Intraluminal thrombus: Innocent bystander or factor in abdominal aortic aneurysm pathogenesis?

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ABSTRACT

Background: Abdominal aortic aneurysms (AAAs) represent a complex multifactorial hemodynamic, thrombotic, and inflammatory process that can ultimately result in aortic rupture and death. Despite improved screening and surgical management of AAAs, the mortality rates have remained high after rupture, and little progress has occurred in the development of nonoperative treatments. Intraluminal thrombus (ILT) is present in most AAAs and might be involved in AAA pathogenesis. The present review examined the latest clinical and experimental evidence for possible involvement of the ILT in AAA growth and rupture.

Methods: A literature review was performed after a search of the PubMed database from 2012 to June 2020 using the terms "abdominal aortic aneurysm" and "intraluminal thrombus."

Results: The structure, composition, and hemodynamics of ILT formation and propagation were reviewed in relation to the hemostatic and proteolytic factors favoring ILT deposition. The potential effects of the ILT on AAA wall degeneration and rupture, including a review of the current controversies regarding the position, thickness, and composition of ILT, are presented. Although initially potentially protective against increased wall stress, increasing evidence has shown that an increased volume and greater age of the ILT have direct detrimental effects on aortic wall integrity, which might predispose to an increased rupture risk.

Conclusions: ILT does not appear to be an innocent bystander in AAA pathophysiology. However, its exact role remains elusive and controversial. Despite computational evidence of a possible protective role of the ILT in reducing wall stress, increasing evidence has shown that the ILT promotes AAA wall degeneration in humans and in animal models. Further research, with large animal models and with more chronic ILT is crucial for a better understanding of the role of the ILT in AAAs and for the potential development of targeted therapies to slow or halt AAA progression. (JVS—Vascular Science 2021;2:159-69.)

Keywords: Abdominal aortic aneurysm; Aortic rupture; Intraluminal thrombus

Abdominal aortic aneurysms (AAAs) are typically asymptomatic, and their rupture has been associated with high morbidity and mortality. AAAs are discrete dilations of the aorta that preferentially develop in the infrarenal segment[1] and typically contain intraluminal thrombus (ILT).[2,3] AAAs are considered for repair in good-risk candidates at maximal aortic diameters of ≥5.5 cm in men and ≥5.0 cm in women (owing to the smaller relative size of the female aorta).[4] However, the use of the AAA size as the primary criterion for intervention is imperfect, because rupture at sizes <5 cm is possible,[5] especially in women.[6] It is also unclear why some AAAs will reach extreme sizes without rupturing,[7,8] and, if size is the major factor, why AAAs rarely rupture at the location of the maximal aortic diameter.[9] The main focus of AAA management has been to predict and prevent rupture. Despite extensive research into the pathogenesis of AAAs, the mortality rates have remained high, with only a slight decrease during the past two decades.[10] Most of the improvement in AAA mortality has resulted from improved screening for AAAs[11] and the increased endovascular management of ruptured AAAs (RAAAs),[10] not from any improvement in nonoperative management.

The development of an AAA is a complex multifactorial thrombotic, inflammatory, and hemodynamic process that ultimately leads to remodeling of the aortic wall connective tissue, resulting in expansion and rupture.[12] The inflammatory nature of the process is evidenced by the infiltration of leukocytes, lymphocytes, and macrophages; with apoptosis of vascular smooth muscle cells (VSMCs).[13,14] This inflammation is associated with increased proteolytic activity, primarily due to the effects of matrix metalloproteinases (MMPs), serine proteases, and cytokines.[15] All are believed to affect the synthesis and degradation of elastin and collagen, leading to irreversible changes in the aortic matrix.[16-18] It is thought that elastin degradation is the initiating step for AAA expansion and that proteolytic degradation of collagen is the final step leading to rupture.

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The changes in the aortic wall in AAAs are similar to those of atherosclerosis and share some similarities with typical arterial thrombosis. However, AAAs represent a form of atherothrombotic disease characterized, not only by matrix degradation, but also by the formation of nonocclusive ILT.[19] This ILT rarely embolizes; however, when that occurs, the morbidity is high.[20] Unlike atherosclerosis, in which remodeling and resolution of arterial injury can occur, the atherothrombotic process in AAAs, once initiated, does not resolve and can, ultimately, lead to vessel rupture.

Of the factors involved in AAA pathogenesis, the potential role of ILT has emerged as an area of current research interest. Nonocclusive ILT, until recently, has been presumed to be inert and to passively accumulate owing to the hemodynamics changes caused by aortic expansion. It is now known that ILT is a complex material containing many active inflammatory cells and proteolytic enzymes.[21,22] The present review critically examined the latest clinical and experimental evidence for possible involvement of ILT in the development, growth, and rupture of AAAs. Understanding any potential role of ILT in AAA pathogenesis could have implications for targeted therapeutic interventions.

