β2-adrenergic receptors are expressed on coronary endothelial and vascular smooth muscle cells and contribute to coronary blood flow regulation [1-3]. They represent dominant adrenergic receptor type at the microcirculatory levels [4-7] and thereby control microvascular resistance in the normal coronary arteries [8].

In atherosclerotic coronary arteries, adrenergic stimulation by cold pressor test and mental stress is known to induce paradoxical vasoconstriction [9,10]. Intravenous infusion of dobutamine, an α1-, β1-, and β2-adrenergic receptor agonist, is associated with a blunted vasodilation in mildly atherosclerotic coronary arteries and lack of vasomotion in stenotic coronary arteries [11]. A local intracoronary infusion of the selective β2-adrenergic receptor agonist, salbutamol, was associated with a reduced but still preserved vasodilation in mildly atherosclerotic coronary arteries [8], confirming a prevalent role of β2-adrenergic receptors of vascular smooth muscle cells [5,12]. In more severely diseased, atherosclerotic coronary arteries, salbutamol did not evoke any significant vasomotion [8]. Thus, in contrast to normal coronary arteries, coronary atherosclerosis is associated with a progressive loss of vasodilatory response to β-adrenergic stimulation.

β2-adrenergic receptor responsiveness can be genetically modulated by various polymorphisms. In particular, the presence of glutamic acid (Glu) allele in codon 27 has been associated with an increased vasodilator response to isoproterenol compared with that of Gln-27 homozygote patients [13]. Dishy and coworkers showed that Arg-16 polymorphism was associated with rapid agonist-mediated desensitization, while Glu-27 polymorphism with enhanced agonist-mediated responsiveness in the vasculature [14]. In the light of a progressive impairment of coronary β2-adrenergic receptor responsiveness in coronary atherosclerosis, one may question the potential importance of genetic variation of the receptor in the setting of coronary artery disease.

In fact, conflicting data were reported on association between β2-adrenergic receptor polymorphisms with extent of coronary atherosclerosis and incidence of cardiovascular clinical events. In a Japanese patient population, Yamada et al. found that none of the β2-adrenergic receptor polymorphisms were associated with an increased risk of myocardial infarction [15]. This finding was further confirmed in a European patient population recruited in the ECTIM study [16]. In another study of elderly patients, Glu-27 allele was even associated with a lower risk of coronary events [17]. On the other hand, the Physicians’ Health Study demonstrated that only specific haplotype combinations ([non-Gly16-Gln27]-Thr164 and Gly16-Gln27-Ile164) were associated with increased risk for myocardial infarction [18]. Yet, this association disappeared after adjustment for other polymorphisms [19]. However, these studies relied solely on the clinical data [20-23] and evidence for coronary atherosclerosis was obtained only in selected patients with myocardial infarction [24,25] and coronary atherosclerosis was not documented in control patients. Thus, these observations could not be directly extrapolated to patients routinely seen in the current cardiovascular practice presenting with clinical symptoms such as angina-like pain or having high risk for coronary artery disease. In fact, lack of direct
detection of coronary artery disease in the previous studies might have been responsible for misdiagnosis or undertreatment of the patients with established coronary artery disease.

We designed recently a study to address the modulatory significance of Glu-27 in a cohort of patients undergoing coronary angiography due to clinical symptoms or high cardiovascular risk [26]. Using this design our data demonstrated that the presence of Glu-27 variant was associated with a nearly 2-fold higher risk for angiographic coronary atherosclerosis. Glu-27 variant remained an independent risk factor after adjustment for other cardiovascular risk factors or analysis for other beta receptor polymorphisms. This finding was independently confirmed in another patient population by Abu-Amero [27]. We hypothesize that the underlying mechanism of the increased risk may be related to resistance to downregulation due to replacement of Gln with Glu in codon 27 resulting in the “gain-of-function” of the receptor [28]. The presence of a “hyper-functioning” receptor would make the target tissues overexposed to catecholamine stimulation. Alternatively, “hyper-functioning” receptor may be exposed to increased sympathetic nervous activity that was previously demonstrated to accelerate the development of coronary atherosclerosis [29,30]. In addition, the BCAPS study demonstrated an anti-atherosclerotic effect of beta-blockers [31].

Nevertheless, despite a marked association between Glu-27 allele and the presence of coronary atherosclerotic disease, we failed to observe differences in the incidence of myocardial infarction or other hard clinical end points between patients carrying Glu-27 allele and Gln-27 homozygote patients. However, it should be noted Glu-27 homozygotes underwent more frequently myocardial revascularization as compared to Gln-27 homozygote patients despite similar medical treatment. Thus, a more aggressive interventional therapeutic strategy performed in Glu-27 homozygotes might have offset the higher burden of coronary atherosclerotic disease present in these patients. Further studies are warranted to test the value of genetic screening as a stratification tool for therapeutic strategy in patients with high risk for coronary atherosclerosis.

References

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