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Chapter 14

Diabetic Autonomic Neuropathy and Circadian Misalignment in Type 1 Diabetes

Elena Matteucci and Ottavio Giampietro

Additional information is available at the end of the chapter

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1. Introduction

Misalignment of circadian rhythms has been evidenced in patients with type 1 diabetes and there is a close relationship between alterations in neuroendocrine sleep architecture, circadian clock oscillations, glucose metabolism, autonomic function, and diurnal profiles of blood pressure and heart rate [1-5]. In turn, circadian misalignment may modify the peak incidence of cardiovascular events in diabetic people [6-9]. Diabetic autonomic neuropathy, particularly cardiac autonomic neuropathy, is considered an important potential factor involved in the disruption of circadian cardiovascular rhythms [10]. This serious chronic complication is rarely diagnosed because it remains for a long times asymptomatic; contrariwise, it seems to have a significant prognostic value [10-12]. The review summarises the battery of non-invasive autonomic function tests available for diabetic autonomic neuropathy diagnosis as well as cross-sectional and follow-up studies supporting their importance in risk stratification for diabetic micro-vascular complications and cardiovascular morbidity/mortality.

2. A bit of history and a bit of anatomy

In 1973, the British Medical Journal and the Lancet published three articles on diabetic autonomic neuropathy [13-15], which would then be followed over the years by an unbroken series of studies and publications. Wheeler and Watkins identified vagal denervation of the heart as a feature of diabetic autonomic neuropathy that could be evaluated by monitoring beat-to-beat variation in heart rate [14]. Ewing et al. found the vascular responses to the Valsalva manoeuvre and sustained handgrip useful in providing an objective assessment of the integrity of the autonomic nervous system in diabetes [15]. Ewing himself later developed

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the cardiovascular autonomic function test battery still in use to provide an objective diagnosis of autonomic nervous system involvement [16]. The battery included: Valsalva manoeuvre, heart rate response to standing up, heart rate response to deep breathing, blood pressure response to standing up, and blood pressure response to sustained handgrip (Appendix 1).

Brief description of the five non invasive cardiovascular reflex tests used by Ewing et al. [15] to assess autonomic function in diabetic subjects.

Valsalva manoeuvre: the subject sits quietly and then blows in a mouthpiece at a pressure of 40 mmHg for 15 s. The heart rate normally increases during the manoeuvre and decreases after release. The ratio of the longest R-R interval shortly after the manoeuvre to the shortest R-R interval during the manoeuvre is measured.

Heart rate response to standing up: the subject lies quietly and then stands up unaided. The heart rate normally increases with a maximum at about the 15th beat after starting to stand and thereafter decreases with a minimum around the 30th beat. Electrocardiogram tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

Heart rate response to deep breathing: the subject sits quietly and then breathes deeply at a rate of six breaths per minute. The maximum and the minimum heart rate during each breathing cycle are measured, and the mean of the differences during successive breathing cycles is measured.

Blood pressure response to standing up: the blood pressure is measured using a sphygmomanometer while the subject is lying down and after standing. The difference in systolic blood pressure is a measure of postural blood pressure change.

Blood pressure response to sustained handgrip: handgrip is maintained at 30% of the maximum voluntary contraction up to a maximum of five minutes and the blood pressure is measured each minute. The difference between the diastolic blood pressure just before release of handgrip, and before starting, is measured.

Based on his 10-yr experience, Ewing et al. 1) stressed the fallacy of relying on a single test, particularly heart rate variation during deep breathing, to make diagnosis of autonomic neuropathy, and 2) stated that the previous classification of tests into parasympathetic and sympathetic (Table 1), although clinically useful, should not be considered physiologically precise because of the complexity of the autonomic pathways [16].

Blood flow adjustments are achieved by local vascular control mechanisms (mechanical forces and chemical stimuli) but require to be coordinated by a remote central neural control [17]. Autonomic motor control is effected by long parasympathetic preganglionic fibres and short sympathetic preganglionic fibres that originate within the central nervous system. The former synapse on short postganglionic fibres arising from ganglia located close to the effector targets, the latter synapse on long postganglionic fibres arising from the paravertebral chain ganglia or collateral ganglia. Parasympathetic neurons limit their influence mainly to the control of cardiac function, whereas sympathetic neurons innervate the heart, blood ves-

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sels, adrenal glands, and kidneys [17]. The arterial baroreflex modulates beat-to-beat blood pressure oscillations: afferent baroreceptor discharge from the carotid sinus and aortic arch is relayed to the nucleus tractus solitarius in the dorsomedial region of the medulla. As a result, changes in the efferent sympathetic and parasympathetic outflow to the heart and blood vessels adjust cardiac output and vascular resistance to return blood pressure to baseline. Similarly, the cardiopulmonary baroreceptors minimise changes in arterial blood pressure in response to changes in blood volume.

Cardiovascular tests in diagnosing diabetic autonomic neuropathy

Parasympathetic	Sympathetic
Resting heart rate	Resting heart rate
Heart rate response to deep breathing	Blood pressure response to standing up
Heart rate response to standing up	Blood pressure response to sustained handgrip
Valsalva manoeuvre	Blood pressure response to cold
Spectral analysis of heart rate variation (high frequency component)	Spectral analysis of heart rate variation (very low frequency component)

Table 1. Classification of cardiovascular tests for the diagnosis of diabetic neuropathy.

The complexity of the autonomic pathways is exemplified by the following quotations. The act of breathing modulates autonomic neural outflow from the brainstem, but the mechanisms underlying the respiratory sinus arrhythmia are still unclear [18]: only fluctuations in efferent cardiac vagal activity or combined vagal/sympathetic heart rate modulation? Moreover, is respiratory sinus arrhythmia driven by respiratory synchronous oscillations in blood pressure via the arterial baroreflex or both respiratory sinus arrhythmia and blood pressure are independently related to respiration via nonbaroreflex mechanisms?

Small negative changes of central volume reduce cardiac output without significant alterations of arterial blood pressure: 1) short-term cardiovascular control through respiratory sinus arrhythmia and baroreflex feedback are optimised at mild hypervolemia; 2) both the time and frequency domain data support the presence of a Bainbridge reflex (i.e. hypervolemia-induced tachycardia) at moderately elevated levels of central volume, to reduce cardiac preload under volume loading conditions. Finally, mild to moderate levels of hypovolemia do not cause significant reductions in arterial pressure, explained in part by a mild tachycardia and increased feed forward gain from heart rate to arterial pressure [19].

Physical activity produces intensity-dependent increases in arterial blood pressure that are mediated by central signals arising from higher brain centres and by peripheral feedback from skeletal muscle (exercise pressor reflex) with further modulation provided by the arterial baroreflex. The sensory component of the exercise pressor reflex is comprised of myelinated group III and unmyelinated group IV skeletal muscle afferents that respond to both

mechanical (mechanoreflex) and metabolic (metaboreflex) stimuli. However, the receptors activating muscle afferent fibres as well as the factors contributing to a decrease in reflex activity in oxidative muscle are still not precisely characterised [20].

3. Current standards of medical care in diabetes

Up to 70% of people with diabetes experience nervous system damage in their lifetime. Diabetic neuropathy compromises quality of life being a major contributing cause of lower limb amputation (http://www.diabetes.org/diabetes-basics/diabetes-statistics/) [11, 21-22].

