

Review

The impact of Cardiovascular Autonomic Neuropathy in diabetes: Is it associated with left ventricular dysfunction?

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Abstract

Cardiovascular Autonomic Neuropathy (CAN) is one of the least understood of all serious complications of diabetes. Besides increasing mortality, CAN may have various clinical sequelae including exercise intolerance, arrhythmias and painless myocardial infarction. But does it also cause left ventricular dysfunction? Patients with diabetes have a greater risk of developing congestive heart failure. Coronary artery disease and hypertension have been notorious in causing left ventricular dysfunction in many of these patients. However, even in their absence, diabetes itself, through several studies, has been proposed to cause the controversial entity, Diabetic Cardiomyopathy (DCM). Various mechanisms have been suggested. CAN through alteration in myocardial blood flow and sympathetic denervation, and through changes in myocardial neurotransmitters, including catecholamines and neurotransmitters of the neuropeptidergic system, has been and is still being studied as one of the main mechanisms to cause left ventricular dysfunction. Earlier detection of CAN and instant initiation of upcoming treatments may be a way to help prevent DCM, and thus improve the morbidity and mortality this causes to patients with diabetes. © 2006 Elsevier B.V. All rights reserved.

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1. Introduction

Diabetic neuropathy is one of the most common and troublesome complications of diabetes mellitus. This disorder encompasses a wide range of abnormalities affecting both proximal and distal peripheral sensory and motor nerves, as well as the autonomic nervous system. Diabetic autonomic neuropathy is one of the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes (Vinik et al., 2003).

The crucial point about diabetic autonomic neuropathy is that sub-clinically it can occur as early as within a year of diagnosis in Type 2 diabetic patients and within 2 years in Type 1 diabetic patients. In a study by Pfeifer et al. (1984) the RR-variation during beta adrenergic blockade (an index of an autonomic nervous system reflex involving the cardiac parasympathetic nervous system pathway) was smaller than that of control subjects in both Type 2 ($P < 0.001$) and Type 1 subjects ($P < 0.01$). The patients had only been known to suffer from diabetes for a year; although, in those with Type 2 diabetes the exact period from the onset of disease is difficult to elicit. The importance of this finding is that, unknowingly, mortality and morbidity may be increased at a very early stage in patients with diabetes. In fact the 5-year mortality rate is five times higher for individuals with cardiovascular autonomic neuropathy (CAN) than for individuals without cardiovascular autonomic involvement (Ziegler, 1999). Rathmann et al. (1993) revealed that the 8-year survival rate estimate in patients with CAN was 77% compared with 97% in those with normal autonomic function ($P < 0.05$). Deaths were mainly due to macrovascular diseases and sudden unexpected deaths. But why mention CAN?

CAN is one of the most overlooked of all serious complications of diabetes (Maser and Lenhard, 2005). The autonomic nervous system modulates the electrical and contractile activity of the myocardium via the interplay of sympathetic and parasympathetic activity (Chow et al., 2001). CAN results from damage to these autonomic nerve fibers resulting in abnormalities in heart rate control and vascular dynamics. Besides increasing mortality, CAN may cause exercise intolerance, orthostatic hypotension, asymptomatic ischaemia, and painless myocardial infarction (Vinik et al., 2003). Therefore could it also be a cause of left ventricular dysfunction?

Diabetic Cardiomyopathy (DCM) is a well-defined complication of diabetes. Accumulating data have shown that diabetes mellitus results in cardiac functional and structural changes, independent of hypertension, coronary artery disease, or any other known cardiac disease, and this supports the existence of DCM. Left ventricular diastolic dysfunction appears to be quite common in well-controlled diabetic patients without clinically detectable heart disease (Poirier et al., 2001). Besides diastolic dysfunction, evidence of systolic dysfunction has also been revealed in patients with diabetes.

These findings are not definite. We must keep in mind that a number of studies have not confirmed the association of left ventricular dysfunction with diabetes mellitus (Salazar et al., 1994). So what is the truth? What causes DCM?

