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Association Between Aortic Vascular Inflammation by PET/CT and Aortic Distensibility by MRI in Psoriasis

PARAG SHUKLA[1,2], AMIT DEY[2], AGASTYA BELUR[2], JACOB GROENENDYK[2], YOUSSEF ELNABAWI[2], ADITYA GOYAL[2], JUSTIN RODANTE[2], LEONARD GENOVESE[2], MARK AHLMAN[2], MARTIN PLAYFORD[2], NEHAL MEHTA[2]

1 PSYCHOLOGY, CCAS '18, pshukla@gwu.edu 2 The National Heart, Lung, and Blood Institute (NHLBI), NIH, Bethesda, MD

ABSTRACT

Introduction:
Globally, 18 million people die from cardiovascular disease (CVD) annually, making it the leading cause of morbidity and mortality worldwide. In recent years, inflammation has been established as a key cause of CVD, but the effects of anti-inflammatory treatment on cardiovascular (CV) risk remains poorly understood. Psoriasis (PSO), a chronic inflammatory skin disease associated with increased CV events, provides an ideal clinical model to study the role of inflammation in CV disease. Aortic vascular inflammation (VI) by [18F]-fluorodeoxyglucose (FDG) PET/CT as well as aortic distensibility (AD) by MRI, are important markers of subclinical CV disease and have been shown to predict future CV events. Following subclinical markers, such as AD, enables physicians to make judicious treatment decisions before CV events such as stroke, myocardial infarction, or angina occur. Our study demonstrates a novel association between VI and AD in patients with chronic inflammatory disease.

Hypothesis:
A reduction in aortic vascular inflammation (VI), measured by PET/CT, will associate with increased AD, measured by MRI at 1-year.

Methods:
Consecutively recruited PSO patients (N=50) underwent whole-body PET/CT scans to quantify VI as target-to-background ratio (TBR). Descending aorta contours on MRI were traced throughout the cardiac cycle [Qflow, Medis] to measure AD. Longitudinal changes in aortic VI and AD were analyzed by multivariable regression.

Results:
The cohort was middle aged (mean ± SEM: 49.8 ±1.9 years), mostly male (56%), had low CVD risk, and mild-to-moderate PSO. At 1-year follow up, patients had a median improvement in PSO severity of 40% ($p<0.001$) with use of biological therapy (28/50 patients) while aortic VI decreased by 8% (1.81 ± 0.05 vs 1.67 ± 0.04, $p<0.001$) and AD increased by 10% (0.61 ± 0.03 vs 0.67 ± 0.04, $p=0.04$). Reduction in aortic VI was associated with an improvement in AD beyond traditional CV risk factors, statin use, and systemic/biologic PSO therapy ($\beta = -0.36$, $p=0.04$).

Conclusion:
Improvement in aortic VI in patients with psoriasis by PET/CT is associated with improvement in AD by MRI at 1-year, suggesting that treatment of inflammation may have a favorable impact on functional characteristics of the aorta. These findings further advance our understanding of the role of inflammation in CVD and the utility of MRI for inflammatory CVD risk prediction. Our novel findings can help improve the accuracy of CVD risk prediction, enable physicians to make evidence-based decisions, and decrease the global economic burden of cardiovascular disease on healthcare systems.

INTRODUCTION

Globally, 18 million people die from cardiovascular disease (CVD) annually, making it the leading cause of morbidity and mortality worldwide (Roth et al., 2017). In recent years, inflammation has been established as a key cause of CVD (Libby, Ridker, & Maseri, 2002), but the effects of anti-inflammatory

treatment on cardiovascular (CV) risk remain to be explored in detail (Lerman et al., 2017). Psoriasis (PSO), a chronic inflammatory skin disease, is associated with innate and adaptive immunity activation, both of which play important roles in PSO pathogenesis (Harrington, Dey, Yunus, Joshi & Mehta, 2017). Chronic inflammatory diseases such as psoriasis are associated with increased CV events, and provide an ideal clinical model to study inflammation and CV risk (Harrington, Dey, Yunus, Joshi & Mehta, 2017). Aortic vascular inflammation (VI) by [18F]-fluorodeoxyglucose (FDG) PET/CT as well as aortic distensibility (AD) by MRI, are important markers of subclinical CVD and have been shown to predict CV events (Abdelbaky et al., 2013; Redheuil et al., 2014). Macrophages are recognized as the cells that drive vascular inflammation thereby causing vessel damage (Libby, Ridker, & Maseri, 2002). FDG as visualized by PET-CT accumulates in the arterial wall proportional to the concentration of macrophages in the arterial wall and is associated with markers of CVD (Mehta et al., 2011a).

