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Artículo original

Validity and reliability of autonomic symptom test

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Summary
Introduction: the cardiovascular autonomic neuropathy increases the risk of silent myocardial ischemia and intraoperative cardiovascular liability. Additionally, from 27 to 56% of the patients with this diagnosis dies in the following 5-10 years. Cardiovascular autonomic neuropathy is detected by means of an electrocardiograph registration that monitors changes in heart rate induced by different stimulus. The autonomic symptom profile evaluates symptoms of autonomic function but it was not considered their reliability and validity with cardiovascular autonomic neuropathy diagnosis. It was carried out a study to determine the validity and reliability of the autonomic symptoms profile in the diagnosis of cardiovascular autonomic neuropathy. Materials and methods: from june to december of 2005, 103 participants responded the questionnaire spanish version twice. Then, 52 participants took the autonomic function test; the validity of the content of the questionnaire was evaluated by the cronbach's alpha and the reliability test-retest by intraclass correlation coefficient. It was considered the prevalence, sensibility and specificity of the score obtained with the presence of cardiovascular autonomic neuropathy. Results: The validity of content was good (cronbach's alpha >0,7). The reliability of the total score questionnaire was poor intraclass correlation coefficient (ICC 0,36 0,06-0,6) and the discriminative capacity of the questionnaire for the detection of cardiovascular autonomic neuropathy was bad for anyone of the selected court points Receiver operating curve (ROC area 0,5). Conclusions: the questionnaire evaluates the symptoms of autonomous function consistently; it has a low reliability and poor discriminative capacity to define the presence of cardiovascular autonomic neuropathy. (MÉD. UIS. 2009;22(2):138-45).
Key words: Autonomic function. Reliability. Validity. Cardiovascular autonomic function. Neuropathy. Diabetes mellitus.

Introduction

The Cardiovascular Autonomic Neuropathy (CAN) is characterized by the deterioration of small myelinized and unmyelinized autonomic fibers that innerve the heart, blood vessels and different organs in the gastrointestinal and urogenital systems[1]. These complications are frequent in diabetes mellitus and the risk both silent myocardial ischemic and intraoperatory liability are higher in this population. Additionally, from 27 to 56% of diabetics with CAN dies in the following 5-10 years[1,2]. The prevalence of CAN is from 7 to 27%, it depends on the population studied and diagnostic criteria used[1]. The CAN diagnosis is made with a continuous electrocardiograph registry that detects the variability of heart rate after different stimulus (e.g. deep breathing, lying to standing). These measurements are the most useful in these people[3-5]. In spite of objectivity and standardized methods, the principal disadvantage is the necessity of specialized laboratory, accessibility and cost in developing countries.

The autonomic symptom profile is a questionnaire with 74 questions created previously and evaluated in face and content validity[6]. In that study, the authors showed that scores in patients with autonomic neuropathy were higher than healthy ones and patients with other neuropathies[6]. However, they did not evaluate the reliability test-retest, internal consistency

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and criteria validity with objectives measurements of autonomic function. It was carried out a study to determine the validity and reliability of the profile of autonomous symptoms in the CAN diagnosis.

Materials and methods

Participants between 15 to 65 years old, with diagnosis of diabetes mellitus, assistants to program of chronic disease in a clinical center of Bucaramanga, Colombia were selected. Participants with deafness or mental incapacity for answer the questionnaire were excluded. The protocol was approved by ethical committee of the Universidad Industrial de Santander. All patients gave their consent in order to participate in the study.

The autonomic symptom profile was translated and retro-translated from English to Spanish by two translators with good understanding of English. The authors had consensus and there was no difference in meaning or sense with the original version.

All participants had an interview with a nurse previously trained, who applied the instrument in a standardized way. The second measurement was realized in similar conditions but by telephone. The questionnaire was graded according to the author's test. The total score was 0-200 for men and 0-170 for women.

The autonomic function test was realized from 10:00 a.m to 4:00 p.m. in an isolated room with temperature approximately of 22 °C. Antihypertensive medicines or other treatment were no suspended due to the usual condition of the patients. By means of an electrocardiography register and used the Wincprs version. 1,1597 the cardiac cycle was measured in three conditions, rest breathing, deep breathing (6 cycles/min) and lying to standing. The deep breathing was controlled by a visual timer that allow to train during a minute before the definitively register. There were obtained the 30/15 ratio, E/I ratio, delta E-I ratio, mean RR and other measurements of heart rate variability. The signal's evaluators were masked to the scores obtained in the questionnaire and the double reading. There were two readings in the autonomic function measurements. The evaluators had two years and three months of experience respectively. Cutoffs default American population data were taken for standardization by Ewing, Ziegler and Gerritsen, et al. (Table 1)[5,8,9].