The development of DCM is likely to be multifactorial. Multiple mechanisms are hypothesized to cause this condition. These include metabolic disturbances, myocardial fibrosis, and small vessel disease. One of the main theories for causation of DCM is CAN (Fang et al., 2004). CAN results in sympathetic denervation altering myocardial blood flow, thus affecting myocardial perfusion (Stevens et al., 1998). It also modifies catecholamine levels and adrenergic receptors in the myocardium (Communal et al., 1998). Another component of the autonomic nervous system is the neuropeptidergic system. Changes in its neurotransmitters, such as vasoactive intestinal peptide or calcitonin gene-related peptide (CGRP), among others, have been implicated in causing DCM secondary to CAN (Ahluwalia and Celtek, 1997).

2. What causes left ventricular dysfunction in diabetes?

Congestive heart failure (CHF) has traditionally been a clinical diagnosis, based on signs and symptoms of circulatory insufficiency in the form of volume overload or target organ hypoperfusion (Adams, 2001). In a recent report by Nichols et al. (2004) from a retrospective cohort study of 8231 patients with type 2 diabetes and 8845 nondiabetic patients of similar age and sex who did not have CHF, patients with diabetes were much more likely to develop CHF than patients without diabetes (incidence rate 30.9 vs. 12.4 cases per 1000 person-years, rate ratio 2.5, 95% CI 2.3–2.7).

There are various reasons why patients with diabetes develop left ventricular dysfunction. The contemporary epidemiology of heart failure in patients with diabetes shows it is a common clinical problem, at least for the elderly and very elderly, and largely a consequence of coronary artery disease and hypertension. But not only! Left ventricular dysfunction can also occur in those with diabetes not suffering from either hypertension or ischaemic heart disease (Zabaloitia et al., 2001).

3. Cardiovascular Autonomic Neuropathy — is it a cause for Diabetic Cardiomyopathy?

Over the past years various studies have proposed that patients with diabetes, due to various mechanisms, may develop cardiac functional and structural changes in the absence of hypertension, coronary heart disease or any other known cardiac disease.

3.1. Does DCM really exist?

Poirier et al. (2001) studied 46 patients with diabetes and no evidence of diabetic complications, hypertension, coronary artery disease, congestive heart failure, or thyroid or overt renal disease. Left ventricular diastolic dysfunction

was found in 28 subjects (60%), of whom 13 (28%) had a pseudonormal pattern of ventricular filling and 15 (32%) had impaired relaxation. The limitations for this study in my opinion are that a small group of well characterised patients were used but one must understand that patients with these characteristics are not easy to find. Besides this, increasing age could have been a factor in causation of ventricular dysfunction, but the pseudonormalized pattern of left ventricular filling represents an advanced stage of left ventricular diastolic dysfunction and is considered abnormal, independently of the age of the subject.

Systolic dysfunction has also been revealed in patients with diabetes. Fang et al. (2003) compared three different groups — one with DM only, other with left ventricular hypertrophy (LVH) and another with DM and LVH. All patient groups showed reduced systolic function compared with controls, evidenced by lower peak strain ($P < 0.001$) and strain rate ($P = 0.005$). Peak strain and strain rate were significantly lower in the DM/LVH group than in those in the DM alone ($P < 0.03$) or LVH alone ($P = 0.01$) groups. Diabetic patients without overt heart disease demonstrate evidence of systolic dysfunction and increased myocardial reflectivity (correlates with amount of collagen deposition).

These findings are independent and incremental to the effects of LVH. Coronary ischaemia in this case was excluded by dobutamine echocardiography with possibility of false negative results, although these latter cases would contribute minimally to systolic dysfunction.

