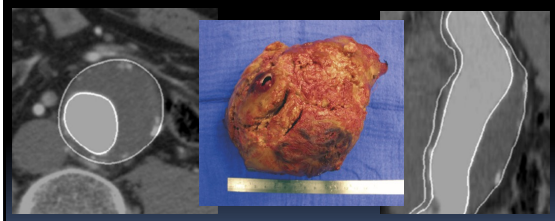
Large Amount of AAA Sac Thrombus Promotes Mortality Without Rupture: What is the Mechanism ?



David H. Deaton, MD FACS
Adjunct Assoc. Prof. Surgery – University of Pennsylvania

Disclosures

- Partner – Healthcare Inroads (healthcare consulting) :
  - multiple clients
  - no conflicts with this subject matter

EVAR is improving…but still eclipsed by OSR by year 3

This makes NO SENSE

VQI infrarenal AAA repair 2003-2018

Journal of Vascular Surgery
Volume 72, Number 2

Rens R. B. Varkevisser, BS,[a] Nicholas J. Swerdlow, MD,[a] Livia E. M. V. de Guerre, MD,[a] Kirsten Dansey, MD,[a] Devin S. Zarkowsky, MD,[a] Philip P. Goodney, MD, MS,[b] Hence J. M. Verhagen, MD, PhD,[c] and Marc L. Schermerhorn, MD,[a] on behalf of the Society for Vascular Surgery Vascular Quality Initiative. Boston, Mass. Rotterdam, The Netherlands. San Francisco, Calif. and Lebanon, NH

Outline

- Thrombus is dead tissue
- Dead tissue initiates an inflammatory response
- Inflammatory states result in increase in ACM
  - Increase CV events
  - Increase malignancy incidence
- Failure to resolve thrombus load after EVAR results in a chronic inflammatory state and thus an increase in ACM

Cell death = Inflammation

ANNUAL REVIEW OF PATHOLOGY: MECHANISMS OF DISEASE Volume 3, 2008

Review Article

The Inflammatory Response to Cell Death

Kenneth L. Rock[1], and Hajime Kono[1]
View Affiliations

Vol. 3:99-126 (Volume publication date February 2008) | https://doi.org/10.1146/annurev.pathmechdis.3.121806.151456

Info Sections Get Access Tools Share

When cells die in vivo, they trigger an inflammatory response. The ensuing hyperemia, leak of plasma proteins, and recruitment of leukocytes serve a number of useful functions in host defense and tissue repair. However, this response can also cause tissue damage and contribute to the pathogenesis of a number of diseases. Given the key role of inflammation in these processes, it is important to understand the underlying mechanisms that drive this response. Injured cells release danger signals that alert the host to cell death. Some of these molecules are recognized by cellular receptors that stimulate the generation of proinflammatory mediators. Other molecules released by dead cells stimulate the generation of mediators from extracellular sources. The resulting mediators then orchestrate the inflammatory response, eliciting its various vascular and cellular components. Dead cells also release danger signals that activate dendritic cells and promote the generation of immune responses to antigens. Here we review what is presently known about the sterile inflammatory response and its underlying mechanisms.

"When cells die in vivo, they trigger an inflammatory response"

I: Aortic Thrombus

Local Inflammatory Effects of AAA thrombus

BASIC RESEARCH STUDIES

Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening

David A. Vorp, PhD,a,b,c Paul C. Lee, MD,a David H. J. Wang, MS,a,b Michel S. Makaroun, MD,a Edwin M. Nemoto, PhD,a Satoshi Ogawa, MD,a and Marshall W. Webster, MD,a Pittsburgh, Pa, and Kanazawa, Japan

