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EDITORIAL COMMENT

Direct Effects of Activation and Inhibition of the Coagulation System on the Atrial Fibrillation Substrate

Is Anticoagulation Antiarrhythmic?*

Stanley Nattel, MD

Atrial fibrillation (AF) is a highly prevalent clinical problem that is becoming more common with population aging, and presents a broad range of therapeutic challenges (1,2). An improved understanding of the underlying pathophysiology is central to improving management options for the arrhythmia (3).

The most significant complication of AF is thromboembolism, particularly stroke (4). AF-related stroke is effectively prevented by oral anticoagulation (OAC), achieved traditionally by vitamin K antagonists (VKAs) such as warfarin, and more recently by direct-acting agents (DOACs) such as the thrombin-antagonist dabigatran and the Factor Xa (FXa) inhibitors rivaroxaban, apixaban, and edoxaban (4). Because of the attendant bleeding risk, OAC therapy has been targeted to patients with elevated stroke risk, although with the reduced bleeding seen with DOACs versus VKAs, the threshold for OAC therapy has decreased and the emphasis has shifted to identifying true low-risk individuals who may safely be managed without OAC (5).

It has long been known that thrombin possesses proinflammatory effects mediated by protease-activated receptor (PAR)-1 (6) and that both thrombin and FXa have profibrotic effects (7). Furthermore, thrombin-inhibition has antifibrotic effects (8). Atrial fibrosis is a major potential contributor to the substrate for AF maintenance (9,10), and therefore beyond its role in clotting, activated thrombin or FXa could contribute to the progression of the AF substrate. Conversely, inhibitors of thrombin or FXa such as the DOACs could have an AF-suppressing effect.

THROMBIN INHIBITION AND THE AF SUBSTRATE IN A RAT MODEL OF CARDIAC DYSFUNCTION

In this issue of *JACC: Basic to Translational Science*, Jumeau et al. (11) study the role of thrombin signaling in a rat model of cardiac dysfunction due to myocardial infarction (MI) (11). MI was created by ligating the left anterior descending coronary artery for 30 min, followed by reperfusion. MI caused ventricular dysfunction, enhanced thrombogenesis, atrial fibrosis and dilation, and an AF substrate (the duration of

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induced AF increased from approximately 3 s to approximately 6 s, $p = 0.02$) over a period of 4 weeks to 8 weeks. Dabigatran or another direct-acting thrombin inhibitor (DTI) suppressed these changes, while attenuating the upregulation of a variety of remodeling-related (connective tissue growth factor [CTGF], brain natriuretic peptide [BNP], α-myosin heavy chain [MHC]) and procoagulant (plasminogen activator inhibitor [PAI]-1) factors/biomarkers. The direct effects of thrombin were studied in rat atrial explants, showing that it increases the expression of BNP, α-MHC, PAI-1, and phosphorylated signal

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From the Department of Medicine, Montreal Heart Institute and Université de Montréal, Montréal, Canada; Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada; and the Institute of Pharmacology, West German Heart and Vascular Center, Faculty of Medicine, University Duisburg-Essen, Essen, Germany. Dr. Nattel has reported that he has no relationships relevant to the contents of this paper to disclose.

TABLE 1 Summary of Studies Addressing the Role of Thrombin Activation and Anticoagulation in Atrial Electrophysiology and AF-Promoting Remodeling

First Author, Year (Ref. #)	Tissue	Experiment	Biochemical Effect(s)	Remodeling Effects	Electrophysiological Effect(s)
Bukowska, 2013 (15)	Human atrium	Exposure to Fxa	Upregulation of PAR2, ICAM-1, IL-8, PAI-1	NT	NT
		Tachypacing + Fxa	Upregulation PAR1/2, ICAM-1, IL-8, PAI-1, LOX-1	NT	NT
		Fxa/TP + RIVA or PAR1-blocker	Effects blocked by RIVA	NT	NT
Chang, 2012 (12)	Rabbit PV	Exposure in vitro	NT	NT	Thrombin decreased PV automaticity and APD L-NAME, dabigatran or PAR-1 blocker attenuated effects
Chang, 2013 (14)	Rabbit LA	LA cells in vitro	NT	NT	RIVA decreased APD and increased diastolic tension RIVA increased $I_{Ca,L}$ and I_{Kur}, no change in I_{to}
Spronk, 2016 (16)	Rat atrial FBs	Exposure in vitro	Thrombin ↑P-Akt, pERK, TGFβ, MCP1 expression Thrombin enhanced ^{3}H-proline incorporation Effects blocked by dabigatran and PAR1 inhibitor		
	TG mice	Procoagulant mice	Atrial fibrosis	Atrial fibrosis	Increased AF inducibility and duration
	AF goats	Nadroparin		Decreased Fibrosis, αSMA positive FBs	Decreased complexity of AF; AFCL unchanged; ?AF duration
Jumeau, 2016 (11)	MI rats	DTI or PAR1 blocker therapy	DTI suppressed CTGF, PAI-1 upregulation DTI decreased BNP, αMHC upregulation	DTI or PAR1 decreased LA size DTI decreased LA fibrosis, hypertrophy	AF promotion suppressed
	Rat atria	Thrombin, PAR1, ROCK blocker	Thrombin increased BNP, αMHC, PAI-1, pSTAT3 Thrombin effect blocked by PAR1, ROCK blocker		

