The Association of Pericardial Fat Volume with Incident Atrial Fibrillation in the Multi-Ethnic Study of Atherosclerosis and the Jackson Heart Study

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Financial Disclosure:

- No relevant financial relationship exits
Atrial fibrillation (AF) is a common arrhythmia
- Complications: stroke, heart failure, cognitive decline

Obesity associated with incident AF
- Association persists after adjustment for CVD risk factors
  - Age, hypertension, diabetes

Fat deposited in pericardium
- Pericardial fat metabolically active
- Few studies of pericardial fat volume and incident AF
Pericardial Fat and AF

Potential Mechanisms:

- Increased pericardial fat
  - Inflammatory cytokine secretion
  - Fatty infiltration
  - Autonomic nervous system modulation?

Electric and Structural remodeling

Atrial Fibrillation
Objective

- To address the questions:
  - Is pericardial fat volume associated with incidence of AF?
Objective

To address the questions:

- Is pericardial fat volume associated with incidence of AF?
- Is pericardial fat volume associated with AF above and beyond the joint association with obesity?
Objective

- To address the questions:
  - Is pericardial fat volume associated with incidence of AF?
  - Is pericardial fat volume associated with AF above and beyond the joint association with obesity?
  - Is the association of obesity with incidence of AF mediated by pericardial fat volume?
Methods
<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Multi-Ethnic Study of Atherosclerosis (MESA)</th>
<th>Jackson Heart Study (JHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 sites</td>
<td>Jackson, MS area</td>
</tr>
<tr>
<td></td>
<td>Baseline 2000-2002</td>
<td>Baseline 2000-2004</td>
</tr>
<tr>
<td></td>
<td>6814 men and women</td>
<td>5301 men and women</td>
</tr>
<tr>
<td></td>
<td>o 45-84 years of age</td>
<td>o 20-95 years of age</td>
</tr>
<tr>
<td></td>
<td>o 53% women</td>
<td>o 64% women</td>
</tr>
<tr>
<td></td>
<td>o Four race/ethnic groups</td>
<td>o All African-American</td>
</tr>
<tr>
<td></td>
<td>• African-American (28%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• White (38%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hispanic (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chinese descent (12%)</td>
<td></td>
</tr>
</tbody>
</table>
### Pericardial Fat Measurement

- Pericardial fat volume by CT scan of the chest
- Same methods, reading center used by both studies

<table>
<thead>
<tr>
<th>MESA</th>
<th>JHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All suitable scans read</td>
<td>Random selection of scans</td>
</tr>
<tr>
<td>Inter-reader reproducibility 0.99</td>
<td>Inter-reader reproducibility 0.96</td>
</tr>
</tbody>
</table>
AF Ascertainment

- Similar methods used in MESA and JHS
  - ICD-9 codes from hospital discharge (any position)
  - Study ECG at a follow-up visit
  - Medicare claims
    - Fee-for-service Medicare
    - Inpatient or outpatient claim (any position)
    - Available through 2011 in MESA; 2012 in JHS

- Date of incident AF = first date AF noted by any source above
Statistical Analysis

• Exclusions:
  o Prior AF at the time of the CT scan

• Analysis:
  o Cox proportional hazards model
    • Covariates: age, sex, race/ethnicity, study, BMI, height, systolic blood pressure, treated hypertension, glucose status (*normal*, *impaired fasting glucose*, *diabetes*)
  o Time from CT scan to incident AF
  o Pericardial fat volume in **standard deviation** units (sd = 41 ml)
  o Mediation analysis: Bootstrap confidence intervals
Results
Baseline Characteristics

- N = 7989 participants, 615 AF cases
  - MESA: N = 6881, 580 AF cases
  - JHS: N = 1308, 35 AF cases
- Average age 62 years (sd = 10)
- 55% women
Mean Pericardial Fat Volume (ml)

- Volume greater with:
  - Male sex
  - Age
  - BMI
  - Treated hypertension
  - Impaired fasting glucose
  - Diabetes

