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

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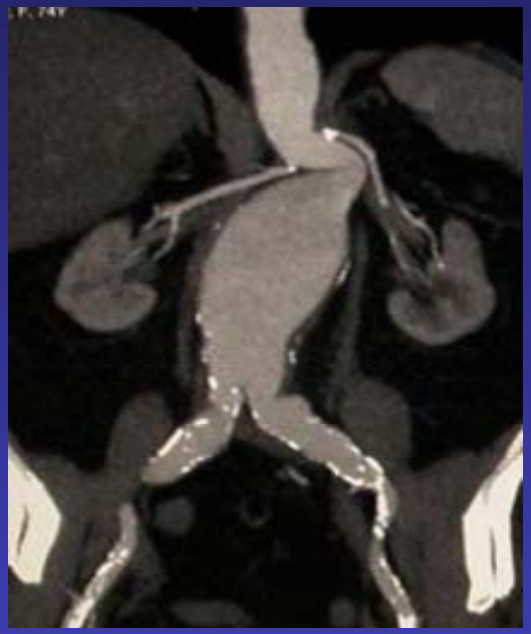
April 23, 2013

DISCLOSURES

None

Abdominal Aortic Aneurysm



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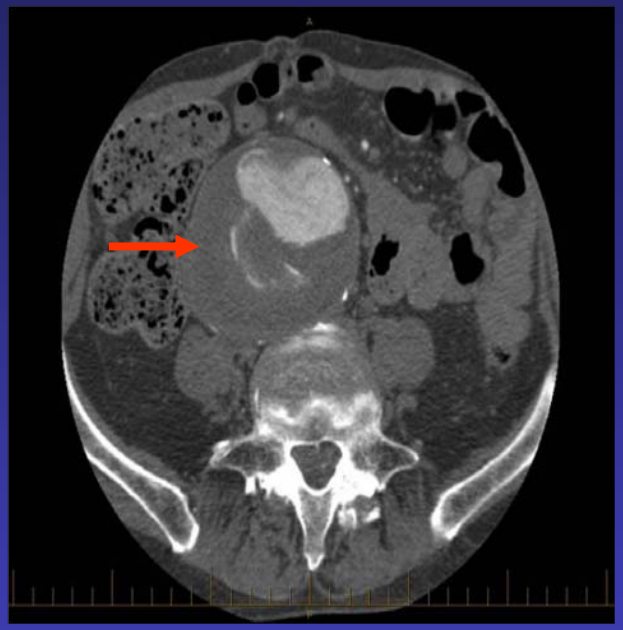
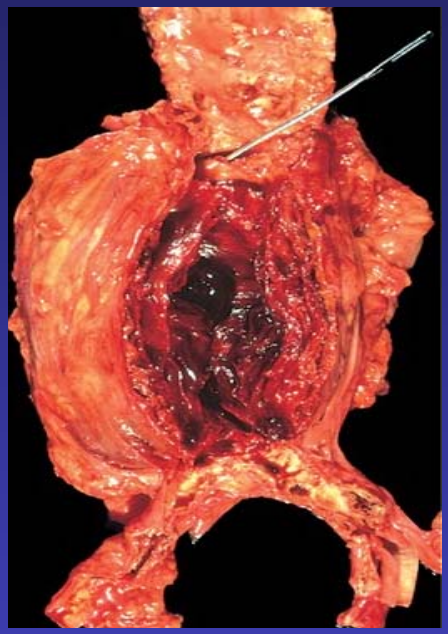


Roy *JVS* 11 April 2008



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

LOCATION = BRANCH POINTS, CURVATURES

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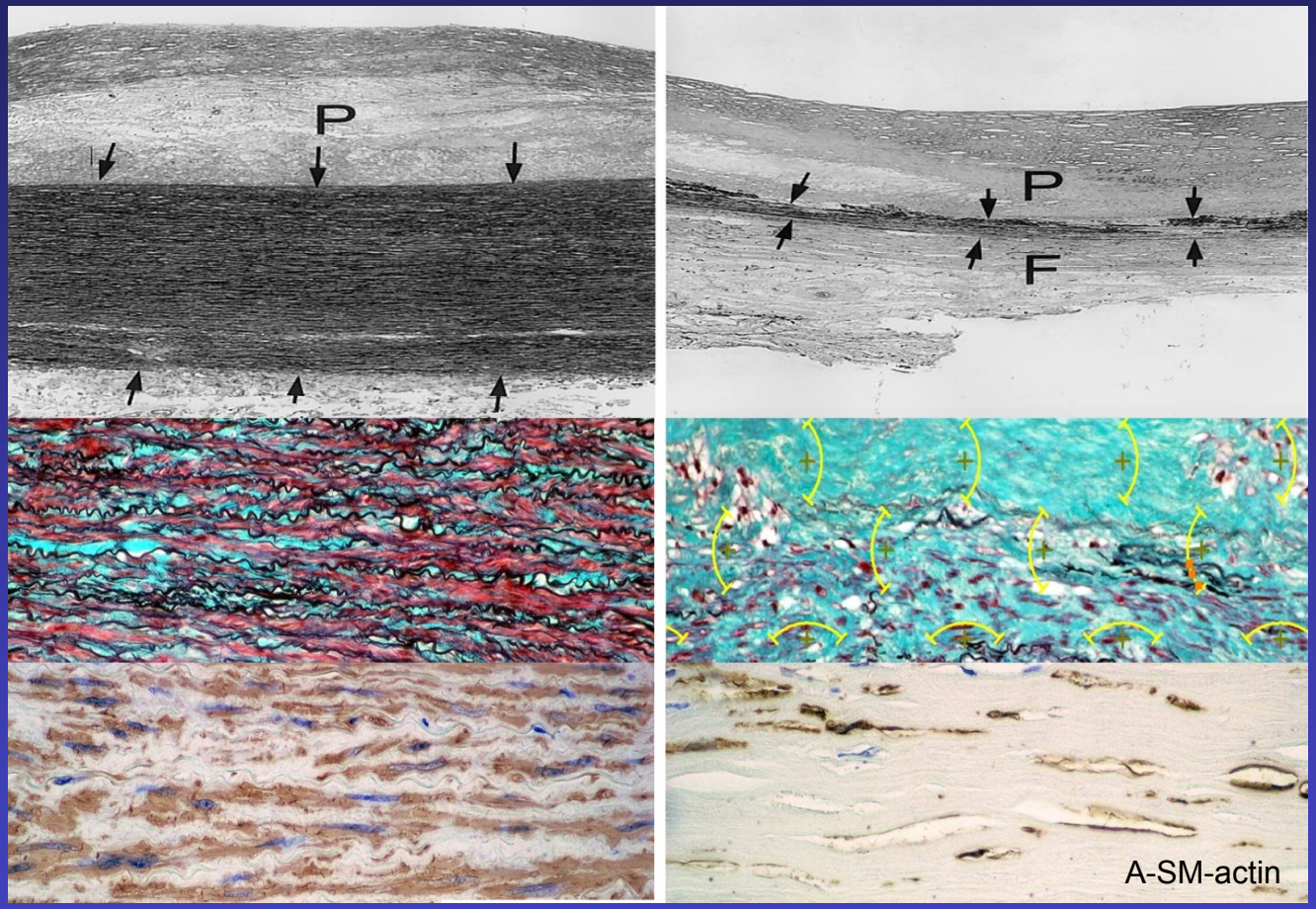
In the current study we sought to determine why some angiotensin-infused animals do, and others do not, develop aortic aneury