But not all studies have proved that patients with diabetes and no other cardiovascular risk factor can develop impaired left ventricular function. Salazar et al. (1994) when studying 61 patients with Type 1 diabetes aged 4 to 20 years showed that there was no echocardiographic data to support the concept of DCM in adolescents with Type 1 diabetes mellitus. The significance of this result may be put in doubt as all patients were young leading to a small specific subset of patients with Type 1 diabetes being studied. Type 1 diabetes is not so prevalent at this age when compared to Type 2 diabetes. Another reason for the lack of cardiac dysfunction might be the beneficial effects of insulin therapy on the heart and lack of or minimal insulin resistance in these patients. Other studies have also shown absence of DCM even in type 2 diabetic patients. Posner et al. (1983) revealed that the mean rate-corrected pre-ejection period, the left ventricular ejection time, electromechanical systole and pre-ejection period/left ventricular ejection time ratio were not significantly different between a group consisting of patients with diabetes and another group of age-/sex-matched healthy persons ($P > 0.05$). One must be careful when assessing reliability of these studies as the technique of assessment might not have been sensitive enough with resultant false negative results.

3.2. Mechanisms for DCM

Various mechanisms for DCM exist. Hyperglycaemia and hyperlipidaemia may result in several major cellular metabolic

perturbations. Formation of advanced glycation end products and reactive oxygen species is followed by deactivation of nitric oxide, myocardial collagen deposition and fibrosis (Ide et al., 2001; Bielawska et al., 1997). Upregulation of the renin–angiotensin system occurs in diabetes (Fein and Sonnenblick, 1985). Angiotensin II and aldosterone are then able to induce cardiac fibrosis (McEwan et al., 1998). Structural and functional abnormalities of small vessels during increased myocardial demand and microvascular spasm cause repeated episodes of myocardial ischaemia leading to cell death. This results in focal fibrosis (Nitenberg et al., 1993). This leads us to another important mechanism suggested to cause DCM; that is CAN.

3.3. The consequences of CAN

CAN is a common form of autonomic neuropathy, causing abnormalities in heart rate control and central and peripheral vascular dynamics. CAN occurs in ~ 17% of patients with type 1 diabetes and 22% of those with type 2. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction (Ziegler, 1999). When assessing for prevalence of CAN different studies use different techniques for assessment and this should be kept in mind when reading epidemiological data. CAN may be present in various ways. Those with CAN have an increased incidence of silent ischemia and myocardial infarction, and have been found to have a decreased likelihood of survival after myocardial infarction (Fava et al., 1993).

There is a strong association between CAN and mortality rates, signifying an important impact of this condition on those suffering from diabetes. Ewing et al. (1980) reported a 5-year mortality rate of 53% in diabetic patients with abnormal autonomic function tests compared with a mortality rate of only 15% over the 5-year period among diabetic patients with normal autonomic function test results. The majority of the deaths were from renal failure while 29% were from sudden death.

In another study by Rathmann et al. (1993), designed to assess the risk of mortality due to CAN among patients with CAN but not suffering from any severe complication of diabetes the mortality of diabetic patients suffering from CAN increased steadily over an 8-year period (6% after 2 years, 14% after 4 years, 17% after 6 years, and 23% after 8 years) compared with an age-, sex-, and duration of diabetes-matched control group where there was one death. Autonomic dysfunction was found to be an independent risk factor with poor prognosis. There are various proposed potential reasons for increased mortality in patients with CAN. These include impaired respiratory response to hypoxia, impaired response to hypoglycaemia, silent ischaemia, or arrhythmias; but could it also be related to DCM?

One of the earliest signs of CAN is an increased resting heart rate with loss of heart rate variability. Initially vagal parasympathetic neuropathy is overcome by cardiac sympathetic activity and heart rate increases. As sympathetic

activity deteriorates the tachycardia may be followed by a decrease in heart rate and, ultimately, a fixed heart rate.

Roy et al. (1989) evaluated the role of parasympathetic nervous system activity on cardiovascular performance on 25 diabetic subjects who lacked symptoms, signs, or objective measurements of ischemia or cardiomyopathy. Those with autonomic neuropathy had a percent increase in cardiac output at matched percent maximum oxygen uptake which was less than those without autonomic neuropathy ($P < 0.01$). Therefore it has been shown that impaired sympathetic and parasympathetic responses, that normally augment cardiac output and redirect peripheral blood flow to skeletal muscles during exertion, may limit exercise tolerance.

