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Von Willebrand Factor and the Right Ventricle (The MESA-Right Ventricle Study)

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Abstract

Elevation in plasma activity of von Willebrand Factor (vWF) reflects endothelial dysfunction and predicts death in pulmonary arterial hypertension (PAH). Higher vWF activity is also associated with lower right ventricular (RV) ejection fraction in PAH. Little is known about the relationship between vWF and RV structure and function in adults without cardiovascular disease. In the current investigation, we included 1,976 participants with MRI assessment of RV structure and function and measurement of vWF activity from the Multi-Ethnic Study of Atherosclerosis. Multivariable linear regression was used to estimate the associations between vWF activity and measures of RV structure and function after adjusting for demographics, anthropometrics, smoking, diabetes mellitus, hypertension and the corresponding left ventricular (LV) parameter. The average vWF activity was $140.7 \pm 57.2\%$. Elevated vWF activity was independently associated with lower RV mass, RV end-diastolic volume and RV stroke volume in models with and without adjustment for the corresponding LV parameter (all $p < 0.05$). There was no association observed between vWF activity and RV ejection fraction. In conclusion, higher vWF activity is associated with lower RV mass, RV end-diastolic volume and RV stroke volume. These associations are independent of common cardiovascular risk factors and LV morphologic changes.

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Keywords

Cardiovascular Imaging; Biomarkers; Pulmonary Hypertension; Right Ventricle

Introduction

Von Willebrand Factor (vWF) is principally released by endothelial cells and mediates the initiation and progression of thrombus formation via platelet aggregation at a site of vascular injury.¹ vWF reflects endothelial dysfunction which can both influence and be affected by left ventricular (LV) dysfunction.^{2,3} Elevated vWF predicts poor prognosis in several diseases including heart failure,⁴ hypertension⁵ and coronary artery disease.¹ Prior work by our group has suggested an independent association between vWF and mortality in patients with pulmonary arterial hypertension (PAH).⁶ We have also shown that elevated vWF activity is associated with lower right ventricular ejection fraction (RVEF) in patients with PAH.⁷ As a marker of endothelial dysfunction, vWF may reflect pulmonary vascular disease severity. However, the relationship between vWF and RV structure and function has not been studied in adults free of cardiovascular disease. A better understanding of the relationship of vWF with RV structure and function in adults without pulmonary hypertension may help to clarify the cardiac role of vWF in disease. We examined the relationship of vWF and measures of RV structure and function in a multiethnic cohort of adults free of clinical cardiovascular disease. We hypothesized that elevated vWF activity would be associated with greater RV mass, larger end-diastolic volume, and decreased RV ejection fraction.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study designed to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in whites, African-Americans, Hispanics and Chinese-Americans. In 2000–2002, MESA recruited 6814 men and women aged 45–84 years old from 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. Exclusion criteria included clinical cardiovascular disease (physician diagnosed heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight >136kg (300 lbs.), pregnancy, or impediment to long-term participation. The Institutional Review Boards of all participating institutions and the National Heart Lung and Blood Institute approved the protocols of MESA and all studies described herein. The MESA-Right Ventricle Study, which includes the present investigation, is an ancillary study focused on RV morphology in MESA participants eligible for MRI at the baseline examination.

The cardiac MRI protocol has been previously described⁸ and methods for interpretation of LV and RV parameters have been previously reported.⁹ Cardiac MRI examinations were transmitted to the reading center at Johns Hopkins University in Baltimore, MD, and image analysis was performed by 2 independent analysts using QMASS software (Medis, Leiden, the Netherlands). Images were magnified to 250%, contrast/brightness set to 55, and window width/level were set with the QMASS auto function.

Endocardial and epicardial borders of the RV were manually traced on short axis cine images at end-systole and end-diastole. Correct placement of RV contours relied on evaluation of cine images to determine the demarcation between the right atrium and the RV. Contours were modified at basal cardiac slices by careful identification of the tricuspid

valve so as to exclude the right atrium and to avoid overestimation of the volumes. The outflow tract was included in RV volume. Papillary muscle and trabeculae were included in the RV volumes and excluded from RV mass, as is commonly done for LV mass. RV end-systolic volume and RV end-diastolic volume (RVEDV) were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at end-diastole as the difference between epicardial and endocardial volumes of the RV free wall multiplied by the specific gravity of the heart (1.05g/mL). RV stroke volume (RVSV) was calculated by subtracting RV end-systolic volume from the RVEDV. RVEF was calculated by dividing RVSV by RVEDV. The intra-reader intra-class correlation coefficient for RV mass was 0.94 (229 scans), RVEDV was 0.99 (230 scans) and RVEF was 0.89 (230 scans). The blinded inter-reader intra-class correlation coefficients on 240 scans for RV mass, RVEDV and RVEF were 0.89, 0.96 and 0.80 respectively.

