PAPER

Sudden cardiac death in diabetes mellitus: risk factors in the Rochester diabetic neuropathy study

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Objectives: To determine risk factors for sudden cardiac death and the role of diabetic autonomic neuropathy (DAN) in the Rochester diabetic neuropathy study (RDNS)

Methods: Associations between diabetic and cardiovascular complications, including DAN, and the risk of sudden cardiac death were studied among 462 diabetic patients (151 type 1) enrolled in the RDNS. Medical records, death certificates, and necropsy reports were assessed for causes of sudden cardiac death.

Results: 21 cases of sudden cardiac death were identified over 15 years of follow up. In bivariate analysis of risk covariates, the following were significant: ECG 1 (evolving and previous myocardial infarctions): hazard ratio (HR) = 4.4 (95% confidence interval (CI), 1.6 to 12.1), p = 0.004; ECG 2 (bundle branch block or pacing): HR = 8.6 (2.9 to 25.4), p<0.001; ECG 1 or ECG 2: HR = 4.2 (1.3 to 13.4), p = 0.014; and nephropathy stage: HR = 2.1 (1.3 to 3.4), p = 0.002. Adjusting for ECG 1 or ECG 2, autonomic scores, QTc interval, high density lipoprotein (HDL) cholesterol, 24 hour microalbuminuria, and 24 hour total proteinuria were significant. However, adjusting for nephropathy, none of the autonomic indices, QTc interval, HDL cholesterol, microalbuminuria, or total proteinuria was significant. At necropsy, all patients with sudden cardiac death had coronary artery or myocardial disease.

Conclusions: Sudden cardiac death was correlated with atherosclerotic heart disease and nephropathy, and to a lesser degree with DAN and HDL cholesterol. Although DAN is associated with sudden cardiac death, it is unlikely to be its primary cause.

In the USA, sudden cardiac death accounts for about 300 000 to 400 000 deaths annually. Sudden cardiac death may account for 50% of all cardiac deaths in developed countries.[1] It may be the first and last manifestation of coronary artery disease. According to recent Centers for Disease Control data, coronary artery disease is the most common risk factor for sudden cardiac death.[2] Other known or suspected risk factors include old age, male sex, hypertension, left ventricular dysfunction, intraventricular conduction defects, congenital heart disease, smoking, obesity, abnormal serum cholesterol, diabetes mellitus, and cardiac autonomic neuropathy. In patients with diabetes mellitus, cardiac autonomic neuropathy has been reported to be a poor prognostic factor associated with an increased incidence of sudden cardiac deaths.[3–6]

The incidence and severity of coronary artery disease is increased in diabetes mellitus, as is diabetic autonomic neuropathy (DAN), but whether sudden cardiac death is caused by coronary artery disease, left ventricular failure, arrhythmias from coronary artery disease, DAN, or combinations of the above is less clear, for several reasons. First, studies were usually not prospective, were not carried out over a long enough time, or were not representative of defined populations. Second, the severity and characteristics of somatic and autonomic neuropathy were not sufficiently studied at periodic intervals using quantitative measures and employing normal test values corrected for age, sex, and anthropomorphic factors, based on studies of a large normal cohort of healthy subjects drawn from the same population. Third, assessment of autonomic neuropathy was incomplete. Finally, factors other than autonomic neuropathy (for example, cardiac and kidney disease) were insufficiently taken into account in multivariate analysis.

In the prospective studies reported here, consenting diabetic patients were representative of diabetic patients in the community, abnormality was identified from population based norms, and both univariate and multivariate analyses were undertaken, which included many risk factors.

Here we evaluate the risk factors for sudden cardiac death in the prospective, population based, Rochester diabetic neuropathy study (RDNS) cohort, by life table analysis of DAN and other risk factors on the outcome of sudden cardiac death; and by analysis of medical records, death certificates, ECG tracings, and available necropsy reports of all cases of sudden cardiac death, looking for additional evidence related to the cause of the death.

