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Short communication

Myocardial perfusion imaging-derived left ventricular strain: Regional abnormalities associated with transthyretin cardiac amyloidosis

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ABSTRACT

Background: Transthyretin (ATTR) cardiac amyloidosis is associated with an apical-sparing strain pattern on TTE. We hypothesize that strain indices derived from myocardial perfusion imaging (MPI) can identify this abnormality.

Methods: A group with ATTR amyloidosis was compared to age-matched controls with LVH but without amyloidosis who underwent PET or SPECT MPI. Strain values were used to calculate the apical strain index (ASI), apex-to-base ratio (ABR), and ejection fraction to global strain ratio in multiple planes.

Results: A direct comparison using Welch's *t*-tests reveals 6 statistically significant metrics. After regression analysis, the circumferential ASI and ABR at rest remain significantly greater in the ATTR group compared to controls.

Conclusion: MPI-derived strain from the circumferential plane at rest may distinguish cardiac amyloidosis from other forms of LVH. If these findings are confirmed with validation studies, routine MPI-derived strain analysis could identify patients with subclinical amyloidosis who may benefit from further testing.

1. Introduction

Transthyretin cardiac amyloidosis (ATTR) is a form of amyloidosis involving a mutation in the transthyretin (TTR) gene that can result in a restrictive cardiomyopathy [1]. These mutations can occur via hereditary mechanisms involving specific amino acid substitutions (ATTRv). However, they can also occur over time due to aging and oxidative stress, without identifiable mutations. If no mutation is noted, this is considered wild-type cardiac amyloidosis (ATTRwt) [1,2]. This is important to note, as the different variants of this disease lead to variable presentations [1,2].

Recent advances in cardiac imaging have favored a non-invasive diagnostic approach to ATTR amyloidosis. This includes screening with transthoracic echocardiography (TTE) and further assessment with a technetium pyrophosphate scan, over a more invasive endomyocardial biopsy [3]. An "apical-sparing" strain pattern on TTE, demonstrating grossly normal strain in the LV apex with abnormal strain in the mid and basal segments, is sensitive and specific for cardiac amyloidosis (approximately 88 % and 85 % respectively) [4]. Myocardial strain values thus have high utility in the diagnostic approach to ATTR amyloidosis. Aside from cardiac MRI, there is limited data to assess myocardial strain derived from other non-invasive cardiac imaging

Abbreviations: ABR, Apex-to-base Ratio; ASI, Apical Strain Index; AUC, Area Under the Curve; EFGCS, Ejection Fraction to Global Circumferential Strain; EFGLS, Ejection Fraction to Global Longitudinal Strain; GLS, Global Longitudinal Strain; HFpEF, Heart Failure with Preserved Ejection Fraction; ATTRv, Hereditary Transthyretin Cardiac Amyloidosis; LVEF, Left Ventricular Ejection Fraction; LVH, Left Ventricular Hypertrophy; MPI, Myocardial Perfusion Imaging; PET, Positron Emission Tomography; ROC, Receiver Operating Characteristics; SPECT, Single-photon Emission Computerized Tomography; TTE, Transthoracic Echocardiography; TTR, Transthyretin; ATTR, Transthyretin Amyloidosis; ATTRwt, Wild-type Transthyretin Cardiac Amyloidosis.

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modalities. Our group recently developed a method to measure left ventricular strain from gated myocardial perfusion images and showed that it correlates well with TTE-derived strain [5]. Apical strain index (ASI), apex-to-base ratio (ABR), and ejection fraction to global strain are three parameters that have been used to distinguish cardiac amyloidosis from other causes of left ventricular hypertrophy (LVH) [6–8]. Previous studies have used TTE-derived strain values to calculate these indices. Here we sought to assess the capability of MPI-derived strain analysis to detect regional abnormalities associated with cardiac amyloidosis.

