Sleep apnoea in children with diabetes mellitus: effect of glycaemic control

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Abstract

Aims/hypothesis. Patients with diabetes mellitus commonly have cardiovascular autonomic dysfunction and an abnormal ventilatory pattern during sleep. Few data are available on these changes in childhood diabetes. We investigated whether young diabetic children with or without diabetic neuropathy have ventilatory dysfunction during sleep and if so, whether these autonomic changes are related to the duration of diabetes and glycaemic control.

Methods. We studied 25 children with insulin-dependent diabetes mellitus (19 boys, mean age 7.72 ± 1.99 years). All patients were insulin-dependent at diagnosis; blood samples for HbA_{1c} assay were collected on the morning before testing and at 3-month intervals during the preceding year. Patients and control subjects (20 age-matched healthy children, 15 boys) underwent overnight polysomnography.

Results. More diabetic patients than control subjects had sleep apnoeas ($p = 0.006$); apnoeas in patients

also lasted longer ($p = 0.07$). Patients with poorly controlled diabetes had more apnoeas than patients with well-controlled diabetes and than healthy control subjects ($p < 0.0001$). Respiratory events during sleep correlated significantly with glycaemic control ($r = 0.360$; $p = 0.09$) and with the duration of diabetes ($r = 0.430$; $p = 0.04$).

Conclusion/interpretation. We conclude that respiratory control is compromised very early in children with diabetes. These anomalies are closely related to the duration of diabetes and to glycaemic control. In young children with diabetes, screening of ventilatory control using recording techniques that are simpler than polysomnography could provide an early indication that an adverse cardiopulmonary reaction has begun. [Diabetologia (2000) 43: 696–702]

Keywords Sleep apnoea, diabetes, children, autonomic nervous dysfunction, glycaemic control.

Autonomic neuropathy is a frequent complication of diabetes mellitus and an additional risk factor for sud-

den death [1–5]. The autonomic dysfunction associated with diabetes mellitus is shown by changes in cardiovascular [3], gastrointestinal and genitourinary system dysfunction, pupillary dysfunction [6–7] and abnormal sweating [8]. The current consensus is that the syndrome of diabetic neuropathy has a relatively early, adolescent onset and develops earlier and more frequently than had previously been thought [3]. The syndrome causes diffuse functional changes [4], the most feared being changes in heart rhythm [9–10], because they pose a risk of death from cardiac arrest, especially during or immediately after surgical interventions [11–14]. Some of these presumed cardiac events might actually be respiratory arrests, resulting from an alter-

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Abbreviations: TSH, Thyroid stimulating hormone; REM, rapid eye movement; NREM, non rapid eye movement; FEV₁, forced expiratory volume at 1 second; FVC, forced vital capacity; FEF_{25–75}, forced expiratory flow at 25–75 % of vital capacity; AI, apnoea index; CAI, central apnoea index; TST, total sleep time.

Table 1. Anthropometric characteristics in the subjects studied^a

Characteristics	Total group (n = 25)	Diabetic patients Glycaemic control		Control subjects (n = 20)
		Good (HbA _{1c} ≤ 7.9 %) (n = 12)	Poor (HbA _{1c} ≥ 8 %) (n = 11)	
Age (years)	7.72 ± 1.99	7.83 ± 2.12	7.64 ± 2.11	8.81 ± 1.88
Sex (Males)	19	10	8	15
BMI (kg/cm ²)	18.74 ± 3.58	19.21 ± 4.48	18.22 ± 2.46	18.54 ± 3.26
Height (cm)	129.64 ± 12.70	131.1 ± 13.04	128.0 ± 13.35	129.07 ± 9.35
Duration of diabetes (years)	2.68 ± 2.61	2.42 ± 0.75	2.96 ± 1.23	
Haemoglobin A _{1c} (%)	7.80 ± 1.09	6.95 ± 0.60	8.72 ± 0.64	

^a Plus-minus values are means ± SD

ation in respiratory control or at least in the central neurovegetative system [15–16]. Some investigators nonetheless suggest a concomitant change in cardiac electrical conduction [11, 12]. During sleep, cardiorespiratory function is almost completely under autonomic nervous system control. Sleep acts as a challenge for autonomic-mediated functions and is thus an ideal state for disclosing autonomic dysfunction, whereas during the awake phase voluntary central control tends to mask defective autonomic control.

