Emerging Importance of Alpha-Adrenergic Coronary Vasoconstriction in Acute Coronary Syndromes and its Genetic Background*

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As compared to the beta-adrenoceptor-mediated effects of sympathetic activation, alpha-adrenoceptor-mediated effects on coronary blood flow have long received little attention. This was largely due to the fact that, in animal experiments under physiologic circumstances, there is very little alpha-adrenergic coronary vasomotor tone at rest, and the increase in coronary blood flow during sympathetic activation is only somewhat blunted. More recent experimental studies, however, clearly demonstrated that, when the coronary circulation is compromised by hypercholesterolemia (1), endothelial dysfunction (2), exhaustion of autoregulation (3), or severe coronary stenoses (4,5), alpha-adrenergic vasoconstriction is unrestrained and powerful enough to reduce coronary blood flow and induce myocardial ischemia (6). Both, alpha1- and alpha2-adrenoceptors mediate such coronary vasoconstriction, with alpha2-adrenoceptors more predominant in the microcirculation (3,7).

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Over the last decade, various studies using quantitative coronary angiography, Doppler flow probes, and positron emission tomography have demonstrated the importance of alpha-adrenergic coronary vasoconstriction in humans (8). As in animal experiments, studies in humans under physiologic conditions show there is no limitation of resting coronary blood flow by alpha-adrenergic coronary vasoconstriction, but there is a limitation of coronary reserve (9). However, again as in the animal experiments, alpha-adrenergic coronary vasoconstriction is enhanced in patients with endothelial dysfunction and atherosclerosis (10–12). In patients with established coronary artery disease (CAD), both selective alpha1- and alpha2-adrenoceptor activation induce augmented coronary vasoconstriction, and alpha2-adrenergic vasoconstriction is then powerful enough to induce net lactate production and electrocardiographic signs of ischemia (11). Notably, reflex alpha-adrenergic coronary vasoconstriction is also elicited during coronary interventions (13,14), and this contributes to postinterventional contractile dysfunction (15,16).

Very recently, a genetic determination of alpha-adrenergic coronary vasoconstriction has emerged (17). A polymorphism in the gene encoding for the Gβ3 subunit of pertussis-sensitive G proteins, which is associated with alternative splicing and enhanced signal transduction (18), induces a pronounced supersensitivity to alpha2-adrenergic coronary vasoconstriction in the 825T-allele carriers, which adds to the augmentation of alpha-adrenergic coronary vasoconstriction in the presence of atherosclerosis (19).

It is against this background that the current study by Snapir et al. (20) in this issue of the Journal provides additional evidence for the importance of alpha2-adrenergic coronary vasoconstriction and its genetic determination. A deletion/insertion polymorphism in the alpha2B-adrenoceptor (21) has previously been shown by these investigators to be a novel genetic risk factor for CAD, insofar as individuals with the deletion/deletion genotype had an increased risk of acute myocardial infarction in a population-based prospective study (22). The study by Snapir et al. (20) extends the prior study and points to the importance of alpha2-adrenergic coronary vasoconstriction in the causal pathogenesis of myocardial infarction and also sudden cardiac death in a well-characterized, unscreened cohort of Caucasian men who had suffered out-of-hospital death. Of note, the classical risk factors for CAD in the deletion/deletion genotype were no different from those in the insertion/deletion and insertion/insertion genotype.

In addition, no difference was observed in the extent of coronary atherosclerosis at autopsy. Finally, there was no evidence for coronary thrombosis at autopsy, further supporting the importance of enhanced alpha2-adrenergic coronary vasoconstriction as the underlying mechanism of acute myocardial infarction and sudden cardiac death.

The major limitation of the present study (20), as with all other association studies, is its purely descriptive nature and the lack of definition of a functional phenotype (17). Of note, such functional phenotype was defined for the Gβ3 subunit polymorphism (19), and this clearly needs to be done for the alpha2B-polymorphism in the future, too. It is also tempting to speculate about a potentially additive genetic risk conferred by a combination of the 825T-allele of the Gβ3 subunit and the deletion/deletion genotype of the alpha2B-adrenoceptor in further enhancing alpha2-adrenoceptor-mediated signal transduction, resulting coronary microvascular constriction and ultimately inducing acute myocardial infarction and sudden cardiac death. Future studies will most certainly resolve this question.

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