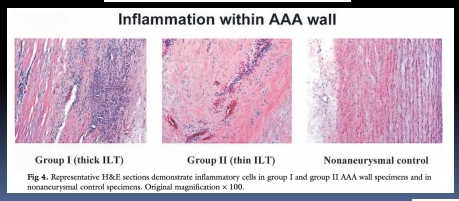
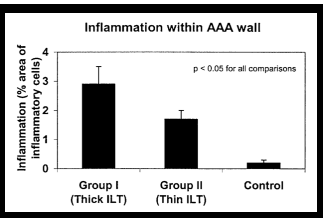
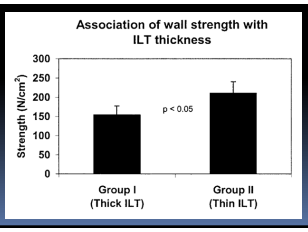


Fig 4. Representative H&E sections demonstrate inflammatory cells in group I and group II AAA wall specimens and in nonaneurysmal control specimens. Original magnification × 100.

JOURNAL OF VASCULAR SURGERY
August 2001

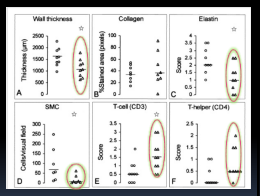




Local Effects of Thrombus and Inflammation on Aortic Wall

Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall

- Aneurysm wall sections from
  - Thrombus covered (triangles)
  - No thrombus (circles)
- Aneurysm wall with thrombus
  - Thinner
  - Fewer elastin and fractured
  - Fewer SMCs, more apoptotic nuclei
  - More inflammatory cells with SMC
- Aneurysm wall no thrombus
  - Dense collagenous matrix
  - Differentiated SMCs



Journal of Vascular Surgery
Volume 38, Issue 6, Pages 1283-1292 (December 2003)
DOI: 10.1016/S0741-5214(03)00792-2

II: Effect of Inflammation on CV outcomes and death

Am J Prev Cardiol. 2020 Dec; 4: 100130.
Published online 2020 Nov 21. doi: 10.1016/j.ajpc.2020.100130
PMCID: PMC8315628
PMID: 34327481

Inflammation and cardiovascular disease: From mechanisms to therapeutics

Abdulhamied Alfaddagh, Seth S. Martin, Thorsten M. Leucker, Erin D. Michos, Michael J. Blaha, Charles J. Lowenstein, Steven R. Jones, and Peter P. Toth*

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Our understanding of atherosclerotic cardiovascular disease (ASCVD) has evolved from being a disease of passive cholesterol accumulation, to a disease that is driven by chronic inflammation which initiates a plethora of biochemical and histologic phenomena that lead to atherosclerotic plaque formation and the triggering of plaque rupture events [9]

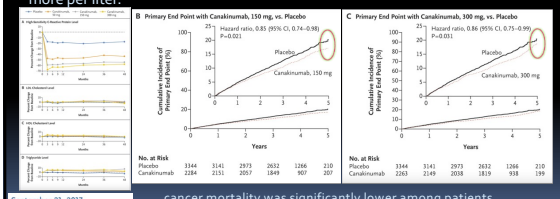
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Paul M Ridker, M.D., Brendan M. Everett, M.D., Tom Thuren, M.D., Jean G. MacFadyen, B.A., William H. Chang, Ph.D., Christie Ballantyne, M.D., Francisco Fonseca, M.D., Jose Nicolau, M.D., Wolfgang Koenig, M.D., Stefan D. Anker, M.D., John J.P. Kastelein, M.D., Jan H. Cornel, M.D., et al., for the CANTOS Trial Group*

...a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter.



September 21, 2017
N Engl J Med 2017; 377:1119-1131
DOI: 10.1056/NEJMoa1707914

...cancer mortality was significantly lower among patients assigned to receive canakinumab than among those in the placebo group.

Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials

Paul M Ridker, Deepak L Bhatt, Aruna D Pradhan, Robert J Glynn, Jean G MacFadyen, Steven E Nissen, on behalf of the PROMINENT, REDUCE-IT, and STRENGTH Investigators

	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)
High-sensitivity CRP, mg/L				
PROMINENT	<1·2	1·2–2·3	2·4–4·8	>4·8
REDUCE-IT	<1·1	1·1–2·1	2·2–4·5	>4·5
STRENGTH	<1·1	1·1–2·0	2·1–4·2	>4·2
LDLC, mg/dL				
PROMINENT	<60	60–78	79–102	>102
REDUCE-IT	<62	62–75	76–89	>89
STRENGTH	<56	56–75	76–99	>99

CRP=C-reactive protein. LDLC=low-density lipoprotein cholesterol.