Aortic Aneurysm - Histopathology

Normal Aneurysmatic



Zarins ,Xu and Glagov 2001 Atherosclerosis 155:157–164

Tonar et al. Microscopy: Science, Technology, Applications and Education A. Méndez-Vilas and J. Díaz (Eds.) 926 ©FORMATEX 2010;

DISRUPTED ELASTICA, DEPLETION OF SMC

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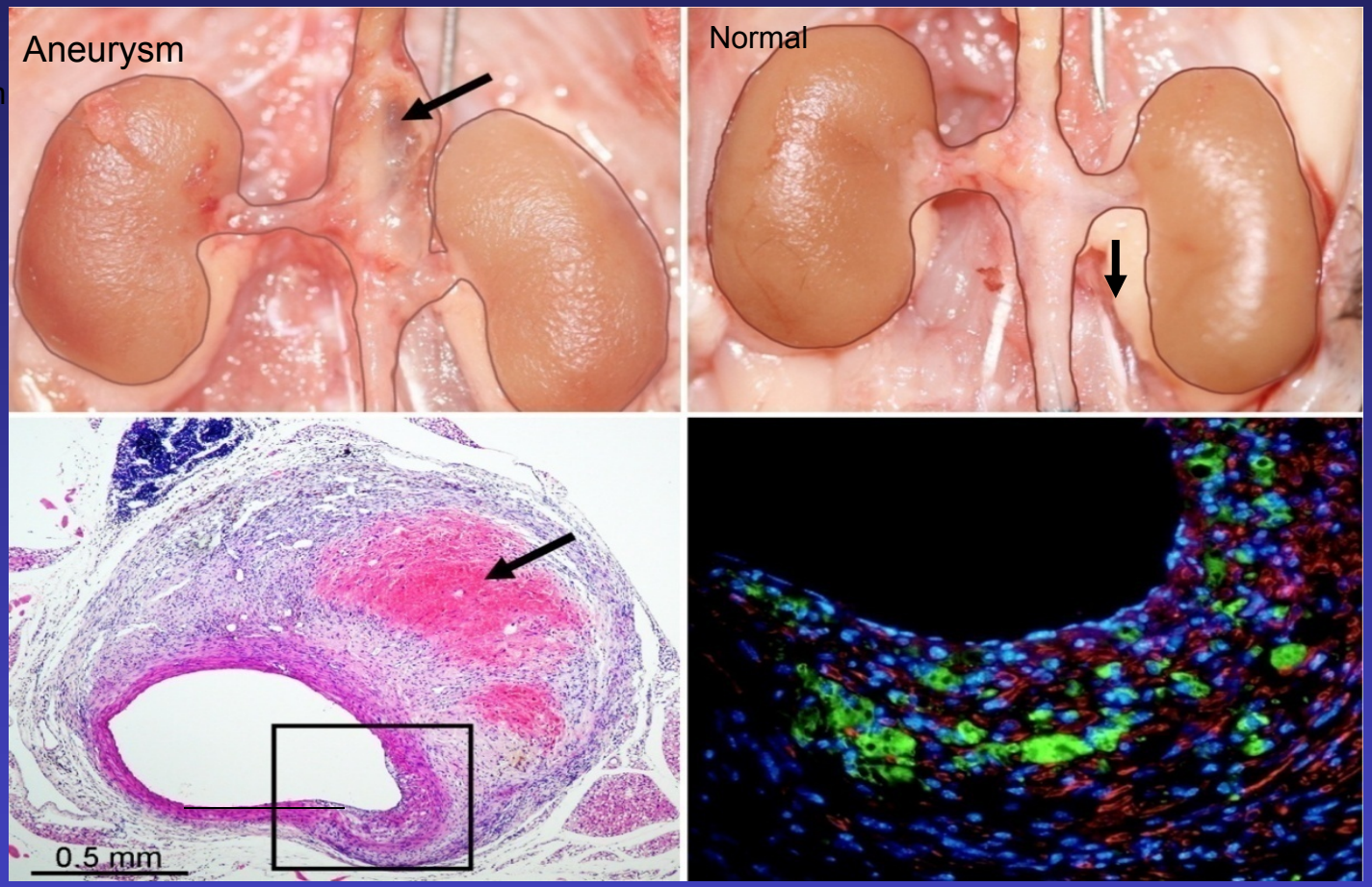
Abdominal Aortic Aneurysm: Angiotensin-Infused Apo $E^{-/-}$- Mouse

