INADEQUATE REINFORCEMENT OF TRANSMURAL DISRUPTIONS AT BRANCH POINTS SUBTENDS AORTIC ANEURYSM FORMATION IN APOLIPOPROTEIN E-DEFICIENT MICE

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Israel Heart Society
Jerusalem, Israel
April 23, 2013
DISCLOSURES

None
Abdominal Aortic Aneurysm

LOCATION = BRANCH POINTS, CURVATURES

http://vasoftas.com/DownloadableContentHandler.ashx?mediaId=0041b032-e9d5-4fa9-ac3b-e82d9457ca8b

Roy JVS 11 April 2008

Kumar et al. Robbins Basic Pathol. 8th ed. www.studentconsult.com

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In the current study we sought to determine why some angiotensin-infused animals do, and others do not, develop aortic aneurysms.
Abdominal Aortic Aneurysm: Angiotensin-Infused Apo E-/- Mouse

Disrupted Elastica; Fibromuscular Hyperplasia; Inflammatory Infiltrates

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Low Level Laser Prevents Aneurysm Formation in Angiotensin-infused Apo E-Deficient Mice

Ratio of U/S diameter of the suprarenal to inter-renal segments:

Baseline vs 28 days:

Control: 1.32±0.11 vs 1.82 ± 0.39, p=0.0002 by 2-tailed t-test

LLLI: 1.29±0.13 vs 1.32 ± 0.014, p=0.49

**Effect of LLLI on Pre-induced AAA in Apo E\(^{-/-}\) Mice**

**Maximal Cross-Sectional Diameter (MCD) of Suprarenal Aorta**
(B-Mode Ultrasonography)

<table>
<thead>
<tr>
<th></th>
<th>0W</th>
<th>2W</th>
<th>4W</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-treated</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>SR SA = L: 1.15 mm</td>
<td></td>
<td></td>
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<tr>
<td><strong>LLLI</strong></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td>SR SA = L: 2.06 mm</td>
<td></td>
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</table>

**Maximal aortic diameter (MCD) 2 vs 4 weeks:**

- **Non-treated** (n=8): 2.10±0.2 vs 2.33±0.28mm, p=0.04 (by paired t-test)
- **LLLI** (n=10): 2.24±0.32 vs 2.09±0.56mm, p=0.2

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Medial Disruption near Aortic Branch Point (superior mesenteric artery [SMA]) Closed off by Increased Fibromuscular Hyperplasia and Collagen Elaboration in an LLLI Mouse
## Experimental Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Infusion</th>
<th>Aneurysm</th>
<th>n</th>
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<tbody>
<tr>
<td>AngII-AAA</td>
<td>Angiotensin-II</td>
<td>+</td>
<td>9</td>
</tr>
<tr>
<td>AngII-no AAA</td>
<td>Angiotensin-II</td>
<td>-</td>
<td>12</td>
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<tr>
<td>Saline</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
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Tramsmural Defect Associated with Aneurysm Near the Origin of the Right Renal Artery
Intermediate Size Transmural Defect of the Aorta Near the Point of Origin of the Superior Mesenteric Artery
Small Transmural Defect of the Aorta Near the Point of Origin of the Celiac Trunk

Movat

C

AA

PSR

PSR under Polarization

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## Transmural Breaks at Branch Orifices
(Celiac, Superior Mesenteric, and L & R Renal)

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<td>AngII-AAA (n=9)</td>
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<td>32.2±10.3</td>
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<td>18.8±10.7</td>
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AngII: AAA vs no AAA
0.29*

AngII vs Sal
<0.005*

MaxMM=missing media; WO=walling off area; %Col/WO = %collagen in the WO; #Mac=number of macrophages per 0.01mm² at the disrupted media and WO area. *by Chi-square or FET as appropriate; **by MW-U test; †by Kruskal-Wallis (p=0.0005) with Conover-Inman as post hoc; NA=not applicable

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AngII: AAA vs no AAA 0.29* 0.0073**

AngII vs Sal <0.005* 0.00003

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| AngII:                 |                                               |           |          |           |                 |
| AAA vs no AAA          | 0.29*                                         | 0.0073**  | 0.0186†  |           |                 |
| AngII vs Sal           | <0.005*                                       | 0.00003   | <0.0006† |           |                 |

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Human Abdominal Aortic Aneurysms-Infrarenal

L: eMedicine, Med/3443, emerg/27, radio/1, MeSH D017544
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Suprarenal AAA in Angiotensin-infused Apo e−/− Mouse

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Conclusions

Transmural defects and inflammatory cell infiltration at branch orifices subtend aneurysm formation in the Ang-II-infused, Apo E^{-/-} mouse.

The extent of the inflammatory response and robustness of the extracellular matrix reinforcement of transmural disruptions at branch orifices by collagen matrix, are important determinants of whether these lesions progress to AAA in the angiotensin-infused Apo E^{-/-} mouse.

Early acceleration of reinforcement of transmural defects would appear to be a potential therapeutic target for management of small, slowly progressing aneurysms.
Collaborators:

Lilach Gavish, PhD  
Ronen Beeri, MD  
Dan Gilon, MD  
Chen Rubinstein, MD  
Yacov Berlatzky, MD  
Leah Gavish, PhD  
Atilla Bulut, MD  
Mickey Harlev, DVM  
Petachia Reissman, MD

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Thank you!