CAN has the propensity to cause a reduction in the cardiac ejection fraction, to impair systolic dysfunction and decrease diastolic filling. Zola et al. (1986) to determine if cardiac autonomic neuropathy (CAN) contributes to DCM, assessed left ventricular function by resting and exercise radionuclide ventriculography. In 37% of patients, ventriculography revealed abnormal left ventricular performance. CAN was found in 91% of all patients. Ventriculography was abnormal in 59% of patients with CAN and in only 8% of patients without CAN ($P < 0.005$). There were significant reductions in mean ejection fractions in patients with CAN at rest and with maximal exercise ($P < 0.001$) compared to patients without CAN. Willenheimer et al. (1998) in a study on patients with Type 1 diabetes found that those with abnormal Expiration/Inspiration ratios (an index of parasympathetic function) had lower E/A ratios (index of cardiac filling) than patients without autonomic neuropathy. In a study to assess the association between CAN and DCM on a group of well controlled Type 2 diabetes patients, the E/A ratios correlated significantly with indices of parasympathetic modulation (Poirier et al., 2003). In these studies a small amount of patients are used but the intense selection of these patients characterized by absent hypertension, coronary heart disease, renal and thyroid disease helps strengthen the results. One must also take into consideration the various techniques used to assess ventricular dysfunction and autonomic neuropathy which vary between studies and are operator dependent.

Through predisposition to arrhythmias autonomic neuropathy may lead to left ventricular dysfunction followed by sudden death. Sivieri et al. (1993) revealed that QT prolongation was higher in diabetic patients with autonomic neuropathy than those without. Tachycardias can reduce the heart's ability to pump by interfering with the ventricular chambers' ability to fill with blood properly. They do this by reducing the time for such filling or by interfering with the booster effect normally provided by timely contraction of the atria such as occurs in atrial fibrillation. When the heart's ability to work is greatly reduced for a prolonged time, cardiac arrest and death are likely. This may result from ventricular tachycardia and ventricular fibrillation.

3.4. How does CAN cause left ventricular dysfunction?

Several theories have been suggested to explain how CAN may cause progressive left ventricular dysfunction leading to DCM.

3.5. Alteration in myocardial blood flow and sympathetic denervation

In a study on 28 diabetics by Di Carli et al. (1999) to assess the effects of autonomic neuropathy on myocardial blood flow, basal flow was regionally homogeneous and similar in the diabetic and normal subjects. However, the increase in flow in response to cold was lower in the diabetics with autonomic neuropathy ($14 \pm 10\%$) than in those without autonomic neuropathy ($31 \pm 12\%$) ($P = 0.015$) and the normal subjects ($48 \pm 24\%$) ($P < 0.001$). This impaired coronary flow response to cold was related to the degree of cardiac sympathetic neuropathy, as assessed by PET. What does this study implicate? It provides evidence that diabetic autonomic dysfunction affecting cardiac efferent sympathetic signals is an important determinant of impaired coronary blood flow during increased sympathetic stimulation, but it also indicates that resultant myocardial necrosis with subsequent areas of fibrosis might be a cause for DCM.

Various studies have revealed presence of sympathetic denervation in patients with heart failure. Hartmann et al. (1999) in a study on patients suffering from dilated cardiomyopathy found not only global reduction but also regional abnormalities of cardiac sympathetic tracer uptake. The degree of abnormality was positively correlated to markers of severity of heart failure. ($P = 0.002$). In this study myocardial blood flow at rest was not impaired, in fact, perfusion scans were all normal. This further strengthens the importance of cardiac sympathetic denervation in the pathology of abnormal myocardial blood flow during a stress response.

Stevens et al. (1998) revealed that rest myocardial blood flow was higher in the neuropathic subjects than in either the nondiabetic ($P < 0.01$) or the nonneuropathic diabetic subjects ($P < 0.05$). On the contrary, during adenosine infusion, global left ventricular myocardial blood flow was significantly less in the neuropathic subjects than in the nonneuropathic diabetic group ($P < 0.05$). The interesting point about this study is that patients with CAN demonstrated heterogeneous distal cardiac sympathetic denervation with persistent proximal innervation and that myocardial blood flow was mostly impaired in the proximal segment. This could reflect regionally exaggerated sympathetic tone or regional vascular hyperresponsiveness in the proximal segments mediated by endothelial inflammatory mediators in patients with diabetes. Besides progressively causing heart failure this condition increases arrhythmogenicity of the myocardium thus increasing mortality.