METHODS

The RDNS cohort

The RDNS is a cross sectional and longitudinal study of all consenting diabetic patients from Rochester, Minnesota (later from Olmsted County, Minnesota) initiated on 1 January 1986, enrolling 502 patients, of whom 462 (151 with type 1 diabetes) provided data for the present study.[7 8] These patients are mainly of northern European extraction. The database from the RDNS has been used to develop and assess neuropathy tests, composite scores, and a staging approach,[9] the prevalence of diabetic complications,[8] progression,[10] and risk factors.[11]

The RDNS healthy subjects study (RDNS-HS)

To develop normative test results (as centiles and normal deviate (z) scores) a large cohort of randomly selected volunteers from Rochester, Minnesota was recruited and examined, excluding persons with neurological disease and

Abbreviations: CASS, composite autonomic severity scale; DAN, diabetic autonomic neuropathy; NIS, neuropathy impairment score; NSC, neuropathy symptoms and change score; QSART, quantitative sudomotor axon reflex test; RDNS, Rochester diabetic neuropathy study

Table 1 Clinical characteristics of the Rochester diabetic neuropathy study cohort at the last evaluation

	Sudden cardiac deaths				Other deaths				Alive			
	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD
Age (years)	21		72.4	11.9	112		70.9	11.5	329		57.3	17.1
Sex (male)	15	71.4			60	53.6			152	46.2		
Diabetes type 1	2	9.5			23	20.5			126	38.3		
Duration of diabetes (years)	21		18.2	8.4	112		20.7	12.3	329		17.1	9.4
FPG, mmol/l (mg/dl)*	20		9.71 (175.0)	1.88 (33.8)	102		9.80 (176.6)	2.91 (52.5)	318		9.73 (175.3)	2.34 (42.2)
Glycosylated Hb (%)*	20		9.8	1.6	100		10.4	2.7	318		10.0	2.0
Calculated HbA1c (%)*	20		8.0	1.0	100		8.4	1.7	318		8.2	1.2
HDLC, mmol/l (mg/dl)*	20		0.83 (32.2)	0.24 (9.2)	88		0.95 (36.8)	0.25 (9.6)	303		1.13 (43.5)	0.36 (14.0)
Cholesterol, mmol/l (mg/dl)*	20		4.70 (181.3)	0.93 (35.9)	88		5.15 (198.8)	0.99 (38.3)	304		4.93 (190.5)	0.93 (35.8)
Triglycerides, mmol/l (mg/dl)*	20		2.05 (181.2)	1.22 (108.2)	88		2.06 (182.7)	1.17 (103.8)	304		1.95 (172.4)	1.46 (129.2)
Creatinine, μmol/l (mg/dl)*	19		123.8 (1.4)	61.9 (0.7)	98		114.9 (1.3)	70.7 (0.8)	317		88.4 (1.0)	17.7 (0.2)
Microalbuminuria (mg/24 h)*	12		712.7	1313.7	50		328.6	666.6	276		133.8	408.3
Total proteinuria (mg/24 h)*	16		739.7	1261.4	78		540.1	1004.2	285		220.7	510.5
Systolic BP (mm Hg)*	20		141.4	17.3	104		146.2	19.0	321		130.3	15.2
CASS total (points)	12		5.4	2.5	64		4.5	2.3	259		2.9	2.3
CASS cardiovagal (points)	13		1.9	1.2	64		1.8	1.0	260		1.2	1.0
JTc (ms)*	18		330.4	18.4	102		330.8	27.1	298		326.0	22.8
QTc (ms)*	15		443.2	17.1	89		446.2	34.1	294		428.1	22.2
Neuropathy stage†												
0	7	53.9			32	43.2			138	49.1		
1a	1	7.7			7	9.5			41	14.6		
1b	4	30.8			19	25.7			48	17.1		
2a	1	7.7			13	17.6			51	18.1		
2b	0	0.0			3	4.1			3	1.1		
Retinopathy stage‡												
0	5	26.3			23	24.7			88	29.2		
1	9	47.4			28	30.1			96	31.9		
2	3	15.8			34	36.6			70	23.3		
3	2	10.5			8	8.6			47	15.6		
Nephropathy stage§												
0	5	31.3			21	26.9			188	65.5		
1	5	31.3			33	42.3			65	22.7		
2	1	6.3			10	12.8			19	6.6		
3	4	25.0			14	18.0			14	4.9		
4	1	6.3			0	0.0			1	0.4		