Aneurysm



DISRUPTED ELASTICA; FIBROMUSCULAR HYPERPLASIA; INFLAMMATORY INFILTRATES

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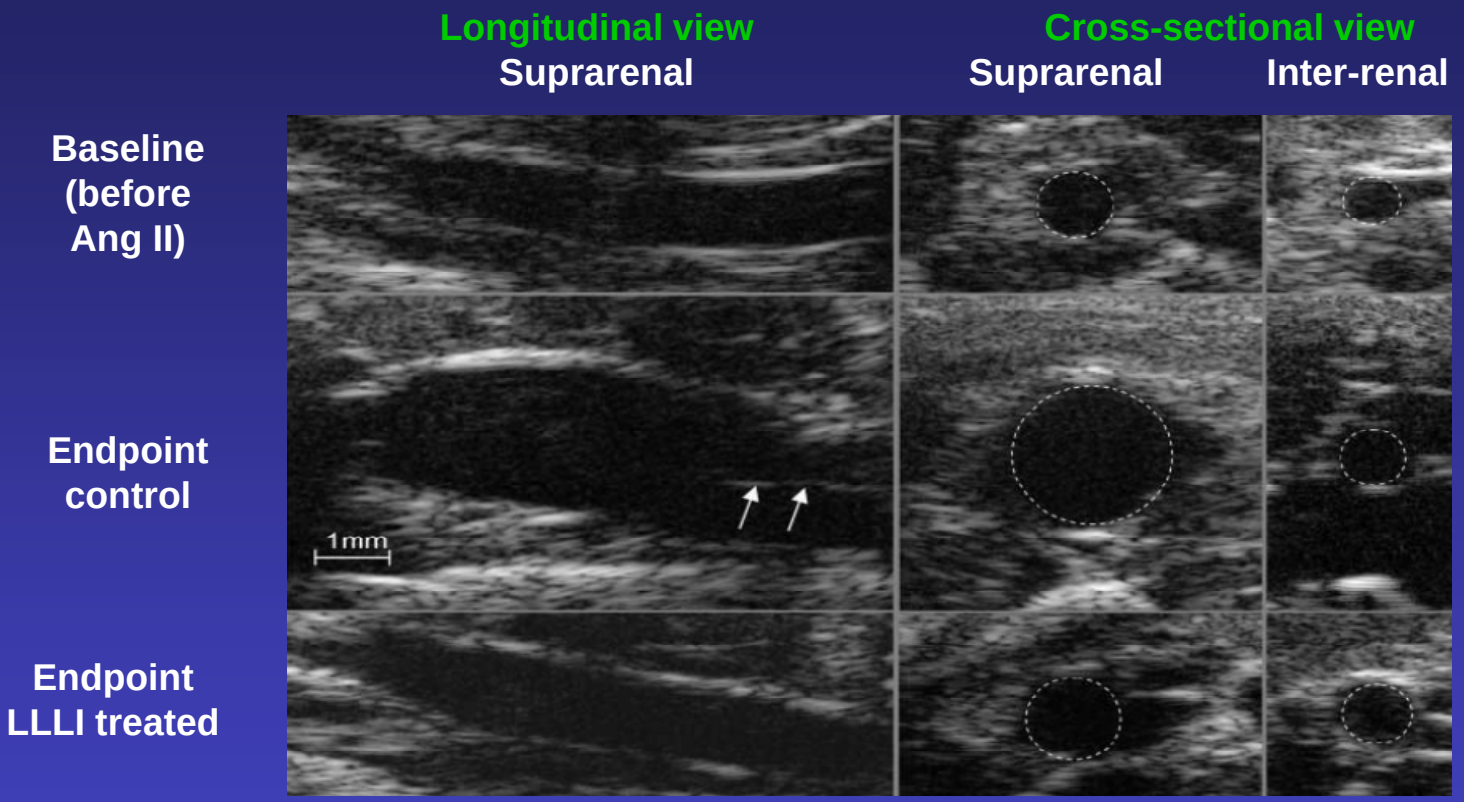
Gavish…Gertz et al. Lasers in Surgery and Medicine. 2012, 44(8):664-74.

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

High Frequency Ultrasonograpy



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 ttest**

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

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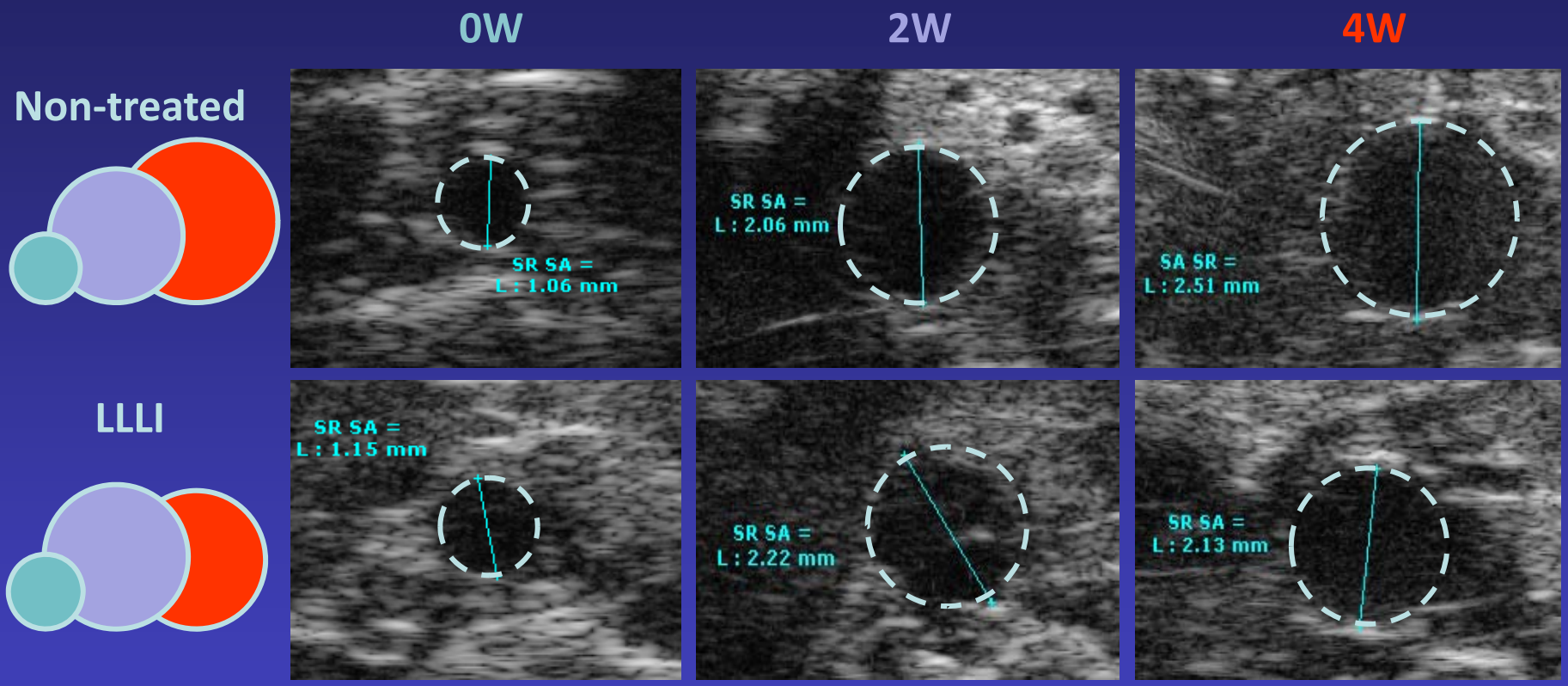
Gavish…Gertz, et al. Cardiovascular Research, 83(4): 785-792, 2009

