Predictive Value of Cardiac Autonomic Neuropathy in Diabetic Patients With or Without Silent Myocardial Ischemia

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OBJECTIVE — The aim of this study was to determine the predictive value of silent myocardial ischemia (SMI) and cardiac autonomic neuropathy (CAN) in asymptomatic diabetic patients.

RESEARCH DESIGN AND METHODS — We recruited 120 diabetic patients with no history of myocardial infarction or angina, a normal 12-lead electrocardiogram (ECG), and two or more additional risk factors. SMI assessment was carried out by means of an ECG stress test, a thallium-201 myocardial scintigraphy with dipyridamole, and 48-h ECG monitoring. CAN was searched for by standardized tests evaluating heart rate variations. Accurate follow-up information for 3–7 years (mean 4.5) was obtained in 107 patients.

RESULTS — There was evidence of SMI in 33 patients (30.7%). CAN was detected in 33 of the 75 patients (38.9%) who were tested, and a major cardiac event occurred in 11 of them. Among these 75 patients, the proportion of major cardiac events in the SMI^+ patients was not significantly higher than that in the SMI^- patients (6 of 25 vs. 5 of 50 patients), whereas it was significantly higher in the CAN^+ patients than in the CAN^- patients (8 of 33 vs. 3 of 42 patients; $P = 0.04$), with a relative risk of 4.16 (95% CI 1.01–17.19) and was the highest in the patients with both SMI and CAN (5 of 10 patients). After adjusting for SMI, there was a significant association between CAN and major cardiac events ($P = 0.04$).

CONCLUSIONS — In asymptomatic diabetic patients, CAN appears to be a better predictor of major cardiac events than SMI. The risk linked to CAN appears to be independent of SMI and is the highest when CAN is associated with SMI.

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Many diabetic patients with severe coronary stenoses are asymptomatic; however, the severity of the symptoms does not predict the outcome. This is supported by the recent finding that within 7 years of follow-up, the rate of coronary deaths in diabetic patients without previous myocardial infarction (MI) is as high as the rate among nondiabetic patients with previous MI (1); this suggests that silent coronary heart disease is probably very frequent in diabetic patients. In diabetic patients without cardiac symptoms or signs, but with other cardiovascular risk factors, silent myocardial ischemia (SMI) has been found in 10–29% of the cases (2–4). However, coronary angiography confirms the presence of significant coronary stenoses in only one- to two-thirds of these patients (2,4). In the remaining patients, the results of the noninvasive tests are considered to be either falsely positive or the consequence of changes in coronary vasomotricity or reduced coronary reserve (5).

Cardiac autonomic neuropathy (CAN) has been found in 30–70% of unselected diabetic patients (6,7). Several longitudinal studies have suggested that CAN is associated with adverse outcomes (6), mainly of cardiac origin. SMI might be involved in the poor prognosis associated with CAN. However, the relationship between SMI and CAN is not clearly established (3,4,8,9), and there are no data available on the respective prognostic value of CAN and SMI.

In asymptomatic diabetic patients with no history of MI or angina (type 1, as described by Cohn [10]), there are very few data on the prognosis related to SMI. The high rate and severity of cardiovascular events in diabetic patients have led to the recommendation of detecting SMI and CAN in asymptomatic diabetic patients with other cardiovascular risk factors (11,12). Although, this strategy does not seem to be sufficiently documented, and longitudinal studies are needed. Therefore, the aim of this study was to determine the predictive value of SMI and CAN in a series of asymptomatic diabetic patients with additional risk factors.

RESEARCH DESIGN AND METHODS

— A total of 120 diabetic patients were recruited in two diabetology units (Jean Verdier Hospital and Robert Debré Hospital) from January 1990 to December 1991 for the assessment of SMI and CAN. All of the patients fulfilled the following criteria for inclusion: *1*) absence of MI or angina; *2*) normal standard 12-lead electrocardiogram (ECG) at rest; *3*) diabetes duration >15 years for type 1 diabetic patients and >5 years for type 2 diabetic patients; and *4*) at least two additional cardiovascular risk factors, either dyslipidemia

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Abbreviations: CAN, cardiac autonomic neuropathy; ECG, electrocardiogram; MI, myocardial infarction; SMI, silent myocardial ischemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(total cholesterol >6.5 mmol/l and/or triglycerides >2.5 mmol/l), blood pressure >140–80 mmHg, BMI >29 kg/m^2, tobacco consumption, lower-limb obstructive arterial disease, nephropathy defined by albuminuria >30 mg/day, or a history of coronary artery disease before 60 years of age in first-degree relatives. None of the patients had valvular heart disease, congenital heart disease or cardiomyopathy, asthma or severe chronic bronchopathy, end-stage renal failure (plasma creatinine >250 μmol/l), thyroid disease, chronic alcohol consumption, or morbid obesity.