3.6. Changes in myocardial autonomic neurotransmitters and their effects

Alterations in sympathetic denervation have modified catecholamine levels and adrenergic receptors in the myocardium of patients with diabetes. Diabetes has been proved to initially cause an increased amount of noradrenaline and β -adrenergic receptor density in the myocardium. Subsequently noradrenaline levels fall to below normal suggesting neuronal damage (Uekita et al., 1997).

As patients develop hyperglycaemia on a background of relative insulin deficiency there is an increase in fatty acids. Increased fatty acids have a stimulatory effect on the sympathetic nervous system with increase in catecholamines. In a study by Manzella et al. (2001) on patients with Type 2 diabetes lipid emulsion infusion increased plasma free fatty acids ($P < 0.001$) and catecholamine concentrations ($P < 0.005$), and mean arterial blood pressure ($P < 0.005$).

As the sympathetic system is stimulated with increasing release of catecholamines, toxic effects on the heart may occur. Norepinephrine causes myocardial cell apoptosis. When rat ventricular myocytes were exposed to either norepinephrine or isoproterenol by Communal et al. (1998) the number of viable myocytes decreased by 35%. Norepinephrine increased the percentage of apoptotic cells from $7.8 \pm 0.7\%$ to $16.7 \pm 2.2\%$ ($P < 0.01$; $n = 6$). Activation of β -adrenergic receptors in cardiac myocytes increases the cellular cAMP concentration. This leads to an increase in intracellular calcium concentration. Increased calcium stimulates transcription of genes involved in the regulation of apoptosis (Stewart et al., 1994). Progressive myocardial cell apoptosis results in heart failure.

Olivettiet et al. (1997) took heart samples from patients who had undergone heart transplantation and evaluated the samples for apoptosis. Heart failure was characterized morphologically by a 232-fold increase in myocyte apoptosis and biochemically by DNA laddering (an indicator of apoptosis). This phenomenon contributes to the progression of cardiac dysfunction. A plausible mechanism for apoptosis is through the formation of oxygen free radicals; the ubiquitous mediators of most destructive mechanisms in diabetes.

The nervous control of the cardiovascular system comprises several transmitters other than the above mentioned classical autonomic neurotransmitters. These non-adrenergic noncholinergic transmitters include vasoactive intestinal polypeptide, calcitonin gene-related peptide, neuropeptide Y and nitric oxide. These particular substances play important roles in the control of vascular tone and altered activity of these mediators have also been found to cause DCM.

Calcitonin gene-related peptide (CGRP) is a vasorelaxant and a positive inotropic and chronotropic peptide that binds to the calcitonin receptor-like receptor. In the heart, upon stimulation CGRP is released from sensory nerve terminals and improves cardiac perfusion and function. Dvoráková et al. (2005) revealed that decreased expression of CGRP

precursor in patients with diabetes, and intra-axonal accumulation of CGRP together with downregulation of the receptors contribute to development of DCM.

Nitric oxide (NO) is a well-characterized neurotransmitter in the central and peripheral nervous systems. NO mediates nonadrenergic noncholinergic relaxant responses. The cardiac effects of NO are complex, and results have been conflicting in terms of a beneficial or deleterious effect of NO.

Sustained hyperglycaemia causes excess formation of mitochondrial ROS (Reactive Oxygen Species) which decrease NO levels, leading to myocardial inflammation and endothelial dysfunction via PARP [poly (ADP-ribose) polymerase] (Rosen et al., 1998). This process promotes cell dysfunction and necrotic-type cell death leading to DCM (Szabo et al., 2002). The impaired availability of NO as a contributor to DCM was shown by Joffe et al. (1999). Exhaled NO was lower in diabetic rats (1.8 ± 0.2 vs. 3.3 ± 0.3 parts per billion, $P < 0.01$) and correlated with Doppler left ventricular filling which was significantly less ($P < 0.0001$) in diabetic rats compared to nondiabetic controls.