Diabetic neuropathy is considered to be a multifactorial process whose contributing factors, yet not completely understood, are metabolic, vascular, autoimmune, oxidative and nitrosative stress, and neuro-hormonal growth factor deficiency [20-21].

The classification of diabetic neuropathy that was originally proposed by Thomas [23] has been recently adapted by Vinik [22, 24] (Table 2).

Clinical Presentation and Diagnosis		**Differential Diagnosis**
Focal neuropathies	Mononeuritis	
	Entrapment syndromes	
Diffuse neuropathies	Proximal motor (amyothrophy)	Co-existing chronic inflammatory demyelinating polyneuropathy
		Monoclonal gammopathy of undetermined significance
		Circulating GM1 antibodies and antibodies to neuronal cells
		Inflammatory vasculitis
Generalised symmetric polyneuropathies	Acute sensory	
	Chronic sensorimotor	
	- Large fibre	
	- Small fibre	
	Autonomic	

Table 2. Classification of diabetic neuropathy proposed by Vinik et al. [22].

Diabetic autonomic neuropathy is the least recognised and understood diabetic complication: clinical symptoms generally do not appear until long after the onset of diabetes, but subclinical autonomic dysfunction can occur within one year of diagnosis in type 2 diabetes and within two years of diagnosis in type 1 diabetes [24]. Diabetic autonomic neuropathy can involve the entire autonomic nervous system leading to a wide range of symptoms

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[21-22, 24]. Cardiac autonomic neuropathy can manifest as tachycardia (heart rate > 100 bpm), decreased exercise tolerance, orthostatic hypotension (a fall in systolic blood pressure > 20 mmHg upon standing without appropriate heart rate response), cardiac denervation syndrome with silent myocardial infarction, paradoxical supine or nocturnal hypertension, intra- and peri-operative cardiovascular instability, left ventricular diastolic dysfunction.

Peripheral diabetic autonomic neuropathy can manifest as decreased thermoregulation, decreased sweating, altered blood flow, impaired vasomotion, and oedema. From the metabolic point of view, there may be hypoglycaemia unawareness with decreased counter-regulatory catecholamine responses as well as hypoglycaemia unresponsiveness with reduction in glucagon and epinephrine secretion in response to hypoglycaemia. Gastrointestinal diabetic autonomic neuropathy can manifest as oesophageal dysmotility, gastro-paresis diabeticorum, diarrhoea or constipation, faecal incontinence. Genitourinary symptoms include erectile dysfunction, retrograde ejaculation, neurogenic bladder and cystopathy, female sexual dysfunction. Sudomotor diabetic autonomic neuropathy may manifest as anhidrosis, hyperhidrosis, heat intolerance, gustatory sweating, and dry skin. Pupillomotor function impairment and pseudo-Argyll-Robertson pupil have also been described.

The American Diabetes Association [11] recommends that:

1. a comprehensive diabetes evaluation should include a history of diabetes related microvascular complications: retinopathy, nephropathy, and neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastro-paresis);

2. a comprehensive diabetes evaluation should include presence/absence of patellar and Achilles reflexes as well as determination of proprioception, vibration, and monofilament sensation;

3. all patients should be screened for distal symmetric polyneuropathy at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter, using simple clinical tests. Electrophysiological testing is rarely needed, except in situations where clinical features are atypical;

4. screening for signs or symptoms of cardiac autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Special testing is rarely needed;

5. medications for relief of specific symptoms related to distal symmetric polyneuropathy or diabetic autonomic neuropathy are recommended as they improve the quality of life of the patient;

6. foot examination should include testing for loss of protective sensation, i.e. 10-g monofilament plus testing for any one of the following: vibration using 128-Hz tuning fork, pinprick sensation, ankle reflex, vibration sensation threshold.

4. Diagnostic tests of cardiovascular autonomic neuropathy

The presence of cardiac autonomic neuropathy may be indicated by resting tachycardia (heart rate > 100 bpm) that is due to an imbalance of the sympathetic/parasympathetic tone. Because neuropathy is seen first in the longest fibres, early in the natural history of diabetes there is impairment of parasympathetic function, followed later by sympathetic denervation that progresses from the apex of the ventricles towards the base of the heart and increases the propensity to dysrhythmias [10, 25]. Moreover, cardiac autonomic neuropathy reduces exercise tolerance by impairing heart rate, blood pressure, and cardiac output responses to exercise. Indeed, subjects with diabetes and suspected cardiac autonomic neuropathy should perform a cardiac stress test before undertaking an exercise program. The assumption of upright posture results in gravity-mediated displacement of blood into the veins of the pelvis and lower limbs, reducing venous return to the heart. In healthy people, this leads to a reflex increase in sympathetic nervous system activity, increasing peripheral vascular resistance and heart rate such that arterial pressure is maintained [26]. In diabetic people, sympathetic vasomotor denervation may lead to orthostatic hypotension that is aggravated when combined with orthostatic bradycardia [25]. Moreover, a large proportion of diabetic patients receive multi-drug therapy that potentially contributes to the fall in blood pressure on assuming the upright posture [24]. Table 3 provides a list of drugs, which may interfere with autonomic function tests.

In diabetes, analysis of 24-h ambulatory blood pressure monitoring (ABPM) showed altered characteristics of blood pressure rhythm [1]. In particular, diabetic patients had a high prevalence of increased night time blood pressure or non-dipping profile [27-32] that could reflect a) the presence of autonomic neuropathy [32-33] resulting in sympathetic predominance during sleep, but also b) the circadian misalignment due to obstructive sleep apnoea in obese subjects with type 2 diabetes [34]. Chronobiologically interpreted ambulatory blood pressure monitoring uncovered that midline estimate statistic of rhythm (MESOR) and mean of systolic blood pressure and diastolic blood pressure were higher in diabetic patients than in healthy subjects [35-42]. Figures 1-2 show the relationship between heart rate response to deep breathing and the circadian blood pressure rhythm parameters midline estimate statistic of rhythm and acrophase.

Abnormalities in respiration-related heart rate variability can be evaluated in a number of different ways, from the simple bedside tests of short-term heart rate differences previously listed to the spectral analysis of heart rate variability, taking into account that normative values of heart rate variability indices are affected mainly by age [10]:

1. Heart rate response to deep breathing, which measures sinus arrhythmia during quiet respiration and primarily reflects parasympathetic function.
2. Heart rate response to standing up induces reflex tachycardia followed by bradycardia and is both vagal and baroreflex mediated.
3. Valsalva manoeuvre evaluates cardio-vagal function in response to a standardized increase in intrathoracic pressure, primarily parasympathetic mediated.
4. Time domain measures of heart rate variability are summarised in Table 4[43]. In a continuous ECG record, each QRS complex is detected, and the normal-to-normal (NN) in-

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tervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarisations) or the instantaneous heart rate is determined.

5. Frequency domain measures of heart rate variability evaluate how power (variance) distributes as a function of frequency using power spectral density (PSD) analysis (Table 5) [43]. Vagal activity is thought to contribute mainly to the high frequency (HF, 0.15-0.4 Hz) component, which is related to respiratory activity, while the sympathetic system is thought to modulate the lower-frequency heart rate variability components. The very low frequency (VLF, <0.04 Hz) components are related to fluctuations in vasomotor tone associated with thermoregulation, and the low frequency (LF, 0.04-0.15 Hz) components are considered to be associated with the baroreceptor reflex [10, 44].