METHODS

A literature search, from 2012 to June 2020, for original reports, meta-analyses, and systematic reviews pertaining to AAAs and ILT was performed using the PubMed search engine MEDLINE database. The search words were "abdominal aortic aneurysm" and "intraluminal thrombus." The titles and abstracts were screened to identify potential relevance and suitability. Studies were included if the full text was available. A total of 250 reports were initially reviewed, with 125 included in the present study.

ILT STRUCTURE

Unlike typical acute thrombus, the ILT associated with AAAs is distinctly different, with two predominant types: continuous and discrete.[23] Continuous ILT is more homogeneous and uniform on gross inspection. Discrete ILT is the most common type, with three distinct layers, known as luminal, medial, and abluminal, which have sharp demarcations and weak attachments between adjacent layers. Discrete ILT has the appearance of being gradually deposited over time.[24] Beneath discrete ILT, and adjacent to the AAA wall, a fluid layer of unknown significance is typically present.[23] Each layer of discrete ILT varies in color, with the luminal layer more characteristically red owing to a greater proportion of erythrocytes, similar to that of typical thrombus, with little fibrinolytic activity.[22,25-27] The medial and abluminal layers are acellular and have greater density toward the abluminal side, reflecting older generations of ILT.[28] These layers tend to be yellow to brown, reflective of increasing erythrocyte degeneration[29] (Fig 1). Fibrin deposition occurs uniformly throughout the ILT; however, fibrinolysis is more active in the abluminal regions.[19,23]

Over time, discrete ILT appears to mature and develop channels known as canaliculi. These canaliculi connect the luminal to abluminal layers in a continuous network that might allow for the penetration of various cell types into the ILT, even after it has been well-established.[21] The cell types found in the luminal layer canaliculi are typically degranulated platelets and macrophages. Macrophages do not appear to be passively trapped in ILT, because they have shown no signs of necrosis or apoptosis.[21] Histologic and immunofluorescent staining showed a distinct activated macrophage population within luminal ILT.[30] These fibrocyte-like macrophages express CD45, but lack CD34 and FLK1, suggesting a unique population of cells not derived from the aortic endothelium. These macrophages secrete various anti-inflammatory cytokines, unlike the macrophages of the adventitia, which produce nitric oxide and reactive oxygen intermediates.[13] The exact contribution of this distinct population of macrophages to ILT formation is unknown.

It is not clear why two grossly different types of ILT are present in AAAs nor whether continuous and discrete ILT differs in terms of physical properties, bioactivity, patterns and timing of deposition, or their potential contribution to AAA growth or rupture. The mechanism of deposition is not fully understood. However, the pattern of ILT deposition appears to depend on the AAA shape and hemodynamics.[31] The onset of macroscopic ILT deposition seems to begin only after aortic expansion had changed the geometry to the point at which the hemodynamic conditions favor significant platelet and erythrocyte deposition.[32] Although ILT can change the deposition pattern with AAA remodeling and growth,[33] it generally continues to accumulate and rarely resolves.[34]

MECHANICAL PROPERTIES AND HEMODYNAMICS OF ILT

Humphrey et al[23] have written excellent review with a more detailed discussion on the biomechanics of ILT in AAAs. In brief, it has been suggested that ILTs might play a protective role in AAA formation by withstanding strain.[3] In a retrospective multicenter study, finite element analysis (FEA) was used to calculate the predicted peak wall stress (PWS), peak wall rupture risk (PWRR), rupture risk equivalent diameter (RRED), and ILT volume on computed tomography angiograms (CTAs) from 13 patients with RAAA with prerupture CTAs available for comparison.[35] A control group of patients with diameter-matched, non-RAAAs was included in the analysis. The prerupture CTAs showed significantly greater PWRR and RRED compared with those of the control group. RAAAs showed the greatest maximum diameters, PWRR, and RRED; however, only one half showed rupture at sites that correlated with the

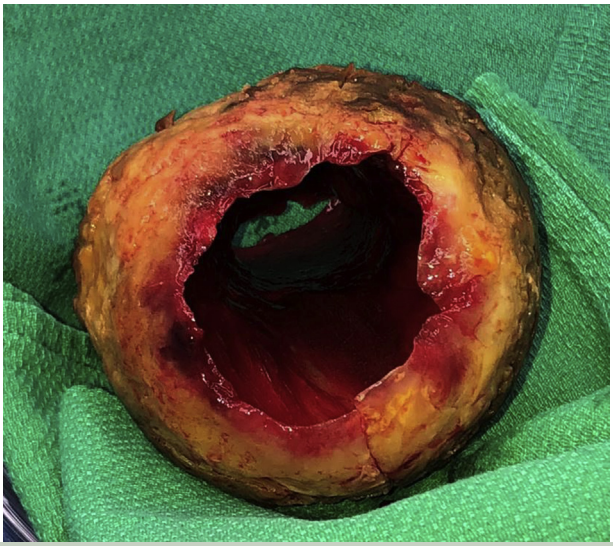

Fig 1. Intraluminal thrombus removed intact from a large abdominal aortic aneurysm (AAA) showing characteristic layers of discrete thrombus.

