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COMMENTARY

Does angiotensin receptor blockade ameliorate the prothrombotic tendency in hypertensive patients with atrial fibrillation? breaking the vicious cycle

Kyosuke Takeshita and Toyoaki Murohara

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Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, contributing directly to morbidity and mortality through its association with thromboembolism events, including stroke. Hypertension is the most common contributing risk factor for the increasing burden of AF in the population, and both clinical and experimental studies have demonstrated a close link between AF and hypertension.[1] Thus, the pathophysiological mechanism of the prothrombotic state in both disease entities is indivisible and is often considered a common pathway. Optimal blood pressure control using antihypertensive drugs is required to maximize the benefit of anticoagulant therapy for stroke prevention in AF patients,[1] and therapeutic targets and the management of both conditions are also similarly considered.

The renin–angiotensin system (RAS) is a key player in blood pressure control and the regulation of electrolytes and body fluid homeostasis. Angiotensin II (Ang II), the main effector of this system, exerts most of its actions via the activation of the Ang II type 1 receptor (AT1R) to promote a hypertensive state through pressure-enhancing mechanisms (for example, fluid retention and vasoconstriction) and structure-modulation mechanisms (for example, the hypertrophy of vascular smooth muscle cells and accumulation of extracellular matrix). Ang II signaling increases oxidative stress, the expression of various adhesion molecules (for example, P-selectin) to recruit leukocytes and the production of proinflammatory cytokines (for example, interleukin (IL) 6 and tumor necrosis factor α (TNFα)) and monocyte chemoattractant protein-1 (MCP-1),[2] resulting in endothelial impairment (Figure 1). The RAS is also mechanically implicated in the initiation and perturbation of AF.[1] RAS activation induces atrial fibrosis, which serves as an arrhythmia substrate and changes the electrophysiological properties of the cell, resulting in atrial structural and electrical remodeling. AF itself also creates and promotes an inflammatory environment through turbulent blood flow and endocardial/endothelial impairment.[3] Indeed, inflammatory markers and mediators (for example, C-reactive protein (CRP), TNF-α, IL-2, IL-6 and MCP-1) are reportedly linked with the presence or outcome of AF.[4] Increasing evidence implicates inflammation associated with AF in the prothrombotic state.

The pathophysiology of hypertension in patients with AF is characterized by blood flow abnormalities, such as atrial blood flow retention and turbulence, endothelial/endocardial dysfunction and activation of platelets as well as the coagulation cascade (Figure 1). The impairment of the endothelium and endocardium, which is induced by turbulent flow and the vicious cycle between inflammation and RAS activation, results in the induction of adhesion molecules, the von Willebrand factor (vWF) and the tissue factor (TF, the main regulator of blood coagulation activity) as well as initiates the prothrombotic state in hypertensive patients with AF (Figure 1). AT1R activation also directly induces TF in the endothelium and monocytes via the intracellular activation of transcription factors NF-κB and activator protein-1.[2] On activated endothelium and monocytes, TF binds to activated factor VII to activate factors IX and X, stimulating the coagulation pathway and thrombin generation, which in turn converts fibrinogen into fibrin. Platelet activation is also involved in this process as is the platelet–leukocyte interaction via P-selectin–PSGL-1 binding to induce TF.[5] Although antiplatelet drugs reduce the risk of stroke less than anticoagulants,[1] platelet aggregation remains an important therapeutic target. Fibrinolysis is the degradation of fibrin by plasmin upon the activation of plasminogen into plasmin by the tissue-type plasminogen activator (t-PA), which is the physiologic activator of fibrinolysis. Fibrinolytic activity is determined by a balance between t-PA and plasminogen activator inhibitor type 1 (PAI-1). PAI-1, which is released from hepatocytes, platelet α−granules, smooth muscle cells and adipocytes in response to proinflammatory cytokines (for example, TNF-α) and AT1R activation, inhibits fibrin degradation to increase thrombus formation and is thus the main inhibitor of fibrinolysis.[6]

Together with anticoagulants, the generation of new antihypertensive agents is anticipated to reduce hypertension-related complications (for example, thrombotic disorders) and to improve prognoses, especially in hypertensive patients with AF. Treatment with AT1R blockers (ARBs) improves known prognostic indices (for example, endothelial and platelet dysfunction) as well as coagulation and fibrinolytic abnormalities.[1–3,7] ARBs, such as losartan, may reverse the balance between coagulation and fibrinolysis through their inhibitory effects on the AT1R-related proinflammatory mechanism[7] (Figure 1). TF expression

K Takeshita and T Murohara are at Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan and K Takeshita is at Department of Clinical Laboratory, Nagoya University Hospital, Nagoya, Japan
E-mail: kyousuke@med.nagoya-u.ac.jp

