BRIEF REPORT

Predictive Value of Differential Pulse Pressure in the Diagnosis of Silent Myocardial Ischemia in Patients With Type-2 Diabetes

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Silent myocardial ischemia occurs more frequently in diabetics. Differential arterial pulse pressure is a valuable predictor of cardiovascular disease. We studied 48 consecutive male patients with type-2 diabetes and no known history of ischemic heart disease. Ambulatory monitoring of arterial pressure was carried out and the presence of silent myocardial ischemia was studied using a protocol that involved: resting ECG, echocardiography, 24-hour Holter ECG, conventional exercise stress testing, and exercise testing with nuclear scanning. Nine patients (19%) had silent myocardial ischemia. Differential pulse pressure had good discriminative ability in identifying the presence of silent ischemia: the area under the receiver operating characteristic (ROC) curve was 0.83 (95% confidence interval [CI], 0.71-0.96; *P*=.002). This predictive ability was also observed on adjusted logistic regression modeling (odds ratio [OR], 1.24, 95% CI, 1.02-1.49). We found that the OR for the risk of silent ischemia for every 10-mmHg increase in differential pulse pressure was 8.5 (95% CI, 1.7-31.2). Age and differential pulse pressure were the only independent predictors of silent myocardial ischemia found in this study.

Key words: *Diabetes mellitus. Differential pulse pressure. Silent myocardial ischemia.*

Valor predictivo de la presión diferencial del pulso en el diagnóstico de isquemia miocárdica silente en pacientes con diabetes tipo 2

La isquemia miocárdica silente es más frecuente en diabéticos. La presión arterial diferencial del pulso tiene valor como predictora de riesgo de enfermedad cardiovascular. Estudiamos a 48 varones diabéticos tipo 2 consecutivos sin antecedentes de cardiopatía isquémica. Realizamos medición ambulatoria de la presión arterial y un protocolo de estudio de isquemia miocárdica silente que incluyó: ECG en reposo, ecocardiograma, Holter-ECG-24 h y ergometría convencional y con isótopos radiactivos. Nueve pacientes (19%) presentaron isquemia miocárdica silente. La presión diferencial del pulso mostró buena capacidad discriminadora para determinar la presencia de isquemia silente (área bajo la curva [COR] = 0,83; intervalo de confianza [IC] del 95%, 0,71-0,96; p = 0,002). El efecto predictor se mantuvo en el modelo de regresión logística ajustado (*odds ratio* [OR] = 1,24; IC del 95%, 1,02-1,49). Estimamos una OR de 8,5 (IC del 95%, 1,7-31,2) por cada incremento de 10 mmHg de la presión diferencial del pulso para el riesgo de presentar isquemia silente. La edad y la presión diferencial del pulso fueron los únicos predictores independientes de isquemia miocárdica silente encontrados en este estudio.

Palabras clave: *Diabetes mellitus. Presión diferencial de pulso. Isquemia miocárdica silente.*

INTRODUCTION

Ischemic heart disease is the most common cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The increased cardiovascular risk in this population results from the diabetes, itself, and the higher frequency of conventional risk factors.[1] The prevalence of T2DM in individuals over 30 years old in Spain ranges from 6% to 10% and half these patients are unaware of the diagnosis.[2]

Silent myocardial ischemia (SMI) is 2 to 7 times more frequent in diabetic patients.[3] Detection of this condition allows treatment to be optimized by adopting a strategy

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to assess the extent of coronary disease and the possibility to achieve revascularization.[4,5] Nevertheless, there is no current consensus as to the recommended method for screening these patients.[6] Along these lines, the importance of blood pressure (BP) status as a determinant of cardiovascular risk and the benefits of treating hypertension have been conclusively established. Among its various components, systolic arterial pressure (SAP) and differential pulse pressure (DPP), defined as the difference between SAP and diastolic arterial pressure (DAP), have shown the highest value as predictors of cardiovascular risk in relation to increased arterial wall rigidity.[7]

The main purpose of this study was to assess the usefulness of DPP for predicting SMI by 24-hour ambulatory blood pressure monitoring (ABPM) in patients with T2DM and no history of ischemic heart disease.

METHODS

Study Population

The study included 48 consecutive male patients with T2DM[8] and no documented history of ischemic heart disease, selected from an endocrinology service to investigate the relationship between several parameters and detection of SMI. The exclusion criteria were physical disability or ECG alteration precluding exercise stress testing, and significant kidney disease (plasma creatinine ≥1.5 mg/dL). In accordance with the Declaration of Helsinki, all patients were informed of the objectives, risks, procedures, and possible benefits of the study and gave consent to participate.