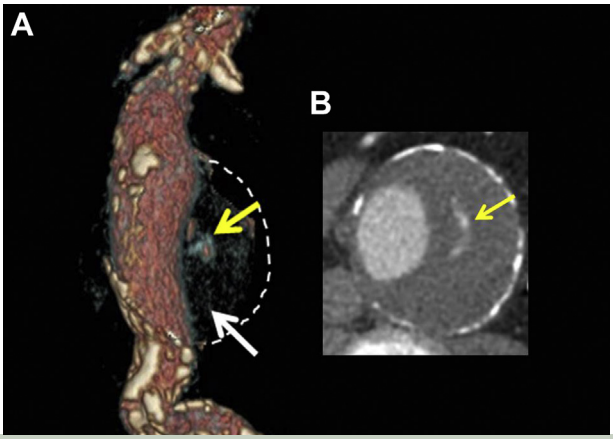

Fig 2. Abdominal aortic aneurysm (AAA) showing active extravasation of contrast (*yellow arrow*) into thick intraluminal thrombus (ILT; *white arrow*) that had preceded rupture by 9 days **(A)** and crescent sign on axial computed tomography angiogram (CTA; *yellow arrow*; **B**).

prerupture PWRR locations.[35] No statistically significant difference was found for PWS and ILT volume; however, the FEA software was not able to measure the variable ILT thickness within the AAAs.[35] Therefore, it was not possible to consider any correlation between PWS, PWRR, or RRED and the location of the AAA rupture or site of maximal ILT deposition.

Haller et al[36] included measures of normalized ILT and percentage of volume of ILT when they examined the PWS and mean wall stress (MWS) in large (≥6 cm) and small (<6 cm) RAAAs and non-RAAAs using FEA. They found the PWS was lower in small RAAAs than in large RAAAs and in small or large non-RAAAs. Small RAAAs had a lower MWS compared with large RAAAs. Small RAAAs also had a greater percentage of volume of ILT and normalized ILT thickness compared with small non-RAAAs. Although increased ILT was associated with lower MWS and PWS, it was also associated with aneurysm rupture at smaller diameters.[36]

Tong et al[37] performed biaxial testing on ILT and suggested that with increasing ILT age, decreased mechanical anisotropy occurred, suggesting a greater propensity for ILT dissection over time. This greater propensity for ILT dissection might explain the fissuring of contrast into thick ILT, which has occasionally been seen as an early sign of impending AAA rupture[38] (Fig 2). In addition, mechanical testing of the aortic wall underlying older ILTs showed an increase in anisotropy, suggesting a loss of strength in these regions. These data suggest that although ILT might initially provide some form of protection against high wall stress, the aging of the ILT causes it to lose this ability. Thus, any biomechanical advantage of ILT in reducing PWS might be offset by weakening of the AAA wall over time.

It is well known that hemodynamics factors favor the preferential formation of AAAs in the infrarenal segment of the aorta and perpetuate continued aortic expansion.[39] Alterations in aortic length and tortuosity result in the development of flow vortexes that ultimately produce turbulent flow.[40-42] Tangential forces exerted on the wall, commonly known as wall shear stress (WSS), result in regions of high, low, and oscillating WSS.[43,44] These altered hemodynamic conditions likely play a major role in initiating and propagating ILT deposition. It has been proposed that high WSS results in intimal denudation that predisposes to ILT formation,[45] with low WSS favoring ILT deposition.[46] Calculation of the time-averaged shear stress on simulated particles in the proximal and middle of an AAA showed a correlation between slower near-wall particle transit times and future ILT deposition.[32] In this sense, low oscillatory WSS is also thought to be proatherogenic.[45] It has been suggested that platelets activate in regions of high WSS and deposit in zones of low WSS.

Bhagavan et al[47] computationally examined the roles of five key morphologic features of AAAs on ILT formation: AAA diameter, AAA length, axial position, tortuosity, and renal artery position. They concluded that the maximum diameter is a key determinant, with vortex flow structures having the potential to induce thrombogenicity and, therefore, ILT deposition. Lozowy et al[33] previously performed a direct numerical stimulation computational fluid dynamics analysis on realistic AAA geometries to study the effects of pulsatile flow on AAA morphology and ILT deposition. In most cases, turbulent vortex structures impinged or sheared along one AAA wall, which tended to be devoid of ILT. In contrast, along the opposite wall, a zone of vortex blood flow was associated with the accumulation of ILT. Expansion occurred to a greater extent in the direction of dominant flow

