500 HEART BEATS FOR ASSESSING DIABETIC AUTONOMIC NEUROPATHY

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ABSTRACT

The objective of the study was to investigate the usage of a new definition of autonomic dysfunction in assessing diabetic autonomic neuropathy (DAN), compared with the existing methods of evaluation, such as changes in heart rate variability (HRV) and autonomic scoring.

In a prospective study, 21 diabetic patients and 9 non-diabetic volunteers were enrolled for assessment of DAN. Three methods were employed: scoring of the autonomic function involving 3 manoeuvres (more than 3000 heart beats), reduction in components of the power spectrum (PSD) of the HRV (Valsalva manoeuvre along less than 600 heart beats) and finally measurement of autonomic dysfunction as provided by the ANSiscope™ (supine position for 572 heart beats). All individual comparisons were taken between the three classifications given by the methods. Pathways leading from one classification to another were thoroughly represented.

From 3 groups in the clinical classification (non-diabetic, diabetic without complications, diabetic with complications), autonomic scoring divided patients in 3 other groups with 15 healthy cases, 14 early cases and 1 case of advanced DAN. These 3 groups of scored patients were transformed in 2 ordered groups of equal size, by consideration of the amount of LF and/or HF component reduction (normal, abnormal). From this PSD distinction between absence and presence of DAN, the ANSiscope™ classified and ordered patients among 5 groups: 7 healthy cases, 7 early cases of DAN, 6 late cases, 7 advanced cases and 3 most advanced. Equivalence was found between the HRV and ANSiscope™ assessments as the latter classification was also brought to 2 groups, only distinguishing between absence and presence of DAN. The additional groups of the ANSiscope™ classification seem to provide evidence of early DAN for the first normal category and relativism in the severity of the neuropathy for the second abnormal category. Autonomic scoring did not convey the same diversity between groups as found with the groups formed by the other methods.

These findings suggest that correct supine assessment of DAN with sole consideration of R-R time intervals is possible in a little more than 500 heart beats, i.e. with 5 to 8 minutes of ECG recording.

KEY WORDS: Diabetic autonomic neuropathy; Autonomic scoring; HRV; Scale covariance; Autonomic dysfunction.

INTRODUCTION

Autonomic neuropathy is a common complication of diabetes that has a significant negative impact on survival and quality of life of the patients (1-3). Diabetic autonomic neuropathy (DAN) may be clinically evident, generally long after the onset of diabetes. Subclinical autonomic dysfunction can occur within a year of type 2 diabetes diagnosis and within 2 years of type 1 diabetes (4). Knowledge of early autonomic dysfunction can encourage patients and physicians to improve metabolic control and use of treatments that are proven to be effective for patients with autonomic dysfunction and particularly cardiac autonomic dysfunction (CAN) (5).

Cardiovascular reflex tests based on changes in heart rate and blood pressure during various manoeuvres allowed, through scoring, to frequently detect CAN at early stages (6, 7). Since introduction of these non invasive tests of the cardiovascular function, results have shown the importance of detecting and monitoring impaired autonomic dysfunction in patients with diabetes (8, 9). However, standard autonomic tests may not be sensitive enough to reveal subtle effects of interventions on autonomic nerve function (10, 11).

Methods based on power spectral analysis of heart rate variability (HRV) were proven useful in evaluating cardiovascular autonomic activity in diabetic patients and further measure decrease of LF and/or HF components (12, 13). The assessed vector Euclidean-norm gives a representation of the reduction of tones which reflects ANS dysfunction (14).

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Based on scale covariance physics, a new mathematical method, implemented in the ANSiscope™ device, allows to measure autonomic dysfunction based on the RR intervals.

The objective of this study was to test the usage of this new method's definition of autonomic dysfunction towards assessing DAN and give a thorough comparison between this new method and existing and validated methods.

MATERIAL AND METHODS

The study involved 2 groups of patients, 9 non diabetic patients (mean age 38 +/- 9 years) and 21 type 2 diabetic patients (mean age 50+/- 9 years). 4 of these diabetic patients had diabetes complications. The institutional review board approved the study for human research. Exclusion criteria were as follows: (1) causes of neuropathy other than diabetes (e.g., chronic alcohol abuse, vitamin B12 deficiency, hypothyroidism, drug induced neuropathy) and significant neurological disease (e.g., Parkinson's disease, epilepsy, recent stroke); (2) coronary artery disease or congestive heart failure; (3) a creatinine clearance <30 ml/min; (4) pregnancy; and (5) use of medications with potential influence on autonomic nerve function (e.g., a- and b-adrenergic) except for angiotensin-converting enzyme inhibitors; (6) history of drug or alcohol abuse. After obtaining informed consent from the patient, a full history was obtained and physical examination was performed. Clinical symptoms of complication of diabetes were reported in patient files.

