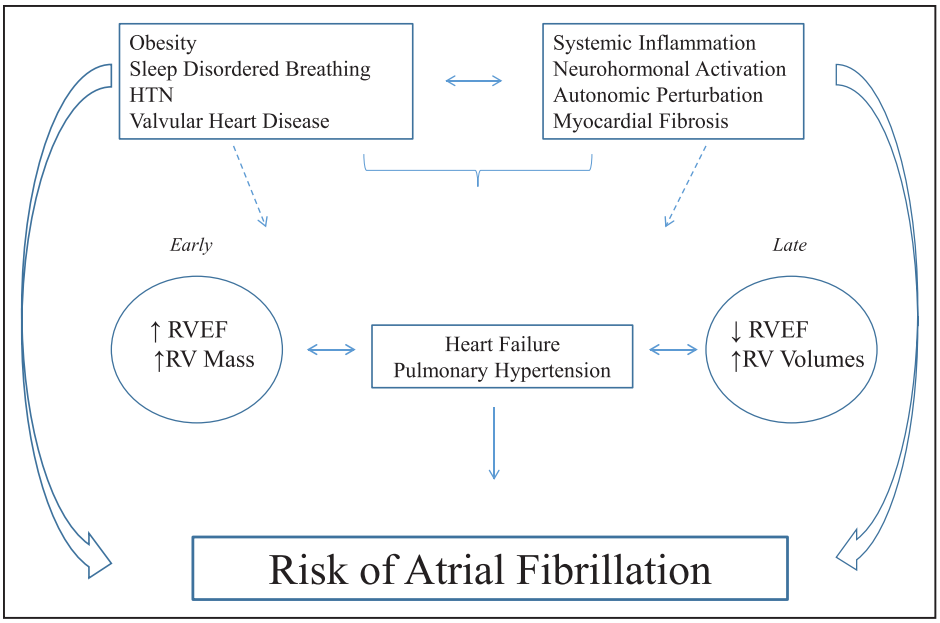


**Figure 3.** Schematic representation of the possible relationships between right ventricular (RV) morphology and atrial fibrillation (AF) pathogenesis. Schematic reflecting the possible relationships between clinical phenotypes, systemic processes, and temporal changes in at-risk RV morphology (early vs late) in the context of AF pathogenesis. EF indicates ejection fraction; and HTN, hypertension.

For example, systemic markers of inflammation, including elevated levels of CRP (C-reactive protein) and interleukin-6, have been associated with atrial electric remodeling and increased risk of AF in healthy community cohorts.[33–36] In MESA, the relationship between RV morphology and markers of inflammation has proven complex, although extreme levels of CRP and interleukin-6 were positively associated with RV mass.[19] Likewise, greater RV mass has been associated with neurohormonal activation,[20] which has been implicated as a risk factor for AF via its influence on myocardial fibrosis, atrial stretch, and modulation of ionic channel function.[36–39] Finally, in a subset of the MESA cohort, higher RVEF was associated with higher levels of estradiol, postulated to reflect myocardial effects of estrogen receptor activation.[39] Elevated estradiol has been associated with an increased risk of AF in healthy community cohorts,[38] and increasing RVEF may reflect a structural signature of sex hormone levels.

Second, individuals with established risk factors for AF (eg, obesity and sleep-disordered breathing) harbor significantly greater RV mass even after adjustment for LV mass.[17] Sleep-disordered breathing has been associated with both LV and RV hypertrophy[40] and independently predicts incident AF.[18,41] In our study, the association between RVEF and RV mass with AF persisted even after adjustment for measures reflective of pulmonary vascular function and RV afterload. Taken together, our findings suggest a potentially unique role of RV structure and function in the pathogenesis of AF. For example, a higher RV mass—and consequently higher RV end-diastolic pressure or increased RV elastance—may lead to the same deleterious consequences on atrial mechanics as higher LV mass (ie, atrial stretch, neurohormonal activation, and atrial fibrosis).[14] Whether early changes in RV morphology (RVEF and RVEDM) serve as a more sensitive barometer of systemic drivers of AF (eg, inflammation and neurohormonal activation)[19,20] that precede atrial remodeling may warrant future investigation.