Table 1. Cutoffs of autonomic measurements.

Measures	Cutoffsw
E/I ratio	< 1,25*
30/15 ratio	< 1*
delta E/I	20-24 years <136 ms
	25-29 years <127,4 ms
	30-34 years <119,4 ms
	35-39 years <111,9 ms
	40-44 years <104,8 ms
	45-44 years < 98,2 ms
	50-54 years <86,2 ms
	56-60 years < 80,8 ms
	61-65 years < 75,7 ms

abbreviations: *No units, ms: milliseconds

Sample size

It was calculated a sample size of 102 participants to detect a prevalence of CAN about 22% with an error in the estimation of 12% and alpha and beta error of 5% and 20% respectively. The study took 50 participants to apply objective autonomic test and maintained minimum 10 participants in the marginal ones the table of two by two with the prevalence estimated[10]. For the reliability study it was estimated a intraclass correlation coefficient between 0,6–0,8 in order to reject the null hypothesis of none agreement between both measurements. This was an alpha error 5% and power of 80%. In agreement with Kraemer[11] it was calculated a delta in the following form: $\Delta = (0,6-0,8)/(1-(0,6*0,8))=0,38$. This value was searched in the master table in the book and it was selected with the power and alpha wished (n = 41 +1).

Statistical analysis

The content validity was evaluated with cronbach's alpha and excluded items that improved or maintained the internal con-sistency among 0,7 to 0,9.[12] The agreement was calculated with the intraclass correlation coefficient and their confidence intervals of 95%[13]. For criteria validity, the measurement of autonomic function was compared with the best reliability and cut-points publicated and the total score. Initially it was calculated the level of the test (Q), the predictive values (PPV, NPV) and confidence intervals directly for each ten points of the total score. In according with the sampling, conditional probability with Bayesian approximation was used to calculate sensibility (S), specificity (E) and prevalence (P)[10]. Then, a ROC curve was constructed. The statistical analysis was done in the STATA 8.0[14].

Autonomic symptom profile

The mean total score in the autonomic symptom profile was 22 points RIQ (8,75-33). The secretomotor symptoms was the highest score compared with the

Table 2. Reliability test-retest, internal consistency autonomic symptom profile.

Variable	P50 (RIQ)	% >0 (IC95%)	alpha cronbach	ICC (IC 95%)
Total score*	22,1 (8.75-33)	100 (42-63)	0,85	0,36 (0,06-0,6)
Orthostatic intolerance	1,3 (0-20)	52 (42-62)	0,85	0,28 (0,01-0,54)
Syncope	0 (0-0)	12 (6-19)	0,79 ¶	0,41 (0,12-0,63)
Vasomotor	0 (0-0)	19 (12-28)	0,79	0,46 (0,18-0,67)
Secretomotor	3 (1,5-6,0)	99 (94-99)	0,76	0,18 (-0,12-0,46)
Gastroparesis	0 (0.0-1,7)	32 (23-42)	0.42	0,21 (-0,09-0,49)
Diarrhea	0 (0-0)	21 (14-30)	0,73¦	0,26 (-0,52-0,04)
Constipation	0 (0-1,5)	39 (29-49)	0,72	0,35 (0,05-0,59)
Slowed down vesical evacuating	0 (0,0-2,0)	39 (29-49)	0,49	0,23 (-0,07-0,5)
Pupillomotor reflex alterations	0,5 (0,0-1,5)	65 (55-74)	0,73	0,51 (0,24-0,7)
Sleep	1,5 (0,0-2,3)	75 (65-83)	0,23	0,17 (-0,14-0,45)
Eréctil dysfunction †	8 (2-9)	27 (19-37)	0,67	0,75 (0,58-0,86)
Ejaculation problems †	0 (0-0)	5 (2-10)	0,63	-0.1 (-0,1-0,39)
Validity scale				
Psychosomatic	0 (0,0-0,0)	11 (5-18)	0,52	0 (-0,3-30)
Understatement index	8,3 (4,9-8,3)	98 (93-99)	0,67	0,15 (-0,15-0,44)