There is evidence that diabetic patients with autonomic nervous system neuropathy have more apnoeic episodes during sleep than diabetic patients without neuropathy [17]. Sleep apnoeas also last longer and are more intense in diabetic patients with neuropathy than in those without [18], suggesting a correlation between changes in the ventilatory pattern during sleep and diabetic neuropathy [19–21]. Most observations come from studies conducted in adult diabetic patients with a long history of diabetes in whom neuropathy had already developed [21–22]. Little information is available about diabetic children with a shorter duration of disease in whom neuropathy is rare. In addition, few studies have yet reported data on respiratory control in childhood diabetes [23].

Most attempts at studying the autonomic nervous system in childhood have encountered difficulties. Ventilatory control is especially difficult to study in children, hence the scarce data on respiratory control in children during wakefulness or sleep.

Sleep is the preferred phase in which to study the autonomic nervous system, therefore we designed this study to find out whether young diabetic children with or without signs of diabetic neuropathy have ventilatory dysfunction during sleep and if so, whether these respiratory changes are related to the duration of diabetes and to metabolic control.

Subjects and methods

We studied 25 children with insulin-dependent diabetes mellitus (19 boys and 6 girls) whose ages ranged from 5–11 years

(mean 7.72 ± 1.99 years). When tested all children had normal growth (mean height 129.64 ± 12.70 cm; BMI 18.74 ± 3.58 kg/cm²). The duration of disease ranged from 1 month to 5 years (mean 2.68 ± 2.61 years); only one patient was tested at the onset of disease (1 month). All patients were insulin-dependent at diagnosis. During the study they continued to receive insulin therapy with regular rapid-acting, intermediate-acting and slow-release insulin, in four daily doses (morning, lunchtime, evening and bedtime). The mean total daily insulin dose per kg at the time of the study was 0.63 ± 0.33 U/kg. All subjects underwent an electrocardiographic (ECG) examination. No patient had signs or symptoms of autoimmune disorders. None had nocturnal snoring or signs of adenotonsillar hypertrophy. None of the patients had clinical signs of diabetic neuropathy. To obtain comparative polysomnographic data we studied 20 age-matched healthy control children (15 boys and 5 girls; age range 5–12 years). Their mean height was 129.07 ± 9.35 cm and BMI 18.54 ± 3.26 kg/cm² (Table 1).

Study protocol. A questionnaire was used to gather information on the history of cardiorespiratory diseases. All patients underwent physical examination to exclude symptoms of concurrent illnesses at the time of testing.

To assess metabolic control in diabetic patients, blood samples were collected for assay of HbA_{1c} (detected by HPLC high-performance liquid chromatography, DIAMAT, Bio-rad, Munich, Germany) on the morning before testing and at 3-month intervals during the preceding year. The patients were divided into two groups according to their mean glycated haemoglobin values: those with good metabolic control (HbA_{1c} ≤ 7.9 %) and those with poor control (HbA_{1c} ≥ 8 %). To exclude hypoglycaemia as a cause of apnoea and to avoid invasive procedures that might alter autonomic nervous system function during sleep, blood glucose concentrations were measured when patients awoke after polysomnography.

Thyroid function was assessed in all patients by radioimmunoassay of T₃, T₄, and thyroid-stimulating hormone (TSH). All patients underwent an ophthalmoscopic examination to assess diabetic retinopathy. Renal function was studied with an assay of microalbuminuria, detected by radioimmunoassay γ-counter. Microalbuminuria was defined as an albumin excretion rate less than 20 µg/min in at least two or three consecutive urine samples collected over 24 h.