Of the 120 patients, 13 moved to another area in France or another country a few months after the investigation. We obtained accurate follow-up information from the remaining 107 patients. The mean age of these patients was 54.7 years (range 30–70). Of these patients, 17 had type 1 diabetes and 90 had type 2 diabetes treated by diet alone or diet with oral hypoglycemic drugs.

SMI and CAN function tests were performed in 75 of the 107 patients. The main clinical and biochemical characteristics of these 75 patients were very similar to those of the 32 patients for whom only SMI tests were available.

Initial assessment

Initial assessment was performed as previously described (4). The patients gave their informed consent, and this study received the approval of a local ethical committee. Treatments such as β-blockers, calcium-channel blockers, or ACE inhibitors were withdrawn ≥2 days before the cardiac investigations.

Assessment of a cardiac ischemic disease was performed in all of the patients by means of three noninvasive tests: an ECG stress test, a thallium-201 myocardial scintigraphy with intravenous infusion of dipyridamole, and ambulatory 48-h ECG monitoring. The investigators agreed on common positive criteria for myocardial ischemia. The tests were performed according to a standard protocol.

Briefly, the ECG stress test consisted of a graded exercise test on a bicycle ergometer, starting from a workload of 30 W and increasing by 30 W every 3 min. The test was considered to be positive if angina occurred; if there was an ST-segment horizontal or downsloping depression ≥0.1 mV at 0.08 s beyond the *J* point; if there was ventricular ectopic activity (>5 ventricular premature contractions per minute or complex ventricular premature contractions: couplets, ventricle tachycardia, or multiform); or if there was atrioventricular blockade or intraventricular bundle blockade. The ECG stress test was monitored by the same investigator in each center, and all ECG recordings were read independently and blindly by both investigators.

Thallium-201 myocardial scintigraphy was performed using pharmacological stress testing, which consisted of infusing 0.56 mg/kg dipyridamole intravenously for 4 min. Then, 3 or 4 mCi of thallium-201 was administered 4 min after the completion of dipyridamole infusion, when body weight was <75 or >90 kg, respectively. Myocardial scintigraphy was performed by a single investigator in each center, and all images were read independently and blindly by both investigators. The test was considered to be positive when transient defects were observed by both investigators. Defects strictly localized to the apex or base were not considered significant.

Ambulatory electrocardiographic monitoring was performed with an Avionics device during hospitalization. Two channel recordings (leads V5 and V5R) were obtained. The test was considered positive if either a horizontal ST-segment depression ≥1.5 mm lasting ≥1 min or a horizontal or convex ST-segment elevation ≥1.5 mm lasting ≥1 min occurred 0.08 s beyond the *J* point for a heart rate <100 beats/min or 0.08 s after the *J* point for a heart rate >100 beats/min (taking the isoelectric line of three consecutive PR-segments as the reference line). All recordings were analyzed by the same investigator.

Coronary angiography was proposed to the patients who had at least one positive test. A coronary stenosis was considered to be significant when ≥50% narrowing was found on the left coronary artery or ≥70% narrowing was found on the left anterior descending artery, the circumflex artery, a well-developed marginal vessel, or the right coronary artery.

Other cardiovascular investigations

Cardiac autonomic function tests were performed as previously described (7). Briefly, they consisted of measuring RR-interval variations during three tests using a computerized device (QMed, Laurence Harbor, NJ) (13). The Valsalva test, conducted with the patient seated, consisted of forcing exhalation and maintaining a pressure of 40 mmHg for 15 s. The result was expressed as the ratio of RR maximum to RR minimum. It was performed consecutively three times, and the mean value for this ratio was taken. The deep breathing test was performed in a previously trained subject and consisted of taking six deep breaths for 1 min in a lying position. The result was expressed as the mean value for the ratio of maximal heart rate to minimal heart rate. During the lying-to-standing test, heart rate variation was determined by calculating the maximal-to-minimal heart rate ratio; the maximal heart rate was approximately the 15th beat, and the minimal heart rate was approximately the 30th beat. The results of the three tests were compared with those from a control series with age taken into account, as previously described (14,15). The reproducibility of these methods has been demonstrated in diabetic patients: the coefficients of variation are 9.2, 12.6, and 6.4% for the Valsalva, deep-breathing, and lying-to-standing tests, respectively (16).

