Impact of the renin–angiotensin system and inflammatory gene polymorphisms on diastolic heart failure

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Heart failure is the final consequence of various heart diseases and the leading cause of mortality worldwide. The morbidity associated with diastolic heart failure (DHF; including the rate of hospitalization) is similar to that associated with systolic heart failure.1

In recent years, impaired calcium homeostasis of cardiomyocytes was proposed to be one of the pathophysiological hallmarks of DHF. Of numerous calcium-regulatory proteins, decreased expression of sarcoplasmic reticulum calcium ATP-ase 2 (ATPα2, SERCA2) and altered regulation of phospholamban levels have been reported to correlate with diastolic function.2,3 The combination of an enhanced tissue renin–angiotensin system (RAS) and hyperglycemia leads to the development of fibrosis and myocyte hypertrophy, a prominent feature of DHF.2 In addition, our recent study found that, through downregulation of SERCA2 gene expression, inflammatory cytokines could cause cardiac diastolic dysfunction by decreasing diastolic calcium reuptake.3 Genetic influences contributed to some extent to serum cytokine levels, but genetic studies of DHF are scarce in the literature. In this article, we discuss recent genetic studies related to the RAS gene, inflammatory gene polymorphisms, and their relationship with DHF.

The ACE gene

Rigat et al first proposed that the D allele of the angiotensin converting enzyme (ACE) gene had a dose-dependent influence in terms of plasma ACE concentration.4 The concentration of plasma ACE is in proportion to the level of hypertension or myocardial fibrosis, both of which are important risks for DHF.

In 2008, we recruited 148 patients with DHF and controls and found that the ACE gene I/D polymorphism had a dose-dependent influence in terms of plasma ACE concentration.4 The concentration of plasma ACE is in proportion to the level of hypertension or myocardial fibrosis, both of which are important risks for DHF.

In 2008, we recruited 148 patients with DHF and controls and found that the ACE gene I/D polymorphism was associated with an increased risk of DHF. Subjects carrying two copies of the D allele had an increased risk of DHF (odds ratio 2.40, p = 0.002).5 In addition, a synergistic interaction of the ACE gene I/D polymorphism and an A1166C polymorphism of the angiotensin II type 1 receptor AGTR1 gene on the risk of DHF was distinguished.

To further elucidate the possible mechanisms, we used the propensity score to control left ventricular (LV) mass and found that different ACE genotypes could predispose to different pathways of development of DHF.6 The ACE gene
II genotype was noted to be associated with a greater LV mass in a well-matched cohort, whereas presence of the D allele was strongly correlated with DHF after removing patient matching for LV mass. The findings suggested that ACE gene polymorphisms may affect DHF in different ways: (1) the ACE II form may have an impact on angiotensin II that then leads to LV hypertrophy and thus to the development of DHF; (2) the ACE DD form may have a direct trophic effect that leads to calcium overload or increased myocardial stiffness, which further leads to DHF, independent of LV hypertrophy.

The AGT gene

There was evidence that plasma AGT concentrations are associated with genetic polymorphisms of the angiotensinogen (AGT) gene. We compared the differences among six AGT gene polymorphisms [G-217A (rs5049), G-152A (rs11568020), A-20C (rs5050), G-6A (rs5051), M235 T (rs699; T4072C), and T174 M (rs4762; C3889 T)] in patients with DHF and controls. Only the A-20C polymorphism of the AGT gene was associated with an increased risk of DHF compared with normal controls. However, the effect was not substantial after multiple testing or after a comparison with risk-matched controls.\(^5,6\) Haplotype analysis for the six-locus haplotype of the AGT gene showed no significant difference in the global haplotype profile in the above two studies.

The AGTR1 gene

An association study has been conducted in a Han Chinese population. Eleven single nucleotide polymorphisms (SNPs) tagging the AGTR1 gene were selected and analyzed.\(^7\) In a single locus analysis, SNPs rs16860760, rs389566, and rs5186 were shown to be associated with DHF. Also, SNP rs389566, with a minor allele frequency of 20.17%, had an odds ratio of 2.03 for the autosomal dominant model [AA + AT: TT, 95% confidence interval (CI) 1.29–3.19; \(p = 0.0012\)] and 1.73 for the additive model (95% CI 1.21–2.48; \(p = 0.0018\)), corresponding to a population attributable risk fraction of 27.21%. The haplotypes in a linkage disequilibrium block of rs389566 (T-A-G and A-A-G) were also significantly associated with DHF after permutation tests. The results revealed that, in addition to A1166C polymorphisms (rs5186), the effects of other genetic variants of the AGTR1 gene were significant for DHF.

Genes associated with inflammation

Recent studies have concluded that the inflammatory process arising from sepsis or even visceral adipose tissue may lead to LV diastolic dysfunction.\(^3,8\) There are few reported studies on inflammatory cytokine gene polymorphisms and DHF. Only one study has evaluated the interleukin-10 gene (IL10) promoter polymorphism at position –1082 and its association with conventional and Doppler echocardiographic and tissue doppler imaging parameters in 112 patients undergoing hemodialysis.\(^9\) The authors concluded that the IL10 genotype may balance the effects of inflammatory cytokines on the myocardium and may be a determinant of LV function in hemodialysis patients.

Pharmacogenetic effects

At present, there is little information about the prognostic influence of RAS genes on DHF and the pharmacogenetic interaction between the RAS gene and ACE inhibitors. We followed a cohort of DHF patients for more than 10 years and evaluated the genetic effects along with pharmacogenetic interactions.\(^10\) In a multiple Cox regression model adjusted...
for the ACE inhibitor effect, the D allele of the ACE gene induced a 2.04-fold hazard compared with the I allele, and the AGTR1 A1166C C allele had a hazard ratio of 2.08 compared with the A allele. Moreover, in the group who received ACE inhibitors, the effect of the ACE gene D allele on survival was no longer significant, suggesting a pharmacogenetic interaction. Therefore, genetic variation or polymorphisms in RAS genes are associated with not only the development of DHF, but also long-term survival; however, the effects can be modified by using ACE inhibitors.

Conclusions and future perspective

In conclusion, recent advances suggest that patients with specific genetic variations in RAS or inflammatory genes may be more likely to develop DHF (Fig. 1). The genetic variants in the RAS genes were also associated with long-term prognosis in DHF patients, but their effects could be modified by the use of ACE inhibitors. By understanding the pharmacogenetic effects related to treatment response, patients who are most likely to benefit from such treatment could be distinguished. This concept of therapy tailored by pharmacogenetics may have a large impact on future clinical practice.

References