6. QT interval prolongation in the ECG has been used to diagnose cardiac autonomic neuropathy with reasonable sensitivity, specificity and positive predictive value [12, 45] although there is no universal agreement on 1) QT measurement and correction techniques, and 2) normality range [46]. Age dependency of cardiovascular autonomic responses is exemplified in Figure 3. Figures 4-6 show the heart rate variability with deep breathing, lying to standing, and Valsalva manoeuvre, respectively, in patients with type 1 diabetes and control subjects.

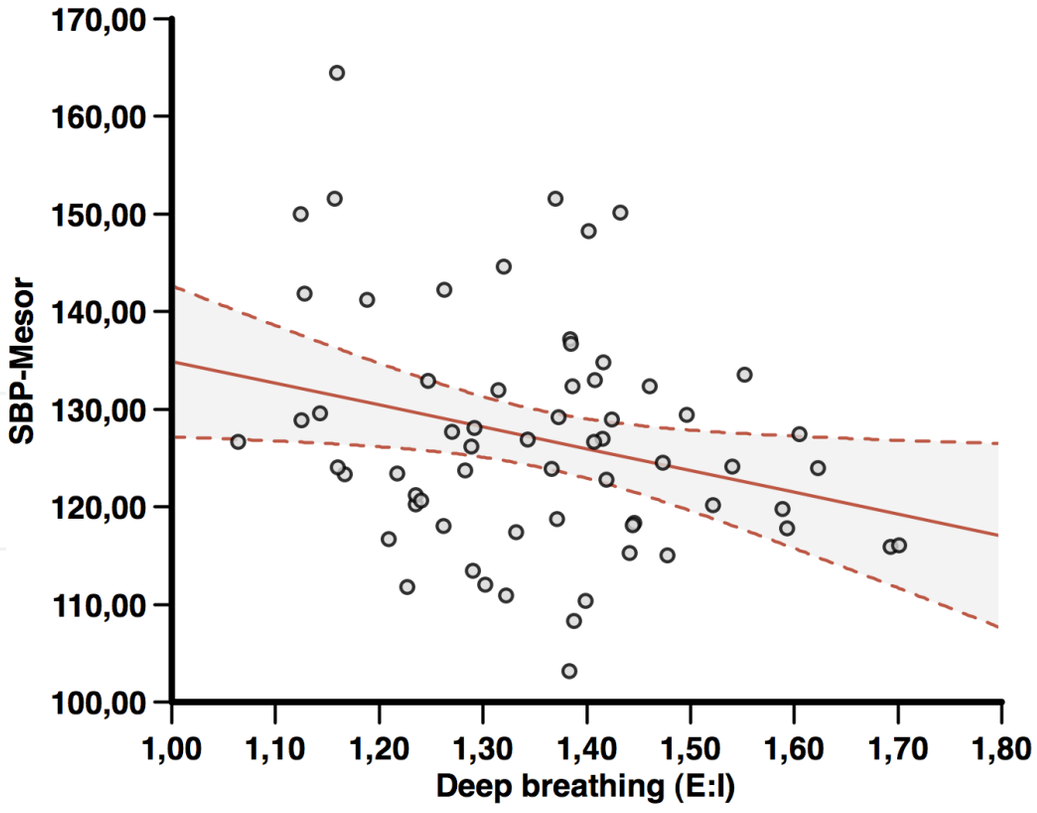


Figure 1. The linear relationship between age and heart rate response to deep breathing expressed as expiratory/inspiratory (E:I) ratio and systolic blood pressure (SBP)midline estimate statistic of rhythm (MESOR) in 20 patients with type 1 diabetes and 25 age-matched control subjects.

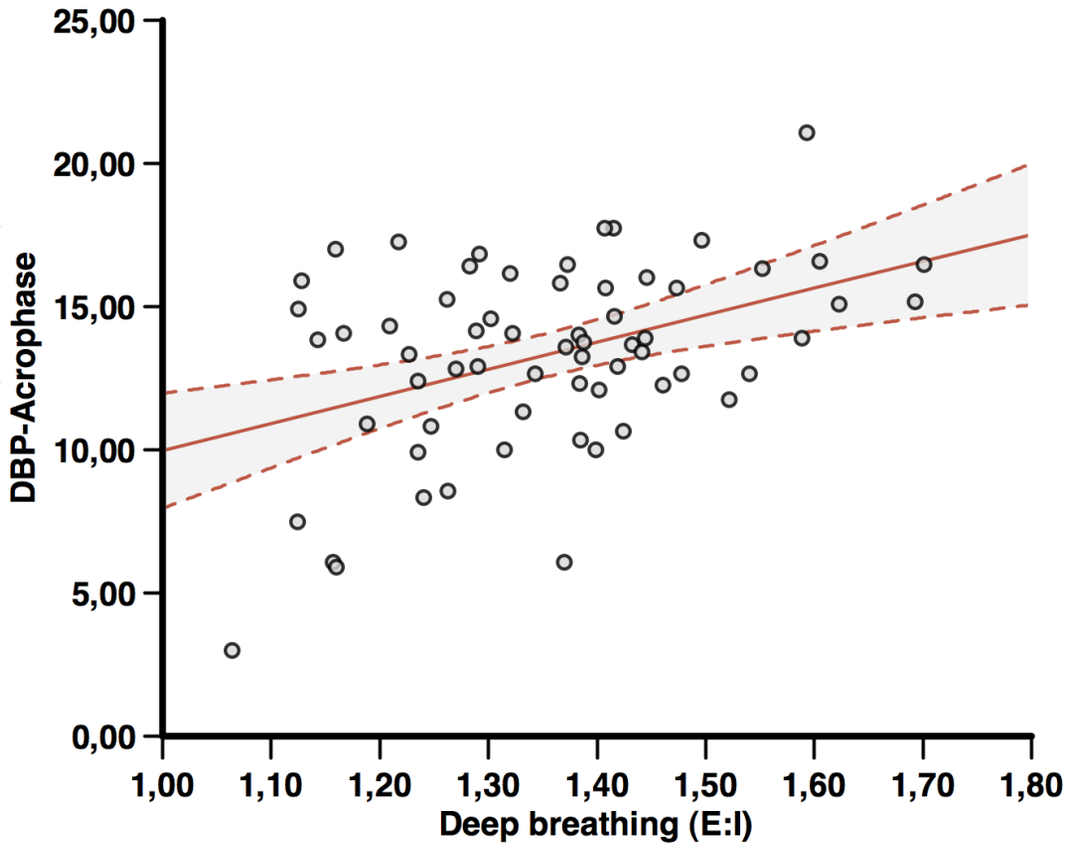


Figure 2. The linear relationship between age and heart rate response to deep breathing expressed as expiratory/inspiratory (E:I) ratio and diastolic blood pressure (DBP) acrophase in the same subjects as in Figure 1.