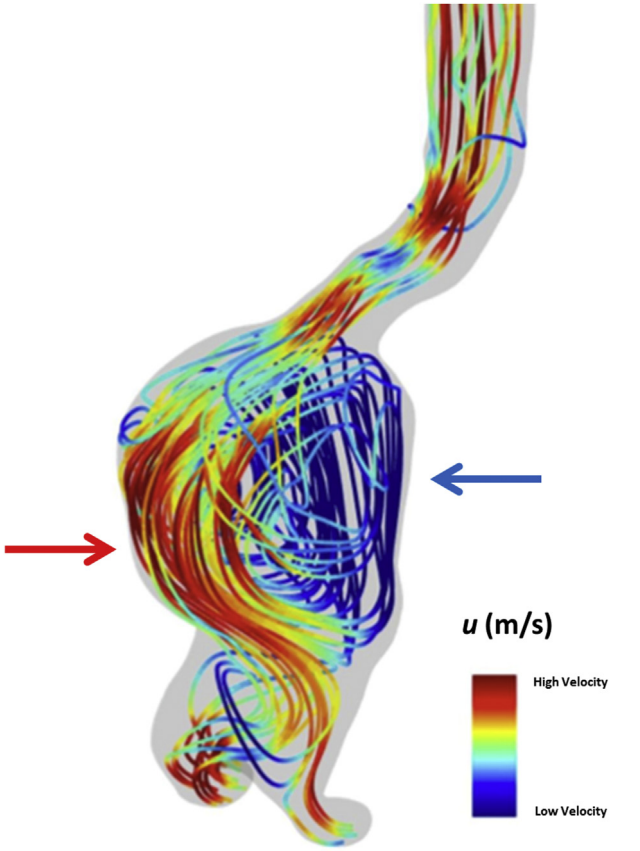

Fig 3. Velocity (μ) in meters/second (m/s) streamlines showing a dominant flow channel (*red arrow* and *red streamlines*) with faster flowing blood in contrast to a zone of vortex flow (*blue arrow* and *blue streamlines*; see also the Video 1). Reproduced, with permission from Boyd et al.[48]

impingement and not at the site of maximal ILT deposition (Fig 3 and Video 1). The results from their small computational study suggest that flow impingement, and not ILT deposition, promotes AAA expansion.[33]

Small AAAs, with average size of 4.0 cm, were followed up for several years with serial CTA imaging until they had reached ~5.5 cm. CTA was used to create realistic AAA geometries, and computational fluid dynamics was used to predict variations in WSS over time. The location and thickness of the ILT was recorded at each time point.[49] In virtually all cases, the ILT had increased over time and its location coincided with the zones of low WSS and vortex flow. ILT deposition tended to increase in the same location in all but one case. In that case, the zone of vortex flow had changed its location over time and coincided with a change in the location of ILT deposition (Fig 4 and Video 2). This finding suggests that ILT deposition is strongly dependent on aortic hemodynamics.

In a rat xenograft model, Etienne et al[50] created saccular or fusiform aneurysms. They showed that saccular aneurysms had lower inflow velocities, greater vortex flow, and thicker ILT, when assessed by magnetic resonance imaging, compared with fusiform aneurysms. Saccular aneurysms also had higher myeloperoxidase, platelet factor 4, advanced oxidation protein products, iron, and MMP-9, suggesting that differential specific hemodynamics can affect inflammatory markers and ILT deposition.

ILT AND RUPTURE RISK

In an autopsy study, AAAs were found to typically rupture in regions of ILT burden in 80% of cases.[9] Kazi et al[51] showed that the aortic wall beneath ILT is thinner, has more inflammatory infiltrate, greater apoptosis of VSMCs, and a greater amount of degraded extracellular matrix. Early evidence indicated that the burden of ILT in AAAs was associated with accelerated growth and rupture risk.[36,52-54] Pillari et al[34] showed a synchronous increase in ILT volumes with AAA growth to 7 cm. In contrast, after 7 cm, aortic expansion was not associated with an increase in ILT volume, suggesting that hemodynamic and procoagulant conditions no longer favor ILT deposition and/or that the advanced stage of AAA growth is unrelated to the presence of ILT.[34]

In contrast, Golledge et al[55] matched RAAAs with non-RAAAs for size and found no difference in ILT thickness. Kontopodis et al[56] showed that ILT was more symmetrical in RAAAs but was slightly reduced at the site of rupture. Qiu et al[57] correlated the rupture location with the ILT content in a small series of RAAAs. AAAs, devoid of ILT, ruptured in areas of low WSS. In contrast, in those with thin ILT, the AAA had ruptured at the site of dominant flow impingement. In those with thick ILT, the rupture had occurred at the border of the dominant flow channel and the region with highest ILT deposition.[57] Although their small study showed variable rupture locations, AAAs with thick ILT ruptured at significantly smaller sizes than did those without ILT, and rupture was more common in AAAs that contained ILT compared with those devoid of ILT.[57] Using a computational fluid dynamics approach, we have previously shown that AAA rupture tends to occurs in zones of vortex flow in AAAs with eccentric ILT deposition, where the predicted WSS was low and ILT deposition was greatest.[48]