Fasting blood samples were drawn, processed and stored using standardized procedures.¹⁰ The MESA parent study originally measured baseline vWF in 1,000 participants of whom 733 also had RV data from cardiac MRI. We selected 1290 additional participants with sufficient plasma and available RV data for measurement of vWF. vWF activity was measured in the Laboratory for Clinical Biochemistry Research at University of Vermont (Burlington, VT, USA). vWF activity was measured by the Liatest (latex immunoturbidometric) assay on the STA analyzer (Diagnostica Stago, Parsippany, NJ). In this assay the degree of agglutination (measured by light absorption) between vWF in the sample and vWF monoclonal antibody in the assay is directly proportional to vWF activity. The intra-assay and inter-class coefficient of variation was 3.7 and 4.5% respectively.

Race/ethnicity was self-reported during the baseline MESA examination according to 2000 US Census criteria. Height was measured to the nearest 0.1 cm with the subject in stocking feet and weight was measured to the nearest pound with the subject in light clothing using a balanced scale. Hypertension was accounted for with systolic blood pressure (mmHg) and current use of anti-hypertension medication. Presence of diabetes mellitus was based on self-reported physician diagnosis, use of medication for hyperglycemia, or fasting glucose value $\geq 126 \text{ mg dl}^{-1}$, measured by rate reflectance spectrophotometry (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY, USA). Fasting glucose of 100–125 mg dl^{-1} was considered impaired fasting glucose. Smoking was classified as current, past or never. Spirometry and computed tomographic (CT) lung density measures of % emphysema were available for a subset of participants.¹¹ Flow-mediated dilation (FMD) as a marker of systemic endothelial dysfunction has been previously described.¹² The brachial artery was occluded by a sphygmomanometer at a pressure of 50mmHg above systolic blood pressure for 5 minutes. Maximal brachial artery dilation over the last 2 minutes of this occlusion was recorded. Percent FMD (%FMD) was the maximum brachial artery diameter minus the baseline diameter divided by the baseline diameter expressed as a percentage. The MESA Typical Week Physical Activity Survey (TWPAS) had been previously described and includes intentional exercise as the sum of metabolic equivalents (METs) from activities that were consciously done for exercise. Intentional exercise was most strongly associated with LV structure and function.¹³

We used linear regression to characterize the relationship between vWF and RV parameters. Covariates were chosen 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 and study site. Adjustment for height and weight avoided the assumptions made in indexing the RV measures to certain parameters of body size (e.g. body surface area), while achieving the same end of accounting for differences in body size between participants. In fully adjusted models we included smoking, hypertension, diabetes mellitus,

cholesterol, impaired glucose tolerance, systolic blood pressure, treatment for hypertension, and CRP. We then adjusted the RV mass analysis by LV mass, the RVEDV analysis by LVEDV and the RVEF analysis by LVEF to evaluate for independence from LV abnormalities (e.g. increased LV mass causing pulmonary venous hypertension leading to increased RV mass) and to better account for differences in body size. Because RVSV and LV stroke volume are interdependent, we adjusted for LV mass in this case. In separate analyses, we adjusted for intentional exercise, lung function (forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC) and % emphysema on chest CT)(n=1,826) and % FMD (n=1,620). Generalized additive models were used to assess possible nonlinearity in the associations between vWF and RV parameters. Statistical significance was defined as $p < 0.05$. Analyses were performed using STATA 11.0 (StataCorp, College Station, TX, USA). We anticipated 99% power to detect a difference of 0.3 standard deviations in RV mass, volumes and ejection fraction from the top quintile to the bottom quintile of vWF in the full sample.