Drug class	Medication	Effect on heart rate	Effect on blood pressure
Anti-inflammatory drugs	acetylsalicylic acid	x	
Angiotensin converting enzyme inhibitors	captopril	x	
	enalaprin	x	
	lisinopril	x	
	quinalapril	x	
	trandolapril	x	
Angiotensin II type 1 receptor blockers	eprosartan	x	
	losartan	x	
α-adrenoceptor antagonists	doxazosin		x
β-blockers	atenolol	x	
	bisoprolol	x	
	metoprolol	x	
	nebivolol	x	

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Drug class	Medication	Effect on heart rate	Effect on blood pressure
Calcium channel blockers	diltiazem	x	
	nifedipine	x	
	verapamil	x	
Cardiac glycosides	digoxin	x	
Diuretics	furosemine, thiazides		x
	spironolactone	x	
Psychoactive drugs		x	
Benzodiazepines	alprazolam	x	x
	diazepam	x	
	lorazepam		
	midazolam	x	
Tricyclic antidepressants	amitriptyline	x	x
	carbamazepine	x	
	desipramine	x	x
	doxepin	x	x
	fluvoxamine	x	x
	imipramine	x	x
	nortriptyline	x	x

Table 3. Drug classes which may interfere with autonomic function tests and some examples of medications [12].

Variable	Units	Description
STATISTICAL MEASURES		
SDNN	ms	Standard deviation (SD) of all normal-to-normal (NN) intervals
SDANN	ms	Standard deviation (SD) of the averages of normal-to-normal (NN) intervals in all 5-minute segments of the entire recording
RMSSD	ms	Root-mean square of the differences of successive normal-to-normal (NN) intervals
SDNN index	ms	Mean of the standard deviations (SDs) of all normal-to-normal (NN) intervals for all 5-minute segments of the entire recording
SDSD	ms	SD of differences between adjacent normal-to-normal (NN) intervals
NN50 count	ms	Number of pairs of adjacent normal-to-normal (NN) intervals differing by more than 50 ms in the entire recording (counting all such NN intervals pairs or only pairs in which the first or the second interval is longer)
pNN50	%	NN50 count divided by the total number of all normal-to-normal (NN) intervals

Variable	Units	Description
GEOMETRIC MEASURES		
Heart rate variability triangular index		Total number of all normal-to-normal intervals divided by the height of the histogram of all normal-to-normal (NN) intervals measured on a discrete scale with bins of 7.8125 ms (1/128 seconds)
Triangular interpolation (TINN)	ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all normal-to-normal (NN) intervals
Differential index	ms	Difference between the widths of the histogram of differences between adjacent normal-to-normal intervals measured at selected heights
Logarithmic index	ms	Coefficient ϕ of the negative exponential curve $k \cdot e^{-\phi t}$, which is the best approximation of the histogram of absolute differences between adjacent NN intervals

Table 4. Time domain measures of heart rate variability described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. The four measures marked in grey were recommended for time domain heart rate variability assessment [43].

Variable	Units	Description
ANALYSIS OF SHORT-TERM RECORDINGS		
5-min total power	ms^2	The variance of normal-to-normal (NN) intervals over the temporal segment
VLF	ms^2	Power in very low frequency (VLF) range
LF	ms^2	Power in low frequency (LF) range
LF norm	nu	LF power in normalized units LF/(total power-VLF)x100
HF	ms^2	Power in high frequency (HF) range
HF norm	nu	HF power in normalized units HF/(total power-VLF)x100
LF/HF	ms^2	Ratio LF [ms^2]/HF[ms^2]
ANALYSIS OF ENTIRE 24 HOURS		
Total power	ms^2	Variance of all normal-to-normal (NN) intervals
ULF	ms^2	Power in the ultra low frequency (ULF) range
VLF	ms^2	Power in the VLF range
LF	ms^2	Power in the LF range
HF	ms^2	Power in the HF range
α		Slope of the linear interpolation of the spectrum in a log-log scale

Table 5. Frequency domain measures of heart rate variability described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [43].

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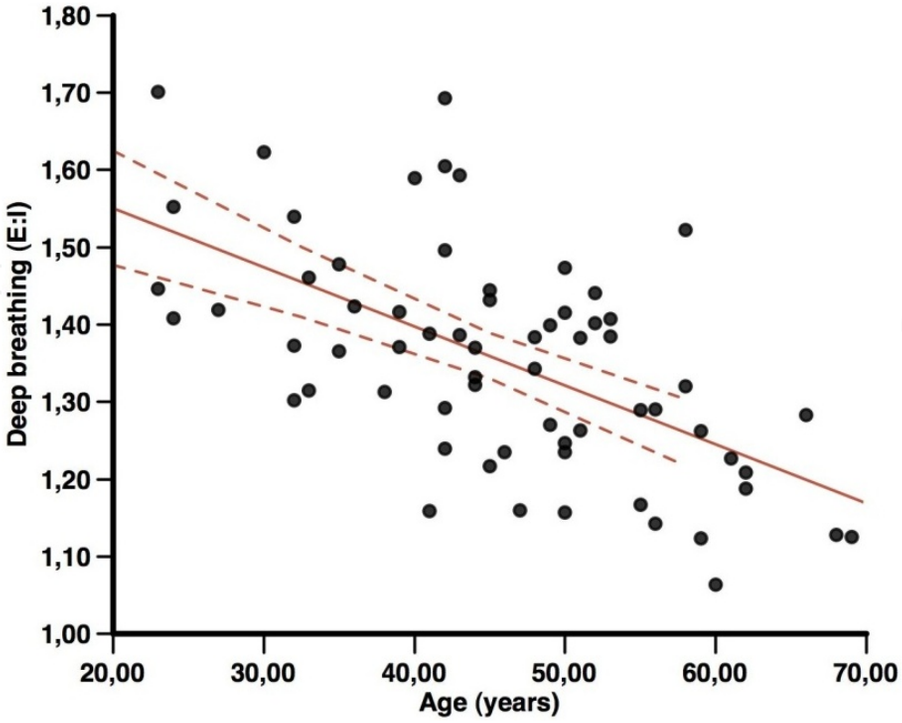


Figure 3. The linear relationship between age and heart rate response to deep breathing expressed as expiratory/inspiratory (E:I) ratio.

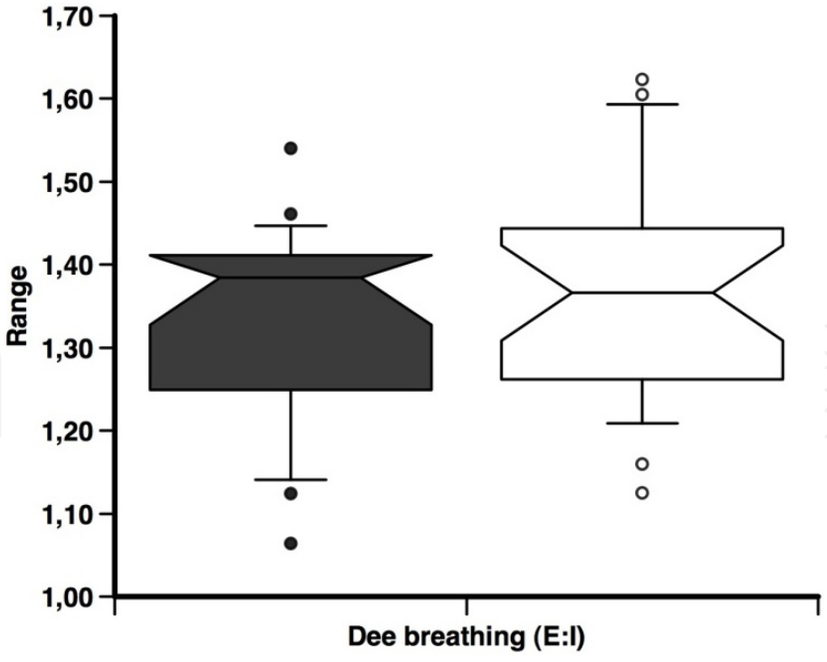


Figure 4. Two-way box percentile plots of heart rate response to deep breathing expressed as expiratory/inspiratory (E:I) ratio in 20 patients with type 1 diabetes (black box) and 25 age-matched control subjects (white box).