Echocardiograms were performed according to a standard protocol by skilled sonographers, one in each center, to exclude a valvular or congenital disease and cardiomyopathy.

Follow-up

A follow-up procedure was agreed on by the investigators and included at least one cardiovascular examination once a year. Most of the follow-up for the patients occurred at our hospitals (Jean Verdier and Robert Debré). Information was obtained for those patients whose follow-up was performed by a general practitioner or cardiologist. The case report files of the patients who were hospitalized in other departments were also obtained. The patients who had not been recently examined in our departments were requested to have an assessment of cardiovascular signs and symptoms and a 12-lead ECG. For the patients who died, the cause of death was documented with the help of the patient's family and general practitioner.

The following events were considered to be major cardiac events: death of cardiac origin (sudden death or death caused by MI or congestive heart failure), nonfatal MI, heart failure, resuscitation from ventricular tachycardia/fibrillation, and need for coronary revascularization. MI was considered to be a major event whether the patient was hospitalized or not. MI was defined by a serum creatinine kinase level >240 U/l with creatinine kinase MB-isoform isoenzymes >15 U/l associated with new Q waves ≥0.04 s on the 12-lead ECG,

or ST-segment depression >1 mm 60 ms after the *J* point for non–Q wave MI. Silent MI was defined by the appearance of new Q waves on the ECG performed during the follow-up. The other cardiovascular events were previously mentioned (the exercise occurrence of angina, nonfatal arrhythmias, stroke, and limb amputation).

Statistical analyses

Data are means ± SD. Continuous variables were compared by the unpaired *t* test and the Mann-Whitney *U* test (as appropriate, according to the gaussian or nongaussian distribution), and categorical data were compared by Pearson's χ^2 test or Fisher's exact test. All of the comparisons were two-sided. Odds ratios were calculated with 95% CIs. The Kaplan-Meier method was used to examine the time-dependent cumulative probabilities of the outcomes. The Mantel-Haenszel χ^2 test was used to evaluate the odds ratio of a variable after adjusting for another variable, and the multivariate stepwise Cox regression analyses were performed to determine the independent predictors of events. Statistical analyses were carried out using SPSS software.

RESULTS

Initial assessment

Among the 107 diabetic patients, the exercise test was positive in 23 cases, the thallium myocardial scintigraphy in 17 cases, and the 24-h ECG recording in 7 cases. Thus, evidence of SMI was obtained in 33 patients (30.7%) who had at least one positive noninvasive test. Coronary angiography was accepted by 28 of these patients and confirmed the presence of significant coronary stenoses in 12 patients, whereas coronary arteries were angiographically normal in the other 16 patients.

Cardiac autonomic function tests disclosed CAN in 33 of the 75 patients who were tested (38.9%). Among these 75 patients, SMI was present in 25, and significant coronary stenoses were present in 12 patients. CAN was found in 10 of the 25 patients with SMI (40%) and in 4 of the 12 patients with coronary stenoses (33.3%). CAN was also found in 23 out of the 50 patients free of SMI (46%). There is no significant statistical difference between these percentages.

Follow-up

Follow-up duration was 3–7 years (mean 4.5). Among the 107 patients, a major cardiac event occurred in 11 patients (10.3%): 2 patients died, there were 5 cases of nonfatal MI, and 4 patients needed a revascularization procedure (coronary angioplasty in 3 patients and coronary artery bypass grafting in 1 patient). Other cardiovascular events occurred in eight patients, consisting of atrial arrhythmia in one patient, transient stroke in two patients, a leg amputation in one patient, and angina with confirmation of significant coronary stenoses on the angiography in four patients.

Variables associated with major cardiac events

Univariate analyses. All of the major cardiac events occurred in the 75 patients who had had both SMI and CAN assessments. The statistical analyses were confined to these 75 patients.

There was no significant difference in age, diabetes duration, type of diabetes, BMI, HbA_{1c} level, plasma total cholesterol, triglycerides, HDL and LDL cholesterol, or creatinine, and urinary albumin excretion rate at the initial assessment between the patients who developed a major cardiac event and patients who did not.

