Diabetic Cardiovascular Autonomic Neuropathy

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Diabetic cardiovascular autonomic neuropathy (CAN) is a serious complication of diabetes associated with an increased mortality, silent myocardial ischemia, and may even predict the development of stroke. According to a recent meta-analysis the overall mortality rates over periods up to 10 years were 30.4% in diabetic patients with CAN detected by reduced heart rate variability (HRV) compared with 13.4% in those without evidence of CAN. The relative risk of mortality with 95% CI from 15 Studies (n=2900) was increased in patients with CAN by 2.14 (1.83-2.51). In a population based epidemiological study in Germany (MONICA/ KORA Study) we recently demonstrated that low HRV and prolonged QTc interval are independent predictors of increased all-cause mortality over 9 years by 1.78 (0.98-3.24) and 1.99 (1.34-2.96), respectively. Among the risk factors for reduced HRV diabetes is the primary determinant in the general population, while hypertension is the primary contributor to prolonged QTc in both sexes. Obesity and smoking contribute to autonomic dysfunction in men but not women. Thus, it is possible that the excess mortality attributed to increased cardiovascular risk may at least in part be explained by autonomic nervous system dysfunction associated with diabetes, hypertension, and, in men, smoking and obesity creating the substrate for life-threatening ventricular arrhythmias.

Apart from reduced HRV, the clinical manifestations of CAN include fixed heart rate, increased resting heart rate, sinus tachycardia, orthostatic hypotension, reduced circadian rhythm of heart rate and blood pressure, abnormal hormonal regulation to standing and exercise, antibodies to autonomic tissue (vagal nerve, sympathetic ganglia), denervation hypersensitivity to α- and β-adrenergic agonists, exercise intolerance, reduced left ventricular diastolic filling/ejection fraction, intraoperative cardiovascular instability, QTc interval prolongation, and increased susceptibility to silent myocardial ischemia/infarction. A recent meta-analysis including 12 studies (n=1468) revealed an increased risk of silent myocardial ischemia during exercise by 1.96 (1.53-2.51) in diabetic patients with CAN compared to those without CAN. Today, sensitive and early assessment of CAN is possible by means of noninvasive autonomic function tests (AFTs). It is estimated that CAN can be detected by abnormal AFTs in at least 1/4 of Type 1 and 1/3 of Type 2 diabetic patients. In some cases autonomic dysfunction may be present as soon as at the time of manifestation of both Type 1 and Type 2 diabetes. There is increasing evidence suggesting that measurement of 24-hour HRV could be more sensitive and reliable in detecting CAN when compared with AFTs. Moreover, 24-h recording of HRV provides
insights into abnormal patterns of circadian rhythms modulated by sympathovagal activity. Simultaneous beat-to-beat measurement of R-R intervals and blood pressure is increasingly being employed to determine spontaneous baroreflex sensitivity (BRS). This noninvasive technique evaluates the relationship between spontaneous changes in blood pressure and RR interval in the time domain (sequence method) and in the frequency domain (cross spectral method). These estimates can be obtained under conditions suitable for routine outpatient evaluation. There is evidence suggesting that reduced BRS is an early marker of autonomic dysfunction at a stage when conventional autonomic function tests do not yet indicate the presence of CAN.

Radionuclide techniques for cardiac mapping have been introduced to directly quantify myocardial sympathetic innervation in CAN. One technique uses the non-metabolized guanethidine derivative [123I]metaiodobenzylguanidine (MIBG), a radiolabelled analogue of norepinephrine which is taken up by the postganglionic presynaptic sympathetic nerve terminals and shares several uptake and storage mechanisms with norepinephrine. Several studies have demonstrated decreased myocardial MIBG uptake in diabetic patients predominantly in the left ventricular inferior and posterior segments. We recently reported that the global left ventricular adrenergic innervation defects do not progress over 12 years in long-term Type 1 diabetic patients, despite continuing progression of vagal dysfunction. However, regional progression of sympathetic dysinnervation in the posterior wall and possibly inferior and apical walls may be slowed by long-term near-normoglycaemia. Thus, the global left ventricular defects in MIBG uptake appear to reflect an irreversible component of CAN characterized by sympathetic denervation, while some regional defects may represent residual functional components susceptible to long-term metabolic intervention.

Furthermore, the norepinephrine analogue [11C]hydroxyephedrine (HED) has been employed to examine cardiac innervation defects. In diabetic patients attenuated HED retention was related to the severity of CAN and was most pronounced in the inferior, apical, and lateral segments. In severe CAN, the myocardial retention of HED was remarkably heterogenous, since as the extent of distal deficits increased, HED retention became paradoxically increased in the proximal myocardial segments which showed the highest deficits in coronary blood flow reserve. Such a proximal hyperinnervation complicating distal denervation could result in potentially life-threatening myocardial electrical instability.

The best possible degree of glycemic control is regarded as the primary approach to a causal treatment of CAN. However, while in Type 1 diabetic patients intensive diabetes therapy resulted in partial prevention and slowing of progression of CAN, conflicting data have been generated in Type 2 diabetic patients. Among the therapeutic approaches based on the pathogenetic concepts of neuropathy favorable effects on HRV have been demonstrated for the aldose reductase inhibitors (e.g. epalrestat), antioxidant treatment with a-lipoic acid and vitamin E, ACE inhibitors, and angiotensin receptor blockers. Symptomatic treatment of orthostatic hypotension in clinical routine includes physical measures and administration of midodrine or fludrocortisone. Before drug treatment is initiated, the risk-benefit ratio has to be thoroughly estimated because of sometimes limited efficacy and frequent significant side effects.