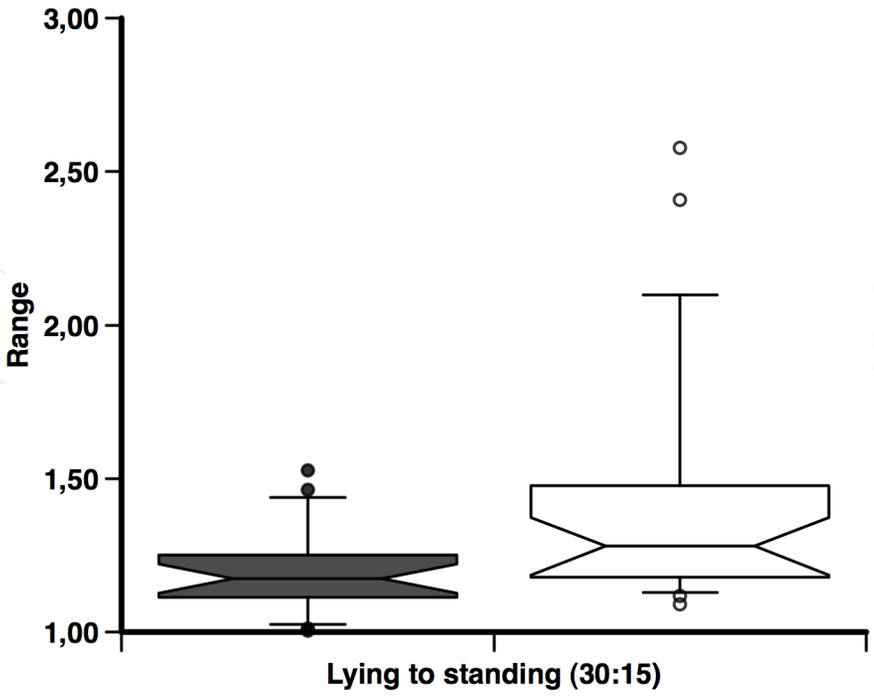


Figure 5. Two-way box percentile plots of heart rate response to standing upcalculated as the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat in 20 patients with type 1 diabetes (black box) and 25 age-matched control subjects (white box).

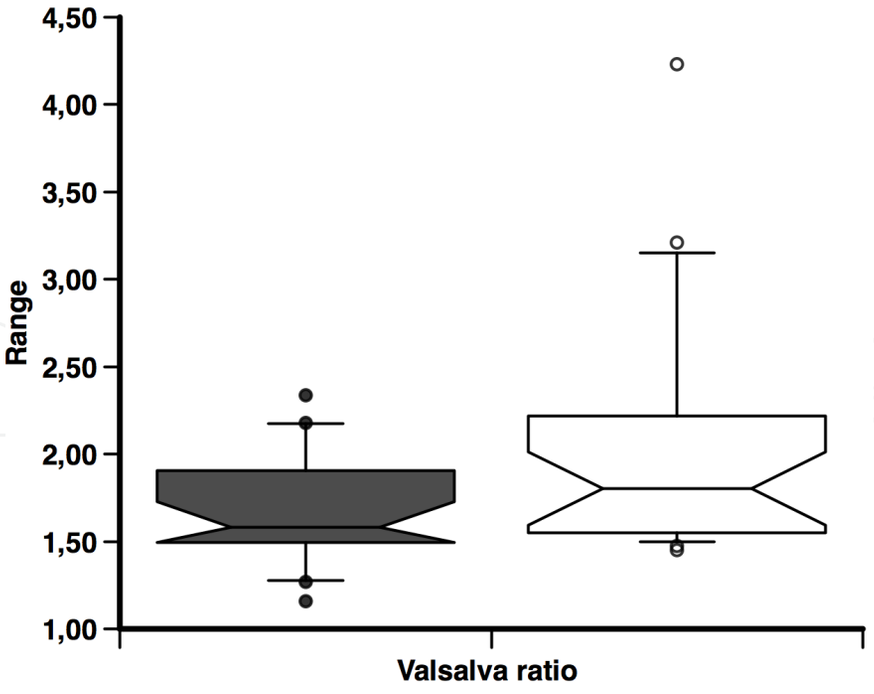


Figure 6. A two-way box percentile comparison plot of heart rate response to Valsalva manoeuvre expressed as the ratio of the longest R-R interval shortly after the manoeuvre to the shortest R-R interval during the manoeuvre in 20 patients with type 1 diabetes (black box) and 25 age-matched control subjects (white box)

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5. What kind of relationship is between cardiac autonomic neuropathy, cardiovascular mortality, and albuminuria

Chronic misalignment between the endogenous circadian timing system and the behavioural cycles may increase the risk of diabetes, obesity, cardiovascular disease and cancer [5] as well as the presence of diseases may affect circadian rhythms. While cardiovascular events generally occur in the early morning hours [47-48], abnormalities in the circadian pattern of cardiovascular events in the diabetic population has been attributed to differences in the duration of diabetes and supposedly the variable extent of underlying diabetic autonomic neuropathy [6-9, 49]. In 1989 Hjalmarson et al. observed two peaks of symptom onset of acute myocardial infarction for patients with diabetes: a peak, 28%, was discernible between 6:01 AM and 12:00 noon and a secondary peak, 25%, between 6:01 PM and midnight. In patients over 70 years of age, smokers, diabetics, those receiving β-blockers, and women, the morning and the evening peaks were of the same size [6]. Moreover, angina has long been considered an unreliable index of myocardial infarction in diabetic patients with coronary artery disease [50-51]. The prolonged anginal perception threshold in diabetic patients was suggested to be partly the result of damage to the sensory innervation of the heart [52]. In the same 1990, to investigate the incidence and mechanism of painless myocardial ischemia on exercise testing in diabetic patients, Murray et al. performed two studies: 1) retrospectively, all exercise tests carried out in the hospital during the past 5 years were reviewed for silent ischemia; 2) prospectively, diabetic patients with known or suspected coronary artery disease underwent autonomic function testing and a second exercise test. They concluded that silent myocardial ischemia on exercise testing was common among patients with diabetes mellitus and was associated with severe autonomic dysfunction [53].

Ambulatory electrocardiographic monitoring in 60 patients with diabetes and coronary artery disease, 25 of whom underwent also autonomic nervous system testing, evidenced that 1) silent ischemia was highly prevalent since 91% of all ischemic episodes were silent, and 2) time of onset of ischemia followed a circadian distribution with a peak incidence in the morning hours, except in patients with moderate to severe autonomic nervous system dysfunction who did not demonstrate such a peak [7]. Using harmonic regression model to evaluate the circadian variation of myocardial infarction symptom onset in patients (n = 3882) who were enrolled in the Onset Study, it was then confirmed that patients with type 1 diabetes and those with type 2 diabetes for 5 or more years had an attenuation of the morning peak in acute myocardial infarction [9]. Authors concluded that inconsistency in observation of such an effect in patients with diabetes in the past might well have been due to differences in the duration of diabetes and thus the variable extent of underlying autonomic dysfunction [9]. To exemplify inconsistencies among clinical observations, the time of onset of ischemic pain in patients enrolled in the Thrombolysis in Myocardial Ischemia (TIMI) III Registry Prospective Study and in the TIMI IIIB trial showed a circadian variation with a peak in the morning hours between 6 AM and 12 noon. This circadian variation was observed both in patients with unstable angina and in those with evolving non-Q-wave acute myocardial infarction and in all subgroups tested, diabetics included [8]. On the contrary, Li

et al. showed there was no a significant morning peak of incidence of acute myocardial infarction in patients with diabetes but was obvious in control subjects; however, disappear of morning peak was not associated with duration of diabetes [49].