Effect of LLLI on Pre-induced AAA in Apo $E^{-/-}$ Mice

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



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 2tttest)
LLLI (n=10): 2.24±0.32 vs 2.09±0.56mm, p=0.2

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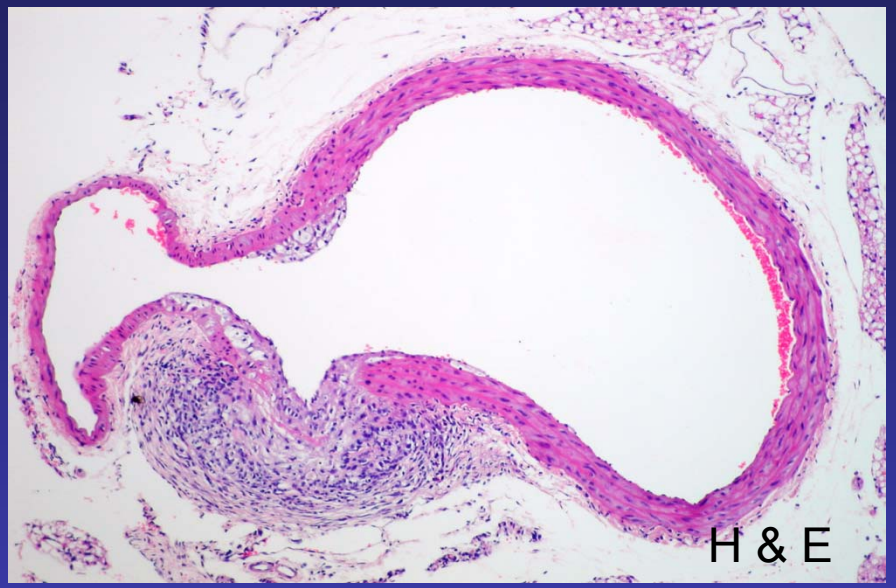
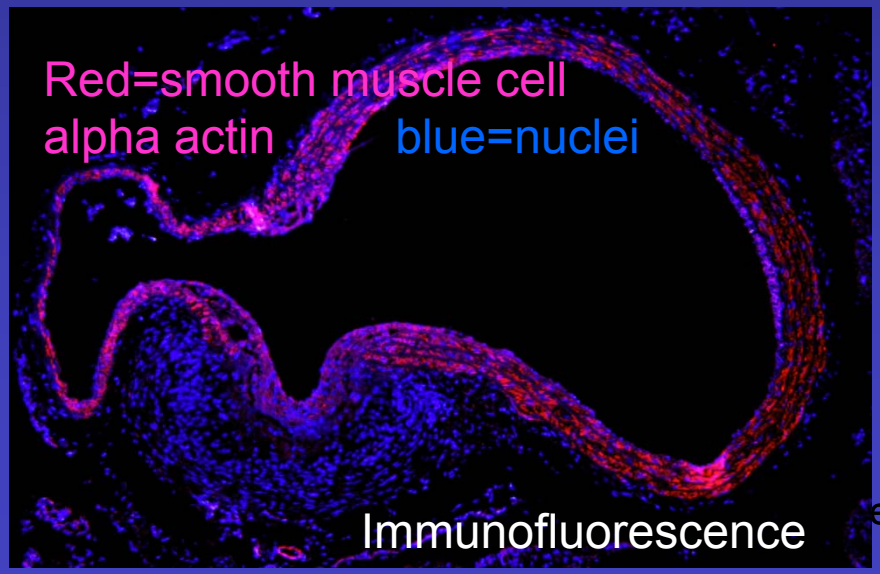
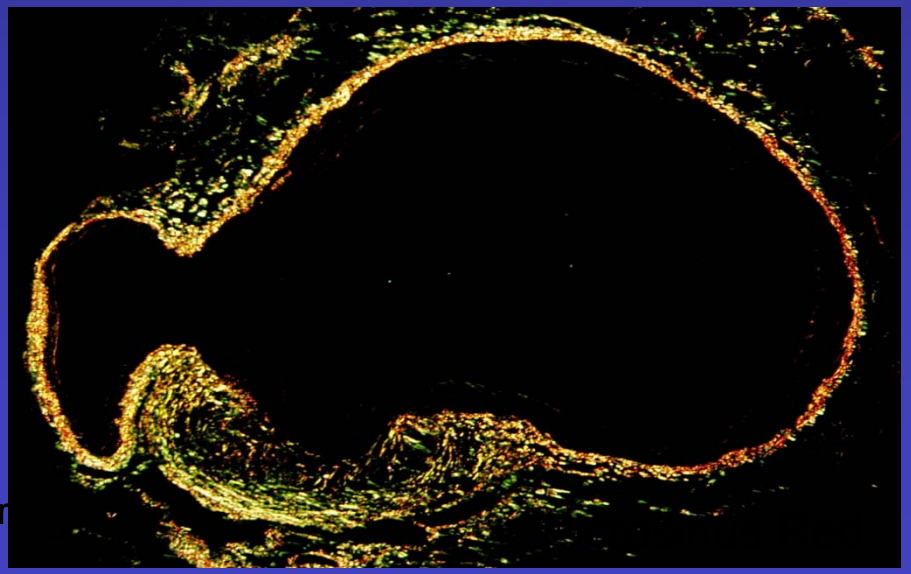
Medial Disruption near Aortic Branch Point (superior mesenteric artery [SMA]) Closed off by Increased Fibromuscular Hyperplasia and Collagen Elaboration in an LLLI Mouse