Table 2: Trial-specific cutpoints for baseline high-sensitivity CRP and baseline LDLC

> 30, 000 patients

www.thelancet.com Vol 401 April 15, 2023

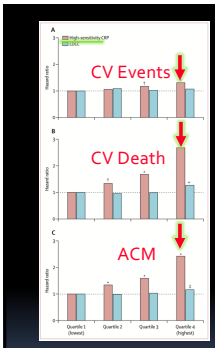


Figure 1: Residual inflammatory risk (as assessed by high-sensitivity CRP) and residual cholesterol risk (as assessed by LDLC) as predictors of future cardiovascular events and death
Combined trial cohort data are shown for major adverse cardiovascular events (A), cardiovascular death (B), and all-cause death (C). CRP=C-reactive protein. LDLC=low-density lipoprotein cholesterol. *p<0·0001. †p<0·01. ‡p<0·05.

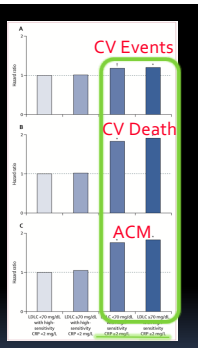
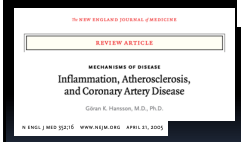
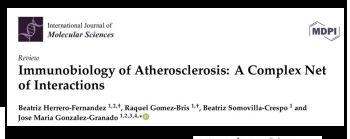
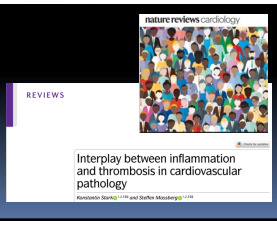


Figure 2: Joint analyses of high-sensitivity CRP and LDLC as predictors of future cardiovascular events and death
Combined trial cohort data are shown for major adverse cardiovascular events (A), cardiovascular death (B), and all-cause death (C). Data are shown in four groups according to baseline LDLC and high-sensitivity CRP concentrations. CRP=C-reactive protein. LDLC=low-density lipoprotein cholesterol. *p<0·0001. †p<0·01.

Inflammation and Atherosclerosis – A Well Established Connection







III: Fate of AAA patients with chronic thrombus burden

Interplay between coagulation and inflammation in open and endovascular abdominal aortic aneurysm repair--impact of intra-aneurysmal thrombus.

Scand J Surg 2007;96(3):229-35 (ISSN: 1457-4969)

Aho PS; Niemi T; Piilonen A; Lassila R; Renkonen R; Lepantalo M

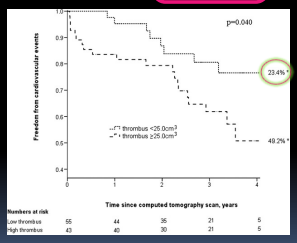
- Volume of pre-op ILT correlates with
  - CRP and PAI-1 ag
- Post-op CRP correlates with volume of ILT in EVAR patients only, not open
- 3 months post-op D-dimer higher in EVAR group than pre-op, not so after open
- ILT after EVAR stimulates both prothombotic and inflammatory mediators

Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms

Adam Parr, MBBS (Hons), Moira McCann, PhD, Barbara Bradshaw, RGN, Anwar Shahzad, MBBS, MRCP UK, Petra Buttner, PhD, and Jonathan Golledge, MChir, *Townsville, Queensland, Australia*

Untreated AAA

- 98 patients / 3 years f/u
- Freedom from CV events
  - 23.4% for large thrombus
  - 49.2% for small thrombus
- CV event RR of 2.4 for large thrombus
  - Independent of other risk factors



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Aneurysm sac expansion is independently associated with late mortality in patients treated with endovascular aneurysm repair

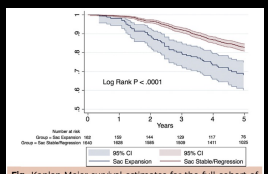


Fig. Kaplan-Meier survival estimates for the full cohort of patients, including those excluded from the remainder of the study because of missing long-term follow-up data. *CI,* Confidence interval.