Abbreviations: % >0= Percent of people with scores higher than cero. *Total score: men 0-200; women 0-170. † Only men. ‡ Only questions 10 y 11. ¶ excluded question 47.

other dominions, mean 3 points RIQ (1,5-6); followed by the upheavals of the sleep, mean 1,5 points RIQ (0-2,3). In the sexual activity symptoms the erectile dysfunction had a high score in this group, mean 8,0 points RIQ (2-9). All participants referred some symptoms; it was found that the vasomotor symptoms were the most frequent, followed by sleep and pupil alterations. Additionally, the sub-scale that measure the presence of previously symptoms related with concentration problems, nausea, diarrhea, loss of appetite or epigastric pain was also high. Only domains of orthostatism, syncope, vasomotor symptoms, secretomotor symptoms, diarrhea, constipation and pupil alteration showed internal consistency among 0,7 to 0,9, cut points recommended to consider good internal consistency (Table 2).

Results

From june to december 2005, 103 persons were included in the study. The mean age was 57 years RIQ (52-62 years), 38% were men. The majorities were diabetic type 2 (69%), received oral treatment (75%) and up to 50% has been diagnosed more than six years before stic RIQ (6-10 years) (Table 3).

Reliability of autonomic measures

Reliability of autonomic symptom profile was low because almost all domains had intraclass correlation coefficient (ICC) lowers than 0,7; except the questions about erectile dysfunction ICC 0,75 (0,58-0,86). Probably

Table 3. Characteristics participants included.

Characteristics	Participants N=103
Demographic	
Age years, p50 (RIQ)	57 (52-62)
Gender, (male) n (%)	39 (38)
Socio-economic level	
Low 0-2, n (%)	46 (45)
Middle / high 3-6, n (%)	56 (55)
Diabetes mellitus	
Type 1, n (%)	20 (19)
Type 2, n (%)	71 (69)
Non Classify, n (%)	12 (12)
Diagnostic time years, p50 (RIQ)	6 (6-10)
Fasting glucose mg/dl, p50 (RIQ)	141 (113-180)
Treatment	
Insulin, n (%)	23 (22)
Oral medicines, n (%)	76 (74)
Exclusive diet / nothing, n (%)	4 (4)
Comorbidities	
Hypertension, n (%)	40 (39)
Antecedent of high cholesterol, n (%)	31 (30)
Antecedent of low thyroid hormone, n (%)	4 (4)
Previous stroke, n(%)	1 (1)
Previous myocardial infarction, n(%)	1 (1)
None, n (%)	26 (25)
Physical exam	
Weight kg, mean (SD)	69 (13.0)
Height mts., mean (SD)	1.6 (0.08)
Body mass index, mean (SD)	27 (4.37)
Cardiac pulse, mean (SD)	73 (10)
Systolic blood pressure (mmHG), mean (SD)	119 (14)

Abbreviations: p50: percentile 50, p25: percentile 25, p75: percentile 75, (SD): standard deviation.

these symptoms were remembered easier and with lowest variation on the time (Table 1). The measurements obtained of the autonomic function test were reliable among evaluators, the most reliable were the Pnn50 and the delta E-I ICC 0.98 (0,97-0,99) (Table 4).

Table 4. Reliability of measures of autonomic function test.

Factor	Evaluator 1 Mean (SD)	Evaluator 2 Mean (SD)	ICC (IC 95%)
Mean R-R, ms	788 (95,3)	791 (91,3)	0,97 (0,95 – 0,98)
Ratio 30/15	1,07 (0,10)	1,08 (0,13)	0,63 (0,42 – 0,77)
Ratio E/I	1,15 (0,01)	1,16 (0,01)	0,97 (0,95 – 0,98)
Delta E-I, ms	118 (66,4)	122 (69,9)	0,98 (0,97 – 0,99)
Minimum, ms	707 (79,5)	711 (98,3)	0,71 (0,55 – 0,83)
Maximum, ms	880 (119)	864 (107)	0,91 (0,85 – 0,94)
CV	2,3 (1,07)	2,2 (1,19)	0,89 (0,83 – 0,94)
RMSSD	18 (9,9)	18 (11)	0,92 (0,86 – 0,95)
Pnn 50, ms	2,8 (6,21)	2,8 (6,73)	0,98 (0,97 – 0,99)

Abbreviations: mean R-R intervals, Ratio 30/15, E/I: Expiration /Inspiration ratio. Delta E-I diferences of the intervals R-R in Expiration and inspiration, Minimum: Mean of R-R intervals minimum. Maximum: Mean of R-R intervals maximum. CV: Varation coefficient, RMSSD: The sum of squares of mean differencess squares among R-R intervals. Pnn 50: Percent of R-R intrvals that differ more than 50ms. Ms milliseconds.