Standardized instantaneous autonomic tests were obtained as recommended for clinical trials (15). The autonomic function tests included (1) beat-to-beat measurement of heart rate variation during timed ventilation, (2) postural heart rate response (30:15 ratio), (3) heart rate variation during standardized Valsalva maneuvers (Valsalva ratio), (4) hemodynamic response to standing. An additional 10 minutes period in supine position were respected with recording of the ECG for further analysis. A composite index of autonomic neuropathy that incorporated results from all autonomic function tests was calculated similar to the method of Bellavere et al. (10) A score from 0 to 2 was allowed for each test, giving a score of 0 when the value of the single test was within the normal range, a score of 1 when it was borderline, and a score of 2 when it was abnormal. The final score was obtained from the sum of the single test scores and provided the classification of the degree of abnormality of the patient's autonomic nervous system as follows: The sum of the scores from each test classified the patient as normal if the total score equaled 0 to 1, affected by early CAN if the total score was 2 to 4, and affected by advanced CAN if >= 5.

Parametric estimation of the power spectrum of HRV (using the Yule-Walker autoregressive model with order 12) was performed, as described by Malik et al. (14).

In a spectrum calculated from short term recording of 512 RR intervals (same quantity as for the next method), three main spectral components are distinguished: VLF (very low frequency), LF (low frequency) and HF (low-frequency) components, respectively for frequencies 0 — 0.04 Hz, 0.04 – 0.15 Hz, 0.15 – 0.4 Hz. The VLF component should be avoided when interpreting the power spectral density of short term ECGs. Vagal activity is the major contributor to the HF component. Prior studies suggest that LF is a quantitative marker of sympathetic activity. The LF/HF ratio is considered by some investigators to mirror the sympatho-vagal balance or to reflect sympathetic modulators (16). This ratio is of no help in the evaluation of autonomic dysfunction (17, 18). Power spectrum analysis in supine is highly correlated with the Valsalva ratio in the time domain (19, 20). Thus, the spectral analysis over the Valsalva manoeuvre was taken rather than only considering the more traditional reduction of components in supine.

Measurements of autonomic dysfunction were also obtained on the supine recordings using the ANSiscope™ (Dyansys Inc., Burlingame CA, USA). The ANSiscope™ extracts beat-by-beat information on the sympathetic and parasympathetic subsystems of the ANS, from the R-R time-intervals of the ECG.

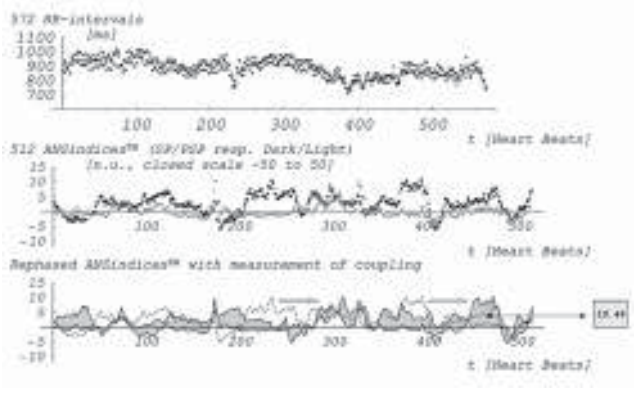

Fig 1: From the Time-intervals Between Heart Beats to the Measure of Autonomic Dysfunction, via Synchronization of ANS Indices. Particular Diabetic Case with no DAN.

Indices are calculated (called ANSindices™), giving activity-degrees of subsystems locally. The ANSiscope™ considers autonomic dysfunction as lack of coupling of these indices and then defines its measurement as a percentage of ANS dysfunction over the time period considered (512 ANSindices™ are required). The lack of coupling is measured by a metric between sympathetic and parasympathetic indices in optimal phase. Figure 1 further illustrates this process. The obtained autonomic dysfunction measurements form aggregates of values whose boundaries define groups, called, in order, Healthy (H), Early (E), Late(L), Advanced(A) and Most Advanced(MA) DAN groups.

The analysis of data for the purpose of thorough comparison is done by representation of all cases, performed at the level of each patient's classification by the different methods under comparison. This case-by-case comparison is not a descriptive study and by such is close to comprehensive.

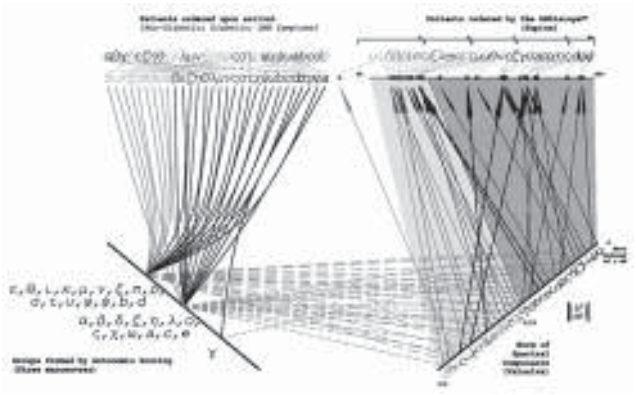

Fig 2: Thorough Comparison Between Four Assessments (Patients upon arrival with their clinical classification; Autonomic Scoring (Healthy, Early, Advanced); Power Spectrum Analysis (reduction of frequency components); Autonomic Dysfunction Measurement (Healthy(H), Early (E), Late (L), Advanced (A), Most Advanced (MA))

RESULTS

In figure 2 we find paths from the prior classification of patients upon their arrival, leading to the three different classification obtained respectively by autonomic scoring, overall reduction of spectral components and that which is obtained by the measurement of autonomic dysfunction (AutDys) provided by the ANSiscope™.