Aortic distensibility is a measure of the degree of stiffness of the aortic wall. Changes in subclinical markers, such as AD over time, enable physicians to make judicious treatment decisions before CV events such as stroke, myocardial infarction, or angina occur (Yonemura et al., 2005). Our longitudinal study demonstrates a novel association between change in VI and change in AD in patients with psoriasis at 1-year.

HYPOTHESIS

A reduction in aortic VI, measured by FDG PET/CT, will associate with increased AD, measured by MRI, at 1-year.

METHODS

Consecutively recruited PSO patients (N=50) underwent whole-body PET/CT and MRI scans to quantify VI as target-to-background ratio (TBR) and aortic distensibility respectively. Following patients' overnight fast, whole body FDG PET/CT images were obtained at 60 minutes after IV administration of 10 mCi FDG in psoriasis. FDG PET/CT images of the aorta for our study were analyzed using an imaging software called Extended Brilliance Workspace (Phillips Healthcare). Two-dimensional regions of interest were drawn on axial slices of the aorta from the level of the aortic root to the level of the iliac bifurcation to obtain a maximal standardized uptake value (SUV_{max}), thus quantifying vascular inflammation in vivo. Regions of interest were placed within the lumen of 10 continuous slices of the superior vena cava and averaged to produce one venous value. SUV_{max} values from each aortic slice were divided by the venous SUV_{mean}, yielding a TBR (Mehta et al., 2011b; Naik et al., 2015). Descending aorta contours on MRI images were traced throughout the cardiac cycle [Qflow, Medis] to measure AD. A contour was created outlining the descending aorta for all of the images. A graph was then generated: time vs. area of the aorta and the largest area and smallest areas were recorded for each patient. Distensibility was calculated as [(maximum area - minimum area) X 1000] / [(minimum area) X (pulse pressure)] (Ohyama et al., 2016). Systolic and diastolic blood pressures, used to calculate pulse pressure, were measured on the day of the scans for all patients in the study. (Figure 1) Pulse pressure is the difference between the systolic and diastolic blood pressures. Longitudinal changes in aortic VI and AD were analyzed by multivariable regression.

RESULTS

The cohort was middle aged (mean ± SEM: 49.8 ±1.9 years), mostly male (56%), and mild-to-moderate PSO (Table 1). Moreover, the cohort was overweight to obese and originally had low CV risk. At the 1-year follow up, patients had a median improvement in PSO severity of 40% ($p<0.001$) with use of biological therapy such as anti-TNF and anti-IL 12/23 (28/50 patients). In conjunction with improvement in psoriasis severity, aortic VI decreased by 8% (1.81 ± 0.05 vs 1.67 ± 0.04, $p<0.001$) and AD increased by 10% (0.61 ± 0.03 vs 0.67 ± 0.04, $p=0.04$). Furthermore, reduction in aortic VI was associated with an improvement in AD beyond traditional CV risk factors, statin use, and systemic/biologic PSO therapy ($\beta=-0.36$, $p=0.04$).

DISCUSSION

We demonstrate that vascular inflammation in the aorta is associated with deleterious consequences in aortic structure and function by simultaneous MRI. Specifically, improvement in aortic vascular inflammation was related to decreased distensibility in the aorta after adjusting for known CVD risk factors. These findings are especially significant given that AD and vascular inflammation either predicts CVD, or relate to its severity.

Vascular inflammation has been shown to drive the formation, propagation and finally rupture of atherosclerotic plaques in injured blood vessels (Libby, Ridker, & Maseri, 2002). Moreover, VI is being increasingly recognized as a robust surrogate marker for vessel wall disease (Mehta et al., 2011a). The use of MRI permitted us to measure aortic distensibility, which has been associated with known CVD risk factors as well as prospective CV events. In a study of 1053 participants, Malayeri et al. linked AD to older age, hypertension, and current smoker status (Malayeri et al., 2008). Therefore, our use of AD provided a reliable surrogate for understanding how vascular inflammation may relate to early atherosclerosis.

Inflammatory blood cells such as neutrophils, monocytes and macrophages play a critical role in vascular inflammation. Elements of the inflammatory