Mechanisms through which cardiovascular circadian rhythms may be altered in diabetes are under current investigation. The tight crosstalk between components of circadian and metabolic cycles in mammals suggests that changes in nutrient-dependent signalling pathways such as in metabolic disorders may transmit cues that affect cardiovascular rhythmicity through transcriptional and non-transcriptional mechanisms [1, 54]. Moreover, a functional antagonism between melatonin and insulin has been supposed on the basis of animal and clinical studies. Melatonin inhibits insulin release through both the pertussis-toxin-sensitive membrane receptors MT_1 and MT_2 and the second messengers 3',5'-cyclic adenosine monophosphate, 3',5'-cyclic guanosine monophosphate and inositol 1,4,5-trisphosphate. In turn, increased insulin levels exert an inhibitory effect on the pineal gland and melatonin[55].

The relationship between cardiovascular prognosis and cardiac autonomic neuropathy has been investigated for a long time since the rate of deaths within a mean follow-up of 5.8 years had been found five times higher in the diabetic patients with cardiac autonomic neuropathy than in the diabetic patients free from cardiac autonomic neuropathy; most of these deaths were from cardiac causes [56]. The reasons why cardiac autonomic neuropathy affects quality and length of life are not well established, but cardiac autonomic neuropathy has been found to be associated with exercise intolerance, silent myocardial ischemia, prolongation of QT interval that may cause arrhythmias, decreased myocardial perfusion reserve, left ventricular hypertrophy and diastolic dysfunction [24, 57-59]. The variability of mortality rates revealed in the studies could be related to the study population, the modality for assessing cardiac autonomic neuropathy, the criteria used to define the presence of cardiac autonomic neuropathy, and the length of follow-up [60]. In 2003, Maser et al. examined by meta-analysis this relationship: 15 studies published from 1966 to 2001 could be included whose follow-up ranged from 0.5 to 16 years. The study-specific relative risks for individuals with cardiac autonomic neuropathy ranged from 0.91 to 9.20 with a pooled relative risk for mortality of 3.45 for studies that used two or more measures to define cardiac autonomic neuropathy, and of 1.20 for those studies defining cardiac autonomic neuropathy with one measure of autonomic function [60].

Our Table 6 summarises the main studies of cardiac autonomic neuropathy and mortality/morbidity in patients with diabetes mellitus restarting from the year 2001 onwards. In that year, a 3-7 year (mean 4.5) follow up was obtained in 107 diabetic patients with no history of myocardial infarction or angina, a normal ECG, and two or more additional risk factors, who underwent ECG stress test, a thallium-201 myocardial scintigraphy with dipyridamole, and 48-h ECG monitoring to assess silent myocardial ischemia. In addition, cardiac autonomic neuropathy was searched for by standardized tests evaluating heart rate variations [61]. The study confirmed that 1) the prevalence of type 1 silent myocardial ischemia was high (about 30%) and significant coronary stenoses were found in approximately one-third of those patients with silent myocardial ischemia; 2) there was only a trend of higher risk of major cardiac events in the diabetic patients with silent myocardial ischemia than in the dia-

betic patients without silent myocardial ischemia; 3) cardiac autonomic neuropathy was significantly associated with an increased risk of major cardiac events. According to the Kaplan-Meier method, the increase in the risk of major cardiac events linked to cardiac autonomic neuropathy was significant after adjusting for silent myocardial ischemia, but the highest rate was found in patients who had silent myocardial ischemia and cardiac autonomic neuropathy. Authors concluded that the poor cardiovascular prognosis related to cardiac autonomic neuropathy in previous studies was probably associated with undetected silent myocardial ischemia in many patients [61].

Ref.	Follow up (years)	Sample size	Tests of CAN	Definition of CAN	Results	Comments
61	4.5	107 patients (of whom 17 with T1DM) and normal ECG	HR variability during deep breathing, Valsalva and lying to standing tests	The results were compared with those from an age-matched control series	CAN was a better predictor of major cardiac events (odds ratio 4.30, 1.07-17.31) than silent myocardial ischemia (evaluated by ECG stress test, myocardial scintigraphy with dipyridamole, and 48-h ECG monitoring)	Limited number of asymptomatic patients with predominantly T2DM
62	3.5	532 patients with DM (483 with T2DM)	HR variability during deep breathing; SBP decrease during standing	Not stated	Increased all-cause mortality associated with the lowest quintile of HR variability (hazard ratio 1.49, 1.01-2.19)	The cohort was predominantly male; no direct adjustment for use of cardio-active medications
63	2.5	715 survivors of AMI (117 with DM)	Spectral analysis of HR variability (24-h Holter ECG)	According to cutpoints previously established	Decreased HR variability remains predictive also in diabetic patients (hazard ratio for SDNN < 50 ms 2.56, 1.26-5.19)	Moderate power due to the small number of death in diabetic patients; DM was not classified
65	5.3	872 of 950 patients with T2DM underwent baseline neuropathy assessment	HR variability during deep breathing	According to age-related range values	Borderline or abnormal expiratory/ inspiratory ratio at baseline was associated with the occurrence of stroke (hazard ratio 2.3, 1.17-4.70)	Only one autonomic test instead of a battery
66	3.8	146 patients with T2DM with suspected coronary artery disease	Deep breathing, Valsalva manoeuvre, lying to standing, postural systolic blood pressure change, handgrip test	Three or more of the tests were abnormal	Although perfusion defects remained a strong predictor of cardiac risk, CAN predicted the occurrence of death and cardiac events independent of perfusion defects	Retrospective design; limited number of subjects; symptomatic diabetic patients
67	15	311 patients with T2DM and 151 patients with T1DM	Quantitative sudomotor axon reflex test, HR response to deep breathing and to the Valsalva manoeuvre, BP responses during tilt and the Valsalva manoeuvre	According to the 10 point score composite autonomic severity scale (CASS)	Sudden cardiac death relates more directly to coronary ischemia, cardiac arrhythmia, or nephropathy than it does to diabetic autonomic neuropathy	Northern European sample; unavailable serial data obtained before and during sudden cardiac death; not all applicable risk factors could be modelled