That NO synthesis is altered in patients with diabetes has been shown in various other studies. Celtek et al. (2003) demonstrate the depletion of neuronal NO synthase content from nerve fibers in the early stages of diabetes with resultant autonomic dysfunction. As diabetes progresses high amounts of NO are produced through inducible NOS (Nitric Oxide Synthase) and endothelial NOS. They reveal that accumulation of endogenous NO in cell bodies causes apoptosis of the nerves by formation of free radicals. Esberg and Ren (2003) further reported that local overproduction of NO seen in the early stages of diabetes, can react with superoxide (O_2^-) to form peroxynitrite ($ONOO^-$). This caused cardiomyocyte contractile dysfunction, secondary to increased NO; in contradistinction to above studies where decreased NO resulted in endothelial dysfunction followed by DCM (Rosen et al., 1998).

Vasoactive intestinal peptide (VIP) is a vasorelaxant peptide that stimulates insulin secretion and mediates anti-inflammatory effects. In the heart, VIP is produced and released primarily by intrinsic neurons and improves cardiac perfusion and function. Downregulation of VIP and altered expression of its receptors was revealed by Dvoráková et al. (2005) in a study on streptozotocin induced diabetic rats with DCM. Changes in receptor expression were observed in atria, ventricles and smooth muscle cells of arterioles.

Substance P is another important neuropeptide which through release of nitric oxide has strong vasodilatory effects. Its role in DCM has never been studied although it has been shown after short ischemic periods to mediate myocardial stunning during reperfusion (Chiao and Caldwell, 1996).

Neuropeptide Y (NPY) is a neurotransmitter also found in the autonomic nervous system. It augments the vasoconstrictor effects of noradrenergic neurons. Zhang et al. (2005) revealed that the activation of PKC may lead to the overexpression of NPY possibly resulting in DCM.

4. Looking optimistically ahead

With no doubt at this stage it is definite that the presence of CAN is of significant importance in any patient suffering from diabetes. Revealing CAN as being one of the principal mechanisms resulting in DCM helps us try and discover treatments and maneuvers to help prevent or delay heart failure, and thus reduce morbidity and mortality in our patients.

One of the main effects of CAN is to alter sympathetic innervation resulting in changes in myocardial blood flow. Drugs like ACE inhibitors may facilitate blood flow through the microcirculation of the heart. Rosen et al. (1995) showed that the intravascular volume was enlarged and the epicardial perfusion rate increased in hearts of diabetic rats treated with captopril as compared to diabetic controls. Quinapril, another ACE inhibitor, significantly increased parasympathetic activity ($P < 0.01$) in patients with CAN 3 months after treatment initiation. It also increased total heart rate variability ($P < 0.05$) (Kontopoulos et al., 1997). So could ACE inhibitors be beneficial if started in patients suffering from CAN and who still have no evidence of left ventricular dysfunction?

CAN alters catecholamine levels with resultant myocardial cell apoptosis. Communal et al. (1998) showed that the use of β -adrenergic antagonists helped abolish this effect. Other drugs have been assessed in treatment of CAN such as anti-oxidants like alpha-lipoic acid. Ziegler et al. (1997) showed that improvement in CAN ($P < 0.05$) occurred in Type 2 diabetes patients treated with alpha-lipoic acid when compared to placebo. But have these drugs been proven to prevent development of DCM?

The effects of aldose reductase inhibitors on patients with CAN have been assessed. In fact sorbinil, in a small study on 14 patients with diabetes but no atherosclerotic disease or cardiomyopathy, helped improve cardiovascular performance after 1 year of treatment ($P = 0.02$) (Roy et al., 1990).

So there is hope! Understanding the pathophysiology of CAN and being sensitive and knowledgeable about its adverse consequences will motivate us not to stop here. Our aim is to establish the scientific means of preventing the multiple complications of CAN, and above all to hopefully prevent DCM.

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