	Baseline N=50	1-year N=50	p-value
Demographic & Clinical Characteristics			
Age, years	49.8±1.9	50.9±1.9	**<0.001**
Males	27 (56)	27 (56)	1.00
Hypertension	13 (27)	11 (23)	0.48
Hyperlipidemia	23 (48)	25 (52)	0.53
Type-2 diabetes	7 (15)	5 (10)	0.16
Body mass index, kg/m^2	28.9±0.82	28.5±0.79	0.17
Waist-to-hip ratio	0.95±0.01	0.95±0.01	0.25
Current smoker	2 (4)	2 (4)	1.00
Statin use	17 (35)	19 (40)	0.16
Laboratory Values			
Systolic BP, (mm/Hg)	126.8±2.4	118.2±1.9	**<0.001**
Diastolic BP, (mm/Hg)	73.3±1.3	69.2±1.1	**0.003**
Total cholesterol, mg/dL	180.5±5.4	176.1±5.4	0.19
HDL-c, mg/dL	56.8±3.1	62.4±3.6	**0.002**
LDL-c, mg/dL	96.3±4.6	89.0±4.7	0.10
Triglycerides, mg/dL	92 (77-139)	110 (76-150)	0.89
C-reactive protein, mg/L	2.1 (0.8-3.7)	1.8 (0.6-3.2)	0.09
Framingham risk score	4 (1-7)	1.5 (1-6)	0.09
Psoriasis Characteristics			
Psoriasis area severity index score	5.2 (2.8-11.7)	3.1 (1.8-5.2)	**0.003**
Systemic or biologic therapy	20 (42)	28 (58)	**0.01**
Vascular Inflammation by 18-FDG PET/CT			
Aortic target-to-background ratio	1.81±0.05	1.67±0.04	**<0.001**
MRI Functional Indices			
Aortic distensibility (X100, mm/Hg)	0.61±0.03	0.67±0.04	**0.04**

Values are reported as mean±SEM or median (IQR) for continuous variables and as n (%) for categorical variables. Comparisons were performed by Paired t-test for parametric and Wilcoxon-signed rank-test for non-parametric continuous variables, and by Pearson's chi-square test for categorical variables. P-value<0.05 deemed significant.

TABLE 1. | *Characteristics of Psoriasis Cohort*

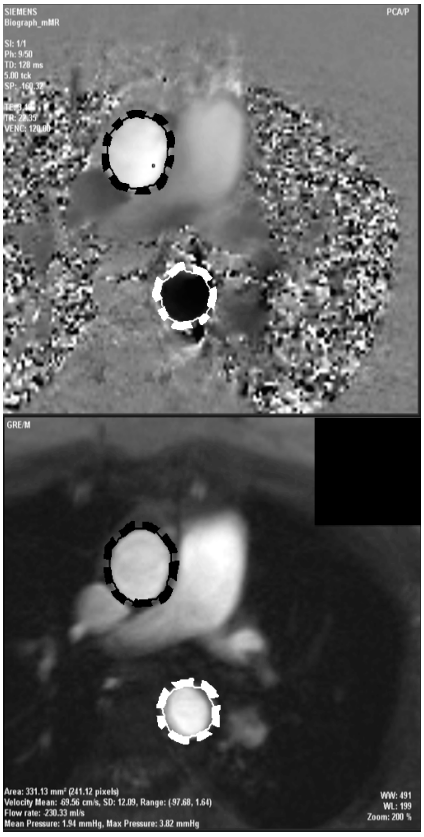

FIGURE 1. | *This image shows contours (region of interest) created around the descending aorta (white dashes) and ascending aorta (black dashes) using the imaging software Medis QFlow to quantify aortic lumen area during a single contraction/expansion of the heart. The largest and smallest aortic lumen area are used to calculate aortic distensibility.*

process inclusive of monocytes are involved in the early stages of atherogenesis from development of the fatty streak and growth of atherosclerotic plaque until plaque rupture (Libby, Ridker, & Maseri, 2002). Furthermore, monocyte-derived macrophages contribute to arterial stiffening through production of proteinases, resulting in abnormal elastin and collagen formation (Rajavashisth et al., 1999). Furthermore, VI can also lead to endothelial dysfunction and activation that can also contribute to the decrease of vessel distensibility (Kinlay et al., 2001). Treatment of psoriasis by anti-inflammatory therapy has been associated with decrease in vascular disease (Bissonnette et al., 2013); therefore, treatment should be accompanied by reduction in inflammatory blood cell characterization and thus aortic inflammation and stiffness.

CONCLUSION

Improvement in aortic VI in patients with psoriasis by PET/CT is associated with improvement in AD by MRI at 1-year, suggesting that treatment of inflammation may have a favorable impact on functional characteristics of the aorta. This longitudinal study's findings further advance our understanding of the role of inflammation in CVD and the utility of MRI for inflammatory CVD risk prediction. Our novel findings can help improve the accuracy of CVD risk prediction, enable physicians to make evidence-based decisions, and decrease the global economic burden of cardiovascular disease on healthcare systems. However, larger studies are needed to validate our findings.

LIMITATIONS

We acknowledge certain limitations in our study, which include a small sample size and a single-center study design. The cross-sectional nature of our study does not enable us to establish causality, or correlate with incidence of cardiovascular events. Finally, we did not characterize inflammatory cells in the blood and thus are unable to show any mechanistic link between VI and AD.

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