Vorp et al[58] hypothesized that the deposition of ILT might lead to a relatively hypoxic environment with increased proteolytic activity in the aortic wall nearest to thick ILT deposition. Under normal circumstances, aortic wall oxygenation and nutrients reach the media and adventitia by diffusion from the lumen and are less dependent on that provided by the adventitial vasa vasorum.[59] With increasing aortic wall inflammation, the vasa vasorum dilates to maintain vessel integrity.[60] In support of the hypoxia theory, Vorp et al[61] demonstrated that thick ILT had lower oxygen pressure compared with areas with thin ILT and resulted in greater inflammation, greater hypoxia-specific peptide, and decreased tensile strength.[61] In addition, it

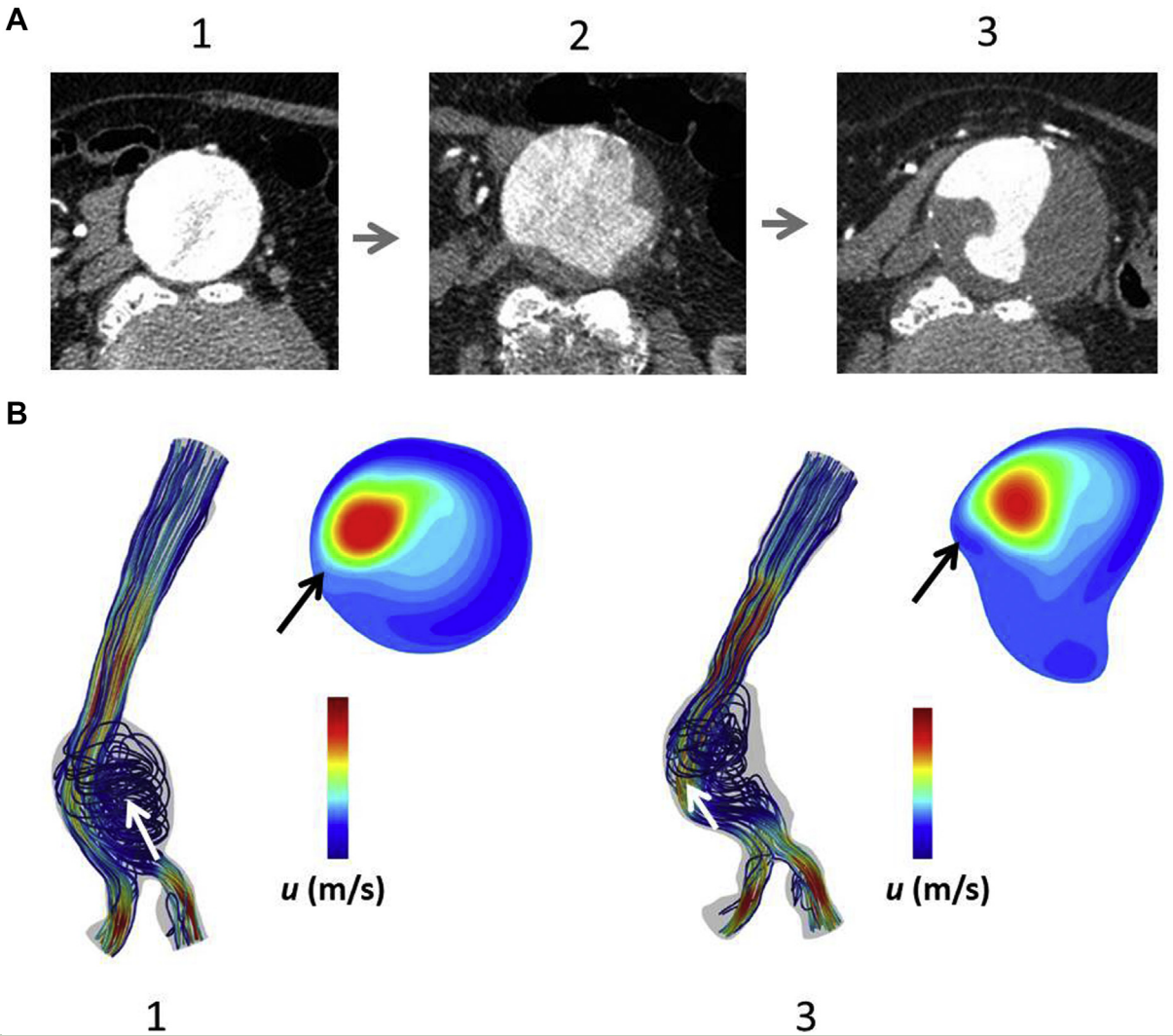

Fig 4. A, Axial computed tomography angiograms (CTAs) of abdominal aortic aneurysm (AAA) from time point 1 (baseline), time point 2 (at 2 years), time point 3 (at 5 years) showing increased intraluminal thrombus (ILT) deposition over time. **B,** Velocity streamlines (*white arrows*) and cross-sectional velocity profiles (*black arrows*) showing changes in location of vortex flow for time points 1 and 3, coinciding with the gradual change in ILT deposition. Reprinted, with permission, from Launcelott et al.[49]

has been shown that macrophages subjected to hypoxia increase their reactivity[62] and promote elastase production.[63] Hypoxia has been shown to have a detrimental effect on the extracellular matrix,[64] in particular, hypoxic fibroblasts produced less collagen, because oxygen is a requirement for the hydroxylation of proline.[65]

Positron emission tomography with fluorine 18-fluorodeoxyglucose (^{18}F-FDG) can detect activated leukocytes by competing with glucose for uptake into metabolically active cells. Xu et al[66] showed that ^{18}F-FDG uptake correlated positively with regions of high wall stress in non-RAAAs and RAAAs and that the location of rupture was associated with regions of higher metabolic activity. Huang et al[67] showed that in small non-RAAAs, ^{18}F-FDG activity was highest in regions of thick ILT and FEA-predicted high mechanical wall stress, suggesting that regions with higher ILT have greater inflammatory activity.