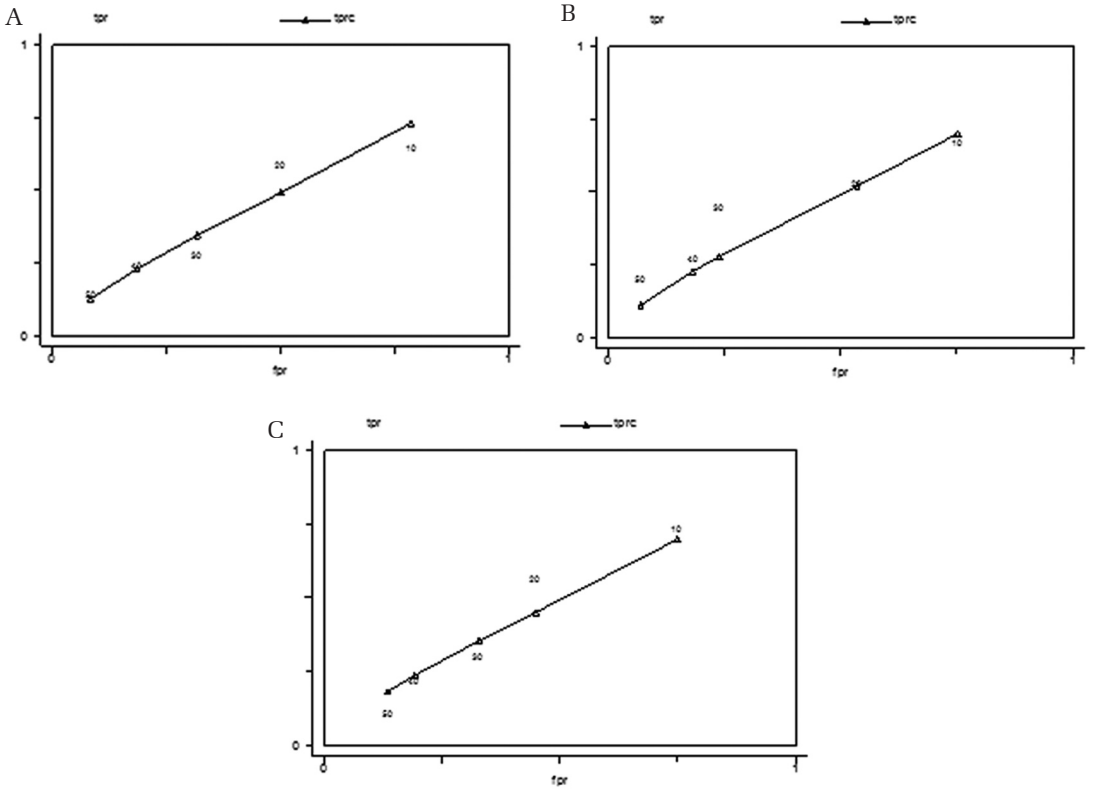
Criteria validity

The prevalence of CAN founded in this study was 43% in the delta e-i, 28% in mean r-r and 85% in e/i ratio. The 72% of participants obtained more than 10 points in the total score (q), there was not a cut-off point with both good specificity and sensibility and the discriminative capacity of the total score for can diagnosis was in the random line in spite of the measurement considered (figure 1). the score with the better sensibility was >10 points (s= 63%) and >50 points for specificity and efficiency (e=91%; eff= 60%). the best (ppv) in the cut off > 20 points was for e/i ratio (Table 5).

Discussion

The dysfunction of the autonomic nervous system is a serious problem in diabetic patients. The

Figure 1. Area under the curve of total score and three measures of autonomic function.



A= delta E-I; B= mean R-R; C= E/I ratio.

Table 5. Validity criteria of autonomic symptom profile and autonomic function test.