Ref.	Follow up (years)	Sample size	Tests of CAN	Definition of CAN	Results	Comments
68	10.1	388 patients with T1DM of whom 197 with diabetic nephropathy	HR variability during deep breathing	HR variability < 10 bpm	CAN predicted cardiovascular mortality and morbidity in patients with diabetic nephropathy (hazard ratio 6.4, 1.5-26.3), but not all-cause mortality	CAN determined by only one test, but well characterised population
69	9.2	104 patients with T2DM of whom 51 with diabetic nephropathy	HR variability during deep breathing	Not stated	Non-dipping phenomenon predicted all-cause mortality (1% increase in dipping was associated with a lower risk 0.97, 0.94-0.998); HR variability was confirmed to be a predictor also in T2DM (1 bpm increase 0.92, 0.87-0.98)	Low patient number, but well characterised population
70	9.0	1560 non diabetic and 160 diabetic subjects (MONIKA/ KORA Study)	Time domain measures, corrected QT interval, and QT dispersion were obtained from a 12-lead resting ECG	Not stated	The relative risk of mortality in subjects with corrected QT > 440 ms increased by twofold and threefold in the non diabetic and diabetic group, respectively; prolonged QT interval predicted cardiovascular mortality only in the non diabetic group (risk ratio 4.47, 2.44-9.22)	Short period of ECG recording (20s) without control for respiration
71	7.1	1458 patients with T2DM	HR variability during deep breathing, Valsalva manoeuvre and postural change	According to age-related reference values (total maximum CAN score of 3)	Hazard ratio for acute stroke events in patients with abnormal CAN scores was 2.7 compared with patients with normal scores; a CAN score of 3 was significantly associated with a new ischaemic stroke event in patients with diabetes	Lack reference values for CAN tests specific for Korean people; the effect of glycaemic control status on the development of stroke has not been assessed; limited number of events
71	13.6	490 individuals from a population-based cohort (Hoorn Study) of whom 135 with T2DM	HR variability during deep breathing and standing up, 5 tests of spectral analyses of HR variability, and one baroreflex sensitivity measurement	Cardiovascular autonomic dysfunction total score	Both microalbuminuria and CAN are independently associated with cardiovascular mortality, and the excess mortality attributable to microalbuminuria cannot be explained by CAN	Moderate level of reproducibility of autonomic function parameters; CAN total score evaluated at baseline only; spectral analyses performed during 3 min; albumin/creatinine ratio measured in one urine sample only
72	15.5	178 diabetic patients of whom 110 with T2DM	HR variability during deep breathing, Valsalva manoeuvre, and lying to standing, postural systolic blood pressure change, diastolic blood pressure response to handgrip test	Two or more abnormal tests	The relative risk of all-cause mortality associated with CAN was 2.85, 1.75-4.65; Valsalva ratio and handgrip had an independent predictive value	Sources of lower sample representativeness: 1) 26% of invited subjects refused to participate (older than responders), 2) patients' ability to cooperate to the function tests
73	15.5	165 diabetic patients of	Time and frequency domain parameters	Not stated	The low frequency band in the frequency domain was the most powerful predictor of all-	Sources of lower sample representativeness: 1) only patients who completed all

Ref.	Follow up (years)	Sample size	Tests of CAN	Definition of CAN	Results	Comments
		whom 97 with T2DM	based on 24-hour ECG recordings		cause mortality (estimated relative risk of death with an increase by 1 standard deviation 0.65)	5 function tests and had an acceptable 24-hour ECG recording could be analysed, 2) ECG was recorded during normal daily activity
74	15.5	136 diabetic patients of whom 77 with T2DM	Five autonomic function tests together with time and frequency domain parameters based on 24-hour ECG recordings	Not stated	Three simple autonomic function tests (Valsalva, 30:15, and handgrip) were superior to HR variability in predicting all-cause mortality in the diabetic population	Sources of lower sample representativeness: 1) percentage of invited subjects who refused to participate (older than responders), 2) patients' ability to cooperate to the function tests and to have an acceptable 24-hour ECG recording

Table 6. Studies that evaluated mortality and morbidity in patients with diabetes mellitus and cardiovascular autonomic neuropathy (CAN) from 2001 onward. AMI, acute myocardial infarction; DM, diabetes mellitus; SBP, systolic blood pressure; SDNN, standard deviation of normal RR intervals; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

Wheeler et al. evaluated short-term all-cause mortality in an elderly cohort of predominantly male veteran patients with diabetes [62]. Among the 532 patients with RR variability measures (evaluated by heart rate response to timed deep breathing), subjects who died (n = 120) had significantly lower heart rat variability than survivors. The lowest quintile of heart rate variability with deep breathing was found to be associated with a 50% increase in mortality. After adjusting for age, smoking status, creatinine, pack-year of cigarettes smoked, diabetes duration, race, history of ischemic heart disease, and hypertension, the hazard ratio was 1.49 with a 95% confidence interval 1.01-2.19 [62].

Whang et al. used data from the Multicenter Post Infarction Program (MPIP, a longitudinal observational study of 715 survivors of acute myocardial infarction, including 117 diabetic patients, enrolled from 1979 to 1980) to test two hypotheses: 1) RR interval variability was lower in diabetic patients, and 2) low RR interval variability was less predictive of mortality in diabetic patients [63]. Six frequency-domain measurements and one time-domain measurement of RR interval variability were evaluated on the basis of 24-hour Holter electrocardiographic recordings. Reduced RR interval variability was significantly more frequent in diabetic patients than in non-diabetic patients for all measurements except high frequency power. Moreover, in diabetic patients, the association between reduced RR interval variability and all-cause mortality was at least as strong as it was in non-diabetic patients for all measurements except high frequency power [63].

Since the risk of fatal and non-fatal strokes were increased in diabetic patients compared with non-diabetic patients over a 7-year follow up period [64], Cohen et al. evaluated the relationship between a number cardiovascular risk factors in normotensive and hypertensive type 2 diabetic patients (enrolled in the Appropriate Blood Pressure Control in Diabetes trial) on the incidence of stroke [65]. Cardiovascular risk factors included also autonomic function testing,

and automated electrocardiographic measure of heart rate response to deep breathing. Expiratory/inspiratory (E:I) ratio was categorised as normal (53.6%), borderline (9.5%), or abnormal (36.9%) based on age-related range values. The presence of a borderline or abnormal expiratory/inspiratory ratio at baseline was significantly associated with the occurrence of stroke in the follow up period (hazard ratio 2.3, 1.17-4.70). Thus, diabetic autonomic neuropathy was a significant independent risk factor also for the occurrence of stroke [65].

In order to investigate the prognostic value of cardiac autonomic neuropathy in relation to myocardial perfusion defects, Lee et al. evaluated 146 consecutive patients with type 2 diabetes mellitus who underwent thallium-201 single photon emission computed tomography (SPECT) for suspected coronary artery disease and who tested for autonomic nerve function within three months of the single photon emission computed tomography study [66]. Cardiac autonomic function tests included deep breathing, Valsalva manoeuvre, lying to standing, postural systolic blood pressure change, and handgrip test; cardiac autonomic neuropathy was defined by the presence of ≥ 3 abnormal tests. Patients were followed up for 46±24 months to record deaths and major cardiac events. Significant predictors of death were perfusion defects, cardiac autonomic neuropathy, and older age; significant predictors of cardiac events were perfusion defects, cardiac autonomic neuropathy, hypertension, and longer history of diabetes [66].