2. Methods

We conducted a retrospective case-control study involving a cohort of 8 individuals with ATTR amyloidosis and 32 age-matched controls with comparable degree of LVH but without evidence of ATTR amyloidosis who underwent ischemic evaluation with either rest/stress positron emission tomography (PET) MPI or single-photon emission computerized tomography (SPECT) MPI. ASI, ABR, ejection fraction to global longitudinal strain (EFGLS) and ejection fraction to global circumferential strain (EFGCS) were calculated for all patients using MPI-derived strain values for each segment of the myocardium at rest and at stress in the longitudinal, circumferential, and radial direction. ASI was defined as the average strain among the apical segments of the left ventricle divided by the sum of average mid and average basal strain values. ABR was defined as the average apical strain value divided by the average basal strain value. EFGLS and EFGCS were defined as MPI-derived ejection fraction divided by the global strain value derived from MPI in the longitudinal and circumferential planes respectively. Welch's *t*-tests and linear regression analysis were performed to assess for differences between the groups. ROC analysis was completed to assess relative sensitivity and specificity of these indices.

3. Results

The ATTR cohort included 6 individuals with ATTRv cardiac amyloidosis based on genetic testing and 2 individuals with ATTRwt cardiac amyloidosis. Among the 6 individuals with ATTRv, 3 patients were diagnosed via pyrophosphate scan and 2 patients were diagnosed via endomyocardial biopsy. One patient deferred endomyocardial biopsy but was diagnosed with ATTRv due to highly suspicious findings on TTE and cardiac MRI with a positive genetic test. One individual with ATTRwt was diagnosed via positive pyrophosphate scan while the other individual was diagnosed with an endomyocardial biopsy. The ATTR cohort included 6 men and 2 women with an average age of 69.5 (± 4.04) years. The control group included 20 men and 12 women with an average age of 66.5 (± 3.65) years. Additional population data can be viewed in Table 1.

The mean value for each of the 16 indices is higher in the ATTR group compared to controls. A direct comparison of the two groups utilizing Welch's *t*-tests revealed 6 metrics that are significantly greater in the ATTR group compared to the control group. After performing linear regression analysis, the circumferential ASI and ABR at rest were noted to be significantly greater in the ATTR group compared to controls. Average circumferential ASI at rest in the ATTR cohort was 0.98 ± 0.19 compared to 0.65 ± 0.13 in controls ($p = 0.002$). Circumferential ABR at rest was 2.36 ± 0.61 in the ATTR cohort compared to 1.38 ± 0.32 in controls ($p = 0.002$). The area under the curve for the circumferential ASI and ABR was 0.96 and 0.95 respectively. Complete statistical analysis can be found in Fig. 1.

4. Discussion

The results suggest that MPI-derived strain indices, particularly within the circumferential plane, may differentiate ATTR amyloidosis from controls and provide a foundation for future studies to test this hypothesis. To our knowledge, this is the first study utilizing MPI-derived myocardial strain analysis to assess regional strain patterns associated with ATTR cardiac amyloidosis. While echocardiography is routinely used to assess for myocardial strain, it also has various limitations. If the "apical-sparing" pattern associated with cardiac amyloidosis can be distinguished with MPI-derived strain, it is possible routine strain analysis could aid in identifying patients who may benefit from further evaluation and might otherwise evade diagnosis.

Table 1
Demographic, clinical, and imaging characteristics of the Control and ATTR groups.

Demographic and Clinical Characteristics	Control Group (***N*** = 32)	ATTR Group (***N*** = 8)	*P*-Value
Age (years)	66.5 ± 3.65	69.5 ± 4.04	0.09
Sex (male n, %)	20 (63 %)	6 (75 %)	0.51
Hypertension (n, %)	27 (84 %)	5 (63 %)	0.17
Diabetes (n, %)	22 (69 %)	3 (38 %)	0.03
Former or Current Smoker (n, %)	10 (31 %)	3 (38 %)	0.74
Coronary artery disease (n, %)	10 (31 %)	4 (50 %)	0.32
Cerebrovascular event (n, %)	0 (0 %)	1 (13 %)	0.42
Troponin Level	–	0.21 ± 0.22	–
BNP	–	412 ± 263	–
NYHA Class	–	3 ± 0.4	–
Imaging characteristics on echocardiography			
Ejection Fraction (%)	57.8 ± 3.60	49.7 ± 5.6	0.14
LV Wall Thickness	2.6 ± 0.71	3.1 ± 0.99	0.23