Table V. Cox regression for long-term mortality

Variable	Death hazard ratio	95% CI	*P* value
Sac expansion	1.5	1.1-2.0	.01
Sac regression	0.6	0.5-0.8	<.001
Age, by decade	1.6	1.4-1.8	<.001
Congestive heart failure	1.4	1.1-2.0	.02
Chronic obstructive pulmonary disease	1.5	1.2-1.8	<.001
Concurrent iliofemoral bypass	3.1	1.5-6.7	<.01

CI, Confidence interval.
Hazard ratio >1 is a risk factor for mortality.
Also adjusted for patient sex, preoperative aneurysm diameter, history of prior aortic surgery, procedure urgency, concurrent hypogastric coverage, and any endoleak or reinterventions at 1-year follow-up.

VSGNE EVAR 2003-2011 / N = 1802

Sarah E. Deery, MD, MPH,[a] Emel A. Ergul, MS,[a] Marc L. Schermerhorn, MD,[b] Jeffrey J. Siracuse, MD,[c] Andres Schanzer, MD,[d] Philip P. Goodney, MD, MS,[e] Richard P. Cambria, MD,[b] and Virendra I. Patel, MD, MPH,[a] for the Vascular Study Group of New England. *Boston and Worcester, Mass. and Lebanon, NH*

Journal of Vascular Surgery
January 2018

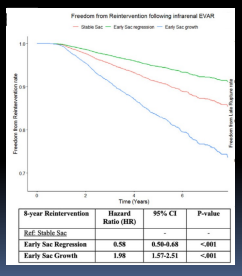
From the Society for Vascular Surgery

One-year aneurysm-sac dynamics are associated with reinterventions and rupture following infrarenal endovascular aneurysm repair

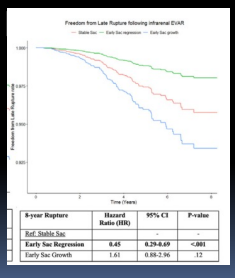
Vinamr Rastogi, MD,[a,b] Thomas F. X. O'Donnell, MD,[c] Christina L. Marcaccio, MD, MPH,[a] Priya B. Patel, MD, MPH,[a,b] Rens R. B. Varkevisser, MD,[a,b] Sai Divya Yadavalli, MD,[a] Jorg L. de Bruin, MD, PhD,[b] Hence J. M. Verhagen, MD, PhD,[b] Virendra I. Patel, MD, MPH,[c] and Marc L. Schermerhorn, MD,[a] *Boston, MA, Rotterdam, The Netherlands, New York, NY, and New Brunswick, NJ*

- All EVAR VQI from 2003-2018
- 16, 102 patients(52%) had 1 year post-op imaging
- At one year:
  - 44% stable
  - 49% regressed
  - 6.2% expanded
- Regression vs. stable sacs: less mortality (p=0.03), less reintervention (p<0.001), less rupture (p<0.001)

Reintervention / Late Rupture



8-year Reintervention	Hazard Ratio (HR)	95% CI	P-value
Ref: Stable Sac		-	-
Early Sac Regression	**0.58**	**0.50-0.68**	**<.001**
Early Sac Growth	**1.98**	**1.57-2.51**	**<.001**

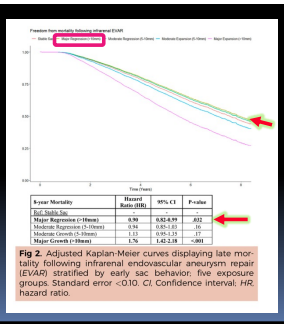


8-year Rupture	Hazard Ratio (HR)	95% CI	P-value
Ref: Stable Sac			
Early Sac Regression	**0.45**	**0.29-0.69**	**<.001**
Early Sac Growth	1.61	0.88-2.96	.12