Polysomnography. Patients and control subjects underwent a polysomnographic study (multichannel polygraph, Medilog SAC 800, Oxford Instruments, Oxon, UK) overnight (from 2100 to 0600 hours). None of the subjects had pharmacologic induction or sleep deprivation. To determine the sleep stages

according to the criteria of Rechtschaffen and Kales [24] we obtained an electroencephalogram (EEG) (C3-A2; C4-A1) monitored through surface electrodes fixed to the scalp; chin and external tibia electromyogram (chin and external tibia); and electro-oculogram for eye movements (with two channels). Thoracoabdominal excursions were measured qualitatively by respiratory impedance plethysmography with pneumatic respiration transducers placed over the rib cage and abdomen. Airflow was recorded qualitatively with an oronasal paediatric thermocouple (MV 1526, EPM Systems, Midlothian, Va., USA). Arterial-blood oxyhaemoglobin saturation (SaO_2) was monitored by pulse oxymetry (Sensor oximeter Y-PROBE 66 Z99, Datex-ohmeda, Louisville, Ky., USA). To determine cardiac function during sleep two electrocardiographic (ECG) channels (precordial leads V_1 , V_3 , and V_6) were recorded during polysomnography. The R-R series (interval tachogram) were obtained from the polysomnographic ECG recording and computed with an algorithm of R-wave recognition [25]. Each tachogram was then divided into segments according to sleep stages.

Studies took place in the sleep laboratory, a comfortable room kept at a constant temperature (21–22°C), where the children slept with their parents.

We also measured transcutaneous partial oxygen and carbon dioxide pressure (TePO_2 and TePCO_2) by TCM3 (Radiometer, Copenhagen, Denmark). Sleep apnoea was defined according to the criteria of the American Thoracic Society for sleep studies in children [26]: apnoea (cessation of inspiratory oronasal airflow lasting for 5 s or more); central apnoea (the absence of rib-cage and abdominal excursions and airflow); obstructive apnoea (absence of airflow in the presence of rib-cage and abdominal excursions); and mixed apnoea (central apnoea followed by a respiratory component). For each apnoeic event, the lowest oxyhaemoglobin desaturation was determined, defined as the smallest fall in SaO_2 (nadir). The number of episodes of apnoea per hour of sleep is referred to as the apnoea index (AI). The index of central apnoea (CAI) was calculated in the rapid eye movement (REM) sleep stage and in the four non-rapid eye movement (NREM) stages.

Respiratory function. Before and after polysomnography, all subjects underwent spirometric pulmonary function testing, including a flow-volume curve recorded for measurement of forced vital capacity (FVC), forced expiratory volume at 1 s (FEV_1), and forced expiratory flow at 25–75 % of vital capacity (FEF_{25-75}) (ALTAIR 1000 COSMED apparatus, Altair Cosmed, Rome, Italy). The best flow-volume curve recorded in three successive trials was chosen for analysis.

Autonomic function tests. In 12 patients we assessed cardiovascular autonomic function with the test battery described by Ewing [27,28]. The results of these cardiovascular tests were compared with normal reference values obtained previously in a group of 54 healthy children matched for age and sex [29]. Before lung function testing began, systolic and diastolic blood pressures were measured twice with a Riva Rocci sphygmomanometer according to the standard method [28], with subjects in the supine position. Heart rate and arterial pressure variabilities were determined by blood pressure recordings during tilt testing and by the Valsalva response beat-to-beat. With the child lying quietly on the couch the heart rate was monitored with an electrocardiograph (ECG) trace. The patient was then rapidly placed upright and the start of the manoeuvre was marked on the tracing. A ruler was used to measure the shortest R-R interval between the 15 ECG complexes and the longest R-R interval in the first 30 complexes. The cardiac response to the manoeuvre was expressed as the ratio be-

tween the longest R-R interval recorded during the 30 complexes after orthostatism and the shortest R-R interval in the first 15 complexes (maximum/minimum 30:15 ratio). Arterial pressures measured with the subject lying down were measured again upright, keeping the arm-cuff at the level of the heart. For the Valsalva manoeuvre, the child inhaled and exhaled forcibly into a mouthpiece connected to a modified sphygmomanometer, until the pressure value reached one-third of the subject's baseline arterial pressure (values ranging around 30 mmHg). The subject maintained that pressure for 15 s under continuous ECG monitoring. Beat-to-beat arterial pressure was measured repeatedly during testing and after the mouthpiece had been removed. The result was expressed for heart rate variations from the ratio between the longest R-R interval after the manoeuvre (rebound bradycardia) and the shortest R-R interval during respiratory effort (expression of tachycardia during the manoeuvres), determined from the ECG trace. Like all manoeuvres measuring heart rate variability, this procedure predominantly explores vagal function.