Among the 11 patients who had a major cardiac event, 6 had evidence of SMI. A coronary angiography was performed in three of them, showing significant stenoses in all three cases. The proportion of major cardiac events was not significantly higher in the SMI^+ patients (6 of 25 patients, 24%) than in the SMI^- patients (5 of 50 patients, 10%). CAN was detected in 8 of the 11 patients who developed a major cardiac event. The proportion of major cardiac events was significantly higher in the CAN^+ patients (8 of 33 patients, 24.2%) than in the CAN^- patients (3 of 42 patients, 7.1%) ($P = 0.04$) with an odds ratio of 4.16 (95% CI 1.01–17.19). The Kaplan-Meier method confirmed that CAN was associated with a higher rate of major cardiac events (log-rank 4.44, $P = 0.03$) (Fig. 1). Of the 10 patients with both SMI and CAN, 5 had a major cardiac event.

The presence of lower-limb arteritis according to Doppler ultrasonography was assessed in 68 of the 75 patients. It was associated with a higher rate of major cardiac events: 4 of 10 cases (40%) vs. 5 of 58 cases (8.6%) ($P = 0.02$); odds ratio 7.07 (95% CI 1.48–33.71). According to the Kaplan-Meier method, this association was also significant (log-rank 8.32, $P = 0.004$).

Variables associated with major cardiac events

Multivariate analysis. The Mantel-Haenszel analysis was carried out with SMI and CAN as independent predictors. It showed that when adjusting for SMI, there was a significant association between CAN and major cardiac events, with an adjusted odds ratio of 4.30 (95% CI 1.07–17.31) ($P = 0.04$). According to the Kaplan-Meier method, this association was also significant independently of SMI (log-rank adjusted for SMI 5.27, $P = 0.02$) (Fig. 1).

CONCLUSIONS

— The aim of the present study was to evaluate the predictive value of SMI and CAN in diabetic patients with additional cardiovascular risk factors. These two complications were searched for at baseline in strictly asymptomatic patients with no cardiac history and with a normal 12-lead ECG. Patients received follow-up for 4–7 years.

Presence or absence of SMI was initially assessed on three noninvasive tests to prevent overlooking coronary heart disease. This study confirms that the prevalence of type 1 SMI is high (~30%) in these patients, and significant coronary stenoses are found in approximately one-third of those patients with SMI (4). CAN was assessed by means of three tests that analyze heart rate variations, which are mainly dependent on parasympathetic control, and age was taken into account as recommended (14). This study also confirms the high prevalence of CAN, as has been previously shown (6,7).

The prognostic value of SMI has been evaluated in many studies (17–20), but the specific data for the diabetic patients included in these studies are not available. The substudy drawn from the Coronary Artery Surgery Study registry showed that in diabetic patients with coronary stenoses, those patients with SMI according to the stress test had a significantly lower survival rate after 6 years of follow-up than nondiabetic patients (59 vs. 82%) and an even lower rate than the diabetic patients free from myocardial ischemia (93%) (21). However, these data must be considered with caution, because this substudy included only 113 diabetic patients, and thallium myocardial scintigraphy is more sensitive than the stress test. In a series of 204 diabetic patients, two-thirds of whom were free from cardiac symptoms (but many of whom had nephropathy), a positive myocardial scintigraphy has been found to be associated with