ILT FORMATION AND COAGULATION FACTORS

Tobacco smoking is the strongest risk factor for AAA development, and active smoking is associated with faster AAA growth and higher rupture rates.[68] Although the inciting mechanisms for vascular dysfunction are not well understood, the endothelial absorption of tobacco smoke constituents induces free radical lipid peroxidation of the vascular endothelium.[69] Whatever the inciting event, vessel injury exposes matrix proteins to circulating platelets, leading to their activation. It is well known that autocrine activation of surrounding platelets,

via adenosine diphosphate and thromboxane A2, leads to the formation of a platelet-rich plug. In addition, exposure of subendothelial tissue factor (TF) and the formation of a complex of factor Xa (FXa) and factor Va occurs; with thrombin cleavage of fibrinogen to fibrin. The subsequent interaction of the primary hemostatic plug with factor XIIIa, cross-linked fibrin, leads to a stable secondary platelet–fibrin thrombus. Increased secondary fibers contribute to fibrin consolidation.[69]

In early ILT formation, platelets exposed to P-selection stimulate the accumulation of neutrophils preferentially in the luminal layer of ILT.[70] Neutrophils have a high affinity for fibrin and undergo constitutive apoptosis after binding,[22] which releases various inflammatory cytokines, proteases, and metalloproteinases,[71,72] as well as myeloperoxidase and elastase.[73]

The glycoprotein IIb/IIIa inhibitor, abciximab, attenuated ILT formation and prevented aortic expansion in a rat xenograft model.[74] This agent also decreased P-selection expression, elastin degradation, and VSMC adhesion. However, P-selectin is not specific to platelets, because it is also expressed by endothelial cells.[75] Administration of the antiplatelet agent, AZD6140 (a P2Y12 receptor antagonist), in this xenograft model reduced AAA growth, ILT deposition, MMP-9 expression, leukocyte infiltration, and elastin degradation.[76] In aortic tissue harvested from hypercholesterolemic rats, aspirin also reduced radical oxidative stress in endothelial cells.[77] In angiotensin II-induced AAAs in mice, the administration of clopidogrel reduced ILT formation, platelet and macrophage accumulation, and rupture-related death. Clopidogrel also decreased MMP-2 and MMP-9, urokinase plasminogen, and tissue plasminogen activator (TPA) levels and platelet factor 4 and platelet-derived cytokines.[78] All these animal models showed a strong correlation between AAA growth and ILT deposition. They also showed strong evidence of the role of platelets in ILT formation and AAA growth. However, no benefit was found from platelet inhibition on AAA progression, rupture, or repair outcomes in humans to date.[79]

In angiotensin II-induced AAAs in apolipoprotein E–deficient mice, AAA size correlated with FXa expression and increased protease activator (PAR-2) expression.[80] When these mice were treated with enoxaparin (FXa/FIIa inhibitor), fondaparinux (FXa inhibitor), or dabigatran (FIIa inhibitor), no effect was found for FIIa inhibition alone on AAA development. In contrast, FXa and FXa/FIIa inhibition was associated with decreased AAA formation and reduced steroid receptor activator levels, PAR-2 expression, MMP-2, Smad 2/3 phosphorylation, and monoclonal macrophage-monocyte antibody 2–positive cells. These findings suggest that FXa/FIIa might limit AAA growth by downregulating PAR-2–mediated Smad2/3 signaling and MMP-2 expression. FXa inhibition alone was associated with decreased ILT formation and increased elastin degradation. These data suggest that FXa/FIIa is important in AAA growth and ILT-mediated elastin degeneration. These findings also suggest that inhibition of FXa/FIIa could be a potential therapy for limiting AAA growth.[80]

ILT AND PROTEASES

Serine proteases and coagulation factors are simultaneously elevated in AAA tissue,[81] suggesting possible cooperation between the hemostatic and proteolytic systems in degrading components of the extracellular matrix (ECM),[82] and the possibility that this interaction might play a significant role in AAA pathogenesis.[22,83-89] ILT might be a source for serine proteases released or activated during coagulation, fibrinolysis, and proteolysis that could weaken the AAA wall.[90-93] TPA and D-dimer concentrations were significantly higher in the plasma of subjects with AAAs.[90] Also, the AAA tissue had greater concentrations of TPA and plasmin, with decreased plasminogen activator inhibitor (PAI-1) activity,[91-96] suggesting that AAAs are associated with hypercoagulability that might promote ILT deposition.

