Influence of Caffeine on Heart Rate Variability in Patients With Long-Standing Type 1 Diabetes

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OBJECTIVE — The effect of caffeine on cardiovascular health remains controversial. Patients with long-standing type 1 diabetes are at risk of autonomic failure and sudden cardiac death. We investigated the effects of caffeine on autonomic dysfunction (as assessed by heart rate variability [HRV]) in this high-risk group and in a control population.

RESEARCH DESIGN AND METHODS — Using a randomized blinded, placebo-controlled, crossover design trial, we examined 2 weeks of caffeine consumption (250 mg twice daily) on HRV in 20 type 1 diabetic patients and 10 matched healthy volunteers.

RESULTS — Baseline HRV was blunted in the diabetic patients ($P < 0.0005$ vs. control subjects) and markedly increased by caffeine in both groups (+103% in the group with diabetes [$P = 0.009$] and +38% in control subjects [$P = 0.002$]). The caffeine-associated increase in HRV was not statistically different between the control and the type 1 diabetes groups ($P = 0.16$).

CONCLUSIONS — Modest amounts of caffeine improved autonomic function in diabetic patients and healthy volunteers. For individuals with abnormal HRV, regular caffeine use may have the potential to reduce the risk of cardiovascular events.

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R educed heart rate variability (HRV), a manifestation of autonomic dysfunction, is associated with increased risk of premature cardiovascular disease and sudden death in both diabetic and nondiabetic populations (1,2). In patients with type 1 diabetes, autonomic dysfunction may be detectable in up to 40% of individuals (3).

Regular use of caffeine may be useful in type 1 diabetic patients at risk of hypoglycemia (4). The intensity of early warning symptoms of hypoglycemia and early hormonal counterregulatory responses are enhanced by caffeine, allowing individuals to take appropriate action before neuroglycopenia develops (5). Ingestion of modest amounts of caffeine in normal subjects is associated with detectable cardiovascular changes, including a transient increase in blood pressure, although these attenuate with sustained use (6). However, the effects of ingestion of caffeine on autonomic function are unknown.

The aim of this study was to assess the effect of caffeine on HRV in patients with long-standing type 1 diabetes and healthy control subjects.

RESEARCH DESIGN AND METHODS — All subjects provided written informed consent, and this study was approved by the local ethics committee. Twenty patients with long-standing (>5 years) type 1 diabetes and 10 control subjects with similar sex and age distribution and without evidence of cardiovascular disease (Table 1) participated in a double-blind, randomized crossover, placebo-controlled study of the effects of caffeine ingestion on HRV.

Patients and nondiabetic control subjects had no clinical evidence of autonomic or structural heart disease from history or examination. Patients were screened by 12-lead electrocardiogram (ECG), echocardiography, and treadmill exercise testing. Those with atrial fibrillation, left-bundle branch block, evidence of left ventricular systolic impairment (left ventricular ejection fraction <50%), or exercise-induced ischemia (ST depression ≥1 mm at ≥85% maximum predicted heart rate during or after exercise using the Bruce protocol) were excluded. No patients had renal failure. All control subjects had normal beats for at least 99% of total QRS complexes on 24-h ambulatory ECG monitoring.

All participants were maintained on a low-caffeine diet (<50 mg/day) for 2 weeks with either 250-mg caffeine capsules supplemented twice daily (equivalent to average caffeine intake in the U.K.) or matched placebo. At the end of the 2 weeks, HRV was assessed over the last 48 h by continuous Holter monitoring recorded on a miniature digital recorder (Life Card; Reynolds Medical). Over the same 48 h, the diabetic patients also underwent simultaneous assessment of interstitial glucose levels using the continuous subcutaneous glucose monitoring system (CGMS) (7). The patients and control subjects were crossed over to the alternate treatment arm, and the final set of measurements were repeated at the end of a further 2 weeks.