*Mean over time.
†Diabetic neuropathy staging: 0, no polyneuropathy; 1a, abnormal tests only; 1b, test abnormalities and neurological signs of polyneuropathy; 2a, condition 1b plus symptoms of polyneuropathy; 2b, condition 2a but ankle dorsiflexion weakness >50%.
‡Diabetic retinopathy staging: 0, no retinopathy; 1, mild background retinopathy; 2, severe non-proliferative retinopathy; 3, proliferative retinopathy.
§Diabetic nephropathy staging: 0, microalbuminuria <30 mg/24 h; 1, microalbuminuria 30–300 mg/24 h; 2, microalbuminuria >300 mg/24 h; 3, stage 1 or 2 and creatinine 141 to 354 μmol/l (1.6 to 4.0 mg/dl); 4, stage 1 or 2 and creatinine >354 μmol/l (4.0 mg/dl).
BP, blood pressure; CASS, composite autonomic severity score; FPG, fasting plasma glucose; Hb, haemoglobin; HDLC, high density lipoprotein cholesterol; JTc, corrected JT interval; QTc, corrected QT interval.

diseases predisposing to neuropathy. The test results from these healthy persons were used to estimate normative test results for quantitative sensation tests, attributes of nerve conduction, and quantitative autonomic tests, taking into account the influence of age, sex, and other applicable anthropomorphic characteristics.[12 13]

Assessment of neuropathy

Assessing for the presence of neuropathy and its severity was done by prospective evaluation of the symptoms, neuropathic impairments, and test results from the patients. Neuropathic deficits were assessed by the neuropathy impairment score (NIS) and symptoms by the neuropathy symptoms and change score (NSC). The neuropathic tests assessed were nerve conduction studies, quantitative sensation, and quantitative autonomic function tests. Criteria for the diagnosis and staged severity of diabetic sensory polyneuropathy have been published.[14 15]

Assessment of autonomic neuropathy

In addition to the history and examination, validated, standardised, quantitative autonomic studies of known sensitivity, specificity, and reproducibility were carried out on the patients to evaluate the distribution and severity of sudomotor, cardiovagal, and adrenergic impairment. Postganglionic sudomotor function was evaluated with a quantitative sudomotor axon reflex test (QSART) recorded from the forearm and three lower extremity sites. Heart rate variability to deep breathing and to the Valsalva manoeuvre was used to evaluate cardiovagal function. Adrenergic function was evaluated using the beat to beat blood pressure responses during tilt and the Valsalva manoeuvre.

The composite autonomic severity scale (CASS) is a 10 point score of autonomic function derived from the three sets of autonomic function tests (sudomotor, cardiovagal, and adrenergic). The scale rates adrenergic deficits by one of four grades, and sudomotor and cardiovagal deficits each by one of three grades. This score of autonomic failure ranges from a value of 0 (normal) to 10 (maximum deficit). Each score is normalised for the effects of age and sex.[16] The procedures and methods of analysis of autonomic tests have been reported previously.[17]

Assessment of metabolic control, diabetic complications, and putative risk factors

Patients in the RDNS cohort underwent measurement of height, weight, body surface area, body mass index (BMI), abdominal to pelvic girth, blood pressure, heart rate, fasting plasma glucose, glycosylated haemoglobin, and calculated HbA_{1c} every three months. Total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and lipoproteins were evaluated every six months. Retinopathy was assessed on seven standard retinal photographs of each eye by the Retinal Eye Reading Center, Madison, Wisconsin (Dr R Klein). Nephropathy was assessed every 12 months by measurement of 24 hour proteinuria, 24 hour microalbuminuria, and plasma creatinine. Other putative risk factors measured over time in the cohort included energy expenditure, alcohol consumption (g/week), smoking (pack-years), and other variables.

Staging of retinopathy, polyneuropathy, and nephropathy are described in table 1 and have been published.[14]

Characterisation of ECG abnormality

A 12-lead ECG was recorded on RDNS participants every two years. The test was also carried out at other times depending on clinical necessity, and stored as digital data on the Marquette MUSE system. In all, 8155 ECGs were available for analysis. These electronic records were analysed using a computer program that characterised each record as:

- ECG 1: consistent with evolving myocardial infarction or previous Q wave changes indicative of myocardial infarction;
- ECG 2: left bundle branch block or electronic pacing;
- other patterns.