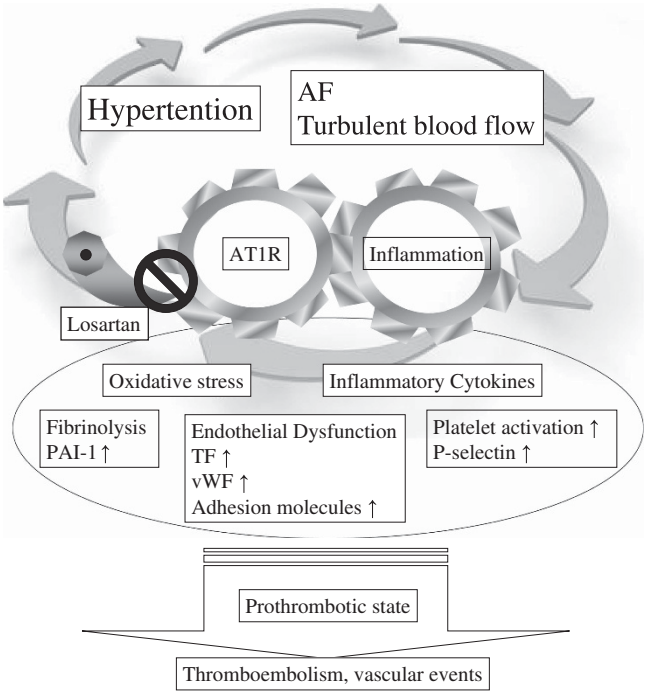

Figure 1 RAS activation and inflammation form a vicious cycle that acts to exacerbate the prothrombotic status in hypertensive patients with AF.

depends on this mechanism, and ARBs can prevent TF induction, thereby reducing the prothrombotic tendency.[7] AT1R blockade reportedly inhibits platelet aggregability and adhesion by stimulating nitric oxide release from platelets and endothelial cells.[2] On the other hand, controversial results have been reported on the inhibitory effects of ARB on PAI-1 induction.[2,7]

In this issue of *Hypertension Research*, Sakamoto *et al.*[8] describe serial changes in the biomarkers of endothelial impairment (plasma vWF and TF), platelet activity (P-selectin and aggregability) and fibrinolysis (plasma PAI-1 activity) in 20 hypertensive patients complicated with AF during treatment with 50 mg of losartan for 8 weeks followed by 100 mg for 4 weeks. The treatment significantly ameliorated the procoagulant state, including platelet activity. Furthermore, blood pressure inadequately but significantly decreased from 156/97 to 140/80 mm Hg. While their study is a small pilot trial, it provides valuable information about the synergic benefits of losartan on lowering blood pressure and blocking ATR1, thus reducing the prothrombotic tendency in hypertensive patients with AF.

Their study, however, has several limitations in its design as well as in the generalization of its results. First, the authors evaluated a small population without control subjects over a relatively short period of time. During the observation period, no thrombotic events were recorded despite the high risk of thrombosis. There is no doubt that the difficulty in finding a sample collection for biomarkers of the prothrombotic state, especially platelet activity in a constant and proper manner, limits the sample size and the observation period. Second, the fibrinolytic capacity cannot be rigorously assessed by only the plasma PAI-1 activity. The effects of PAI-1 reduction, and the restoration of the balance between t-PA and PAI-1 activity are reported to be influenced by the observation period and the so-called 'drug class effects' of the respective ARBs.[2,7] More importantly, this study does not seem to support the beneficial effects of Ang II receptor blockade on hypertensive patients with AF beyond its blood pressure-lowering effect. Interestingly, both the ACTIVE I and GISSI-AF studies demonstrated that the AT1R blockade itself hardly reduced thrombotic events beyond the hypotensive effects.[9,10] According to the SPORTIF study, the systolic blood pressure level correlated with the risk of systemic thromboembolism and stroke in patients with nonvalvular AF.[1,11] Admittedly, it is difficult to compare previous clinical trials of ARBs on the prevention of stroke and thrombosis in AF patients because the prothrombotic status is not always directly linked to the incidence of stroke or other thrombotic disorders. The stroke-associated risk factors and endpoints in these studies also differ.[1] Larger clinical trials are needed to define the antithrombotic mechanism of the respective ARBs.

Finally, despite several study limitations, this study is of great interest to the scientific community because it demonstrates that the AT1R blockade with losartan provides additional benefit to hypertensive patients with AF through an improvement in the prothrombotic tendency. Because losartan can also potentially prevent the development of AF in patients with left ventricular hypertrophy,[3] these results suggest that ARBs can ameliorate the prothrombotic status in hypertensive patients with AF based on their pleiotropic effects on Virchow's triad (hemodynamic changes (maintenance for sinus rhythm and prevention from turbulent blood flow in AF), improvement of endothelial impairment (reduction in TF and vWF) and amelioration of hypercoagulability (reduction in platelet and plasma PAI-1 activity)).[3]

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