Results

There were 6814 men and women enrolled in MESA (Figure 1). Of them, 5098 underwent cardiac MRI and 5004 (98%) had interpretable exams for the LV. We selected 4634 scans and attempted reads in 4484 scans before reaching our goal of 4204 participants with successful RV interpretation (94% of 4484 attempted). vWF was available for 2011 of these participants. Thirty-five participants were excluded for missing covariates leaving 1976 in the study sample. Table 1 shows characteristics of the study sample compared with those excluded. The mean age was 60.2 years and 47.2% were men. As compared with MESA participants not included in the analysis, the study sample was slightly younger with a slightly lower prevalence of hypertension and diabetes. Mean RV mass in the sample was 21.4 ± 4.4 g, the mean RVEDV was 127.2 ± 31.5 mL and mean RVSV was 88.7 ± 20.9 mL. The mean RVEF was $70.2 \pm 6.6\%$. All analyses were adjusted for height and weight (accounting for differences in body size), so that indexing to certain measures (e.g., body surface area) was not necessary and was not performed.

vWF was independently associated with RV mass (Table 2, Figure 2). Higher vWF was associated with lower RV mass. This relationship was not meaningfully altered by adjustment for cardiovascular risk factors or LV mass. Adjustment for intentional exercise, %FMD (n=1620) (as a proxy for systemic endothelial function) or FEV1, FVC and radiographic % emphysema (n=1826) did not alter the relationship between vWF and RV mass in participants with these measures (Table 3).

Higher vWF was associated with lower RVEDV (Table 2, Figure 2). This relationship was unchanged after adjustment for cardiovascular risk factors and diminished but remained significant after adjustment for LVEDV. Adjustment for intentional exercise, systemic endothelial dysfunction or lung function did not alter or attenuate the inverse relationship between vWF and RVEDV (Table 3).

vWF was independently associated with RVSV (Table 2, Figure 2). Higher vWF was associated with a lower RVSV. This relationship was unchanged after adjustment for cardiovascular risk factors. The relationship persisted after adjustment for LV mass. Adjustment for intentional exercise, systemic endothelial dysfunction or lung function did not alter or attenuate the inverse relationship between vWF and RVEDV (Table 3).

Elevated vWF activity was not associated with RVEF (Table 2, Figure 2). Adjustment for cardiovascular risk factors, intentional exercise, systemic endothelial dysfunction and lung function did not change this result (Table 3). There was no effect modification between vWF

and age, gender, race or respective LV parameters (all $p>0.25$). All analyses were repeated using generalized additive models. No significant non-linearity was detected (all $p>0.3$).

Discussion

We have shown that elevated vWF activity is associated with lower RV mass, RVEDV, and RVSV. This finding is opposite from that reported for the left ventricle. Previous publications have reported that elevated vWF and systemic endothelial dysfunction are associated with increased LV volumes and mass.¹⁴ Our finding of the inverse relationship in the RV reinforces the limited ability to extrapolate findings from left to right ventricles.

The association between vWF and LV hypertrophy is likely mediated by the strong correlation between vWF and hypertension.¹⁵ We found instead that the RV has smaller volumes and lower mass with increasing vWF. vWF was recently described as a potent angiogenesis inhibitor and our findings may represent a paucity of angiogenesis with impaired blood flow to active myocardium and restricted RV growth.¹⁶ Alternatively, elevated vWF activity may indicate coronary endothelial dysfunction accompanied by the inability of coronaries to dilate and provide increased blood flow to support cardiac growth.^{1,17} Inhibiting angiogenesis and/or coronary dysfunction leads to decreased cardiac mass and volumes in otherwise healthy animal models.¹⁸

If elevated vWF activity does reflect the inability to augment blood flow in active cardiac muscle, this may contribute to the increased mortality we previously described in patients with pulmonary hypertension and elevated vWF activity.^{6,7} Increased perfusion is part of normal myocardial growth and imbalance between myocyte growth and perfusion leads to heart failure.¹⁹ Abnormal RV perfusion reserve in diseases with pathologic afterload leads to weaker contraction, frank ischemia and chamber dilation such as that seen in the failing RV of advanced PAH.^{18,20} Recent work has further reinforced the importance of angiogenesis in cardiac disease. Animal studies have demonstrated that estrogen-dependent angiogenesis rescues the failing RV in rats with PAH.²¹ Further study is necessary to test the role of vWF in controlling RV angiogenesis; however, the question about myocardial perfusion reserve in RV structure and function raised by our current findings is both interesting and may be clinically relevant in diseases characterized by increased RV afterload.