Endothelial inflammation results in the secretion of von Willebrand factor, which is involved in the formation of platelet-rich thrombus. The plasma of 30 patients with asymptomatic AAAs was tested for von Willebrand factor activity, thrombin generation time, factor XII levels, and prekallikrein concentrations, with the findings correlated with the CTA-assessed ILT volume.[97] A positive correlation between the ILT volume, von Willebrand factor activity, and prekallikrein concentrations in plasma was found, indicating that these factors might be important in initiating ILT formation.[97]

Carrell et al[98] investigated fibrinolytic and proteolytic activity in the human AAA wall in relation to the luminal and abluminal layers of the ILT. They found 100-fold greater TPA and 6-fold higher urokinase plasminogen activator activity in the aortic wall compared with either location of the ILT. Luminal ILT had had significantly lower levels of PAI-1 compared with the AAA wall and the abluminal layer of the ILT. The MMP-9 levels were high in the ILT and in the AAA wall, suggesting that ILT might be the source of plasmin activation of endogenous MMPs.

It has also been suggested that thin, as opposed to thick, ILT might allow for greater penetration of inflammatory cells and localized proteolytic degradation. Siennicka et al[99] demonstrated inhomogeneity of coagulation and fibrinolytic activity in human AAAs according to the ILT thickness. The relative concentrations of TF, plasma, PAI-1, α_2-antiplasmin (α2AP), and TPA in ILT and the AAA wall adjacent to thin and thick ILT were measured in 35 patients with eccentric ILT undergoing elective open AAA repair.[99] TF and α2AP levels were highest in the aortic wall adjacent to thin ILT where the greatest inflammatory infiltration had occurred. The TPA levels were highest in the aortic wall. In contrast, plasminogen was highest in ILT, suggesting cooperation in generating active plasmin. Plasmin, depending on the level of α2AP, might then activate various MMPs

responsible for proteolytic degeneration of the wall. Wiernicki et al[100] also showed that thin ILT (<1 cm) correlated with higher oxidative stress—related enzymes and MMP-9 expression in full-thickness human AAAs, suggesting that ILT might be the contributing source of plasmin and MMP-9 activation, leading to proteolytic degeneration of the AAA wall.

The continued elaboration of ILT in AAAs without complete vessel occlusion or distal embolization involves a balance between procoagulant and anticoagulant factors.[101] Like AAAs, popliteal artery aneurysms (PAAs) are characterized by similar ILT deposition and atherothrombotic pathology, although PAAs are more prone to ILT embolization and significantly less likely to rupture.[102] Histologic assessments of PAAs compared with AAAs showed more signs of intramural hemorrhage, greater intimal inflammation, and higher matrix MMP-2 activity. MMP-9 activity was similar in both types of aneurysms.[103] Abdul-Hussien et al[104] showed that AAAs had higher interferon-γ, interferon-inducible protein 10, tumor necrosis factor-α, monocyte chemotactic protein-1, and macrophage inflammatory protein-1α and -1β compared with PAAs. AAAs also had significantly higher B cell, plasma cell, and cytotoxic T cell infiltration compared with PAAs.

The reasons for the relative differences in the inflammatory and protease profile between AAAs and PAAs is unknown. It is possible that size is still the major factor for the greater rupture rates of AAAs compared with PAAs. PAAs have greater rates of ILT embolization owing to the potentially increased local trauma, as evidenced by the more frequent intramural hemorrhage. All studies to date have compared the PAA and AAA differences in the aneurysm wall, and none has compared the constituents or activity of ILT in these two conditions. Understanding the differences in ILT between PAAs and AAAs could be important in determining the possible role of ILT, if any, in the pathophysiology of all aneurysms.

ILT AND CYTOKINES

Upregulation of cytokines occurs, which suggests an immune component to the inflammatory nature of AAAs. Tumor necrosis factor-α, transforming growth factor-β (TGF-β), interleukin (IL)-1β, IL-6, IL-8, IL-17, and IL-18, and CD40 ligand are all elevated in AAAs compared with controls.[105-108] Only selected cytokines appear to play a role in ILT formation in AAAs. One such proinflammatory cytokine is IL-8, which stimulates neutrophil recruitment and migration.[109-111] The luminal layer of ILT is the main source of IL-8, with a gradient of decreasing IL-8 levels toward the abluminal layer, and the aortic wall showing four times lower levels.[112] IL-8 might be a factor in the continued deposition of ILT via continued recruitment of neutrophils.