Welch's t-test assuming unequal variance used for Age, Ejection Fraction, and Wall Thickness. Pearson's $\chi 2$ test for categorical variables. ATTR: Transthyretin amyloidosis. NYHA: New York Heart Association.

While these results are promising, there are limitations to consider. The most notable limitation is the small sample size within the ATTR cohort. This sample size limited our ability to account for other population characteristics besides age and LVH. This proved to be important, as preliminary statistical analysis via Welch's *t*-test assuming unequal variance revealed six of the metrics met the threshold for statistical significance. Five additional metrics were noted to be trending toward significance. However, after performing linear regression analysis to account for other characteristics, only the circumferential ASI and ABR at rest remained significant. It is notable that the variance for fourteen out of sixteen indices is higher in the ATTR group compared to controls. Considering the mean value for each of the sixteen indices was higher in the ATTR group compared to the control group, it is plausible that a larger ATTR cohort may demonstrate less variability and could reveal a greater number of significant indices. Conversely it is possible a larger sample may not reveal significant differences, as the size of the ATTR population reduces the power of the study.

Another potential limitation is the number of indices evaluated. Given the novelty of this topic, the intent was to create a thorough assessment of potentially significant metrics. It is possible that the significant results are spurious in the setting of multiple hypotheses. As per the above discussion, it is also plausible that more indices could be significant if a larger sample size is studied, given the differences in mean and variance between the two groups. This underscores the exploratory nature of this study and the need for validation studies.

5. Conclusion

This novel study explores the utility of MPI-derived myocardial strain analysis to detect regional strain patterns associated with cardiac amyloidosis. Our results suggest that MPI- derived strain from the circumferential plane at rest may be best suited to distinguish patients with cardiac amyloidosis from other forms of LVH. Larger studies are required to confirm this finding and determine whether routine LV strain analysis with MPI can identify patients likely to benefit from further evaluation for amyloidosis.