While we believe that restricted cardiac growth may be the most plausible explanation for a smaller RV along a gradient of increasing vWF, it is not the only possibility. One report does suggest that vWF stimulates platelet-mediated production of nitric oxide, which could decrease pulmonary vascular resistance, pulmonary artery pressure, and RV workload²²; however, this report conflicts with others that suggest increased vWF is associated with decreased nitric oxide.²³

Alternatively, because our study was cross-sectional, reverse causation could explain the findings. Diastolic dysfunction of the LV, with smaller than expected volumes, has been hypothesized to lead to diminished blood flow with subsequent systemic endothelial dysfunction and vWF elevation.²⁴ While our association of higher vWF with smaller RVEDV (independent of LVEDV) could suggest impaired RV relaxation, we did not measure RV diastolic function directly.

In MESA as in other studies, vWF is associated with structural and morphologic changes in the LV.^{14,25} While other studies suggest increased LV mass with elevated vWF, decreased LV mass was seen in the MESA cohort.²⁵ In comparison with other studies MESA was notable for a lower severity of systemic hypertension and may have had less confounding by afterload. Impaired angiogenesis with increased vWF would be thought to affect both

ventricles, however, while associations between vWF and RV parameters were weakened after adjustment for LV structure and function, these associations persisted. This may reflect a shared bi-ventricular mechanism but a disproportionate effect on the RV perhaps due to the presence of systemic hypertension but lack of pulmonary hypertension. Alternatively adjustment by LV parameters may reduce residual confounding by body size.²⁶ Adjustment for intentional exercise, which has previously been associated separately with cardiac hypertrophy and decreased vWF, had no effect on our observed associations.^{13,27} Finally, adjustment for systemic endothelial dysfunction (FMD%) and lung structure and function had no effect on the observed inverse association between vWF and RV mass and volumes, suggesting that systemic vascular dysfunction and pulmonary dysfunction may not confound our findings.

There was no association between vWF and RVEF. This may represent the absence of a relationship between vWF and contractile function. Alternatively, ejection fraction is a load-dependent measure of contractile function.²⁸ Therefore, RVEF may be poorly able to detect changes in contractility in the setting of very low RV afterload, which is presumed in the MESA population.

Not all patients underwent MRI or had available vWF levels, although the study sample was fairly similar to MESA participants lacking these measures. As is possible in all observational studies, residual or unmeasured confounding could account for the results. Our study was cross-sectional and, while a discussion of mechanism is relevant, causality cannot be confirmed. While agreement between MRI readers was excellent, measurement error could impact our findings and measurement of invasive pulmonary hemodynamics was not feasible in this large study of community dwelling participants free of cardiovascular disease. In addition, vWF activity assays have variable precision, which may contribute to misclassification. These assays do not, however, have a systematic bias and it is unlikely that vWF assay differences alone account for our results.²⁹ Finally, the absence of clinical cardiovascular disease in this cohort led to relatively small effect estimates. However, the difference in RV mass from the uppermost to lowermost quintiles of vWF was 3.8%, greater than the 2.8% increase in LV mass seen with diabetes in MESA.³⁰ These small changes may still reflect important pathophysiologic processes.

Acknowledgments

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. We thank the other investigators, staff, and participants of the MESA and MESA-Lung Studies for their valuable contributions. A full list of participating MESA Investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

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Figure 1. Study Sample

Figure 2. The association between vWF and RV parameters

Linear regression adjusted for age, gender, race/ethnicity, study site, height, weight, education, smoking, systolic blood pressure, treatment for hypertension, diabetes mellitus, cholesterol, impaired glucose tolerance, and c-reactive protein.