The data for heart rate and blood pressure variability were compared with those obtained in an earlier study in a group of 54 healthy children matched for age and sex [29].

Our study was approved by the local research ethics committee and verbal informed consent was obtained for each child.

Statistical analysis. A two-tailed paired Student's *t* test and one-way ANOVA were used to determine the statistical significance of differences between groups. Associations between variables were determined with the *r* correlation index. Data were computed with the software program SPSS. *P* values less than 0.05 were considered to indicate statistical significance. Values are reported as means $\pm$ SD.

Results

Anthropometric data were within the normal range for all subjects (Table 1). Thyroid function tests were also within the normal range (T_3 : 2.25 ± 0.45 nmol/l, T_4 : 114.54 ± 24.7 $\mu\text{mol/l}$, and TSH : 2.3 ± 0.61 mU/ml). Values for HbA_{1c} (detected in 23 subjects) 8.21 ± 1.41 % on the day of testing and 7.80 ± 1.09 % during the preceding year indicated 12 patients as having good glycaemic control ($\text{HbA}_{1c} \leq 7.9$ %) and 11 with poor control ($\text{HbA}_{1c} \geq 8$ %) (Table 1). The mean blood glucose concentration on awakening in the 25 patients was 12.3 ± 3.9 mmol/l; range 5.5–20.6 mmol/l (%). No patient had retinopathy (microangiopathy) on ophthalmoscopic examination, altered renal function, or microalbuminuria. None of the subjects snored, neither did they have adenotonsillar hypertrophy, dental malocclusion or craniofacial abnormalities.

Overnight polysomnograms disclosed more apnoeas in diabetic patients than in control subjects (AI: 2.62 ± 1.73 n/h vs 1.40 ± 0.88 n/h; $p = 0.006$); apnoeas in diabetic patients also lasted longer (15.1 ± 4.65 s vs 12.6 ± 4.40 s; $p = 0.07$). When patients were divided according to glycaemic control, patients with poorly controlled diabetes had more apnoeas than patients with well-controlled diabetes (AI: 3.28 ± 1.64

Fig. 1. Central sleep apnoea index (number of events for hour of recording) in children with insulin-dependent diabetes mellitus and healthy control subjects

n/h vs 2.03 ± 1.78 n/h ; $p = 0.04$) and more than healthy control subjects (AI: 3.28 ± 1.64 n/h vs 1.40 ± 0.88 n/h ; $p < 0.0001$) (Table 2). Diabetic patients with poor glycaemic control also had significantly more central apnoeas than control subjects (CAI: 2.54 ± 1.27 n/h vs 0.78 ± 0.73 n/h ; $p < 0.0001$) and than diabetic patients with good metabolic control (CAI: 2.54 ± 1.27 n/h vs 1.34 ± 1.29 n/h ; $p = 0.03$) (Fig. 1). In diabetic patients, episodes of central apnoea were more frequent in REM sleep than in the NREM sleep stages (REM 17.8% of total sleep time (TST); NREM 72% of TST. REM CAI: 3.7 ± 3.0 n/h vs NREM CAI 1.9 ± 2.8 n/h ; $p < 0.05$). In normal subjects, no difference was found in the CAI during the various sleep stages (REM 21.2% of TST; NREM 79% of TST. REM CAI 0.3 ± 0.4 n/h vs NREM CAI 0.4 ± 0.4 n/h ; $p = NS$).

No difference was found for REM cycles (2.9 ± 1.1 vs 3.0 ± 1.3 cycles; $p = NS$) or in REM latencies

(81.2 ± 49.3 min vs 108.3 ± 57.4 min; $p = NS$) in diabetic subjects and control subjects. All subjects had $TcPco_2$ values within the normal range (37.7 ± 39.3 mmHg).