From the Society for Vascular Surgery

One-year aneurysm-sac dynamics are associated with reinterventions and rupture following infrarenal endovascular aneurysm repair

Vinamr Rastogi, MD,[a,b] Thomas F. X. O'Donnell, MD,[c] Christina L. Marcaccio, MD, MPH,[a] Priya B. Patel, MD, MPH,[a,b] Rens R. B. Varkevisser, MD,[a,b] Sai Divya Yadavalli, MD,[a] Jorg L. de Bruin, MD, PhD,[b] Hence J. M. Verhagen, MD, PhD,[b] Virendra I. Patel, MD, MPH,[c] and Marc L. Schermerhorn, MD,[a] *Boston, MA, Rotterdam, The Netherlands, New York, NY, and New Brunswick, NJ*



5-year Mortality	Hazard Ratio (HR)	95% CI	P-value
Ref: Stable Sac	-	-	-
Major Regression (>10mm)	**0.59**	**0.52-0.69**	**.032**
Moderate Regression (5-10mm)	0.94	0.85-1.03	.19
Moderate Growth (5-10mm)	1.13	0.95-1.35	.17
Major Growth (>10mm)	**1.76**	**1.42-2.18**	**<.001**

Fig 2. Adjusted Kaplan-Meier curves displaying late mortality following infrarenal endovascular aneurysm repair (*EVAR*) stratified by early sac behavior, five exposure groups. Standard error <0.10. *CI,* Confidence interval; *HR,* hazard ratio.

Mortality a function of degree of sac regression

Conclusions

- Aortic thrombus creates a chronic inflammatory state
- Chronic inflammatory states are highly associated with :
  - Increased CV event rate
  - Increased CV death rate
  - Increased all cause death(more cancer)
- Effective aortic aneurysm therapy must resolve thrombus burden

But honestly…Hence is right…as he always is

- Aneurysms with no thrombus burden create the largest fresh thrombus burden after EVAR…and thus the most robust inflammatory response
- Aneurysms with no thrombus, patent IMA, >6 patent lumbars, and age 70 have 36-fold increased risk for persistent T2 endoleak
- Aneurysms with endoleak don't regress….and often grow
- So, yes, thrombus free aneurysms have a high rate of endoleak and create the largest acute thrombus burden following EVAR and thus have the highest rupture, reintervention and ACM

From the New England Society for Vascular Surgery

Preoperative variables predict persistent type 2 endoleak after endovascular aneurysm repair

Christopher J. Abularrage, MD,[a] Robert S. Crawford, MD,[a] Mark P. Conrad, MD, MSHs,[a] Hang Lee, PhD,[b] Christopher J. Kwolek, MD,[a] David C. Brewster, MD,[a] Richard P. Cambria, MD,[a] and Glenn M. LaMuraglia, MD,[a] *Boston, Mass*

Table IV. Composite hazard ratio high-risk analysis of variables predictive of persistent type 2 endoleak

Variables	*No.*	*HR (95% CI)*
Patent IMA plus		
>6 patent lumbar arteries	57	8.76 (3.33-23.06)
Age >70 years	109	8.94 (3.16-25.17)
MALD >30 mm	98	9.14 (3.36-24.86)
>6 patent lumbar arteries and age >70 y	46	17.70 (5.91-52.87)
Patent IMA and MALD >30 mm plus		
>6 patent lumbar arteries	46	18.10 (6.26-52.32)
Age >70 y	81	18.47 (5.98-56.78)
>6 patent lumbar arteries and age >70 y	35	36.57 (11.23-118.76)

CI, Confidence interval; *HR,* hazard ratio; *IMA,* inferior mesenteric artery; *MALD,* maximum aneurysm luminal diameter.

Thank you