We also analysed the QT interval and JT interval corrected for heart rate. The QTc and JTc were measured according to the following formulae:

$$QTc = [\text{QT wave duration}]/\sqrt{[60/\text{ventricular rate}]};$$
$$JTc = [\text{QT wave duration} - \text{R wave duration}]/\sqrt{[60/\text{ventricular rate}]}.$$

A QTc interval was not calculated if the ECG was paced or showed a left bundle branch block. A JTc interval was not calculated if the ECG was paced. This computer program has been validated by comparison with interpretation by experts in the Minnesota ECG Coding Laboratory at the University of Minnesota.[18]

Review of death certificates, medical history, and necropsy reports

The medical records, death certificates, and necropsy reports of all deaths in both RDNS cohorts were reviewed. Deaths were categorised as cardiac and non-cardiac. A cardiologist (TEK) categorised the cardiac deaths as sudden or non-sudden. Sudden death was defined as follows: the individual was found dead or died within one hour of symptom onset; or the individual was resuscitated from a cardiac arrest but died during the same hospital admission. The necropsy records were reviewed for the degree of coronary atherosclerosis, degree of myocardial damage, and left ventricular failure.

Statistical analysis

Life table methods were used to evaluate associations between potential risk factors and sudden cardiac death using Cox regression analysis (SAS software, version 8). Because of the small number of sudden cardiac deaths, bivariate analysis was used. Extreme caution was exercised when analysing time dependent covariates.[19] Subjects who died a non-sudden cardiac death were censored at time of death. Three versions of each continuous risk factor (such as fasting plasma glucose) were considered for the analyses—the value at baseline and two time dependent variables. The time dependent variables were continuously updated during follow up. At each time (t) during follow up, we computed the variable at t (current value) and the mean from baseline to t (mean over time). To illustrate this, for analyses associated with a sudden cardiac death at three years, the ''current value'' of fasting plasma glucose entered into the analysis at that time point for all subjects would be the most recent fasting plasma glucose at three years. For stage of neuropathy, retinopathy, nephropathy, ECG 1 and ECG 2, and the autonomic tests, only the values at baseline and at time t were used.

RESULTS

Disease characteristics

At analysis, death had occurred in 133 (29%) of persons in the RDNS cohort and in 18 (4%) of persons in the RDNS-HS cohort. Deaths from non-cardiac causes (cancer, vehicle accidents, and so on) occurred in 81 RDNS and 12 RDNS-HS. Of the 462 RDNS patients, 21 died suddenly, 112 died from other causes, and 329 were still alive. Of the 21 subjects who

Table 2 Univariate risk factors for sudden cardiac death (life table analysis): RDNS sudden cardiac deaths (n = 21) *v* all other deaths + alive (n = 441)

Risk factor	HR	95% CI	p Value
Age (10 years), at last evaluation	2.20	1.36 to 3.56	**0.001**
Type of diabetes mellitus	4.54	1.06 to 19.52	**0.042**
Renal disease, at last evaluation	1.64	0.64 to 4.25	0.306
FPG (10 mg/dl (0.56 mmol/l))*	1.01	0.92 to 1.11	0.822
Glycosylated Hb (10%)*	0.96	0.77 to 1.20	0.717
Calculated HbA1c (10%)*	0.94	0.66 to 1.34	0.717
HDLC (10 mg/dl (0.26 mmol/l))*	0.50	0.29 to 0.87	**0.014**
Cholesterol (10 mg/dl (0.26 mmol/l))*	0.95	0.82 to 1.09	0.434
Triglycerides (10 mg/dl (0.11 mmol/l))*	1.01	0.98 to 1.05	0.362
Creatinine (mg/dl)*	1.88	1.33 to 2.65	<**0.001**
Microalbuminuria (1000 mg/24 h)*	2.38	1.50 to 3.76	<**0.001**
Total proteinuria (1000 mg/24 h)*	1.69	1.24 to 2.30	<**0.001**
Systolic blood pressure (10 mm Hg)*	1.35	1.00 to 1.82	**0.047**
Smoking (10 pack years), at last evaluation	1.17	0.97 to 1.39	0.094
Calcification of vessels in foot, at last evaluation	6.73	1.23 to 36.86	**0.028**
ECG 1*†	6.27	2.23 to 17.62	**0.001**
ECG 2*†	7.47	2.43 to 22.99	<**0.001**
ECG 1 or 2*	10.59	4.06 to 27.64	<**0.001**
JTc (ms)*	1.01	0.99 to 1.03	0.589
QTc (ms)*	1.02	1.01 to 1.04	**0.005**
CASS total (points)*	1.52	1.20 to 1.91	<**0.001**
CASS adrenergic (points)*	2.06	1.06 to 4.00	**0.032**
CASS sudomotor (points)*	1.10	0.39 to 3.11	0.860
CASS cardiovagal (points)*	2.50	1.37 to 4.55	**0.003**
Nephropathy stage*	2.76	1.60 to 4.76	<**0.001**
Neuropathy stage*	0.84	0.44 to 1.59	0.589

