Cardiovascular autonomic neuropathy – prevention, identification and management

Cardiovascular autonomic neuropathy (CAN), a common microvascular complication of type 1, type 2 and prediabetes, is underdiagnosed yet has a 5-year mortality rate greater than most cancers, according to this review in *Diabetologia*. Three key clinical signs help clinicians identify CAN: resting tachycardia, fixed heart rate resulting in exercise intolerance and orthostatic hypotension. Early glycaemic control, ACE inhibitor or ARB use, and multifactorial cardiovascular risk factor management can reduce the risk of CAN developing and slow its progression. In practice, we can help reduce risk of CAN by optimising early management, having a high index of suspicion and hence improving diagnosis, and ensuring that people with CAN receive appropriate lifestyle advice and specialist management.

Pam Brown
GP in Swansea

Cardiovascular autonomic neuropathy (CAN) is a common but poorly recognised microvascular complication of diabetes which results in alterations in function of the cardiovascular autonomic nervous system. It occurs in 20–90% of people with diabetes, including those with type 1 and type 2 diabetes, and also in prediabetes/non-diabetic hyperglycaemia. In the present review published in *Diabetologia*, Eleftheriadou and colleagues summarise the evidence base regarding the pathophysiology, diagnosis and management of CAN.

CAN is asymptomatic in the early stages, with non-specific symptoms later. Optimising glycaemic control and cardiovascular risk factors early may both prevent CAN and, once established, slow its progression. Advanced CAN has a 16–50% mortality rate at 5 years depending on the study, and many of these deaths are attributed to sudden cardiac arrhythmias.

The pathophysiology of CAN is complex and likely to be multifactorial with several different mechanisms, such as the formation of advanced glycation end-products, increased oxidative stress with increased production of free radicals, and activation of the polyol and protein kinase C pathways, all of which may damage autonomic nerve fibres.

Clinical signs and symptoms

There is parasympathetic dysfunction first, which results in sympathetic predominance with tachycardia (up to 130 beats per minute) and later a fixed heart rate resulting in exercise intolerance. Orthostatic hypotension (≥20 mmHg reduction in systolic and ≥10 mm in diastolic blood pressure on standing) occurs, with dizziness or syncope on standing. If symptomatic, treatment should be initiated, including full-leg elastic stockings, abdominal binders, bed tilt-up and midodrine or droxidopa drug treatment (although the latter is not available in the UK).

People with CAN have almost twice the risk of silent cardiac ischaemia compared to those without CAN. Cardiac dysfunction also results in reduced ejection fraction, impaired systolic heart function and decreased left ventricular diastolic filling, presenting as heart failure. Non-dipping of overnight blood pressure can also occur due to parasympathetic dysfunction.

Although CAN may make people more prone to severe hypoglycaemia, and impaired counter-regulatory responses to hypoglycaemia can lead to hypo unawareness, the latter is not directly linked to CAN, and coexistence of CAN does not determine irreversibility of impaired hypo awareness.

Clinical diagnosis of CAN, as recommended by the American Diabetes Association (ADA Professional Practice Committee, 2024), uses changes in heart rate variability (HRV) with deep breathing, resting tachycardia (>100 beats per minute) and orthostatic hypotension.

Future research is needed to clarify how best to reduce the development of CAN. Wearable devices which can accurately measure HRV may greatly simplify and augment CAN diagnosis.

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Cardiovascular autonomic neuropathy in diabetes: an update with a focus on management

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Management

Intensive glycaemic management has stronger evidence for reducing the risk of CAN developing in type 1 than type 2 diabetes. In the US Diabetes Prevention Program, weight loss with diet and exercise interventions improved cardiac autonomic function as measured by HRV. There is also a small amount of evidence for benefit from bariatric surgery in the STAMPEDE study. Metformin has demonstrated HRV improvement, and ACE inhibitors and ARBs may help prevent CAN as well as, possibly, peripheral neuropathy in people with type 2 diabetes.

In those with CAN, beta-blockers such as bisoprolol can be helpful in decreasing resting heart rate and improving HRV by helping to balance the autonomic nervous system. There is variable data on statins and alpha-lipoic acid in different studies.

There are currently no disease-modifying treatments for CAN; therefore, newer glucose-lowering drug classes have been explored for potential benefit. A meta-analysis demonstrated that SGLT2 inhibitors reduced the risk of sudden cardiac death, with an odds ratio of 0.72, and it has been suggested that some of their effects are mediated through direct or indirect effects on the autonomic nervous system; however, this remains to be confirmed. Although GLP-1 receptor agonists have demonstrated cardiovascular benefits, they increase heart rate and decrease HRV.

The paper also provides a detailed discussion on the impact of hypoglycaemia on the autonomic nervous system, resulting in cardiac abnormalities including prolonged corrected QT interval (QT-c), arrhythmias and sudden death. In the ACCORD study, people who suffered severe hypoglycaemia, both in the intensive and standard treatment arms, had greatly increased mortality rates.

A recent systematic review confirmed a potential relationship between peripheral neuropathy and autonomic neuropathy in people with diabetes. This association could prompt clinicians to be more proactive in finding CAN, resulting in earlier management (de Paula et al, 2024).

A previous systematic review of 11 studies involving 1730 people highlighted increased risk of microalbuminuria in people with impaired glucose tolerance, and in people with prediabetes/non-diabetic hyperglycaemia there was a doubling of cardiovascular mortality, increased risk of peripheral neuropathy and a higher than expected prevalence of CAN (9–18%) (Eleftheriadou et al, 2021). The modest hyperglycaemia, combined with obesity, dyslipidaemia, hypertension and inflammation, contribute to the increased risk of CAN. The present review stresses the importance of good glycaemic control and risk factor modification in people with prediabetes to reduce the risk of all these complications, in line with more recent guidance encouraging prediabetes remission rather than just prevention of progression to type 2 diabetes (see our recent *Diabetes Distilled*).

Implications for practice

Think back to the last time you saw someone with a diagnosis of CAN – my guess is that you will have few people coded with this diagnosis, despite it being relatively common. CAN is rarely diagnosed despite its significant impact on quality of life and mortality. Greater awareness of potential signs and symptoms of CAN – resting tachycardia, exercise intolerance due to fixed heart rate and orthostatic hypotension – should encourage us to refer more people with type 1, type 2 and prediabetes for expert assessment to confirm the diagnosis. The close association between diabetic peripheral neuropathy (DPN) and CAN means we should assess carefully for DPN if not already diagnosed in those who are diagnosed with CAN.

This review highlights the important role of early intensive glycaemic and multifactorial risk factor management in people with diabetes, as seen in the Steno-2 study, in potentially reducing the risk of CAN development and progression. We could all use ACE inhibitors and ARBs more consistently, which is likely not only to benefit CAN but also to provide renal protection.

As research into CAN continues, we need to be aware that specific therapies such as SGLT2 inhibitors may influence mortality risk and it is, therefore, increasingly important that we have a high index of suspicion and refer appropriately for CAN investigation and diagnosis. In the meantime, optimising glycaemia and lipids and encouraging lifestyle changes to achieve weight loss in those with prediabetes and type 2 diabetes, as well as optimising our use of ACE inhibitors and ARBs early, may reduce the number of people who develop this high-risk microvascular complication. ■

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