In diabetic patients, the apnoea index during sleep correlated significantly with glycaemic control ($r = 0.360$; $p = 0.09$) and with the duration of diabetes ($r = 0.430$; $p = 0.04$), the central apnoea index correlated significantly with glycaemic control ($r = 0.420$; $p = 0.05$) and duration of diabetes ($r = 0.44$; $p = 0.04$) (Fig. 2). No correlation was found between the number of apnoeas or central apnoeas and the age at onset of diabetes.

Spirometric lung function tests were within the normal range (FVC 97% of the predicted value, FEV_1 98%, and FEF_{25-75} 109.6%). Heart rate and arterial pressure variability (tilt testing and Valsalva manoeuvre) did not differ significantly in diabetic patients and control children (Table 3).

Beat-to-beat heart rate variability showed that neither of the variables tested (mean R-R and total power) differed from control subjects (Table 3).

Table 2. Respiratory variables during sleep in diabetic children and control subjects^a

Variable	Total group ($n = 25$)	Diabetic patients Glycaemic control		Control subjects ($n = 20$)
		Good ($HbA_{1c} \leq 7.9\%$) ($n = 12$)	Poor ($HbA_{1c} \geq 8\%$) ($n = 11$)	
Apnoea index (no. of episodes/h)	2.62 ± 1.73^b	2.03 ± 1.78	3.28 ± 1.64^d	1.40 ± 0.88
Central apnoea index (no. of episodes/h)	1.93 ± 1.34	1.34 ± 1.29^f	2.54 ± 1.27^e	0.78 ± 0.73
Apnoea-hypopnoea index (no. of episodes/h)	6.02 ± 2.78	5.81 ± 2.89	6.30 ± 2.96	5.13 ± 2.56
Mean duration of apnoea (s)	8.67 ± 1.54	8.66 ± 1.75	8.9 ± 1.34	8.2 ± 2.70
Maximum duration of apnoea (s)	15.1 ± 4.65^c	14.9 ± 6.18	15.6 ± 2.93	12.6 ± 4.40
Mean low SaO_2 (%)	90.0 ± 2.50	89.8 ± 2.35	91.2 ± 3.74	91.2 ± 4.1

^a Plus-minus values are means $\pm$ SD

^b $p = 0.006$ vs controls; ^c $p = 0.07$ vs controls; ^d $p < 0.0001$ vs controls; ^e $p < 0.0001$ vs controls; ^f $p = 0.03$ vs poor controls

Fig. 2. Relation between sleep apnoea, glycaemic control and duration of diabetes in 23 children with insulin-dependent diabetes mellitus. **a.** Relation between apnoea index and glycaemic control (HbA_{1c}) $r = 0.360$; $p = 0.09$, **b.** Relation between apnoea index and duration of disease $r = 0.430$; $p = 0.04$, **c.** Relation between central apnoea index and metabolic control (HbA_{1c}) $r = 0.420$; $p = 0.05$, **d.** Relation between central apnoea index and duration of disease $r = 0.440$; $p = 0.04$, $\circ$ good glycaemic control; $\blacktriangledown$ poor glycaemic control

Discussion

Despite having no clinical signs of diabetic neuropathy, the diabetic children in this study all had ventilatory dysfunction during sleep. These changes are related to the duration of diabetes and to metabolic

control. Our findings suggest that this impairment possibly develops very early in the course of diabetic disease. It is not known yet whether it develops before other signs of autonomic dysfunction become evident.

Although diabetes mellitus impairs cardiocirculatory and neuromuscular autonomic nervous system function even in childhood, little is known about its influence on respiratory control in children [19]. Our polysomnographic findings suggest that diabetes mellitus damages the central respiratory control mechanisms.