Table 1

Characteristics of the study sample compared with excluded MESA subjects

Variable	Study Sample (n=1976)	Excluded (n=4838)
Age (years)	60.2±9.9	62.9±10.3
Male	47.2%	47.1%
Race/Ethnicity		
White	43.3%	36.5%
Chinese	10.9%	12.1%
African-American	25.6%	28.6%
Hispanic	20.1%	22.7%
Educational attainment		
No high school degree	14.5%	19.5%
High school degree	16.2%	19.0%
Some college	16.6%	16.2%
Bachelor's Degree	19.7%	16.2%
Higher than bachelor's degree	22.0%	16.4%
Height (cm)	167.0±10.1	166.1±10.0
Weight (kg)	77.8±16.6	79.0±17.6
Body mass index (kg/m ²)	27.8±5.0	28.6±5.7
Cigarette smoking status		
Never	52.1%	49.6%
Former	35.2%	37.2%
Current	12.7%	13.2%
Hypertension	40.6%	46.6%
Systolic blood pressure (mmHg)	123.6±20.2	127.8±21.9
Diastolic blood pressure (mmHg)	71.7±10.1	72.0±10.3
Diabetes mellitus	10.4%	14.9%
vWF activity	140.7±57.2%	145.2±57.5% *

cm indicates centimeters; kg, kilogram; m², meters squared; mmHg, millimeters of mercury; and vWF, von Willebrand Factor

* 309 subjects with measured vWF not included in the study sample because of missing MRI or covariates

Table 2

Multivariable linear regression for von Willebrand Factor activity and right ventricular parameters

Right Ventricular Parameter	Per 50% increase in vWF activity		
	Coefficient	(95% CI)	p-value
Mass (g), Limited model	-0.2	(-0.4, -0.1)	<0.001
Mass (g), Adjusted model	-0.2	(-0.4, -0.1)	<0.001
Mass (g), Adjusted model + left ventricular mass	-0.2	(-0.4, -0.1)	<0.001
End-diastolic volume (mL), Limited model	-1.2	(-2.1, -0.4)	0.005
End-diastolic volume (mL), Adjusted model	-1.2	(-2.1, -0.4)	0.005
End-diastolic volume (mL), Adjusted model + left ventricular end-diastolic volume	-0.7	(-1.3, -0.1)	0.03
Stroke volume (mL), Limited model	-0.8	(-1.4, -0.1)	0.02
Stroke volume (mL), Adjusted model	-0.7	(-1.4, -0.1)	0.02
Stroke volume (mL), Adjusted model + left ventricular mass	-0.6	(-1.2, 0.0)	0.04
Ejection fraction (%), Limited model	0.1%	(-0.1, 0.3)	0.4
Ejection fraction (%), Adjusted model	0.1%	(-0.1, 0.4)	0.4
Ejection fraction (%), Adjusted model + left ventricular ejection fraction	0.1%	(-0.1, 0.3)	0.4

Limited model: age, gender, race/ethnicity, study site, height and weight

Adjusted model: limited model + education, smoking, systolic blood pressure, treatment for hypertension, diabetes mellitus, cholesterol, impaired glucose tolerance, and c-reactive protein

Table 3

Multivariable linear regression for von Willebrand Factor and right ventricular parameters accounting for differences in lung function, systemic endothelial dysfunction and exercise

Right ventricular parameter	Per 50% increase in vWF activity		
	Coefficient	(95% CI)	p-value
<u>Adjusted for lung function</u>			
Mass (g)	-0.2	(-0.4, -0.1)	<0.001
End-diastolic volume (mL)	-1.1	(-2.0, -0.2)	0.01
Stroke volume (mL)	-0.7	(-1.3, -0.1)	0.04
Ejection fraction (%)	0.2%	(-0.1, 0.4)	0.2
<u>Adjusted for systemic endothelial dysfunction</u>			
Mass (g)	-0.3	(-0.4, -0.1)	<0.001
End-diastolic volume (mL)	-1.4	(-2.3, -0.4)	0.006
Stroke volume (mL)	-0.8	(-1.5, -0.1)	0.03
Ejection fraction (%)	0.1%	(-0.2, 0.4)	0.5
<u>Adjusted for Exercise</u>			
Mass (g)	-0.2	(-0.4, -0.1)	<0.001
End-diastolic volume (mL)	-1.2	(-2.0, -0.3)	0.007
Stroke volume (mL)	-0.7	(-1.3, -0.1)	0.03
Ejection fraction (%)	0.1%	(-0.1, 0.4)	0.4

Lung function adjustment: adjusted model+ forced expiratory volume at 1 second, forced vital capacity and % emphysema on CT

Systemic endothelial dysfunction adjustment: adjusted model+ flow mediated dilation of the brachial artery

Exercise adjustment: adjusted model+ intentional exercise (METS)