*Mean over time.
†ECG 1, ECG diagnostic of acute myocardial infarction or evolving diagnostic; ECG 2, ECG with left bundle branch block or electronically paced complexes.
Significant values in bold.
CASS, composite autonomic severity score; CI, confidence interval; HDLC, high density lipoprotein cholesterol; HR, hazard ratio; JTc, corrected JT interval; QTc, corrected QT interval; RDNS, Rochester diabetic neuropathy study.

died suddenly, one was successfully defibrillated and resuscitated but remained unresponsive for four days until life support measures were discontinued. Unsuccessful resuscitation attempts were documented for nine patients, and no resuscitation attempts were documented for 11.

The age, sex, disease, and diabetic complications of the three groups of patients in the RDNS are shown in table 1. Statistical significance is not shown because the average values are provided for descriptive purposes only and not for hypothesis testing. At the time of death or at the last examination, the group who died was older. Mean fasting plasma glucose and mean glycosylated haemoglobin were similar among the three groups. The plasma creatinine was slightly higher in the two groups who had died. There were

Table 3 Multivariate life table analysis: RDNS sudden cardiac deaths (n = 21) *v* all other deaths + alive (n = 441)

	Adjusted for ECG 1†			Adjusted for ECG 2†			Adjusted for nephropathy stage		
Risk factor	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
ECG 1	–	–	–	4.41	1.60 to 12.16	**0.004**	2.13	0.63 to 7.24	0.224
ECG 2	8.64	2.94 to 25.44	<**0.001**	–	–	–	5.30	1.35 to 20.77	**0.017**
ECG 1 or 2	–	–	–	–	–	–	4.25	1.35 to 13.41	**0.014**
JTc (ms)*	1.01	0.99 to 1.02	0.583	1.01	0.99 to 1.03	0.515	1.00	0.97 to 1.02	0.840
QTc (ms)*	1.02	1.00 to 1.03	**0.019**	1.02	1.01 to 1.04	**0.008**	1.01	0.99 to 1.04	0.244
FPG (10 mg/dl (0.56 mmol/l))*	1.01	0.92 to 1.11	0.803	1.01	0.92 to 1.11	0.765	1.00	0.89 to 1.12	0.986
Glycosylated Hb (10%)*	0.69	0.07 to 6.92	0.750	0.51	0.05 to 5.35	0.575	0.46	0.03 to 6.95	0.576
Calculated HbA1c (10%)*	0.55	0.01 to 21.56	0.750	0.34	0.01 to 14.32	0.575	0.29	0.00 to 21.69	0.576
HDLC (10 mg/dl (0.26 mmol/l))*	0.53	0.30 to 0.94	**0.028**	0.52	0.30 to 0.91	**0.022**	0.56	0.30 to 1.04	0.068
Cholesterol (10 mg/dl (0.26 mmol/l))*	0.92	0.80 to 1.07	0.275	0.92	0.80 to 1.06	0.243	0.93	0.79 to 1.09	0.365
Triglycerides (10 mg/dl (0.11 mmol/l))*	1.01	0.98 to 1.05	0.485	1.02	0.98 to 1.05	0.383	0.99	0.93 to 1.05	0.707
Creatinine (mg/dl)*	1.91	1.34 to 2.73	<**0.001**	1.47	1.00 to 2.15	0.051	1.65	0.88 to 3.08	0.117
Microalbuminuria (1000 mg/24 h)*	2.18	1.33 to 3.57	**0.002**	2.37	1.47 to 3.80	<**0.001**	2.15	0.96 to 4.83	0.062
Total proteinuria (1000 mg/24 h)*	1.65	1.19 to 2.28	**0.003**	1.68	1.21 to 2.34	**0.002**	1.22	0.73 to 2.03	0.439
Systolic blood pressure (10 mm Hg)*	1.31	0.97 to 1.78	0.080	1.31	0.97 to 1.79	0.080	1.32	0.89 to 1.94	0.165
CASS total (points)	1.47	1.18 to 1.83	<**0.001**	1.43	1.15 to 1.78	**0.001**	1.19	0.91 to 1.56	0.210
CASS adrenergic (points)	2.05	1.26 to 3.33	**0.004**	1.92	1.20 to 3.06	**0.006**	1.27	0.65 to 2.47	0.481
CASS sudomotor (points)	1.04	0.50 to 2.19	0.911	0.90	0.42 to 1.90	0.772	0.66	0.27 to 1.60	0.360
CASS cardiovagal (points)	2.09	1.26 to 3.47	**0.004**	2.03	1.23 to 3.35	**0.006**	1.49	0.82 to 2.72	0.189
Nephropathy stage	2.12	1.32 to 3.41	**0.002**	2.06	1.30 to 3.26	**0.002**	–	–	–
Neuropathy stage	0.92	0.59 to 1.43	0.717	0.91	0.59 to 1.40	0.661	0.64	0.37 to 1.10	0.108

