

Does Insulin Play a Role in Cardiovascular Autonomic Regulation?

Cardiovascular autonomic neuropathy (CAN) is a major contributor to the increased morbidity and mortality rates in the diabetic population. Cardiovascular disease accounts for ~50% of the mortality in diabetic patients (1). Both sudden death and silent myocardial infarction have been attributed to CAN. Not long ago, CAN was believed to be a late complication of diabetes. This was due to the fact that clinically overt manifestations of CAN are only evident when preceding dysregulatory phenomena reach a decompensated stage. As newer techniques have developed for their detection, it has become clear that diabetic cardiovascular autonomic function may become abnormal early in the course of diabetes. Cardiorespiratory reflexes are therefore commonly abnormal in patients without clinical evidence of neuropathy (2) or even at the time when diabetes is diagnosed (3). These findings parallel those of somatic diabetic neuropathy, in which "hyperglycemic" neuropathy may be present at the time of diagnosis, as assessed by nerve conduction studies (4). CAN occurs in both type 1 and type 2 diabetes and, therefore, has been associated with hyperglycemia per se and its effects on the function of the afferent and efferent limbs of the autonomic cardiovascular control. Other identified risk factors of CAN include blood lipids, blood pressure, age, BMI, smoking, and physical fitness (5). It is also evident that diabetic women have a greater cardiovascular risk than matched diabetic men (6). Premenopausal diabetic women have a multifold higher risk to develop heart disease than their matched male counterparts, suggesting a role for sex hormones. It is therefore increasingly clear that apart from hyperglycemia, there are other factors contributing to the development of CAN. The prominent role of dysglycemia in the pathogenesis of cardiovascular disease has been demonstrated repeatedly (7–9). These studies show an increased risk for cardiovascular death in nondiabetic patients who show impaired glucose tolerance or even in those with fasting blood glucose levels in the upper normal range. In the 22-year follow-up study of nondiabetic men by Björnholt

et al. (5), individuals with a fasting blood glucose level >85 mg/dl showed a significantly increased mortality rate from cardiovascular disease (17.1%) compared with those with a fasting blood glucose level <85 mg/dl (11.0%). This was true even after correction for confounding factors like blood pressure, blood lipids, BMI, age, and smoking. However, of those subjects with blood glucose levels >85 mg/dl, 20% developed clinical diabetes during the follow-up period. A similarly increased mortality was also evident in the Whitehall study (10) of nondiabetic men who showed higher percentiles of 2-h postload values. Undoubtedly, there is an association between impaired glucose tolerance and/or high normal fasting glucose levels and future cardiovascular disease. However, it is unclear whether high normal glucose levels per se contribute to cardiovascular disease or whether they merely indicate the impending development of overt diabetes. The latter phenomenon appeared in part to be the case in the Norwegian study (5). If this is the case, factors other than hyperglycemia, particularly hyperinsulinemia, could potentially contribute to the development of accelerated atherosclerosis and cardiovascular disease. However, in the studies previously cited, fasting insulin levels were not measured or considered a potential contributing factor to CAN.

In this issue, Watkins et al. (11) confirm, in a cross-sectional study of 162 healthy volunteers, an association between spectral analysis–derived baroreflex sensitivity (BRS) and high normal fasting blood glucose levels. However, after corrections for confounding factors, such as age, BMI, and blood pressure, this correlation was no longer significant. Interestingly, a highly significant correlation was found between fasting insulin levels and BRS, even after covariant adjustments. These findings tend to suggest that at least in the early development of cardiac autonomic dysregulation, hyperinsulinemia may be a more important risk factor than hyperglycemia. It is worth noting, however, that the only covariant that predicted both fasting blood glucose and insulin levels was BMI. One may there-

fore speculate that low leptin levels or leptin receptor defects may play, if not a primary, an indirect role in the development of CAN by elevating insulin levels.

Cardiovascular autonomic control is mediated by a complex interplay between sensory afferents, CNS modulation and processing, and efferent effectors. In previous studies, investigating the diabetogenic effects on arterial baroreflex control of the heart rate, bolus injections of vasoactive drugs have been used to produce transient changes in arterial blood pressure (12,13). Use of these methods allows predominantly for assessment of parasympathetic components of baroreflex activation, because of the longer time constant needed for sympathetic components (14). This potential shortcoming was eliminated in the study by Watkins et al. (11) by using a noninvasive technique for the estimation of BRS. Sympathetic nerve activity, reflected by plasma norepinephrine levels and sympathetic responses to unloading of cardiopulmonary receptors, are affected early in diabetic patients (15,16). Furthermore, insulin itself is known to increase plasma norepinephrine and to reduce parasympathetic control of heart rate (17).

Little information is available regarding the effect of diabetes on CNS-mediated control of cardiovascular reflexes. Experimental studies have suggested that early impairments of baroreflex regulation of vagal heart rate are mediated by central mechanisms, occurring before abnormalities of baroreceptor sensory afferents and sympathetic efferents (18,19). Furthermore, in autonomic neuropathy of the spontaneously diabetic rats, sensory afferents are involved before abnormalities of the efferent limb (20). It is not known whether the central modulating effects are insulin-mediated or whether they are a result of dyssynchronous central coupling of afferent input and efferent output.

Hence, baroreceptor dysregulation may potentially occur at several levels of the reflex arch, and it is manifested before the development of overt autonomic neuropathy of the cardiovascular system. This early dysregulation probably heralds overt CAN

and may be mediated by both hyperglycemia and hyperinsulinemia, as indicated by the study by Watkins et al. (11). From this study, hyperinsulinemia appears to be a more independent risk factor. Their findings underpin an often forgotten aspect of diabetic neurological complications, namely the neuroendocrine and neurotrophic consequences of insulin dysmetabolism itself. Today, little is known about its contribution to the development of diabetic complications. Insulin dysmetabolism is, however, likely to become an integral component in the complex web of pathogenetic mechanisms responsible for the neurological complications of diabetes (21). Until now, though, it has been operating undisturbed in the dark shadow of hyperglycemia.

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