Assessment of autonomic function
The Reynolds Life Card has a crystal-generated time reference track that allowed for recording and replay of speed errors to within 0.5%. Recordings were

Table 1—*Details of participants*

	Type 1 diabetic patients	Control subjects	P
n	20	10	—
Sex (male)	10	5	—
Age (years)	44.3 ± 9.2	41.4 ± 10.8	0.44
Duration of diabetes (years)	19.2 ± 10.4	—	—
Heart rate (bpm)	79 ± 8	73 ± 5	0.055
Blood pressure (mmHg)	125 ± 14/73 ± 7	124 ± 15/73 ± 7	0.88/0.94
HbA$_{1c}$ (%)	8.4 ± 1.1	—	—
Microalbuminuria (albumin-to-creatinine ratio 3.5–30 mg/mmol)	0.8 ± 1.1	—	—
Retinopathy	25 (5)	—	—
Sensory neuropathy	10 (2)	—	—
Antihypertensives	25 (5)*	0 (0)	0.089

Data are *n,* means ± SD, or % (*n*). *ACE inhibitor or angiotensin-receptor blocker.

relayed through a Pathfinder 700 arrhythmia analyzer. After initial arrhythmia assessment, time-domain analyses of HRV were performed. For the purposes of the study, counts of RR interval >50 ms (sNN$_{50}$) averaged over the 48-h period were used as a measure of HRV (8).

Frequency domain variables of the HRV were calculated by fast Fourier transformation throughout the whole recording period (9,10). A low-pass filter was used to exclude ectopic beats and movement artifacts. A fast Fourier transformation was computed every 5 min of each hour over the 48 h of ECG recording, with the resulting power spectrum corrected for filtering and sampling effects. We calculated the 24-h spectral density and assessed the power with two frequency bands. The low frequency (LF) power (0.04–0.15 Hz) reflects modulation of sympathetic and parasympathetic tone by baroreflex activity, and the high frequency (HF) power (0.15–0.4 Hz) reflects modulation of vagal tone (sympathetic activity). The LF-to-HF ratio reflects sympathetic activity (11).

Statistical analysis
Statistical analysis was performed using Excel (Microsoft) and SPSS for Windows version 11. For each individual at the end of each phase of the study, the hourly counts of RR >50 ms over the 48-h period were summarized by calculating the area under the curve. These summary statistics were then used for the data analysis. RR counts >50 ms, LF, HF, and the LF-to-HF ratio were assumed to be nor-mally distributed (all Kolmogorov-Smirnov *Z* statistics had *P* values of >0.05). Comparison of changes between caffeine and placebo phases within people with diabetes and healthy control subjects were made using the paired *t* test, and mean changes were presented with 95% confidence intervals. Comparisons between diabetic and control groups were made using the independent samples *t* test, assuming equality of variance, and mean differences were presented with 95% confidence intervals. Because there were differences in baseline HRV between the groups, data on HRV has been analyzed using both percentage changes and absolute changes between caffeine and placebo phases. All tests were two tailed and used a 5% critical *P* value.

RESULTS — Clinical and laboratory characteristics of the diabetic and control groups are shown in Table 1.

Diabetes control in this study is similar to our clinic type 1 diabetic population, which was recently estimated at 8.6% for 669 patients. In the diabetic group, there were no episodes of severe hypoglycemia (i.e., no hypoglycemic events requiring external help) throughout each study period. There were episodes of biochemical hypoglycemia (interstitial glucose <63 mg/dl) during the 48 h of CGMS in both the better and more poorly controlled patients, with a median of 140 min. However, there was no correlation between hypoglycemia and HRV (Spearman correlation coefficient 0.12, *P* = 0.62).

On placebo, the mean ± SD HRV for type 1 diabetic patients was 70 ± 72 counts per hour and was significantly lower than that for the nondiabetic control subjects (213 ± 86 counts per hour, mean difference 141 counts per hour [95% CI 78–205], *P* = 0.0005 using independent samples *t* test) (Fig. 1).

After regular caffeine use, HRV increased in diabetic subjects by 103% ([95% CI 34–173], mean increase [±SD] in sNN$_{50}$ 36 ± 55 counts per hour [95% CI 10–63], *P* = 0.009) and in healthy control subjects by 38% ([95% CI 18–60], mean increase [±SD] in sNN$_{50}$ 55 ± 40 counts per hour [95% CI 27–83], *P* = 0.002) when compared with placebo. The caffeine-associated increase was not statistically different between the control and the type 1 diabetic groups (mean percentage difference 70% [95% CI −27 to 168], *P* = 0.16; mean absolute difference 18 [95% CI −22 to 58]) (Fig. 2).