*Mean over time.
†ECG 1, ECG diagnostic of acute myocardial infarction or evolving diagnostic; ECG 2, ECG with left bundle branch block or electronically paced complexes.
Significant values in bold.
CASS, composite autonomic severity score; CI, confidence interval; FPG, fasting plasma glucose; Hb, haemoglobin; HDLC, high density lipoprotein cholesterol; HR, hazard ratio; JTc, corrected JT interval; QTc, corrected QT interval; RDNS, Rochester diabetic neuropathy study.

differences in the severity of diabetic retinopathy, polyneuropathy, and nephropathy among the groups—notably the stage of nephropathy was more severe in the two groups who died (table 1).

Life table analysis of risk factors for sudden cardiac death

In univariate analysis, many risk covariates were statistically associated with sudden cardiac death (table 2). The relative hazard for sudden cardiac death associated with each risk factor is shown in table 2. Since the increase in hazard depends on the amount of increase in the corresponding risk factor, we have indicated the increase in risk associated with a clinically meaningful increase in the risk factor. For example, a 1000 mg/24 hour increase in 24 hour microalbuminuria is estimated to result in a 2.38-fold increased risk of sudden cardiac death. The largest relative hazards were observed for the three ECG variables and calcification of vessels in the foot. In bivariate analysis of risk covariates (table 3), ECG 1 (evolving and previous myocardial infarction), ECG 2 (bundle branch block or electronic pacing), ECG 1 or ECG 2, and nephropathy stage were significant risk factors. Adjusting for ECG 1 or ECG 2, the following factors were significant: CASS total, CASS adrenergic, CASS cardiovagal, QTc interval, HDL cholesterol, 24 hour microalbuminuria, and 24 hour total proteinuria. However, after adjusting for nephropathy stage, none of the autonomic scores, QTc interval, HDL cholesterol, microalbuminuria, or total proteinuria was significant.

Review of death certificates, medical records, and necropsy reports

All patients who died suddenly had either severe coronary atherosclerosis with myocardial damage at necropsy, or a clinical history of atherosclerosis with clinical left ventricular dysfunction, or both. Unexpected death from arrhythmia had not occurred in the absence of severe coronary atherosclerosis or left ventricular impairment.

DISCUSSION

The present study provides two lines of evidence that sudden cardiac death relates more directly to coronary ischaemia, cardiac arrhythmia, or nephropathy than it does to diabetic autonomic neuropathy. Based on bivariate life table analysis, ECG evidence of evolving or past myocardial infarction, bundle branch block, and stage of nephropathy were stronger risk covariates than were indicators of autonomic neuropathy or HDL cholesterol. In fact, in bivariate analysis and adjusting for nephropathy stage, autonomic test results were not statistically significant factors. Second, our survey of death certificates, medical records, and necropsy reports revealed evidence of preceding severe atherosclerosis and myocardial damage in all patients dying suddenly. The latter changes were judged to be sufficiently advanced to be the direct cause of death. In other words, cardiac autonomic neuropathy in the absence of severe atherosclerosis or myocardial damage was not found to be associated with sudden cardiac death.