The cytokine, TGF-β, is also involved in ILT development in AAA pathogenesis. TGF-β is bound to fibrillin,[113] where it regulates fibroblast differentiation and proliferation, immune response, and protease activity[114,115] in the ECM, and is considered to be involved in the maintenance of vascular integrity. In mice that underwent AAA induction by external elastase application, inhibition of TGF-β activity enhanced neutrophil infiltration into both the ILT and the aortic wall and increased AAA growth, ILT deposition, ECM degradation, and the susceptibility rupture.[116] Early blockade of IL-1β in this model significantly decreased the extent of ILT deposition and AAA formation. In contrast, late administration of IL-1β had no effect, suggesting that neutrophils are involved in early AAA formation.[116] However, aortic wall proteolysis in most animal models of AAA is so acute and severe that it causes sudden aortic dilation, not infrequently leading to acute rupture. ILT in animal models more closely resembles the typical features of the luminal layer of discrete ILT and does not develop the features of the deeper more chronic ILT.

ILT AND MMPs

MMPs are a family of calcium-dependent zinc endopeptidases most widely implicated in AAA pathogenesis. MMP-2 and MMP-9 are two of the most widely studied MMPs in AAA pathology. Both MMP-2 and MMP-9 are type IV collagenases and are found at higher levels in the plasma, aortic wall, and ILT of patients with AAAs[22,117-119] and are associated with increased VSMC apoptosis and elastin degradation.[13,14] MMP-9 levels will also be significantly elevated in RAAAs, in particular at the site of rupture compared with other sites in the aortic wall.[92]

AAAs will typically have varying thicknesses of ILT from 1 mm to several centimeters.[120,121] The highest levels of MMP-2 and MMP-9 were found in the luminal layer of ILT compared with the deeper layers closer to the aortic wall.[73] However, in the aortic wall, the MMP-9 and tissue inhibitor of MMP-1 levels were highest in regions with thin ILT,[122] suggesting that thinner ILT might undergo more active proteolysis. In contrast, when full-thickness human aortic tissues samples were stereographically biopsied over the entire aorta from patients undergoing open AAA repair and correlated with computationally derived hemodynamics, high MMP-9 levels correlated positively low WSS and high ILT deposition, increased inflammatory infiltrate, and decreased elastin and collagen content.[123]

The reason for the discrepancy between thick and thin ILT might reflect the location of tissue sampling, because the former study had taken biopsy specimens of AAA tissue only from the area of maximal aortic diameter.[122] In contrast, in the latter study, biopsies were taken from a representative section of the entire aorta and mainly compared the ILT and no-ILT regions.[123] In addition, thin ILT might have been recently deposited and, thus, might have had greater inflammatory activity, similar to that seen in the luminal layer of discrete ILT. Samples

of thick ILT likely had deeper, more inert, layers included in the sample, which might have diluted the measurements of the inflammatory markers. A comparison of the surface layer of thick ILT with that of thin ILT might explain the differences in inflammatory and proteolytic activities and might explain the discrepant findings regarding the rupture location in relation to the ILT. Regardless, the cited studies have shown that the aortic wall nearest the ILT had the greatest MMP-9 activity, suggesting that local variations in MMP-9 proteolytic activity might explain the tendency for AAAs to rupture at regions of higher ILT deposition in several studies.

CONCLUSIONS AND FUTURE DIRECTIONS

The development of ILT in AAAs involves a concerted interaction between hemodynamics, the coagulation cascade, acute and chronic inflammatory cell activation, and cytokine/protease release. The initiation of ILT deposition in AAAs is likely in response to endothelial injury and, therefore, might initially be protective. Despite computational evidence of a possible protective role of ILT in reducing wall stress, AAAs devoid of ILT do not rupture at smaller diameters nor at greater rates than those with circumferential ILT. In contrast, evidence has shown smaller AAAs with a higher ILT burden having a tendency to be at an increased risk of rupture, with rupture occurring preferentially at the site of ILT deposition in AAAs with eccentric ILT. Increasing evidence has shown the instability of ILT with increasing age and/or thickness, the potential for aortic wall hypoxia, and increased proteolytic degradation in AAA regions with associated ILT. Thus, the question remains regarding why would thrombus be protective in AAAs but detrimental in other vascular beds.

As with most computational and animal model AAA research, issues exists with translation of the findings to the human condition. However, the present review found both animal and human evidence of the potential role of ILT deposition in AAA formation and increased rupture risk. A purely hemodynamic approach to understanding the potential role of ILT is insufficient, because the possible proteolytic effect of ILT on the AAA wall itself must also be considered. In addition, the shape and pattern of ILT distribution varies in AAAs, and most studies have been underpowered to properly assess the potential role of the ILT deposition pattern and thickness on local proteolysis and AAA rupture risk.

Therefore, ILT is likely not an innocent bystander in AAA pathophysiology; however, its potential role remains undefined. With increasing endovascular AAA management, samples of aortic tissue and ILT will be less frequently available. Animal models will become increasingly more important in understanding the molecular mechanisms and controversies regarding the location and thickness of ILT and its effect on AAA rupture risk. However, no current animal model has completely represented the complexity, chronicity, and outcomes of human AAAs nor have any shown a protective effect of ILT. Large animal models with more chronic ILT are needed to mimic the conditions in human AAAs and will be crucial to determine whether therapies targeted toward ILT will have any significant effects on AAA growth and rupture risk.

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