Spectral analysis showed that the increase in HRV was a consequence of enhanced parasympathetic activity with a concomitant reduction in sympathetic activity (Table 2).

Half of both the control subject and diabetic patient groups were either randomized to placebo or caffeine first. The subjects randomized to caffeine first were considered to be "caffeine tolerant"—they had continued directly from their caffeine-replete diet to ongoing caffeine supplementation. The "caffeine naïve" subjects underwent a period of caffeine withdrawal on the placebo arm before reintroduction to caffeine on the active arm. All subjects were analyzed together, and the differences in HRV between the caffeine and placebo phases were calculated for each subject. There was no statistically significant difference (*P* = 0. 80) in the increase in HRV between the caffeine-tolerant and caffeine-naïve groups, demonstrating that the influence of caffeine on HRV did not attenuate with sustained use. Ingestion of caffeine was not associated with any dysrhythmia (supraventricular tachycardia, aberrant beats, or ventricular tachycardia) in either group.

CONCLUSIONS — In this study, ingestion of modest amounts of caffeine (equivalent to two to three cups of drip brewed coffee) was associated with improvement in HRV in both healthy volunteers and diabetic patients. There was no
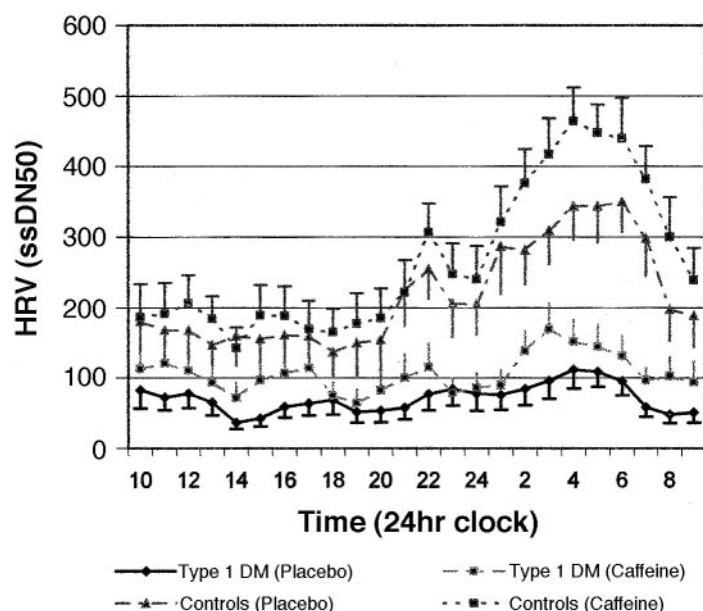
Figure 1—*Diurnal variation of HRV (as measured by total sNN$_{50}$ averaged for each individual over 48 h) and the influence of caffeine in type 1 diabetic and control groups.*

evidence that caffeine caused cardiac dysrhythmia or tolerance (attenuation of the effect on HRV with sustained caffeine use).

Diabetic autonomic neuropathy is characterized by widespread neuronal degeneration of small nerve fibers of both sympathetic and parasympathetic tracts. Although standard bedside autonomic function tests may identify individuals at high risk of cardiac morbidity and mortality (12), HRV appears to be a sensitive marker of autonomic dysfunction at an earlier stage (13,14). In our study, we used sNN$_{50}$ per hour as a measure of HRV. This is considered to be a threshold beyond which each RR interval must pass in order to be counted and has been suggested to be the most sensitive test for the detection of diabetic autonomic neuropathy (15). A reduction in HRV indicates increased cardiovascular risk independently of traditional coronary risk factors (16).

Power spectral analysis can be used to differentiate the various components of sympathovagal activity on HRV. In this study, the HF domain was used as a marker of parasympathetic activity, and the LF-to-HF ratio was used as a measure of sympathetic activity (17). Impairment in parasympathetic function with relative sympathetic overactivity predisposes to ventricular dysrhythmias post–myocardial infarction (18) and to

subsequent coronary events in patients with non–ST segment elevation myocardial infarction (19). The improvement in HRV observed here was as a result of increased parasympathetic activity. While this may be associated with a reduction in the tendency for dysrhythmias, there was no difference in the prevalence of dysrhythmia between the groups, which was probably due to the small number of events in each group.

