Polymorphism of Inhibitory Renin-Angiotensin System as a Genetic Risk Factor for Atrial Fibrillation

To the Editor:

We read with great interest the study by Tsai et al. The authors showed that patients who have a specific genetic variation or polymorphism in the renin-angiotensin system (RAS) genes may be more likely to develop atrial fibrillation (AF) when exposed to environmental factors that elevate atrial pressure.

Although we mostly agree with the authors, we believe AF is associated with reduced activation of the RAS in patients with certain types of cardiovascular disease. We recently reported that the insertion/insertion (II) genotype of the angiotensin I–converting enzyme (ACE) gene is a significant risk factor for atrial fibrillation in patients with hypertrophic cardiomyopathy (HCM). Plasma ACE activity is significantly higher in individuals with the deletion allele than in individuals with the I allele. Patients with the ACE I/I genotype can be thought to be in a more circulatory ACE-inhibitory state than patients with the other genotypes. The RAS regulates sodium balance and intravascular volume and interacts with other blood pressure control mechanisms, including the sympathetic nervous system and baroreflexes. Because patients with HCM have a small left ventricular cavity size (SLVC) due to hypertrophy, reduction of intravascular volume may reduce cardiac output, leading to systemic hypotension. Therefore, activating the RAS may be a protective means for maintaining intravascular volume and a normal systemic circulation in these patients. In fact, vasodilator agents were reported to be unhelpful or even dangerous in patients with severe concentric left ventricular hypertrophy. In addition, acute ACE inhibition in patients with obstructive HCM is known to lead to hypotension with significant reductions in both end-diastolic and end-systolic volumes.

Thomson et al. suggested that hypotension during central volume unloading provides an additional or alternative trigger for arrhythmias in some patients with HCM. The mechanism by which central volume unloading would trigger AF is unknown, but it might be related to autonomic effects on pulmonary venous foci. Although in general, excessive volume overload is harmful in most types of cardiovascular disease, it may actually be beneficial to patients with an SLVC and reduction of intravascular volume. Patients with a genotype of inhibitory RAS genes may have unstable systemic circulation due to comparatively reduced intravascular volume compared with patients with another genotype of activating RAS genes in certain types of cardiovascular disease. Therefore, the reduced activation of the RAS in patients with an SLVC may play an important role in the development of AF.

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Response

We appreciate Dr Ogimoto’s interest in our article and the opportunity to respond to his letter. He has raised an interesting issue about the relationship between the renin-angiotensin system (RAS) and hypertrophic cardiomyopathy (HCM). The hemodynamic characteristics of HCM are much different from those of systemic hypertension. As Dr Ogimoto pointed out, reduction of intravascular volume may increase the severity of outflow obstruction, thereby leading to systemic hypotension and a detrimental hemodynamic condition, which may subsequently trigger cardiac arrhythmias, including atrial fibrillation (AF). However, cardiac arrhythmia in HCM may also be due to a defect in the afferent limb of the cardiopulmonary reflex arc, not necessarily through systemic hypotension. Furthermore, we believed that the increased left ventricular outflow obstruction due to central volume unloading may also impair left ventricular filling, and consequently stretch the left atrium and increase the incidence of AF.

Therefore, we do agree with Dr Ogimoto that not all of the AFs were associated with an activation of RAS. In AF due to a small left ventricular cavity size, such as HCM or hypertension with a very severe concentric left ventricular hypertrophy (LVH), genotypes associated with inhibitory RAS may be associated with the occurrence of AF. However, in our study,3 less than 1% of the patients with AF had HCM, and the degree of LVH in our hypertensive patients was not as severe as that of HCM. Therefore, we still concluded that genotypes associated with an activating RAS were associated with the occurrence of AF.

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Circulation. 2004;110:e329
doi: 10.1161/01.CIR.0000142882.58972.51

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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