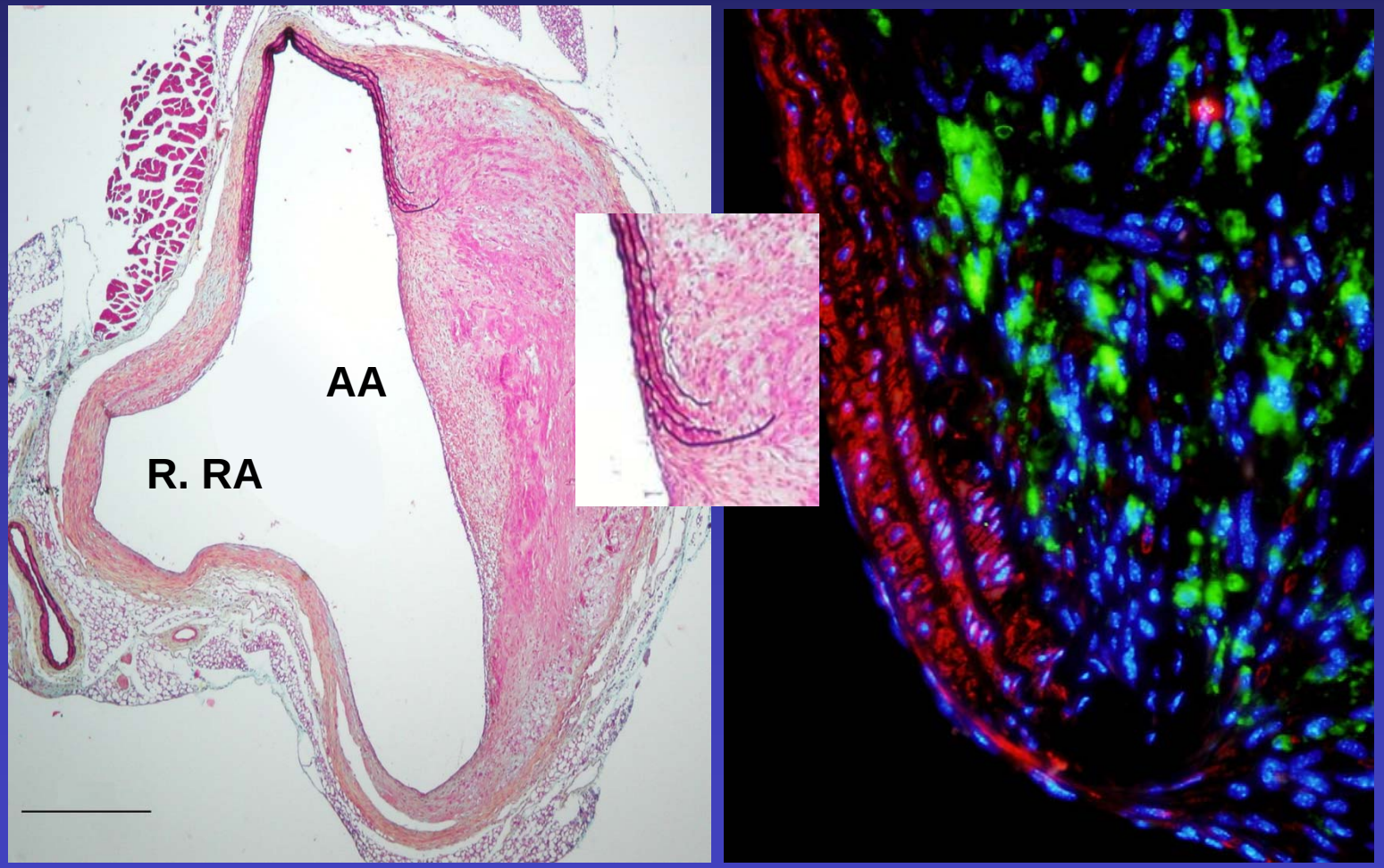




Experimental Groups

Group	Infusion	Aneurysm	n
AngII-AAA	Angiotensin-II	+	9
AngII-no AAA	Angiotensin-II	-	12
Saline	Saline	-	6
		Total	27

Tramsmural Defect Associated with Aneurysm Near the Origin of the Right Renal Artery



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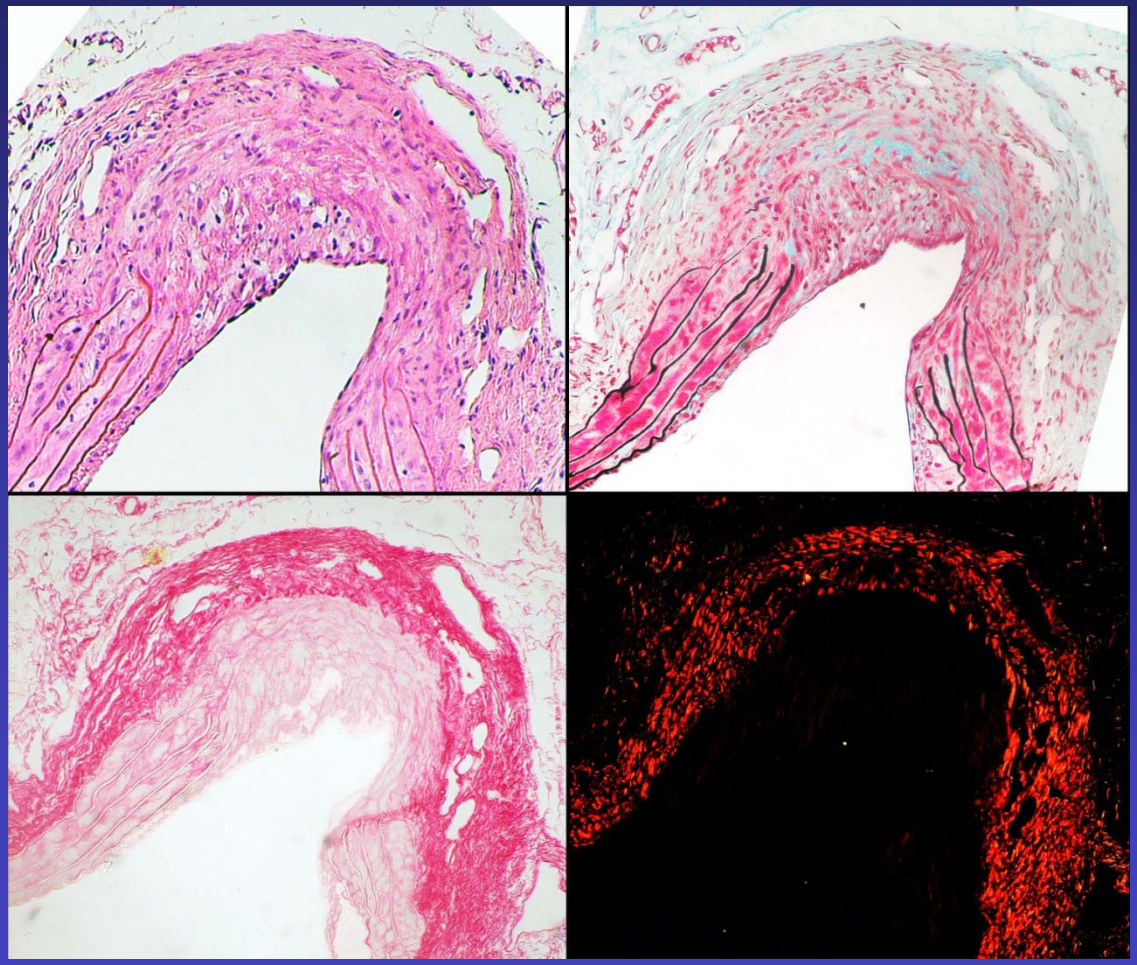
Intermediate Size Transmural Defect of the Aorta Near the Point of Origin of the Superior Mesenteric Artery