Study Variables

After performing a meticulous anamnesis and physical examination, which included calculation of the waist-hip ratio, body mass index, ankle-brachial index, and study of the fundus of the eye by an ophthalmologist, ABPM was performed with recording of the diurnal, nocturnal, maximum, minimum, and mean SAP and DAP values. In addition, BP fluctuation patterns were examined according to the nocturnal BP dip, categorizing patients as non-dipper (0%-10%), dipper (10%-20%), extreme dipper (>20%) or riser, when there was an increase.

Blood samples were drawn from all patients to determine the following parameters:

– Lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C], and triglycerides)

– Glycosylated hemoglobin (HbA_{1c})

– Baseline insulin. The HOMA (Homeostasis Model Assessment) index was calculated according to the following formula: insulin (μU/mL)×glucose (mmol/L)/22.5. Insulin resistance was defined as a value ≥3.5

Screening Protocol for Silent Myocardial Ischemia (Figure)

We began with a baseline electrocardiogram (ECG). If a Q-wave indicating prior myocardial necrosis was seen (defined as duration >0.04 s and depth >1/3 of the QRS complex in at least 2 anatomically consecutive leads), echocardiography was performed. If this test showed regional contractility alterations consistent with the ECG findings, the patient was classified as positive. Otherwise, Holter monitoring of the ECG was continued for 24 hours. Positive status was defined as ≥1 mV of horizontal ST segment depression or 1.5 mV of ST segment elevation for at least 1 min of the recording in the absence of symptoms of angina. If the result was negative, the patient underwent exercise stress testing according to the Bruce protocol; the results were obtained following the recommendations of the Sociedad Española de Cardiología (Spanish Cardiology Society).[9] When the results of this test were negative, SMI was ruled out. If the test was inconclusive, exercise stress testing and nuclear scanning were performed, with positive status established by the criteria of the Sociedad Española de Medicina Nuclear (Spanish Society of Nuclear Medicine).[10]

Statistical Analysis

Quantitative data are expressed as the mean (standard deviation [SD]), and as the median (interquartile range, 25th-75th percentile) when the distribution of the variables was not normal. Qualitative data are expressed as total number and percentage. Student *t* test was used to compare means and the χ^2 test to compare percentages. For variables with a non-normal distribution, the nonparametric Mann-Whitney test was used. To assess the capacity of DPP to discriminate between patients with and without SMI, a ROC curve was constructed. The effect of DPP on the risk of presenting SMI was assessed after adjusting for age and other cardiovascular risk factors by a logistic regression model. A *P* value less than .05 was considered significant.

RESULTS

Nine (19%) patients presented SMI (8 diagnosed by exercise stress testing and one by Holter-ECG). The clinical characteristics of these patients are shown in Table 1. Patients with SMI were older, and had a higher frequency of diabetic retinopathy, poorer recent diabetic metabolic control, higher DPP (only ABPM variable that reached statistical significance) (Table 2), and a nonsignificant trend (*P*=.08) toward longer duration of T2DM.

The DPP showed good discriminative capacity for determining the presence of SMI, as is deduced from the