- Lowest volume in AA
- Greatest volume in whites and Hispanics
AF Incidence Rate

AF incidence per 1000 person-yrs

Sex
- Women
- Men

Age (yrs)
- 30-54
- 55-69
- 70-94

Race
- AA
- Chinese
- Hispanic
- White

Graph showing AF incidence rate by sex, age, and race.
Hazard ratio (HR) for the association of pericardial fat volume with incident AF

<table>
<thead>
<tr>
<th>Model 1</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled MESA and JHS</td>
<td>1.17 (1.09-1.26)</td>
</tr>
</tbody>
</table>

Model 1: age, sex, race/ethnicity, study
Main Results

Hazard ratio (HR) for the association of pericardial fat volume with incident AF

<table>
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<tr>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled MESA and JHS</td>
<td>1.17 (1.09-1.26)</td>
</tr>
</tbody>
</table>

Model 1: age, sex, race/ethnicity, study

Model 2: Model 1 + height
systolic blood pressure
treated hypertension
glucose status (normal, IFG, diabetes)

Hazard ratio per 1 standard deviation pericardial fat volume (41 ml)
# Main Results

Hazard ratio (HR) for the association of pericardial fat volume with incident AF

<table>
<thead>
<tr>
<th></th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled MESA and JHS</td>
<td>1.17 (1.09-1.26)</td>
<td>1.15 (1.06-1.24)</td>
<td>1.04 (0.95-1.14)</td>
</tr>
</tbody>
</table>

Model 1: age, sex, race/ethnicity, study

Model 2: Model 1 + height
- systolic blood pressure
- treated hypertension
- glucose status (*normal, IFG, diabetes*)

Model 3: Model 2 + BMI

Hazard ratio per 1 standard deviation pericardial fat volume (41 ml)
Mediation Analysis

Does pericardial fat volume mediate the association of obesity with incident AF?

- Association of BMI with incident AF*
  - HR 1.31, 95% CI (1.19-1.45)
  - HR 1.28, 95% CI (1.13-1.43) [+ pericardial fat volume]

* adjusted for age, sex, race, study, height, systolic blood pressure, treated hypertension, glucose status
Mediation Analysis

- Does pericardial fat volume mediate the association of obesity with incident AF?
  - Association of BMI with incident AF:
    - HR 1.31, 95% CI (1.19-1.45)
    - HR 1.28, 95% CI (1.13-1.43) [+ pericardial fat volume]
  - Significance Testing
    - Indirect effect of BMI on AF through pericardial fat volume:
      - HR 1.03, 95% CI (0.97-1.10)
    - HR for indirect effect nonsignificant = little evidence of mediation by pericardial fat volume

* adjusted for age, sex, race, study, height, systolic blood pressure, treated hypertension, glucose status
Discussion

- Greater pericardial fat volume associated with incident AF when adjusted for age, sex, race, and other AF risk factors.

- Association attenuated after adjustment for BMI

- Little evidence that association of obesity with incident AF mediated by pericardial fat volume
Strengths/Limitations

- **Strengths:**
  - Large and diverse study population
  - Consistent methods for exposure and outcome measurement
  - Extensive, high-quality covariate data available
  - Large number of incident AF cases
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- Large and diverse study population
- Consistent methods for exposure and outcome measurement
- Extensive, high-quality covariate data available
- Large number of incident AF cases

Limitations:
- ICD-9 codes high specificity, imperfect sensitivity
- May have missed paroxysmal AF cases
- Identification of AF may vary by race/ethnicity or study
Conclusions

- Findings not consistent with initial hypothesis:
  - Greater pericardial fat volume is not associated with incidence of AF above and beyond obesity
  - Little evidence that association of obesity with incident AF mediated by pericardial fat volume

- More research on mechanisms needed

- Control of body weight important for AF prevention
## Acknowledgements

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Thank You

Questions?
Extra Slides
**Epicardial** fat = Outer wall of myocardium to visceral pericardial layer