Autonomic symptom profile	Delta E/I		Mean R-R		E/I ratio	
	Positive	Negative	Positive	Negative	Positive	Negative
> 20	11	12	6	16	20	2
< 20	10	17	8	20	22	6
Total	21	29	14	36	42	8
P (%)	43		28		85	
Q (%)	53 (43-63)		53 (43-63)		53 (43-63)	
S (%)	59		52		56	
E (%)	51		47		56	
PPV (%)	44 (31-57)		25 (16-41)		84 (74-94)	
NPV (%)	63 (49-67)		70 (57-84)		22 (10-34)	

Abbreviations: Mean R-R: Mean of R-R intervals, Ratio 30/15, E/I: Expiration/Inspiration ratio. P: Prevalence; Q: level of the test; S: sensibility; E: Specificity; PPV: positive predictive value; NPV: negative predictive value; CI 95%: confidence interval 95%.

cardiovascular autonomic neuropathy is the most important autonomic dysfunction for its implication in the increase of mortality rate[2], therefore the importance of detecting and quantifying the symptoms of autonomic dysfunction. The patients with CAN present episodes of silent myocardial ischemia that can evolve easily into a myocardial infarction[15-17], also presents intraoperative cardiovascular lability representing morbidity and mortality two to three times higher compared to non-diabetics[18]. Burgos and cols. showed that the induction of anesthesia caused a large decline in heart rate and blood pressure in these patients, and the administration of vasopressors is most frequently used[19], Kitamura and cols. found an association between severe intraoperative hypothermia and CAN, which would generate a decrease in the metabolism of the drug and problems in the healing of the wound[20] and Sobotka and cols. showed that diabetic patients with CAN have reduced the hypoxic ventilatory response induced[21]. Therefore, the investigation of CAN in all diabetics to be subjected to surgery is essential to identify patients at risk and plan carefully anesthetic treatment for the patient.

Being important the recognition of autonomic symptoms, Suarez and cols. describe a questionnaire (Autonomic symptom profile) that measures a wide range of symptoms related to different aspects of autonomic disorders in grouping domains that provide a scoring system called the Composite Autonomic Symptom Scale (COMPASS)[2]. The questionnaire has an internal validity demonstrated to compare the results with the Symptom Composite Autonomic Scoring Scale (CASS)[22], derived from a group of non-invasive tests sensitive, specific, reproducible and standardized that detect and quantify symptoms of autonomic dysfunction, having a good correlation ($p < 0{,}001$).

In the present study, the psychometric characteristics of autonomic symptom profile were analyzed since different aspects such as reliability, internal consistency and criteria validity in front of objectives measurements of autonomic cardiovascular function.

The tests were evaluated in diabetic people with a long term evolution of the disease in whom the CAN have high prevalence and the performance of the test could be best way of diagnose the condition[10]. However, it could not be demonstrated that the presence of autonomic disease is related with the presence of autonomic symptoms. This results are explained by the chronic condition of the disease, since in other methodological reports have been detected problems to apply questionnaires in patients with this type of diseases[12]. This participants can overestimate or underestimate their symptoms and to lose the discriminative capacity of the instrument[12].

In previous studies the autonomic symptoms were evaluated using other standardized instruments that ask about the frequency of symptoms in the last 30 days. The Diabetes control and complications trial (DCCT study (diabetic 26 to 34 years), used this type of instrument and the most frequent symptom was postural hypotension (3,9%) followed by hypoglycemic unadvertised (8,7%)[23]. Ziegler and Cols. found postural dizziness (11%) and erectile dysfunction as more frequent (19%)[24]. It was founded the erectile dysfunction with the highest score (8 points).

Low and Cols. applied the autonomic symptom profile in a study and the results were similar than the obtained in this study. For example, the vasomotor symptoms they found mean 0,98 points ($SD=1{,}98$) and in the evaluated people the mean was 0,86 ($SD=2$)[25]. However, this shows the necessity to modify the scale, because it probably does not reflect the state of the patients.

In the other side, the reliability of the autonomic symptoms was poor showing the variability of its occurrence. This situation reduces the reliability of the measurement and induces a misclassification. In epidemiological research it is recognized that a no reliable instrument reduces the discriminative capacity and increase a sample size of the studies[26].

The measurements of objective autonomic measures were a good reliability among two evaluators, independent of their experience. This guarantees the precision of measures for diagnosis in CAN but do not guarantee the presence of the disease. This was not a scope of this study because the evaluation of real autonomic function does not have a gold standard. However, it is accepted with expert consensus that the autonomic function must be evaluated with the Ewing tests. The Experts recommend at first line the delta E-I in diabetic people[4].