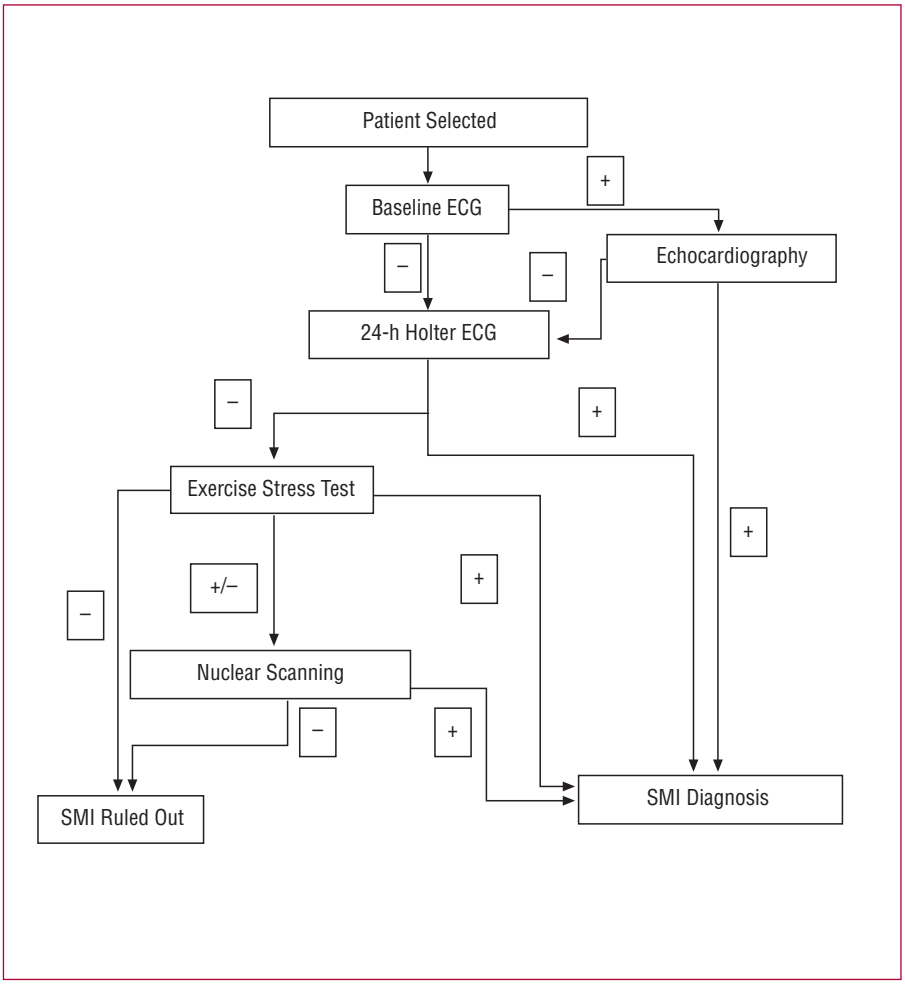

Figure. Flow chart of the protocol used for the diagnosis of silent myocardial ischemia. ECG indicates electrocardiogram; SMI, silent myocardial ischemia.

area under the curve (AUC) obtained from the ROC curve (AUC=0.83; 95% confidence interval [CI] 0.71-0.96; *P*=.002). The predictive effect was maintained in the logistic regression model after adjusting for age, major cardiovascular risk factors (hypertension, smoking, and dyslipidemia) and duration of T2DM, and was significant and independent (odds ratio [OR]=1.24; 95% CI, 1.04-1.49). An OR of 8.5 (95% CI, 1.7-31.2) was estimated for each 10-mm Hg increase in the DPP, for the risk of presenting SMI. The other variable showing an independent relationship in the model was age (OR=1.41; 95% CI, 1.04-1.91).

DISCUSSION

Type 2 diabetes mellitus causes earlier and more severe diffuse coronary atherosclerosis that progresses at a faster rate.[11] Ischemic heart disease in patients with T2DM is often asymptomatic or shows few symptoms, a fact that can lead to a delay in the diagnosis. Scientific evidence indicates that the diabetic population has the same risk of presenting a first cardiovascular event as nondiabetic

TABLE 1. **Characteristics of the Study Population***

	With SMI	Without SMI	All Patients
No. of patients	9 (18.75)	39 (81.25)	48
Age, years†	60.8 (5.4)	54.5 (7.1)	55.72 (7.19)
DM duration, years	12 (2.5-21.5)	4.5 (2-13)	5.00 (2.3-13.5)
BMI	30.1 (4.5)	30.3 (3.3)	30.23 (3.56)
WHR	0.9 (0.06)	1.0 (0.07)	1.003 (0.068)
HbA_{1c}	7.8 (2.5)	6.6 (1.6)	6.8 (1.8)
ABI	0.91 (0.16)	0.96 (0.13)	0.95 (0.14)
HT	4 (44.4)	20 (51.3)	24 (50.0)
Dyslipidemia	4 (44.4)	19 (48.7)	23 (47.9)
Smoking	3 (33.3)	12 (30.8)	15 (31.3)
Insulin resistance	3 (33.3)	19 (48.7)	22 (45.8)
Diabetic retinopathy	7 (77.8)	11 (28.2)	18 (37.5)

*ABI indicates ankle-brachial index; BMI, body mass index; DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; HT, hypertension; SMI, silent myocardial ischemia; WHR, waist-hip ratio.
†*P*<.05.
Quantitative variables with a normal distribution (age, BMI, WHR, HbA_{1c}, and ABI) are expressed as the mean (standard deviation), and variables with a non-normal distribution (DM duration) as the median (25th-75th percentiles).
Qualitative variables (number of patients, hypertensive patients, dyslipidemic patients, active smokers, insulin-resistant patients, and those with diabetic retinopathy) are expressed as total number (percentage).