## Clinical Implications

The RV is a unique morphological structure—sensitive to changes in the pulmonary and left heart circulation, with unique myofibril geometry, distinct developmental origins, and incompletely understood modes of remodeling.[8,42] As such, it represents a novel and potentially integrative measure of systemic processes, hemodynamic perturbation, and local myocardial changes (Figure 3).[8,42] Historically, the prognostic role of RV structure and function has been limited to patients with established cardiopulmonary disease, where a lower RVEF and more dilated RV is associated with morbidity and mortality.[27,28,43,44] In this study, we extend the prognostic relevance of the RV to individuals without prevalent cardiovascular disease, identifying a different phenotype (ie, greater RVEF and mass) associated with AF risk. We would highlight that a similar phenotype has been associated with cardiopulmonary pathology in the MESA population. For example, greater RV mass has been associated with increased heart failure and cardiovascular mortality,[7] and smaller RV volumes have been associated with worsening lung function.[11] To that end, this structural phenotype (ie, increased RVEF and increased RV mass) may represent early, compensatory remodeling of the RV—a process which to date remains incompletely understood.[42] Indeed, while similar compensatory remodeling has been well described for the LV,[45,46] our findings suggest that a similar intermediate phenotype for the RV may have prognostic implications.

An improved understanding of the influence of systemic processes (inflammation and neurohormonal activation) and cardiopulmonary changes (pulmonary vascular function and LV morphology) on RV morphology may help refine our understanding of RV adaptation and its related impact on AF pathogenesis. Morphological and structural features of the left heart—including fibrosis and ventricular strain—have been associated with incident AF in healthy populations, as well as

clinical outcomes after AF ablation (ie, recurrence and recovery of LV function).[47–49] Whether similar changes in RV morphology and function influence clinical outcomes in AF may warrant future exploration. Given its suggested integrative role, RV morphology may serve as a potent marker of incident cardiovascular risk, although its practical use remains untested.

## Limitations

Our study has several strengths, including its prospective design, large sample size of multiethnic participants, comprehensive evaluation of CMR-based cardiac structural measures, time-varying adjustment of clinical risk factors, and blinded adjudication of end points. There are some additional limitations. First, not all MESA participants tolerated CMR examination, and not all CMR scans were interpretable. There were minor differences in age, sex, medication use, and smoking history in those included compared with those excluded (Table I in the Data Supplement), which may influence generalizability. Second, assessments of LA volumes were not included in the original MESA protocol and were only available for a subpopulation of study participants in which there was limited power to assess RV–AF associations. Within this subpopulation, we demonstrate that RVEF retained significant association with incident AF, even after adjustment for LA volumes. Whether the identified association between RV mass and incident AF is confounded by LA volume could not be assessed in this study, although we would note that the association persisted even with adjustment for LVH, a significant structural driver of LA enlargement.[14] Third, RVEF is optimally assessed after accounting for tricuspid regurgitation which was not assessed in MESA, although we would note that participants with a history of valve replacement or significant valvular heart disease at baseline were excluded from enrollment. Although we cannot exclude the possibility of interval valvular heart disease after study enrollment, we do not think that the association between baseline RV measures and incident AF was meaningfully influenced by right- or left-sided heart disease in this healthy population. Participants with significant valvular heart disease were excluded from the MESA trial. Fourth, given the methodology of AF ascertainment, we were unable to detect asymptomatic AF or AF not associated with hospitalization. In addition, AF subtype was not assessed and may be differentially associated with abnormal RV morphology. Finally, given the design of the MESA study, we were unable to account for temporal changes in RV and LV function during study follow-up, although all models included time-varying clinical covariates which could have influenced cardiac structure during the study follow-up period.

## Conclusions

In conclusion, greater RVEF and mass were associated with an increased risk of AF in a multiethnic population free of clinical cardiovascular disease at baseline. Additional investigation of the relationship between RV morphology and AF may help to refine our understanding of RV morphological adaptation, its potential role as a structural biomarker of AF risk, and ultimately an improved understanding of AF pathogenesis.



## Appendix

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## Disclosures

None.