Suarez et al. investigated the risk factors for sudden cardiac death in the prospective, population based, Rochester Diabetic Neuropathy Study (RDNS) cohort: 462 diabetic patients (of whom 115 with type 1 diabetes) were followed up over 15 years [67]. At baseline, patients underwent 1) neuropathy assessment by the neuropathy impairment score, neuropathy symptoms and change score, nerve conduction studies, and quantitative sensation; 2) autonomic neuropathy assessment by quantitative sudomotor axon reflex test, heart rate variability to deep breathing and to the Valsalva manoeuvre, beat to beat blood pressure responses during tilt and the Valsalva manoeuvre; 3) assessment of other putative risk factors, metabolic control, diabetic retinopathy and nephropathy; 4) recording of a 12-lead ECG every two years. The medical records, death certificates, and necropsy reports of all deaths were reviewed and 21 cases of sudden cardiac death were identified. In bivariate analysis of risk covariates, evolving and previous myocardial infarction, bundle branch block or pacing, and nephropathy stage were stronger risk covariates than were indicators of diabetic autonomic neuropathy and HDL cholesterol. In bivariate analysis and adjusting for nephropathy, diabetic autonomic neuropathy was not statistically significant factor [67].

In a prospective observational follow up study, Astrup et al. evaluated the predictive value of cardiac autonomic neuropathy for cardiovascular mortality and morbidity (primary end point), all cause mortality and progression of diabetic nephropathy (secondary end points) in 197 patients with type 1 diabetes and diabetic nephropathy and 191 patients with long standing diabetes and normoalbuminuria who were followed for 10.1 years [68]. After adjustment for cardiovascular risk factors, autonomic dysfunction was a predictor of cardiovascular mortality and morbidity in type 1 diabetic patients with diabetic nephropathy (hazard ratio 6.4, 1.5-26.3), whereas the impact of heart rate variability on all-cause mortality was not significant. Moreover, there was no correlation between abnormal heart rate varia-

bility and rate of decline of glomerular filtration rate [68]. One year later, Astrup et al. published the results of a study aimed at evaluating the prognostic significance of cardiovascular risk factors, including cardiac autonomic neuropathy and 24-hour blood pressure level and rhythm, for all-cause mortality in type 2 diabetic patients (n = 104) with and without diabetic nephropathy [69]. In a Cox regression analysis, predictors of all-cause mortality included cardiac autonomic neuropathy (1 beat/min increase 0.92, 0.87-0.98) together with age, male sex, left ventricular hypertrophy, haemoglobin A1c, daytime systolic blood pressure, glomerular filtration rate (or albuminuria, alternatively) and dipping (1% increase in dipping was associated with a lower risk 0.97, 0.94-0.998). After adjusting for traditional cardiovascular risk factors, non-dipping of night blood pressure remained a significant predictor of all-cause mortality [69].

Prolonged QT corrected (QTc > 440 ms) interval was an independent predictor of mortality over 9 years in the non-diabetic (n = 1560) and diabetic (n = 160) elderly general population of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, whereas QT dispersion did not predict mortality in non-diabetic or diabetic subjects. On the contrary, reduced heart rate variability appeared to be a more specific marker only in the diabetic elderly general population [70]. Ko et al. investigated whether cardiac autonomic neuropathy was associated with acute ischaemic stroke in 1458 patients with type 2 diabetes during 7.1 year follow up [71]. At follow-up, 131 patients (11.6%) had developed newly diagnosed acute ischaemic stroke. Baseline cardiac autonomic neuropathy score was significantly associated with the development of ischaemic stroke in patients with type 2 diabetes. Indeed, the hazard ratio for acute stroke events in patients with abnormal cardiac autonomic neuropathy scores was 2.7 compared with patients with normal scores [71]. In order to investigate whether cardiac autonomic neuropathy could explain the relationship between microalbuminuria and cardiovascular mortality, 490 individuals from a population-based cohort (Hoorn Study) were followed for a median period of 13.6 years [72]. At baseline, were evaluated glucose tolerance status, HbA1c, and albuminuria. Cardiovascular autonomic function tests included four tests that reflected heart rate or blood pressure changes due to deep breathing or standing up, five tests of spectral analyses of heart rate variability, and one baroreflex sensitivity measurement. Both microalbuminuria and cardiac autonomic neuropathy were independently associated with cardiovascular mortality. However, after adjustment for age, sex, glucose tolerance status, and other cardiovascular risk factors, microalbuminuria (relative risk 1.33, 0.83–2.13), in contrast to cardiovascular autonomic dysfunction total score (1.52, 1.11–2.09), was not independently associated with all-cause mortality. The excess of mortality attributable to microalbuminuria could not be explained by cardiac autonomic neuropathy [72].

Finally, May and Arildsen have evaluated long-term predictive power on all-cause mortality of five function tests for cardiac autonomic neuropathy as well as of heart rate variability based on 24-hour ECG recordings (both time domain analyses and frequency domain analyses were performed) in the same sample during a 15.5-year follow up period [73-75]. When considering the five function tests for cardiac autonomic neuropathy (heart rate variability during deep breathing, Valsalva manoeuvre, and lying to standing, postural systolic blood

pressure change, diastolic blood pressure response to handgrip test) it was apparent that the relative risk of all-cause mortality associated with cardiac autonomic neuropathy was 2.85, 1.75-4.65; Valsalva ratio, heart rate response to standing up (30;15 ratio), and handgrip had an independent predictive value with regard to long-term all cause mortality [73]. When considering separately time and frequency domain parameters of heart rate variability calculated on the basis of a 24-hour ECG recording, the power in the low frequency band was the only heart rate variability parameter with an independent predictive value on all-cause mortality [74]. When considering long-term predictive power of heart rate variability together with a battery of five autonomic function tests, the latter ones were superior to the former ones; particularly, Valsalva, 30:15 ratio, and handgrip were independent predictors of death [75].

6. Concluding remarks

Several studies have evaluated the predictive value of various cardiac autonomic neuropathy parameters for all cause mortality and/or cardiovascular mortality and morbidity. They almost all agree that cardiac autonomic dysfunction is associated with a high-risk excess mortality/morbidity in diabetic patients. Toward a general consensus, however, many challenges remain to be addressed by the research community. Drawbacks and limitations mainly concern the following features that deserve attention and discussion [76]:

1. Establishing appropriate study design for evaluating the particular association. Prospective cohort studies are considered less vulnerable to bias than retrospective studies, because the outcomes have not occurred when the cohort is assembled and the exposures are assessed. In cohort studies the population may be fixed or open: undoubtedly, in long-term follow ups, the prevalence of cardiac autonomic neuropathy progressively increases in a direct proportion to age, duration of diabetes, and poor glycaemic control.

2. Defining clear health outcomes that should require confirmation by masked investigators in order to guarantee their accuracy.

3. Establishing the length of follow up interval, which depends on the particular outcome under study. It has been shown that the longer the follow up, the higher the likelihood of attrition.

4. Calculating the required sample size on the basis of anticipated differences between the groups, the background rate of the outcome, and the probability of making some statistical errors.

5. Using suitable cardiovascular autonomic reflex tests to diagnose cardiac autonomic neuropathy taking into account that a) the diagnostic definition of cardiac autonomic neuropathy based on several tests (of both vagal and sympathetic functions) reduces the probability of false positives, b) the gold standard for clinical autonomic testing includes heart rate response to deep breathing, standing, and Valsalva manoeuvre, and blood pressure response to standing [12].

6. Identifying in advance the various cardiovascular prognostic factors (how many and which ones?) to reasonably adjust for in the analysis. Risk adjustment is essential to making fair comparisons and first requires strict definition of each specific outcome, particularly in diabetic people provided the complex association of traditional, non-traditional and disease-specific risk factors with mortality/morbidity.

Author details

Elena Matteucci* and Ottavio Giampietro*

*Address all correspondence to: elena.matteucci@med.unipi.it

Department of Clinical and Experimental Medicine, Italy

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