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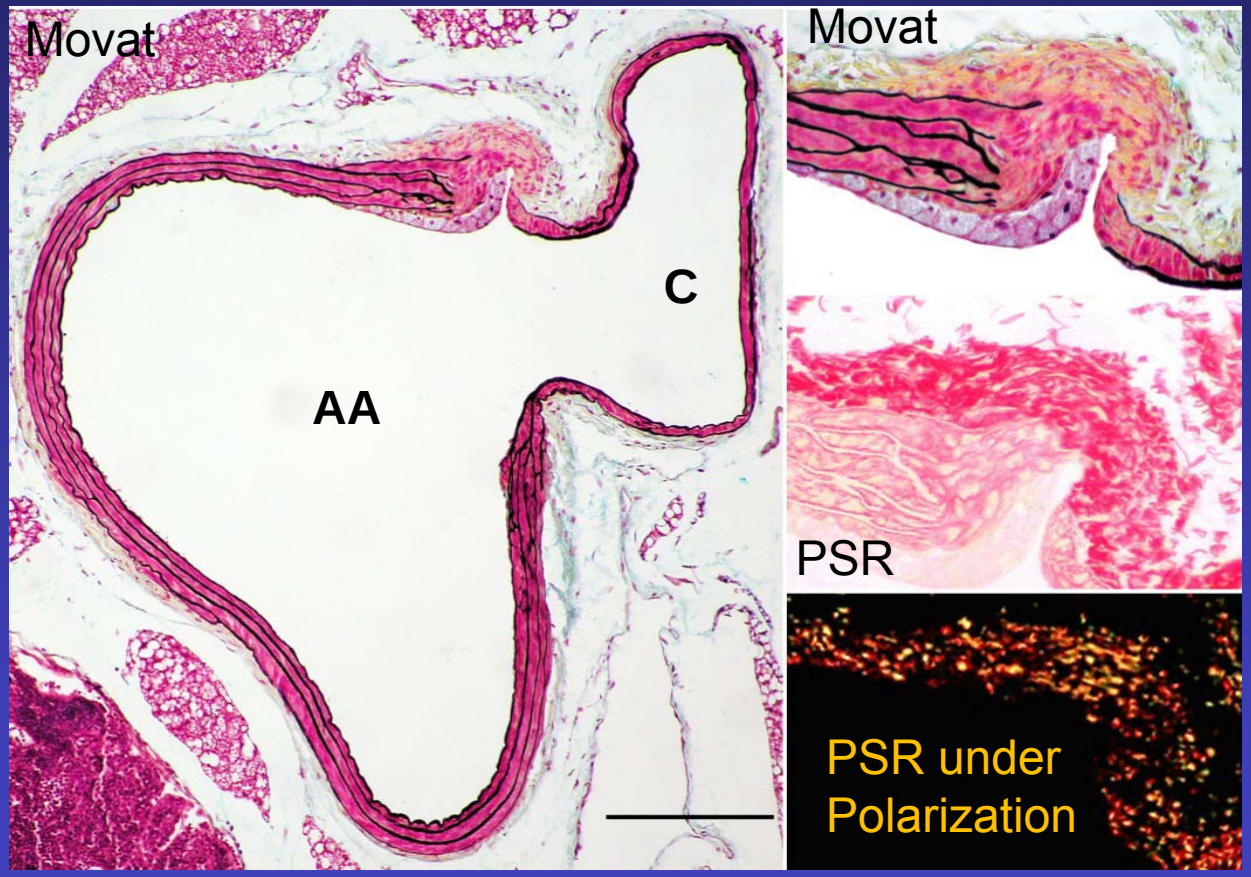
Small Transmural Defect of the Aorta Near the Point of Origin of the Celiac Trunk



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Transmural Breaks at Branch Orifices

(Celiac, Superior Mesenteric, and L & R Renal)

Group	%Branches with Breaks (Mean #Breaks per mouse)	MaxMM	#Mac	%Col/WO	Col/WO per MaxMM
AngII-AAA (n=9)	**69% (2.8±0.7)**				
AngII-no AAA (n=12)	**58% (2.3±1)**				
Sal (n=6)	**17% (0.7±0.8)**				
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 0.01mm^2 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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Transmural Breaks at Branch Orifices

(Celiac, Superior Mesenteric, and L & R Renal)

Group	%Branches with Breaks (Mean #Breaks per mouse)	MaxMM	#Mac	%Col/WO	Col/WO per MaxMM
AngII-AAA (n=9)	**69% (2.8±0.7)**	**1.94±1.57**			
AngII-no AAA (n=12)	**58% (2.3±1)**	**0.65±0.48**			
Sal (n=6)	**17% (0.7±0.8)**	**0.07±0.08**			
AngII: AAA vs no AAA	0.29*	0.0073**			
AngII vs Sal	<0.005*	0.00003			

MaxMM=missing media; WO=walling off area; %Col/WO = %collagen in the WO; #Mac=number of macrophages per 0.01mm^2 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

Transmural Breaks at Branch Orifices

(Celiac, Superior Mesenteric, and L & R Renal)

