J Thromb Thrombolysis (2009) 27:119–121
DOI 10.1007/s11239-009-0307-5

Thrombogenesis in atrial fibrillation contributing mechanisms and natural history

Richard C. Becker

Published online: 28 January 2009
© Springer Science+Business Media, LLC 2009

Atrial fibrillation and its closely related counterpart, atrial flutter are not only common arrhythmias, but also contribute directly to unparalleled morbidity, mortality, and health care expenditures worldwide by virtue of their relation with cardioembolic stroke. While an existing thrombotic substrate is widely recognized, less well described are the natural history of thrombus initiation and development, specifically the sequence of events and contribution of both local (tissue level) and circulating factors, and the participation of thrombus in left atrial/left atrial appendage remodeling.

How important is stasis of blood flow in left atrial appendage thrombogenesis?

Virchow's triad, a time-honored paradigm that offers mechanistic insights for thrombus initiation and development regardless of origin, does indeed apply to atrial fibrillation and left atrial appendage thrombogenesis. While stasis of blood flow is a contributing element, additional local factors originating at the tissue level, and circulating factors with delivery to sites of endocardial injury, may predominate. Experimental models of flow fields in expansive orifices have shown that blood stagnation is associated with thrombin generation, particularly with entrainment of stagnant fluid [1].

The etiology of blood flow stagnation in atrial fibrillation, may for a variety of reasons, be a more important contributor to localized thrombogenesis than stasis itself. Structural remodeling of the left atrial appendage to include the pectinate muscles and multiple lobes of the lumen occurs in patients with permanent atrial fibrillation [2]. Morphologic studies have shown larger volumes and luminal surface areas when compared to patients without atrial fibrillation; however, both the absolute and relative surface areas of the pectinate muscles are reduced. In addition, there is significant endocardial thickening with fibrous and elastic tissue (endocardial fibroelastosis) [2]. Endothelial progenitor cells from patients with permanent atrial fibrillation have an intrinsic tendency to differentiate into cells expressing cardio (myocyte) markers atrial natriuretic polypeptide and myocyte enhances factor-2. Whether the endothelial cell progenitor profile represents a biological response that facilitates endocardial repair and, with it, normal functionality of a more general protective mechanism that prompts fibrosis (and thrombogenicity) requires further investigation [3].

Considered collectively, dilation, stretching, and reduced pectinate muscle volume, coupled with the loss of a normal endocardial surface that is designed specifically to attenuate inflammation and thrombosis, may create a highly prothrombotic environment.

Tissue factor and thrombogenesis in atrial fibrillation

An understanding of left atrial—left atrial appendage thrombogenesis may have its roots in distinguishing hemostatic and thrombotic clotting. Studies performed by Hoffman and Monroe offer potential mechanistic insight. In a series of wounding experiments, skin punch biopsy tissue was placed on the dorsal skin of C57 black mice [4]. Samples containing the wound specimens were then collected. For comparison, thrombus was provoked in saphenous veins by application of 10% ferric chloride.

R. C. Becker (✉)
Duke University School of Medicine, Durham, USA
e-mail: becke021@mc.duke.edu

After complete occlusion, tissue blocks containing the clotted vessels were collected. Histologic evaluation revealed extensive tissue factor staining within saphenous vein thrombi. In distinct contrast, tissue factor staining in hemostatic clots was localized to squamous endothelial cells at the wounds edges—not within the thrombus itself.

The experimental findings suggest that a large volume of blood must flow over an injured surface, such as the left atrial—left atrial appendage endocardium in a person with atrial fibrillation for significant tissue factor, derived from both circulating cells and microparticles [5, 6], to accumulate in high concentrations. Further, and of fundamental teleological relevance, hemostasis occurs rapidly, with tissue factor of local origin determining the rate of thrombus development.

The cell-based model of coagulation translates well to left atrial-left atrial appendage thrombogenesis and supports a primary role for tissue factor-based thrombin generation, with a secondary role being played by platelets. While the results of clinical trials [7, 8] and meta-analyses are consistent with this hypothesis, several biological constructs potentially provide a mechanistic platform as well.

The integrated complexity of coagulation in general and platelet-dependent thrombin generation in particular is becoming evident. One of the most interesting and clinically relevant observations over the past decade is the concomitant interdependence and independence of platelet activation and thrombin generation. The former is best considered in the context of primary hemostasis and possibly arterial thrombosis-both highly dependent on platelet activation, platelet aggregation and thrombin generation (in concentrations sufficient to provoke further platelet activation). In the latter instance, platelet subpopulations with distinct intracellular calcium signaling properties yield procoagulant domains [9]. The down regulation of platelet αIIb/β_3, in turn, attenuates proaggregatory potential.

Thrombin and tissue remodeling

The relationship between atrial fibrillation and remodeling of the left atrium/arterial appendage is traditionally explained by the absence of contractility and altered flow dynamics. This hypothesis is not entirely fulfilling for several reasons, not the least of which is its inability to substantiate the mechanism of progressive structural change. A contemporary view considers the contribution of coagulation factors and thrombus substrate itself as both initiators and perpetuators of the prothrombotic environment that includes remodeling.