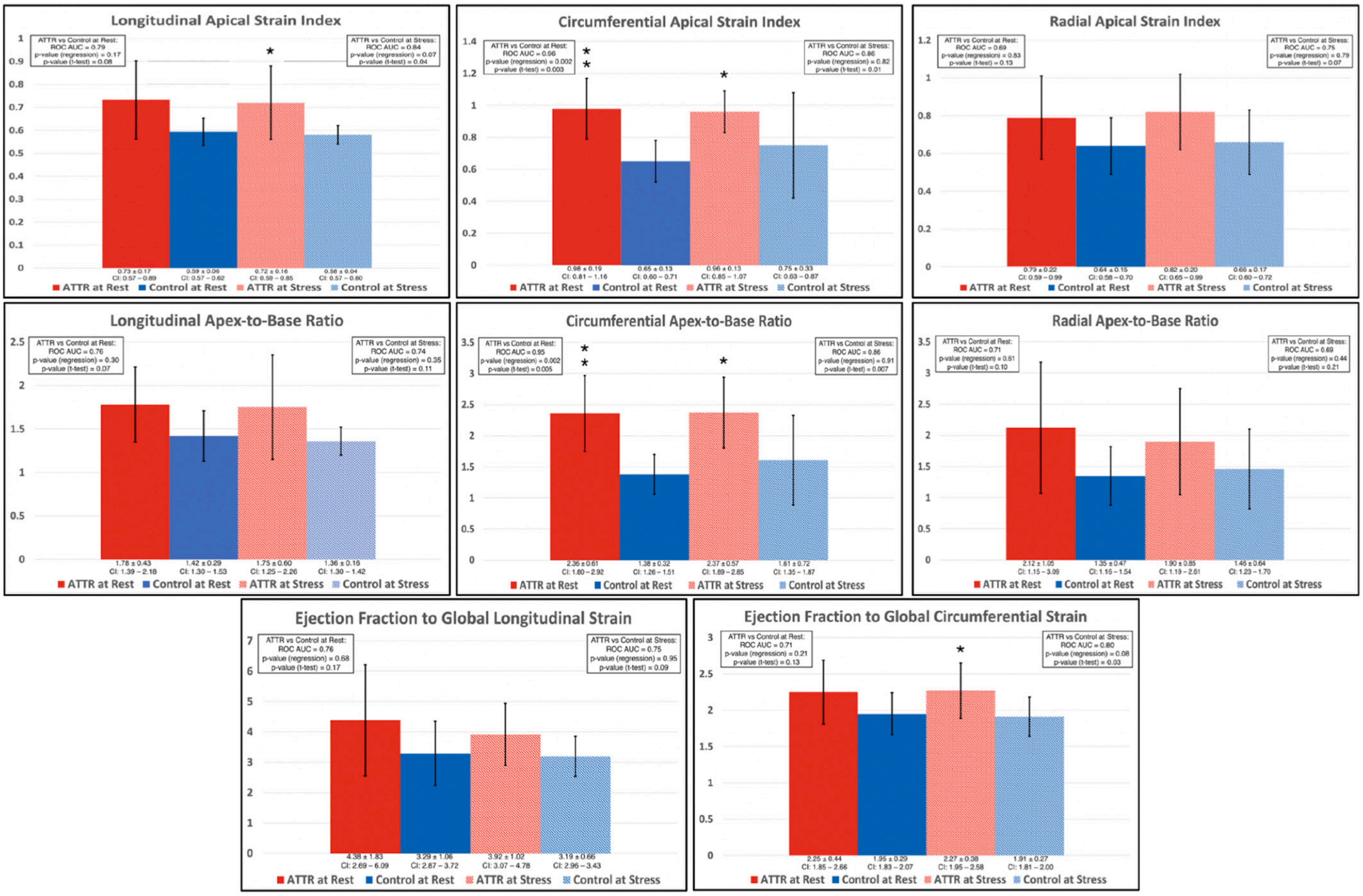

Fig. 1. Bar graphs showing the mean and standard deviation for each index of myocardial strain at rest and stress in the ATTR cohort and control cohort. Welch's *t*-test *P*-value: Comparison of ATTR cohort to all controls. Linear Regression P-value: Comparison of ATTR to all controls, accounting for other covariates. ROC: Receiver Operating Characteristic. AUC: Area Under the Curve.

Ethical statement

The studies involving human participants were reviewed and approved by Emory University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

The current manuscript represents the authors' own original work and has not been published elsewhere. Moreover, the paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the contributions of co-authors.

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CRediT authorship contribution statement

Steven Lewis: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Jingwen Huang:** Writing – original draft, Methodology, Formal analysis. **Nidhi Patel:** Writing – original draft, Visualization, Formal analysis, Data curation. **Russell Folks:** Data curation. **James Galt:** Resources, Methodology. **C. David Cooke:** Resources, Methodology. **Ziduo Zheng:** Validation, Formal analysis. **Rebecca Zhang:** Validation, Formal analysis. **Ernest Garcia:** Software, Methodology. **Jonathon Nye:** Writing – review & editing. **Marina Piccinelli:** Writing – review & editing. **Valeria Moncayo:** Writing – review & editing. **Kunal Bhatt:** Resources, Data curation. **Adam Mitchell:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ernest Garcia reports a relationship with Syntermed Inc. that includes: board membership and equity or stocks. C. David Cooke reports a relationship with Syntermed Inc. that includes: board membership and equity or stocks. Russell Folks reports a relationship with Syntermed Inc. that includes: equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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