TABLE 2. **Results for Outpatient Blood Pressure Measurement***

ABPM Variables	With SMI	Without SMI	Total
Mean SAP, mm Hg	133.11 (13.98)	125.46 (13.16)	126.88 (13.55)
Mean DAP, mm Hg	72.44 (8.28)	76.15 (8.07)	75.25 (7.94)
Diurnal SAP, mm Hg	136.00 (13.13)	129.33 (14.70)	130.23 (14.69)
Diurnal DAP, mm Hg	74.56 (7.90)	79.79 (9.53)	78.37 (9.14)
Nocturnal SAP, mm Hg	127.11 (16.53)	118.74 (13.46)	120.87 (14.17)
Nocturnal DAP, mm Hg	68.22 (10.06)	70.28 (8.41)	70.10 (8.62)
Maximum SAP, mm Hg	165.00 (14.85)	157.54 (16.88)	158.63 (16.58)
Maximum DAP, mm Hg	97.22 (7.36)	98.97 (13.60)	98.73 (12.28)
Pulse pressure, mm Hg†	6.067 (9.41)	49.31 (7.78)	51.63 (9.70)
Mean BP, mm Hg	92.67 (9.55)	92.59 (9.37)	92.46 (9.07)
BP fluctuations			
Non-dipper	5 (55.56)	20 (51.28)	25 (52.08)
Dipper	3 (33.33)	15 (38.46)	18 (37.50)
Extreme dipper	0 (0)	0 (0)	0 (0)
Riser	1 (11.11)	4 (10.26)	5 (10.42)
Total number of patients	9 (18.75)	39 (81.25)	48

*ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; DAP, diastolic arterial pressure; SAP, systolic arterial pressure; SMI, silent myocardial ischemia.
†$P<.05$.
Qualitative variables with a normal distribution (mean SAP, mean DAP, diurnal SAP, nocturnal SAP, nocturnal DAP, maximum SAP, maximum DAP, pulse pressure and mean BP) are expressed as the mean (standard deviation). The remaining variables are qualitative and are expressed as the total number (percentage).

patients with established coronary disease.[12] A diagnostic strategy that allows detection of coronary disease in the early phases can decrease later complications. Diabetic patients with no history of ischemic heart disease have shown a high incidence of SMI. Our results, in which 19% of patients presented SMI, are in line with those obtained in other studies using a similar diagnostic protocol (12%-22%).[3]

High blood pressure is a fully established cardiovascular risk factor. Recent debate has focused on the precise component of blood pressure assessment that best predicts the risk of developing cardiovascular disease. The latest data from the Framingham Heart Study,[12] which are supported by other studies, have indicated that DPP, an indirect measure of arterial rigidity, is a better predictive factor of coronary risk than SAP or DAP alone, at least in persons over 50 years of age; the value of this parameter decreases in younger individuals.[13,14]

Increased arterial rigidity can be a component of the association between cardiovascular risk factors and the development of atherosclerosis. In our study, DPP was associated with the presence of SMI, independently of the remaining cardiovascular risk factors analyzed or the baseline clinical characteristics of the patients. Although this association does not necessarily predict atheroma plaque vulnerability, plaque rupture, and subsequent coronary syndrome, follow-up studies in patients with T2DM have demonstrated that the DPP is a good predictor of cardiovascular events.[7]

Although mean SAP was higher in the SMI group, neither this parameter nor DAP, in themselves, were predictive of myocardial ischemia. The related literature contains discordant data on the prognostic value of BP fluctuation patterns determined by ABPM with respect to cardiovascular risk. In a study performed in a hospitalized population, Sander et al[15] showed that high BP variation was associated with an increase in cardiovascular events. On the other hand, in a population with hypertension, a wide BP range, and a baseline risk profile, Verdecchia et al[16] reported no association between BP fluctuation and an adverse prognosis after adjusting for confounding factors. Our study also found no significant differences between the various ABPM patterns and the incidence of SMI, possibly because of the limited size of the sample.

Taking into account the high risk diabetic patients have of presenting coronary disease, the results of the present study are applicable to this population and to male patients followed up in endocrinology and family medicine services, who have not developed any clinical signs or symptoms of this condition.

In conclusion, the frequency of SMI in patients with T2DM and no history of cardiac disease was 19% in this study. Differential pulse pressure and age were independent predictive factors of SMI. Moreover, SAP or DAP alone were not predictive of myocardial ischemia, and ABPM patterns did not prove to be useful for this purpose.

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