# Cardiovascular Autonomic Neuropathy: Diagnosis and Management

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Cardiovascular autonomic neuropathy increases morbidity and mortality, and reduces quality of life and activities of daily living of the patients with diabetes. The reduced cardiovascular autonomic function as measured by heart rate variability is strongly associated with an increased risk of silent myocardial ischemia and mortality. Currently, no specific therapeutic strategies can be recommended for cardiac autonomic neuropathy, but management of hyperglycemia and the use of angiotensin-converting enzyme inhibitors and β blockers should be instituted.

## Introduction

Diabetic autonomic neuropathy is among the least recognized and understood complications of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes. Because of its association with a variety of adverse outcomes, including cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important form of diabetic autonomic neuropathy. The prevalence of autonomic impairment is 54% in type 1 and 73% in type 2 diabetic patients [1•]. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics. CAN has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction (MI), and decreased likelihood of survival after MI [2•]. Advances in technology, built on decades of research and clinical testing, now make it possible to objectively identify early stages of CAN with the use of careful measurement of autonomic function. In a review of several epidemiologic studies among individuals diagnosed with diabetes, it was shown that the 5-year mortality rate from this serious complication is five times higher for individuals with CAN than for individuals without cardiovascular autonomic involvement [3].

## Pathogenesis of CAN

The pathogenesis of cardiac autonomic neuropathy is incompletely understood. Persistent hyperglycemia increases polyol pathway activity with accumulation of sorbitol and fructose in nerves, damaging them by an as yet unknown mechanism. This is accompanied by decreased myoinositol uptake and inhibition of the $Na^+/K^+$ adenosine triphosphatase, resulting in $Na^+$ retention, edema, axoglial disjunction, and nerve degeneration. Microvascular dysfunction with local ischemia leading to nerve fiber death has been proposed. Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability. Alternately, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons, a process referred to as nitrosative stress. In a subpopulation of individuals with neuropathy, immune mechanisms may also be involved. Reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products (localized in endoneurial blood vessels) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function. The result of this multifactorial process may be activation of polyADP ribosylation depletion of adenosine triphosphatase, resulting in cell necrosis and activation of genes involved in neuronal damage [2•].

## Epidemiology of CAN

The reported prevalence of CAN varies, depending on whether studies have been carried out in the community, clinic, or tertiary referral center. The variance among prevalence studies also reflects the type and number of tests performed and the presence or absence of signs and symptoms of cardiac autonomic neuropathy. For example, in a community-based population study of diabetic neuropathy, the prevalence of autonomic neuropathy as defined by one or more abnormal heart rate variability (HRV) test results was 16.7% [4]. In a further study, Ziegler et al. [5] evaluated