Editorial Comment

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Autoantibodies in Type 2 Diabetes Patients with Left Ventricular Dilatation: Biomarkers and/or Risk Markers?

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Type 2 diabetes is a major cause of illness and death. In the USA, for example, at least 65% of patients with type 2 diabetes die of some form of heart disease or stroke [1]. These patients are at increased risk for the presence of vulnerable coronary plaques but also left ventricular dilatation, which is the primary reason for sudden cardiac death (see [2] and references therein). There is increasing evidence that autoimmunity may play an important role in the pathogenesis and progression of left ventricular dilatation in type 2 diabetes patients because many circulating cardiac autoantibodies have been found in those patients with myocarditis and dilated cardiomyopathy (summarised in [3]).

In this issue of *Cardiology*, Zhao et al. [4] report on their study, in which they analysed the presence of two well-characterised autoantibodies against G protein-coupled receptors in cardiovascular disease, autoantibodies against the beta-1-adrenergic receptor and the angiotensin II receptor type 1. Both autoantibodies are directed at the second extracellular loop of the respective receptor [5, 6]. Zhao et al. [4] recruited 179 type 2 diabetes patients with hypertension and 106 normotensive type 2 diabetes patients. Next, they determined autoantibodies against the second extra-cellular loops of the beta-1-adrenergic receptor and the angiotensin II receptor type 1 by ELISA. They found that the patients with hypertension were more often positive for these autoantibodies – 43.0% for the beta-1-adrenergic receptor and 44.1% for the angiotensin II receptor type 1 – than the normotensive patients (16.0 and 10.4%, respectively).

Knowledge about the contribution of autoantibodies and the underlying mechanisms to the development of left ventricular dilatation has increased within the last 15 years. In 1999, Jahns et al. [5] described autoantibodies against the second extra-cellular loop of the beta-1-adrenergic receptor in patients with dilated cardiomyopathy. In an experimental proof-of-principle study, they immunised rats with a peptide against the second extra-cellular loop of the beta-1-adrenergic receptor, which resulted in the development of antibodies against the peptide followed by progressive severe left ventricular dilatation and dysfunction after 9 months [7]. Isogenic transfer of sera from animals positive for the antibodies resulted in a similar phenotype of left ventricular dilatation and dysfunction in the recipient animals within a similar time frame [7]. At the functional level, autoantibodies against the second extra-cellular loop of the beta-1-adrenergic receptor are agonist-stimulating [5] and can induce apoptosis in isolated cardiomyocytes from adult rats [8]. In addition, autoantibodies against the second extra-cellular loop of the beta-1-adrenergic receptor are associated with serious ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy, and the presence of these autoantibodies independently predicts sudden death [9, 10]. These findings are confirmed by the results of Zhao et al. [4] that autoantibodies against the second extra-cellular loop of the beta-1-adrenergic receptor are a risk factor for left ventricular dilatation and that autoantibodies against the angiotensin II receptor type 1 were identified as risk markers for left ventricular dilatation in patients with type 2 diabetes [4].

Zhao et al. [4] also screened their patients for autoantibodies against the second extra-cellular loop of the an-

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giotensin receptor type 1, which have been described for patients with malignant hypertension and pre-eclampsia [6, 11]. Immunisation of rats with a peptide corresponding to the second extra-cellular loop of the angiotensin receptor type 1 resulted in an increase in systolic blood pressure, heart rate and the ratio of heart weight to body weight compared to the control group [12]. However, even though their involvement in hypertension is commonly accepted, the role of these autoantibodies in the development of cardiac arrhythmias is still unclear.

The antibody-positive rates observed by Zhao et al. [4] confirm previous published data for autoantibodies against the beta-1-adrenergic receptor in myocarditis and dilated cardiomyopathy [3]. Depending on the sensitivity of the ELISA used, the rate can be up to 60% for patients with dilated cardiomyopathy [13]. However, there is no experimental proof that these autoantibodies are actually responsible for or involved in the development of type 2 diabetes, as autoantibodies against the beta-1-adrenergic receptor are associated with left ventricular dilatation and autoantibodies against the angiotensin II receptor type 1 are associated with hypertension. Furthermore, the possibility that the autoantibodies were present before the onset of type 2 diabetes cannot be ruled out for the patients in the study by Zhao et al. [4].

Zhao et al. [4] treated their patients with metoprolol and valsartan for 7 months which resulted in a decreased left ventricular diameter in those patients identified as positive for the aforementioned autoantibodies, indicating that the detrimental effects of the autoantibodies may be reversed or slowed down. Although the autoantibody status was not analysed after the 7 months, this study is important because it shows that autoantibodies can serve as biomarkers for left ventricular dilatation and as risk markers for sudden death. The results infer that hypertensive patients with type 2 diabetes may benefit from pharmacological treatment with beta-blockers and angiotensin II receptor blockers. Nonetheless, monitoring status for autoantibodies against the beta-1-adrenergic receptor and the angiotensin II receptor type 1 in hypertensive patients with type 2 diabetes could be an option for identifying those type 2 diabetes patients with the highest risk for developing left ventricular dilatation. This could indeed be helpful for providing an individual, target-oriented therapy for each patient.

Conflict of Interest

The author declares no potential conflicts of interest.

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