In patients with diabetes, abnormalities of HRV may precede clinical expression of autonomic failure (20). Some investigators have described an association between autonomic dysfunction and abnormal cardiac repolarization, manifested by a prolonged QT interval (21,22). These abnormalities may predict subsequent fatal ventricular dysrhythmias and sudden death. Factors exacerbating QT prolongation include hypokalemia, which may be provoked by low prevailing glucose (23) and by hypoglycemia per se (24). We did not find a consistent relationship between fluctuations in interstitial glucose levels as assessed by the CGMS and HRV.

Despite the caffeine-associated improvement in HRV, values do still fall short of the normal range. However, the increase is still important. With older technology, subtle differences in HRV were missed, and only cases with severely impaired HRV were identified. In those cases, mortality was as high as 50% over 5 years (12). In our study, patients with severely impaired or no HRV at all did not benefit from caffeine. This may be because the disease process associated with autonomic neuropathy has progressed irreversibly. This highlights the importance of identifying and treating patients at risk of developing autonomic neuropathy earlier in an attempt to improve cardiovascular morbidity. Any improvement in HRV is likely to be of potential benefit to car-
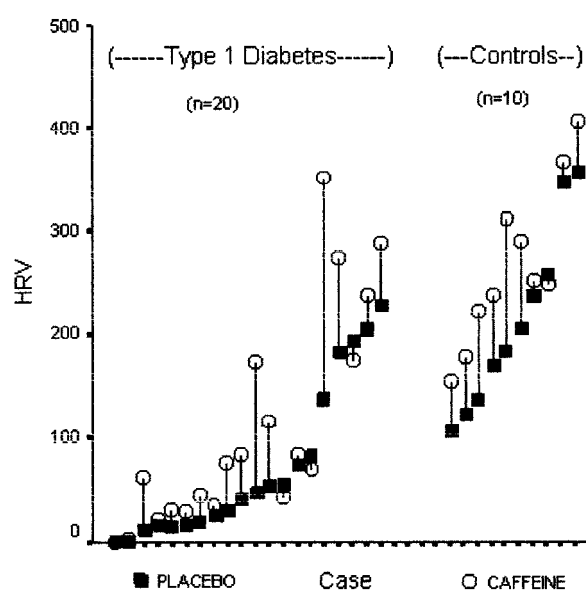
Figure 2—*Absolute change in HRV with caffeine in patients with type 1 diabetes and in control subjects (HRV measured as sNN$_{50}$).*

Table 2—*Influence of caffeine on HRV (time domain and spectral analysis) in type 1 diabetic and control subjects*

	HRV			
	Time domain	Spectral analysis		
	sNN_{50}	LF	HF	LF-to-HF ratio
Control subjects				
Placebo	213 ± 89	77 ± 5	16 ± 4	5 ± 2
Caffeine	268 ± 79	77 ± 4	16 ± 4	5 ± 1
Mean absolute change	$+54$ ($P = 0.009$)	$+0.39$ ($P = 0.64$)	$+0.52$ ($P = 0.51$)	-0.25 ($P = 0.44$)
Type 1 diabetic subjects				
Placebo	70 ± 72	74 ± 13	17 ± 13	4 ± 1
Caffeine	107 ± 101	73 ± 14	19 ± 14	4 ± 1
Mean absolute change	$+36$ ($P = 0.002$)	-0.8 ($P = 0.10$)	$+1.4$ ($P = 0.012$)	-0.4 ($P = 0.006$)

Data are means $\pm$ SD.

diovascular health, as there is no evidence of a cutoff for HRV-associated cardiovascular morbidity. The benefit of caffeine is that it is readily available to the majority of the population.

Caffeine is present in a wide variety of foods and beverages and is the most widely consumed stimulant drug in the world. A cup of percolated coffee contains between 104 and 117 mg of caffeine, and a cup of filter coffee contains 142 mg (25). In patients with cardiac disease, coffee has been reported to decrease the refractory time in the atrioventricular node (26) but not to predispose to ventricular dysrhythmias following myocardial infarction. The majority of studies have found no association between coffee and coronary heart disease (27).

In conclusion, the effect of caffeine in doses resembling average daily coffee intake improved HRV in diabetic subjects and healthy volunteers. Longer-term studies are required to investigate whether caffeine may be associated with a reduction in arrhythmias and sudden cardiac death in people with diabetes and other high-risk groups.

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