**Paracardial** fat = External to the parietal pericardial layer

**Pericardial** fat = **Epicardial** fat + **Paracardial** fat
EAT = *Epicardial* adipose tissue
PAT = *Paracardial* adipose tissue
Parietal pericardium indicated by arrow

*Pericardial* fat is made up of the combination of EAT plus PAT.
CT Scan Region

18 2.5-mm slices:
1.5 cm above to 3.0 cm below superior extent of left main coronary artery
Existing Studies

- **Framingham Heart Study**
  - Cross-sectional study of prevalent AF
  - Only 54 participants had AF
  - All participants were white
  - OR = 1.28 (CI 1.01-1.63)* per sd of pericardial fat volume

- **Heinz Nixdorf Recall Study**
  - Prospective cohort study
  - 50 incident AF events
  - AF ascertained only by two 12-lead ECGs, 5 years apart
  - OR = 1.19 (CI 0.88-1.61)* per sd of pericardial fat volume

*Multiply adjusted, including BMI

Thanassoulis G. *Circ Arrhythm Electrophysiol* 2010;3:345-50
Mahabadi AA. *J Am Coll Cardiol Img* 2014;7:909-16
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>JHS AA</th>
<th>MESA AA</th>
<th>MESA White</th>
<th>MESA Hispanic</th>
<th>MESA Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1308</td>
<td>1855</td>
<td>2568</td>
<td>1470</td>
<td>788</td>
</tr>
<tr>
<td><strong>Age (yrs), mean</strong></td>
<td>60</td>
<td>62</td>
<td>62</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td><strong>Men, %</strong></td>
<td>34</td>
<td>45</td>
<td>48</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), mean</strong></td>
<td>32</td>
<td>30</td>
<td>28</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td><strong>SBP (mm Hg), mean</strong></td>
<td>127</td>
<td>132</td>
<td>123</td>
<td>127</td>
<td>125</td>
</tr>
<tr>
<td><strong>Treated hypertension, %</strong></td>
<td>66</td>
<td>47</td>
<td>27</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td><strong>Current smoking, %</strong></td>
<td>9</td>
<td>18</td>
<td>12</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td><strong>IFG, %</strong></td>
<td>45</td>
<td>15</td>
<td>11</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>27</td>
<td>17</td>
<td>6</td>
<td>17</td>
<td>13</td>
</tr>
</tbody>
</table>
AF Incidence

MESA
- 9.2 yrs follow-up (avg)
- 580 cases incident AF

JHS
- 4.5 yrs follow-up (avg)
- 35 cases incident AF
Results: AF Incidence - Men

A. Men

AF incidence per 1000 person-yrs

Age group (yrs)

30-54
55-69
70-94

0
10
20
30
40

• White
• Chinese
• Hispanic
• MESA AA
• JHS AA

- White
- MESA AA
- Chinese
- JHS AA
- Hispanic
Results: AF Incidence - Women

A. Women

AF incidence per 1000 person-yrs

Age group (yrs)

30-54, 55-69, 70-94

White, MESA AA, Chinese, JHS AA, Hispanic
Existing studies – from Susan - modify

- Framingham Heart Study
  - Cross-sectional study of prevalent AF
  - Only 54 participants had AF
  - All participants were white
  - OR = 1.28 (CI 1.03-1.58) per SD of pericardial fat volume

- Clinical study
  - Cross-sectional
  - 197 patients with AF
  - No information on race
  - Found greater pericardial fat volume associated with AF

Thanassouli G. Circ Arrhythm Electrophysiol 2010;3:345-50
Al Chekakie MO. J Am Coll Cardiol 2010;56:784-8
AF incidence per 1000 person-yrs

Sex

Women
Men

Age (yrs)
30-54
55-69
70-94

Race
AA
Chinese
Hispanic
White

38
AF Incidence Rate