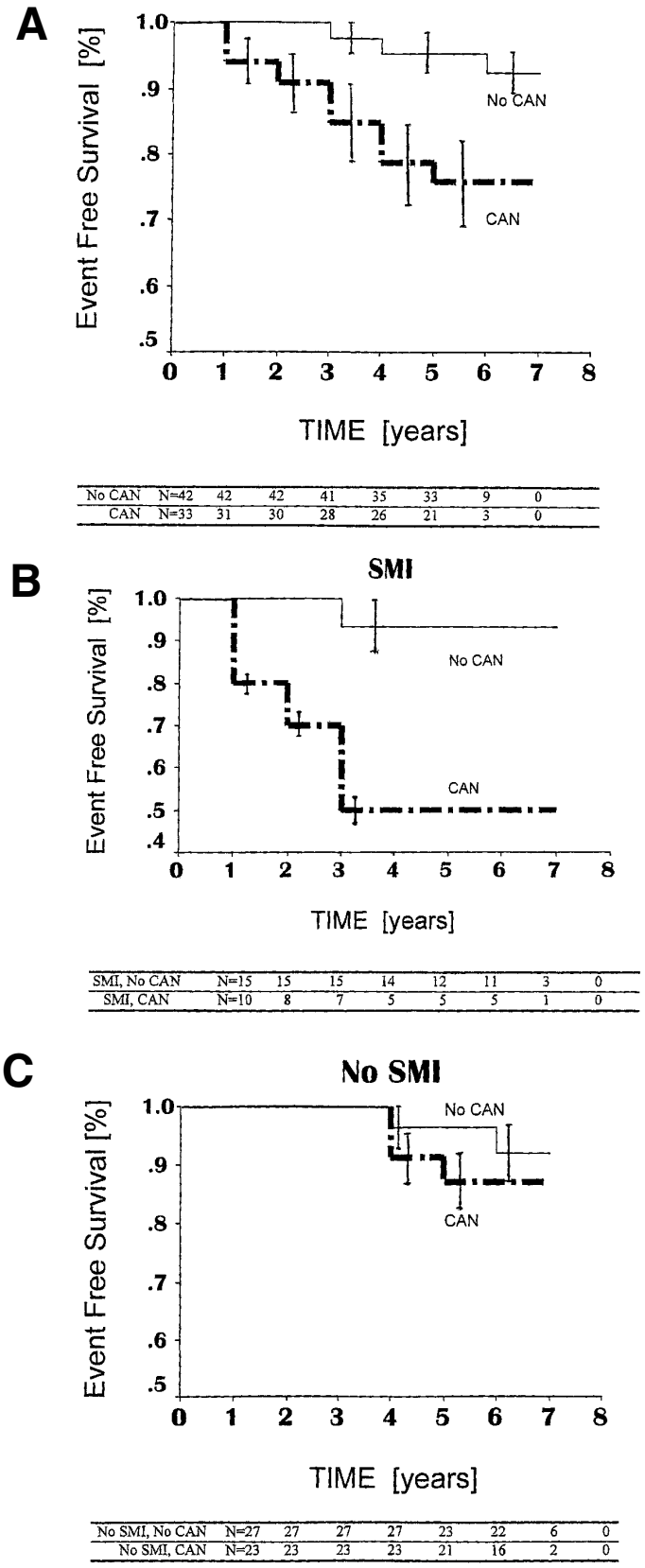

Figure 1—*Kaplan-Meier survival curves for the occurrence of major cardiovascular events according to the presence or absence of CAN. A: The entire series of 75 patients. Log-rank test:* P = *0.03.* B *and C: Patients with SMI or without SMI, respectively. Log-rank adjusted for SMI,* P = *0.02.*

an increased risk of major cardiac events after 0.2–7.0 years of follow-up (22).

A recent review has shown that CAN is also associated with a poor cardiovascular prognosis, the rate of deaths within a mean follow-up of 5.8 years being five times higher in the diabetic patients with CAN than in the diabetic patients free from CAN (6). Moreover, most of these deaths were from cardiac causes. Many of the patients included in these studies probably had coronary heart disease or nephropathy. Indeed, at least one-third of the patients with CAN probably had SMI (3,4,9), and CAN has been found to be associated with microangiopathic complications (23). Unfortunately, very few clinical data are provided in these studies.

The present study has shown that there was only a trend of higher risk of major cardiac events in the diabetic patients with SMI than in the diabetic patients without SMI, whereas CAN was significantly associated with a markedly increased risk of such events. According to the Kaplan-Meier method, the increase in the risk of major cardiac events linked to CAN was significant after adjusting for SMI. However, the highest rate of major cardiac events was found in patients who had SMI and CAN (5 of 10 patients). These data suggest that the poor cardiovascular prognosis related to CAN in previous studies was probably associated with undetected SMI in many patients. The relationship between CAN and SMI is not clearly defined in previous reports, and data are contradictory (3,4,8,9). Nevertheless, our results strongly suggest that SMI should be assessed in diabetic patients with CAN, because prognosis seems to be much poorer when SMI is associated. In addition, the prognostic value of lower-limb arteritis for major cardiac events was very high in the present study. This suggests that SMI should be assessed in diabetic patients with peripheral arterial disease and should be assessed again a few years later.

Other cardiovascular events were reported in the present series. In particular, four patients free from SMI began suffering from angina within 4 or 5 years after the initial assessment. This might suggest that another ECG stress test should be performed a few years after the first one in patients with two or more cardiovascular risk factors.

In conclusion, this study suggests that in asymptomatic diabetic patients, CAN is a better predictor of major cardiac events than SMI. The risk linked to CAN appears to be

independent of SMI and appears to be highest when CAN is associated with SMI. Therefore, CAN should be searched for in the largest possible number of diabetic patients, as previously recommended (12,24). In patients with traditional cardiovascular risk factors, SMI should be assessed, particularly in patients with CAN. This strategy would permit a better selection of patients who would benefit from noninvasive tests used for detecting SMI and therefore reduce the cost of cardiac assessments. However, the present findings must be regarded as preliminary facts that need to be confirmed in a larger series of patients.

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