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# Right Ventricular Structure and Function Are Associated With Incident Atrial Fibrillation: MESA-RV Study (Multi-Ethnic Study of Atherosclerosis–Right Ventricle)

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# Supplemental Material

**Supplementary Table 1.** Baseline Characteristics of Participants Included and Excluded from Study

| Demographic and Clinical Characteristics | Study Sample (N=3,819) | Excluded (N=2,995) |
|---|---|---|
| Age, year | 61.2±10.0 | 63.3±10.4 |
| Male gender, n (%) | 1,774 (46.5) | 1,439 (48.0) |
| Race/ethnicity, n (%) | | |
| Caucasian | 1,485 (38.9) | 1,137 (38.0) |
| African American | 976 (25.6) | 917 (30.6) |
| Hispanic | 859 (22.5) | 637 (21.3) |
| Chinese | 499 (13.1) | 304 (10.2) |
| Education level, n (%) | | |
| Less than high school | 636 (16.7) | 589 (19.8) |
| High school/GED | 690 (18.1) | 546 (18.4) |
| Less than college (more than high school) | 1,100 (28.8) | 837 (28.2) |
| Bachelor degree | 685 (17.9) | 486 (16.4) |
| Graduate degree | 708 (18.5) | 514 (17.3) |
| Body mass index, $kg/m^2$ | 27.9±5.0 | 29.0±6.0 |
| Smoking status, n (%) | | |
| Never | 2,017 (52.8) | 3,418 (50.3) |
| Former | 1,343 (35.2) | 1,144 (38.5) |
| Current | 459 (12.0) | 428 (14.4) |
| Smoking pack-years | 10.7±23.0 | 12.3±21.3 |
| Diabetes mellitus, n (%) | 432 (11.3) | 427 (14.2) |
| Hypertension, n (%) | 1,616 (42.3) | 1,442 (48.1) |
| Medications, n (%) | | |
| RAAS inhibitor | 632 (16.5) | 601 (20.1) |
| β-blocker | 352 (9.2) | 297 (9.9) |
| Anti-arrhythmic | 21 (0.5) | 15 (0.5) |

GED, general education development test; RAAS, renin angiotensin aldosterone system

**Supplementary Table 2.** Proportional Hazards Models for Right Ventricular Structure and Function and Incident Atrial Fibrillation in Participants with Lung Function Assessment

| | HR | 95% CI | P |
|---|---|---|---|
| RV EF | | | |
| Unadjusted | 1.29 | 1.11 – 1.49 | <0.001 |
| Adjusted* | 1.21 | 1.03 – 1.43 | 0.02 |
| Adjusted + LV EF | 1.23 | 1.03 – 1.46 | 0.02 |
| RV EDM | | | |
| Unadjusted | 0.97 | 0.84 – 1.12 | 0.70 |
| Adjusted† | 1.31 | 1.09 – 1.57 | 0.004 |
| Adjusted + LV EDM | 1.26 | 1.04 – 1.54 | 0.02 |
| RV EDV | | | |
| Unadjusted | 0.98 | 0.85 – 1.14 | 0.82 |
| Adjusted* | 1.27 | 1.04 – 1.55 | 0.02 |
| Adjusted + LV EDV | 1.14 | 0.88 – 1.46 | 0.32 |
| RV ESV | | | |
| Unadjusted | 0.85 | 0.73 – 1.00 | 0.04 |
| Adjusted* | 0.99 | 0.81 – 1.20 | 0.88 |
| Adjusted + LV ESV | 0.93 | 0.75 – 1.14 | 0.47 |

Hazard ratios are per standard deviation increase. *Adjustment is for age, sex, race, body mass index, hypertension, diabetes, medication use (RAAS, β-blocker, anti-arrhythmic), smoking (status, pack-years), education level, left ventricular hypertrophy, and forced expiratory volume at one second ($FEV_1$). †Initial adjusted model for RV EDM does not include adjustment for left ventricular hypertrophy; adjustment for LV mass (LV EDM) is performed subsequently. HR, hazard ratio; CI, confidence interval; RV, right ventricular; LV, left ventricular; EF, ejection fraction; EDM, end-diastolic mass; EDV, end-diastolic volume; ESV, end-systolic volume.

**Supplementary Table 3.** Proportional Hazards Models for Right Ventricular Function with Adjustment for Left Atrial Volume: Nested Case:Control Analysis

| | **HR** | **95% CI** | **P** |
|---|---|---|---|
| RV EF | | | |
| Age, Sex Adjusted | 1.31 | 1.10 – 1.56 | 0.002 |
| Multivariable Adjusted* | 1.38 | 1.14 – 1.66 | <0.001 |
| Adjusted + LA volume | 1.27 | 1.06-1.53 | 0.011 |

Hazard ratios are per standard deviation increase. *Adjustment is for age, sex, race, body mass index, hypertension, diabetes, medication use (RAAS, β-blocker, anti-arrhythmic), smoking (status, pack-years), education level, and left ventricular hypertrophy. HR, hazard ratio; CI, confidence interval; RV, right ventricular; EF, ejection fraction.