Thrombin, a serine protease, beyond its widely recognized role in hemostasis and thrombosis, is directly involved in tissue repair and remodeling through an endothelial mesenchymal transdifferentiation process [10]. Thrombin also exerts an effect on endothelial cell junctions (reviewed in [11]), endothelial cell and smooth muscle cell migration and smooth muscle cell proliferation via protease activated receptor (PAR)-1 [12].

Thrombin-induced membrane-type matrix metalloproteinase (MMP)-2 gene transcription and activity [13] may also contribute to structural changes in the atrium/atrial appendage, as may thrombin-augmented fibroblast-mediated collagen gel contraction [14]. Locally generated thrombin has been shown in tissue culture to upregulate tissue factor expression and activity [15].

While thrombin is known to possess a variety of cell-regulating capabilities, one must not overlook the contribution of other coagulation proteases in the remodeling process. Indeed, factor Xa has been shown to promote fibroblast proliferation, migration and differentiation into myofibroblasts through a PAR-2 specific mechanism [16].

Considering the principles presented herein, one may conclude that atrial fibrillation and its natural history, to include atrial/atrial appendage remodeling, loss of normal endocardial thromboresistance, and propensity for thrombus formation and embolization is highly dependent on circulating tissue factor expressed on cellular elements, leading to incremental clot growth, and the contribution of two coagulation proteases—factor Xa and thrombin each exhibiting procoagulant, proliferative and tissue remodeling potential. Accordingly, the development of oral/direct factor Xa and thrombin inhibitors provides an unprecedented opportunity to investigate fundamental pathological mechanisms in atrial fibrillation.

References

1. Fallon AM, Dasi LP, Marzec UM, Hanson SR, Yoganathan AP (2008) Procoagulant properties of flow fields in stenotic and expansive orifices. Ann Biomed Eng 36:1–13. doi:10.1007/s10439-007-9398-3
2. Shirani J, Alaeddini J (2000) Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol 9:95–101. doi:10.1016/S1054-8807(00)00030-2
3. Goette A, Jentsch-Ullrich K, Lendeckel U et al (2003) Effect of atrial fibrillation on hematopoietic progenitor cells: a novel pathophysiological role of the atrial natriuretic peptide? Circulation 108:2446–2449. doi:10.1161/01.CIR.0000102968.19341.FC
4. Hoffman M, Whinna HC, Monroe DM (2006) Circulating tissue factor accumulates in thrombi, but not in hemostatic plugs. J Thromb Haemost 4:2092–2093. doi:10.1111/j.1538-7836.2006.02085.x
5. Lechner D, Weltermann A (2008) Circulating tissue factor-exposing microparticles. Thromb Res 122:S47–S54. doi:10.1016/S0049-3848(08)70019-7

6. George FD (2008) Microparticles in vascular diseases. Thromb Res 122:S55–S59. doi:10.1016/S0049-3848(08)70020-3
7. Connolly S, Pogue J, Hart R et al (2006) Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 367:1903–1912. doi:10.1016/S0140-6736(06)68845-4
8. Healey JS, Hart RG, Pogue J et al (2008) Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke 39:1482–1486. doi:10.1161/STROKEAHA.107.500199
9. Munnix IC, Kuijpers MJ, Auger J et al (2007) Segregation of platelet aggregatory and procoagulant microdomains in thrombus formation: regulation by transient integrin activation. Arterioscler Thromb Vasc Biol 27:2484–2490. doi:10.1161/ATVBAHA.107.151100
10. Archiniegas E, Neves CY, Candelle D, Cardier JE (2004) Thrombin and its protease-activated receptor-1 (PAR1) participate in the endothelial–mesenchymal transdifferentiation process. DNA Cell Biol 23:815–825. doi:10.1089/dna.2004.23.815
11. Vandenbroucke E, Mehta D, Minshall R, Malik AB (2008) Regulation of endothelial junctional permeability. Ann N Y Acad Sci 1123:134–145. doi:10.1196/annals.1420.016
12. Gluck N, Schwob O, Krimsky M, Yedgar S (2008) Activation of cytosolic phospholipase A2 and fatty acid transacylase is essential but not sufficient for thrombin-induced smooth muscle cell proliferation. Am J Physiol Cell Physiol 294:C1597–C1603. doi:10.1152/ajpcell.00206.2007
13. Dahi S, Lee JG, Lovett DH, Sarkar R (2005) Differential transcriptional activation of matrix metalloproteinase-2 and membrane type-1 matrix metalloproteinase by experimental deep venous thrombosis and thrombin. J Vasc Surg 42:539–545. doi:10.1016/j.jvs.2005.04.051
14. Fang Q, Mao L, Kobayashi T et al (2008) PKCdelta mediates thrombin-augmented fibroblast-mediated collagen gel contraction. Biochem Biophys Res Commun 369:1199–1203
15. BelAiba RS, Djordjevic T, Bonello S et al (2006) The serum- and glucocorticoid-inducible kinase Sgk-1 is involved in pulmonary vascular remodeling: role in redox-sensitive regulation of tissue factor by thrombin. Circ Res 98:828–836. doi:10.1161/01.RES.0000210539.54861.27
16. Borensztajn K, Stiekema J, Nijmeijer S, Reitsma PH, Peppelenbosch MP, Spek CA (2008) Factor Xa stimulates proinflammatory and profibrotic responses in fibroblasts via protease-activated receptor-2 activation. Am J Pathol 172:309–320. doi:10.2353/ajpath.2008.070347