In our study, episodes of apnoea were more numerous and lasted longer in patients who had higher HbA_{1c} values than in those with lower HbA_{1c} . Because apnoeas in our patients never altered blood-gas homeostasis (hypoxia or hypercapnia) and no

Table 3. Cardiovascular test results variables in diabetic children with insulin-dependent diabetes mellitus in groups according to glycaemic control and in control children^a

		Total group	Diabetic patients		Control subjects
			Glycaemic control		
			Good ($\text{HbA}_{1c} \leq 7.9\%$)	Poor ($\text{HbA}_{1c} \geq 8\%$)	
		(n = 12)	(n = 8)	(n = 5)	(n = 54)
Variable					
Age (years)		8.24 ± 1.61	7.79 ± 1.49	8.86 ± 1.88	9.22 ± 1.10
Valsalva manoeuvre		1.49 ± 0.37	1.42 ± 0.32	1.56 ± 0.47	1.22 ± 0.18
Maximum/minimum 30 : 15 ratio		1.50 ± 0.33	1.45 ± 0.18	1.60 ± 0.37	1.20 ± 0.19
Blood pressure (mm Hg)	Systolic	110.67 ± 9.61	106.00 ± 11.40	113.75 ± 9.16	121.22 ± 10.00
	Diastolic	64.67 ± 6.40	62.00 ± 8.37	65.00 ± 5.35	74.24 ± 9.21
		(n = 25)	(n = 12)	(n = 11)	(n = 20)
R-R Mean (sec)	NREM	0.89 ± 0.09	0.90 ± 0.11	0.88 ± 0.08	0.90 ± 0.09
	REM	0.85 ± 0.10	0.84 ± 0.09	0.85 ± 0.07	0.84 ± 0.12
Total power (sec^2)	NREM	0.008 ± 0.006	0.009 ± 0.05	0.007 ± 0.005	0.008 ± 0.009
	REM	0.009 ± 0.008	0.010 ± 0.006	0.009 ± 0.008	0.014 ± 0.01

^a Plus-minus values are means $\pm$ SD

other sleep disturbances were apparent from our patients' histories, these abnormal respiratory events apparently do not affect gas homeostasis. In our patients, blood carbon dioxide presumably was not a primary cause of ventilatory dysfunction during sleep.

Although the precise clinical importance of central apnoeas is still not clear [19–21], autonomic involvement appears likely [19, 22, 30]. None of our patients had either clinical or physical signs of autonomic dysfunction. All subjects tested ($n = 12$) had normal findings on cardiovascular testing, a normal Valsalva response and normal blood pressure responses to tilting. None of them had microalbuminuria or retinopathy. One of the two autonomic tests yielded pathologic findings (30:15 ratio = 1:10) in one subject only, a child who had an altered apnoea index during nocturnal sleep (AI = 2.4), a disease duration of 1 year and 10 months and an HbA_{1c} of 8.80%. In none of our patients did we find a correlation between cardiovascular test results and respiratory events during sleep.

Our results indicate that in children with diabetes impaired respiratory control during sleep could be a sign of beginning autonomic nervous system dysfunction. A study of adults with diabetic neuropathy, all of whom had pathologic findings on cardiovascular testing, has reported long-lasting nocturnal apnoeas at high respiratory frequencies [19]. None of our patients had appreciably altered respiratory patterns such as irregular breathing, episodes of tachypnoea or oxygen desaturation.

Our cardiovascular and ventilatory findings show that the ventilatory control system is one of the first systems affected by autonomic nervous system damage in diabetic children. This possibility is not only supported by beat-to-beat heart rate variability data in this study but also by published data [31].

Nocturnal observation of cardiorespiratory functions therefore seems important because sleep can disclose very early anomalies not discernible during the awake phase or by other tests. During the sleep state, especially during REM sleep, cardiorespiratory function comes predominantly under sympathetic control [32, 33]. An unstable sympathetic system poses a real threat to life and it is important to note that our patients' apnoeic events occurred mainly in the REM stage.

In our patients we explicitly excluded other possible causes of the nocturnal respiratory pauses. Spirometric lung function values measured in our patients with diabetes mellitus came within the normal range [34] and none of our subjects had pulmonary disorders or craniofacial abnormalities (for example retrognathia or deep bite) that could have caused the nocturnal respiratory events. To avoid invasive procedures that might influence the results of an autonomic nervous system study, we did not monitor blood glucose during polysomnography. We found no clinical evidence (increased sweating, for example) nor chan-

ges in neurological variables that indicated hypoglycaemia associated with the apnoeic events. We therefore think it unlikely that nocturnal hypoglycaemia caused the extremely large number of apnoeas, although another study confirms frequent respiratory complications in diabetic patients [35]. This is also in line with our earlier study showing that diabetic children who had no signs of peripheral diabetic neuropathy nonetheless had a loss of vagal function in the bronchial receptors. They tolerated high doses of the bronchoconstrictor carbachol without having signs of bronchoconstriction [36]. A loss of bronchial reactivity could be one of the first signs of vagal dysfunction in children with diabetes mellitus.