The criteria validity of autonomic symptom profile was analyzed with a prospective sample, this had an advantage in saving money and time because it wasn't needed to do the objective measures in all sample. This methodology is a simple application of Bayesian theory used in evaluating medical test. Confidence intervals for prevalence, sensibility and specificity weren't calculated because they did not found directly unlike the predictive values[10].

The autonomic symptom profiles does not only evaluate cardiovascular symptoms and one of the limitations is doing measurements of autonomic function in other organs. However, the study was interested in evaluate autonomic symptom profile in the detection of CAN mainly. In the other side, it's shown how a reliability of the measures between evaluators is enough for use in clinical practice and research.

Additionally, autonomic symptom profile could be modified with questions about of acute autonomic symptoms related with diseases like sepsis or systemic inflammatory response syndrome where autonomic system is a modulator in cardiovascular answer mediated by endotoxin[27].

The results of this study does not assign to a systematic bias in patients selection because these were included in a consecutive and the performance of autonomic measures was masking of the score of autonomic symptom profile. The patients with measurements without interpretation were not excluded[11].

In clinical practice, this questionnaire can be used to identify diabetic patients with autonomic neuropathy and also to diagnose the disease early to treat diabetes more intensively because only the approach and maintenance of near glucose blood levels are the most effective way to prevent the cardiovascular autonomic neuropathy in the diabetic patients[23,28,29].

Conclusion

The autonomic symptom profile has a good internal consistency, poor reliability test-retest and did not have a discriminative capacity for the diagnosis of autonomic cardiovascular function. The test identifies diabetic patients who have symptoms of cardiovascular autonomic neuropathy of those who do not have. This is important in clinical practice for its implication in the increase of the mortality rate, allowing the selection of diabetic patients in which diabetes should be treated more intensively. Another important feature of the test is the potential ability to recognize clinically important changes, such as improvement or worsening of symptoms, which may translate into scores useful to monitor the progression of disease and to evaluate the response to treatment but further testing is needed to assess it. Our new research proposal is to establish the frequency of the autonomic neuropathy symptoms and evaluate their association with the duration of diabetes and socioeconomic and therapeutic variables, because this information is unknown in the colombian and latin-american population. It's also interesting the investigation of the presence of acute autonomic symptoms related with sepsis or SIRS, since the topic has not been explored so far.

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Resumen

Validez y confiabilidad de la prueba de síntomas autonómicos. Introducción: la neuropatía autonómica cardiovascular incrementa el riesgo de isquemia miocárdica silente y de inestabilidad cardiovascular intraoperatoria. Además, el 27 al 56% de los pacientes con este diagnóstico muere en los siguientes 5 - 10 años. La neuropatía autonómica cardiovascular es detectada por medio de un registro electrocardiográfico que monitorea cambios en la frecuencia cardíaca inducida por diferentes estímulos. El perfil de síntomas autonómicos es un test que evalúa síntomas de función autonómica pero no se ha considerado su confiabilidad y validez con el diagnóstico de neuropatía autonómica cardiovascular. Se realizó un estudio para determinar la validez y confiabilidad del test de perfil de síntomas autonómicos en el diagnóstico de la neuropatía autonómica cardiovascular. Materiales y métodos: de junio a diciembre de 2005, 103 participantes respondieron la versión en español del cuestionario de perfil de síntomas autonómicos en dos oportunidades. Después, 52 participantes tomaron la prueba de función autonómica, la validez del contenido de cuestionario fue evaluada por medio del *alfa de cronbach* y la confiabilidad test-retest por medio del coeficiente de correlación intraclase. Se consideró la prevalencia, sensibilidad y especificidad del puntaje obtenido con la presencia de neuropatía autonómica cardiovascular. Resultados: la validez del contenido fue buena (alfa de cronbach >0,7). La confiabilidad del resultado total del cuestionario fue pobre coeficiente de correlación intraclase (ICC 0,36 0,06-0,6) y la capacidad discriminativa del cuestionario para la detección de neuropatía autonómica cardiovascular fue mala para cualquiera de los puntos de corte seleccionados (Área ROC 0.5). Conclusiones: el cuestionario evalúa los síntomas de función autonómica sistemáticamente; tiene una baja confiabilidad y pobre capacidad discriminativa para definir la presencia de síntomas de neuropatía autonómica cardiovascular. **(MED. UIS. 2009;22(2):138-45).**

Palabras clave: Función autonómica. Confiabilidad. Validez. Función autonómica cardiovascular. Neuropatía. Diabetes mellitus.

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