AF = atrial fibrillation; APD = action potential duration; BNP = brain natriuretic peptide; DTI = direct thrombin inhibitor; FB = fibroblast; FXa = Factor Xa; $I_{Ca,L}$ = L-type Ca^{2+} current; ICAM = intracellular adhesion molecule; I_{Kur} = ultrarapid delayed rectifier K^{+} current; IL = interleukin; I_{to} = transient outward K^{+} current; LA = left atrium; L-NAME = N(G)-nitro-L-arginine methyl ester; LOX = lysyl oxidase; MCP = monocyte chemoattractant protein; αMHC = α myosin heavy chain; NT = not tested; PAI = plasminogen activator inhibitor; pAkt = phosphorylated Akt; PAR = protease-activated receptor; pERK = phosphorylated extracellular signal-related kinase; pSTAT3 = phosphorylated STAT3; PV = pulmonary vein; RIVA = rivaroxaban; ROCK = Rho-associated coiled-coil kinase; SMA = smooth muscle actin; TGF = transforming growth factor; TG = transgenic; TP = tachypacing.

transducer and activator of transcription-3, or STAT3 (pSTAT3), and that these effects are prevented by a PAR-1 blocker and an inhibitor of Rho coiled-coil kinase (ROCK) signaling. These results indicate a contribution of activated thrombin to profibrillatory atrial remodeling post-MI and suggest that in addition to their anticoagulant effects DTIs may attenuate the development of an AF-supporting substrate.

RELATIONSHIP TO OTHER STUDIES IN THE LITERATURE

A range of other investigators have addressed the effects of OACs on atrial electrophysiology and remodeling, as summarized in Table 1. Chang et al. (12) showed that thrombin decreases pulmonary vein (PV) cellular automaticity and left-atrial (LA) action potential duration (APD) while increasing PV triggered activity, effects that were blocked by dabigatran, a PAR-1 blocker and N(G)-nitro-L-arginine methyl ester (L-NAME) (a nitric oxide synthase inhibitor). An APD reduction should promote re-entry circuits that maintain AF, whereas increased triggered activity should enhance spontaneous AF-initiation (13). In a follow-up study, the same investigators showed that rivaroxaban reduces LA APD in rabbit LA-cells, while increasing L-type Ca^{2+} current and ultrarapid delayed rectifier K^{+} current (14). If applicable to man, these results would suggest that thrombin promotes AF, an effect that can be prevented by a DTI, but that rivaroxaban might be profibrillatory. Bukowska et al. (15) showed that FXa causes proinflammatory signaling in human atrial tissue, upregulating PAR2, phosphorylated extracellular signal-related kinase, intracellular adhesion molecule (ICAM)-1, interleukin-8, and PAI-1. These effects were enhanced by atrial tachypacing to mimic the remodeling effects of AF and suppressed by PAR-1

or PAR-2 blockade. In a very recent study, Spronk et al. (16) used several models to examine the potential role of hypercoagulability and its suppression in AF remodeling. They noted that in rat atrial fibroblasts, thrombin enhances the expression of the profibrotic factor transforming growth factor-β1 and the proinflammatory substance monocyte chemoattractant protein-1 while enhancing ^{3}H-proline uptake, suggesting increased collagen production. These actions were blocked by dabigatran and a PAR-1 blocker. In a transgenic mouse model with coagulation enhanced by a thrombomodulin gene mutation, atrial fibrous-tissue content was increased and AF-duration was enhanced, although the effects of anticoagulation do not appear to have been assessed. In a goat model of persistent AF induced by prior electrical AF-maintenance, the FXa inhibitor nadroparin reduced thrombin generation and reduced AF complexity, without affecting AF cycle length. Changes in AF sustainability were not reported.

SYNTHESIS OF RESULTS TO DATE

Taken together, the available data suggest that the thrombosis-promoting effect of AF may, in addition to leading to thromboembolic events, contribute to the ability of AF to cause electrical and structural changes that favor its own maintenance and recurrence. However, there are some aspects of the findings that are unclear. Two studies suggest direct electrophysiological effects of activated thrombin and OACs (12,14). This action should lead to detectable clinical electrophysiological and electrocardiogram changes in AF populations, but these have not been reported. Promotion of the AF substrate in association with increased coagulation has been described in rodent models. For one of these, reversal by DTI was shown (11), but for the other, DOAC effects were apparently not tested (16). AF-promoting effects have been modest and reported only in rodent models. The stimulation of proinflammatory and profibrotic factors by activated thrombin and/or FXa seems to be a fairly constant finding, as is its inhibition by DOACs.

WHERE DO WE GO FROM HERE?

It will be very important to determine the relevance of these findings to atrial electrophysiology and remodeling in man. The data indicating that thrombin activation promotes atrial remodeling have been obtained principally in specific rodent models and in vitro cell systems (11,16) that cannot necessarily be assumed to apply to clinical AF. Modern imaging methods allow for the AF substrate to be quantified (17); direct comparisons among matched patients taking various DOACs and VKA therapy, versus those not on such therapy, should be possible. Of even greater interest would be longitudinal studies on patients with AF before and after initiation of a DOAC. Extensive databases are available for patients randomized to VKA versus DOAC therapy—these should be interrogated to identify any signal for antiarrhythmic actions of DOACs. Finally, serious consideration should be given to prospective randomized studies of DOAC therapy versus placebo in paroxysmal AF patients at lower risk of stroke than would presently be considered to require OAC treatment, in order to determine whether OACs favorably influence the natural history of AF progression. If they do, the stroke-risk threshold for OAC treatment will certainly move even lower than it is today, and a new and attractive treatment to suppress AF will have been identified.

CONCLUSIONS

The study of Jumeau et al. (11) lends credence to the idea that OACs may have beneficial effects in AF that go beyond simply preventing clot formation, to influencing the natural history of the arrhythmia itself. If confirmed clinically, such findings would be of great practical importance.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Stanley Nattel, Department of Medicine, Montreal Heart Institute and Université de Montréal, 5000 Belanger Street East, Montreal H1T1C8, Quebec, Canada. E-mail: stanley.nattel@icm-mhi.org.

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