Group	%Branches with Breaks (Mean #Breaks per mouse)	MaxMM	#Mac	%Col/WO	Col/WO per MaxMM
AngII-AAA (n=9)	**69% (2.8±0.7)**	**1.94±1.57**	**32.2±10.3**		
AngII-no AAA (n=12)	**58% (2.3±1)**	**0.65±0.48**	**18.8±10.7**		
Sal (n=6)	**17% (0.7±0.8)**	**0.07±0.08**	**1.3±1.5**		
AngII: AAA vs no AAA	0.29*	0.0073**	0.0186†		
AngII vs Sal	<0.005*	0.00003	<0.0006†		

MaxMM=missing media; WO=walling off area; %Col/WO = %collagen in the WO; #Mac=number of macrophages per 0.01mm^2 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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Transmural Breaks at Branch Orifices

(Celiac, Superior Mesenteric, and L & R Renal)

Group	%Branches with Breaks (Mean #Breaks per mouse)	MaxMM	#Mac	%Col/WO	Col/WO per MaxMM
AngII-AAA (n=9)	**69% (2.8±0.7)**	**1.94±1.57**	**32.2±10.3**	**17.0±12.6**	
AngII-no AAA (n=12)	**58% (2.3±1)**	**0.65±0.48**	**18.8±10.7**	**43.5±15.4**	
Sal (n=6)	**17% (0.7±0.8)**	**0.07±0.08**	**1.3±1.5**	**NA**	
AngII: AAA vs no AAA	0.29*	0.0073**	0.0186†	0.0009**	
AngII vs Sal	<0.005*	0.00003	<0.0006†	NA	

MaxMM=missing media; WO=walling off area; %Col/WO = %collagen in the WO; #Mac=number of macrophages per 0.01mm^2 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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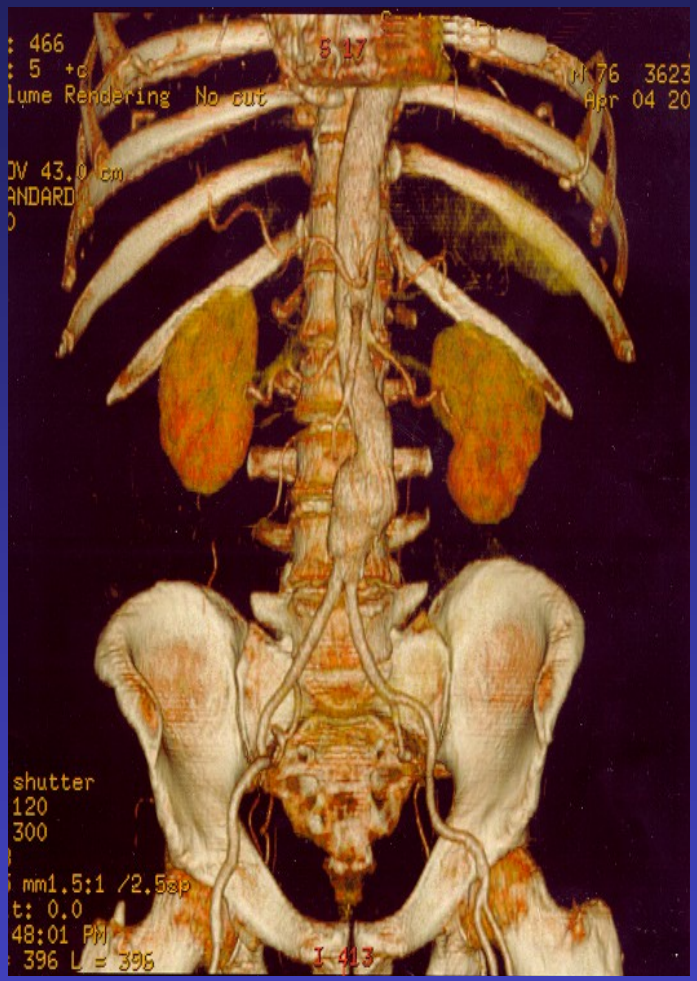
Transmural Breaks at Branch Orifices

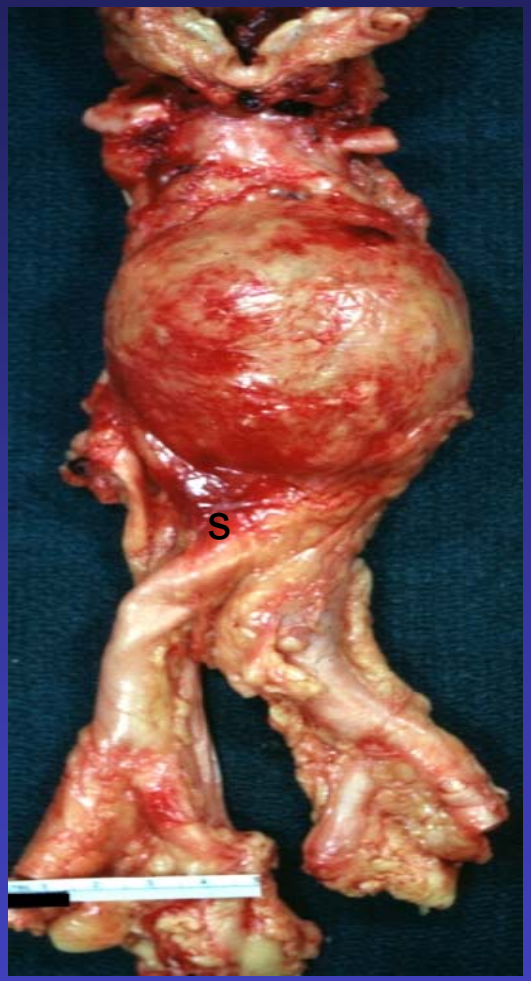
(Celiac, Superior Mesenteric, and L & R Renal)