In the light of our results, the role of autonomic neuropathy as the pivotal event in sudden cardiac death in diabetic patients probably needs revision. Ewing *et al*[3] first reported an association between DAN and sudden cardiac death. These investigators suggested that autonomic neuropathy and an abnormal brain stem mechanism might be involved in sudden cardiac death. Other workers[20 21] have also noted an increased frequency of sudden unexpected death in patients with DAN. The hypothesised mechanisms of sudden death have included silent myocardial ischaemia and infarction, impaired central control of respiration, reduction in heart rate variability,[22–24] sympathovagal imbalance, and predisposition to cardiac arrhythmias because of alterations in the QTc interval.[25–28] However, actual studies of these functional events at death are not available. In addition, we have also analysed the possible association of the increase in the QTc and JTc intervals with sudden cardiac death. The QTc interval was statistically significant in univariate analysis but like many other putative risk factors this association was not supported in the multivariate life table analysis. Crow and colleagues reported that the JTc interval was a significant independent predictor of incident coronary heart disease in men.[29] In our study, the JTc interval was not a significant factor associated with sudden cardiac death.

Previous studies suggesting that DAN causes sudden cardiac death have not been sufficiently rigorous. Jouven and colleagues[30 31] studied the risk factors associated with sudden death in a large cohort of patients followed for more than 20 years (Paris prospective study I). They identified parental involvement in sudden death as an independent risk factor. In addition, they found an association between diabetes mellitus and sudden cardiac death after adjusting for other cardiovascular risk factors, but no measurement of autonomic neuropathy was actually undertaken. Other investigators[22] postulated an alteration in the parasympathetic–sympathetic balance in which a reduction in parasympathetic (vagal) tone secondary to DAN leads to a relative overactivity of the sympathetic system; this enhanced sympathetic tone may also play a role in nocturnal hypertension, ventricular arrhythmias, and increased risk of cardiovascular events in diabetic and non-diabetic patients. Our data do not conform to this hypothesis, as we found impairment of both cardiovagal and adrenergic responses. In addition, the coexisting coronary atherosclerosis, myocardial injury, and kidney disease appeared to be sufficient to account for sudden cardiac death.

Scintigraphic studies that analyse the sympathetic innervation of the ventricle may help us to understand the complex relations between ischaemic heart disease, DAN, and sudden cardiac death. Cardiac positron emission tomographic (PET) studies after myocardial infarction have shown regional cardiac sympathetic denervation.[1] Metaiodobenzylguanidine (MIBG) single photon emission computed tomography (SPECT) studies have shown that diabetic patients with poor glycaemic control have greater areas of left ventricular sympathetic denervation.[32] Stevens *et al*[33] carried out cardiac PET studies and found that diabetic patients with mild DAN had only distal left ventricular sympathetic denervation, but patients with severe DAN showed a pattern of distal cardiac sympathetic denervation associated with proximal ventricular islands of hyperinnervation. These proximal areas also had significant impairment of blood flow.[34] These areas of denervation and hyperinnervation may cause unstable regions of electrical, vascular, or autonomic heterogeneity conducive to lethal ventricular arrhythmias.[35] These findings may explain the cardioprotective benefits of β blockers and amiodarone—drugs that stabilise autonomic balance—in reducing sudden cardiac death after myocardial infarction.[36] Although we did not carry out cardiac PET studies in our patients, our findings complement these observations.

Nephropathy was an independent risk factor for sudden cardiac death in our study. In the sudden cardiac death group of our cohort, 31% of patients had nephropathy stages 3 and 4. Previous studies[37 38] have documented the increased mortality of diabetic patients with renal failure. Mogensen[39] reported that the presence of microalbuminuria in patients with diabetes mellitus type II was a predictor of clinical proteinuria and increased mortality. Other studies[40] have also shown that microalbuminuria is a strong independent risk factor for cardiovascular disease in diabetic and non-diabetic

individuals, and may be a useful marker of diffuse endothelial dysfunction. The data presented here support this observation. We suggest that nephropathy is not the cause of sudden cardiac death but rather a marker of generalised vascular dysfunction, which, in conjunction with other risk factors, contributes to the causal process.

Our study had limitations. First, serial data obtained before and during sudden cardiac deaths (for example, from an ECG or implanted cardiac recording device) were not available on our patients. Second, we may not have modelled for all applicable risk factors—for example, a family history of sudden cardiac death and the presence of inflammatory markers (C reactive protein) may be important. Third, the study sample was predominantly of northern European extraction and the results may not apply to other ethnic groups.

Conclusions

Our findings suggest that coronary artery disease causing ischaemia and renal disease are the main risk factors for sudden cardiac death in the Rochester diabetic neuropathy study cohort. It is possible that DAN may act as the transient factor conducive to the final event, but further studies are necessary to determine this.

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