Our findings show that a lack of metabolic control leads to the onset of diabetic neuropathy and its severe consequences. The central apnoea events in our patients could thus be linked to poor glycaemic control and the duration of diabetes. Extensive research confirms that hyperglycaemia is related to the severity of diabetic neuropathy, to diabetic blindness, and to the risk of myocardial infarction and sudden death [11–17]. Our observation that in young children with a short history of diabetes these changes had already begun raises the doubt that they might be intrinsic to the disease itself rather than simply being a consequence. The question remains whether glycaemic control is a sufficiently strong trigger to bring about rapid changes in such sophisticated control mechanisms. Our finding that sleep apnoea correlated with glycaemic control and with duration of disease appears to show that the ventilatory changes or autonomic nervous system dysfunction or both are linked to metabolic mechanisms rather than to inherent or genetic features of the disease.

In conclusion, young diabetic children with or without signs of diabetic neuropathy already have evident signs of ventilatory dysfunction (central nocturnal apnoea) during sleep. These changes are closely related to the duration of disease and to metabolic control. Whether they develop before other signs of autonomic dysfunction become evident is not known. Our findings also indicate that the main reason for these autonomic changes is hyperglycaemia. In young children with diabetes, screening of ventilatory control using recording techniques that are simpler than polysomnography could indicate early on that an adverse pulmonary reaction has begun. Nevertheless, it is most important to achieve good glycaemic control from the earliest stages of disease.

References

1. Vikin AI, Holland MT, Le Beau JM, Liuzzi FJ, Stansberry KB, Collen LB (1992) Diabetic neuropathies. *Diabetes Care* 15: 1926–1974
2. Menzinger G, Spallone V (1997) Neuropatia diabetica. In: Greco V, Ghirlanda F (eds) *Diabete Mellito. Principi e*