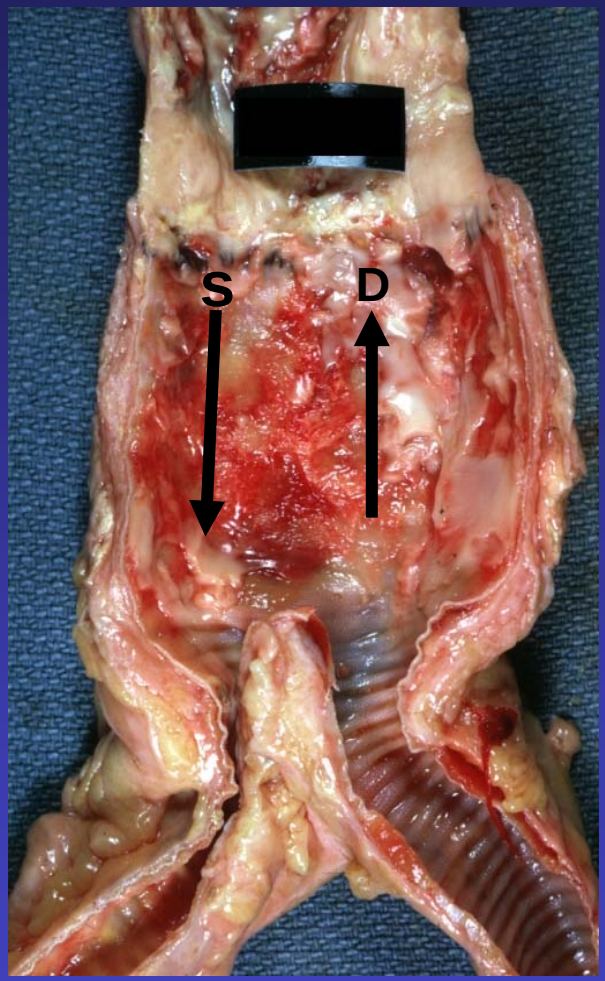
Group	%Branches with Breaks (Mean #Breaks per mouse)	MaxMM	#Mac	%Col/WO	Col/WO per MaxMM
AngII-AAA (n=9)	**69% (2.8±0.7)**	**1.94±1.57**	**32.2±10.3**	**17.0±12.6**	**0.13±0.15**
AngII-no AAA (n=12)	**58% (2.3±1)**	**0.65±0.48**	**18.8±10.7**	**43.5±15.4**	**1.14±1.01**
Sal (n=6)	**17% (0.7±0.8)**	**0.07±0.08**	**1.3±1.5**	**NA**	**NA**
AngII: AAA vs no AAA	0.29*	0.0073**	0.0186†	0.0009**	0.0001**
AngII vs Sal	<0.005*	0.00003	<0.0006†	NA	NA

MaxMM=missing media; WO=walling off area; %Col/WO = %collagen in the WO; #Mac=number of macrophages per 0.01mm^2 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

Human Abdominal Aortic Aneurysms-Infrarenal







L: eMedicine, Med/3443, emerg/27, radio/1, MeSH D017544

M: http://www.wikidoc.org/index.php/Image:Aortic_aneurysm_35.jpg

R: http://www.wikidoc.org/index.php/Image:Aortic_aneurysm_35.jpg

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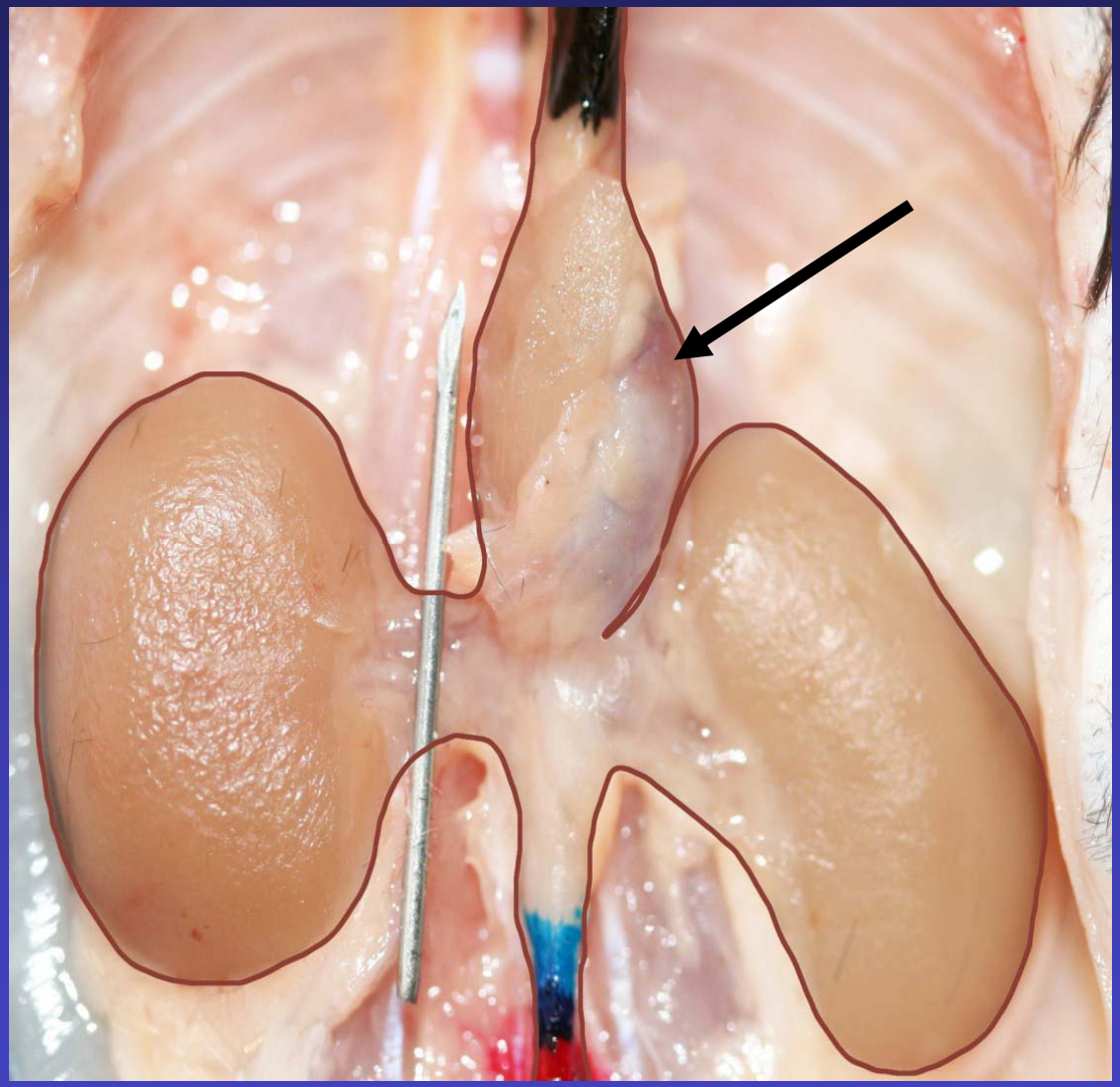
Suprarenal AAA in Angiotensin-infused Apo $e^{-/-}$ Mouse



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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:

Thank you!

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

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