- Pratica, vol 51. Verducci Ed Europress Guidonia (Roma), pp 490–501
3. Ewing DJ, Martyn CN, Young RJ, Clarke BF (1985) The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 8: 491–498
 4. Watkins PJ (1992) Clinical observation and experiments in diabetic neuropathy. *Diabetologia* 35: 2–11
 5. Ewing DJ, Campbell IW, Clarke BF (1980) The natural history of diabetic autonomic neuropathy. *QJM* 49: 95–108
 6. Schwingshandl J, Simpson JM, Donaghue K, Bonney MA, Howard NJ, Silink M (1993) Pupillary abnormalities in type I diabetes occurring during adolescence. *Diabetes Care* 4: 630–633
 7. Karachaliou F, Karavanaki K, Greenwood R, Baum JD (1997) Consistency of pupillary abnormality in children and adolescents with diabetes. *Diabet Med* 14: 849–853
 8. Pena MM, Donaghue KC, Bonney M, Schwingshandl J, Howard NJ (1995) The prospective assessment of Autonomic Nerve Function by pupillometry in adolescents with type 1 diabetes mellitus. *Diabet Med* 12: 868–873
 9. Ewing DJ, Clarke BF (1986) Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab* 33: 177–180
 10. Mantysaari M, Kuikka J, Mustonen J, Uusitupa M (1993) Impaired ventricular repolarization associated with disturbed left ventricular sympathetic function and diastolic filling in diabetes. *Am Heart J* 125: 1458–1460
 11. Garcia-Bunel L (1978) Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* 1: 14–16
 12. Menzinger G, Spallone V, Maiello MR, Felici MG, Gambardella S (1988) Mortality in diabetic autonomic neuropathy. *Diabetes Res Clin Pract* 5:[Suppl 1]S317
 13. Bellavere F, Ferri G, Guarini L et al. (1988) Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? *Br Heart J* 59: 379–383
 14. Ewing DJ, Boland O, Neilson JMM, Cho CG, Clarke BF (1991) Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 34: 182–185
 15. Page MM, Watkins PJ (1978) Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* 1: 14–16
 16. Lawrence IG, Weston PJ, Bennett MA, McNally PG, Burden AC, Thurston H (1997) Is impaired baroreflex sensitivity a predictor or cause of sudden death in insulin-dependent diabetes mellitus? *Diabet Med* 14: 82–85
 17. Rees PJ, Prior JG, Cochrane GM, Clark TJ (1981) Sleep apnoea in diabetic patients with autonomic neuropathy. *J R Soc Med* 74: 192–195
 18. Schmid H, Neumann C, Martinez D (1991) Arterial oxygen desaturation during sleep in patients with severe autonomic neuropathy. *Diabetes* 40[Suppl 1]:326A–329A
 19. Mondini S, Guilleminault C, Hayes B (1985) Abnormal breathing patterns during sleep in diabetes. *Ann Neurol* 17: 391–395
 20. Guilleminault C, Mondini S, Boyd Hayes (1985) Diabetic autonomic dysfunction, blood pressure, and sleep. *Ann Neurol* 18: 670–675
 21. Katsumata K, Okada T, Miyao M (1991) High incidence of sleep apnea syndrome in a male diabetic population. *Diabetes Res Clin Pract* 13: 45–52
 22. Strohl KP (1996) Diabetes and sleep apnea. *Sleep* 19: S225–S228
 23. Barkai L, Madacsy L, Kassay L (1990) Investigation of sub-clinical signs of autonomic neuropathy in the early stage of childhood diabetes. *Horm Res* 34: 54–59
 24. Rechtschaffen A, Kales A (1968) A manual of standardized terminology and techniques on scoring system for sleep stage of human subjects. UCLA Brain Information Service, Bethesda
 25. Villa MP, Calcagnini G, Pagani J, Paggi B, Massa F, Ronchetti R (2000) Effects of sleep stage and age on short-term heart rate variability during sleep in healthy infants and children. *Chest* 117: 460–462
 26. Standards and indications for cardiopulmonary sleep studies in children (1995) American Thoracic Society. *Am J Respir Crit Care Med* 153: 866–878
 27. Ewing DJ, Clarke BF (1982) Diagnosis and management of diabetic autonomic neuropathy. *BMJ* 285: 916–918
 28. Ewing DJ, Borsley DQ, Bellavere F et al. (1981) Cardiac autonomic neuropathy in diabetes: comparison of measures of R-R interval variation. *Diabetologia* 21: 18–24
 29. Villa MP, Paggi B, Pagani J et al. (1999) Autonomic nervous system anomalies in children with asthma. *Ital J Pediatr (IJP)* 3: 446–453
 30. Javaheri S (1999) A mechanism of central sleep apnoea in patients with heart failure. *N Engl J Med* 341: 949–954
 31. Wawryk AM, Bates DJ, Couper JJ (1997) Power spectral analysis of heart rate variability in children and adolescents with IDDM. *Diabetes Care* 20: 1416–1421
 32. Barkai L, Madacsy L (1995) Cardiovascular autonomic dysfunction in diabetes mellitus. *Arch Dis Child* 73: 515–518
 33. Molgaard H, Christensen PD, Hermansen K et al. (1994) Early recognition of autonomic dysfunction in microalbuminuria: significance for cardiovascular mortality in diabetes mellitus? *Diabetologia* 37: 788–796
 34. Buckingham B, Perejda AJ, Sandborg C, Kershner AK, Uitto J (1986) Skin, joint, and pulmonary changes in type I diabetes mellitus. *Am J Dis Child* 140: 420–423
 35. Santos e Fonseca CM, Manco JC, Gallo JL, Barreira AA, Foss MC (1992) Cholinergic bronchomotor tone and airway caliber in insulin-dependent diabetes mellitus. *Chest* 101: 1038–1043
 36. Villa MP, Cacciari E, Bernardi F, Cicognani A, Salardi S, Zapulla F (1988) Bronchial reactivity in diabetic patients. Relationship to duration of diabetes and degree of glycaemic control. *Am J Dis Child* 142: 726–729