First, we find the order upon arrival which is followed by the clinical classification between non-diabetics, diabetics and cases with symptoms (respectively 9, 17 and 4 patients). Second, we are given the three unordered groups formed by the autonomic scoring; 15 are considered healthy, 14 early and only 1 as advanced. Third, patients are reordered by consideration of the reduction of the LF and/or HF components of the power spectrum of HRV during Valsalva manoeuvres. The order follows decrease of the norm of spectral components considered as a vector. Fourth, patients are ordered according to their AutDys on a scale ranging from -11% to 80%, from what is qualified as a vagal tonus to a thorough dysfunction of the ANS. This range covers the aforementioned five groups, divided as follows: H(7 elements), E(7 elements), L(6 elements), A(7 elements), MA(3 elements).

A cut in the last two classifications was sought in order to minimize the contradictions between them. This divides the plane of passage, between assessment by reduction of spectral components and the increasing AutDys measurements, in two. This division only distinguishes the healthy ANS cases from the unhealthy as observed by both classifications. This division also provides the power spectrum reduction scale with a cut in the values of the norm, from ¼ to 1/10, and from 1/10 to 0 (in normalized units). This minimal cut in fact divides the patients in two groups of equal size. We observe a general equivalence between these last two classifications (reduction of Valsalva spectral components and AutDys) at a two-valued (healthy/unhealthy) level of DAN assessment. This equivalence is only contradicted by 5 cases, marked on the figure by black dashed arrows.

Taking back the case at hand in figure 1, we observe that this case lettered "b" possesses an AutDys value of 10.4% (group H) which was reflected from a normal value for the norm of spectral components (healthy), was considered healthy by autonomic scoring and in fact was diabetic without symptoms. This is a case of agreement.

Now taking all four diabetic cases with symptoms, we observe that autonomic scoring considered one as healthy, two as early and one as correctly advanced. They were all considered as non-healthy by spectral analysis over the Valsalva manoeuvre. In supine, the AutDys values correctly classified them as having advanced DAN, 3 in A, 1 in MA.

For non-diabetic patients, autonomic scoring

matches 6 of them with the healthy group and 3 with the early group. Reduction of the spectral components during a Valsalva manoeuvre keeps 7 as healthy and only 2 as unhealthy (reduced norm). AutDys values divide the non-diabetic patients in two, with 5 in H and 4 in E.

Diabetic cases without symptoms are seen by autonomic scoring as healthy for 9 cases and early for 8. With the spectral classification, this division between 9 and 8 patients is also found, here between what is seen as healthy and unhealthy. AutDys values further varies the DAN assessment by finding 2 and 3 patients respectively in H and E, 6 in L, 4 in A and 2 in MA.

DISCUSSION

While the groups formed by Autonomic Scoring do not correspond to the stratification of patients given by the reading of the ANSiscope™ (and require more than 3000 heart beats for assessment), the presence and absence of reduced LF&HF components of the Power Spectrum during a Valsalva manoeuvre are corroborated (respective agreement of 13/15 and 4/5) by the distinction between H/E and L/A/MA groups given by the ANSiscope™ under supine condition. Five groups are formed through the attendance of four aggregations of autonomic dysfunction percentage values, which none-the-less divide the space of neuropathy into two distinct planes. Extreme cases are classified in rather equivalent groups between the different assessments. Remarkable agreement between control subjects (non-diabetics) is found with the spectral and ANSiscope™ measurements. Non-diabetic volunteers can be classified as Early DAN but DAN Groups L/A/MA only contain diabetic patients. One healthy case with a vagal tonus was found, the parasympathetic predominance was expressed as a negative measurement. This distinction between autonomic failures is not possible through the sole consideration of autonomic dysfunction as a reduction in activity (e.g. spectral analysis); this is not the case with the ANSiscope™. As can be observed with the non-diabetic volunteers, the ANSiscope™ fosters detection of early autonomic dysfunction which we can interpret as a functional disorder or which may be part of the degenerative process of aging. Where the ANSiscope™ both revealed meaningful divisions between the diabetic patients and emerging disorders for the non-diabetics, the other two methods could do no more than halve both the populations of diabetics and non-diabetics. We further note that autonomic scoring provided its healthy and early groups with similar compositions (pertaining to the original clinical classification). In summary, the autonomic dysfunction readings given by the ANSiscope™ in supine position provide a strict order between patients which, while being finer and more accurate, does not contradict the reduction in spectral components (the LF/HF ratio is here of no help) during a Valsalva manoeuvre, and just requires a little more than 500 heart beats, 5-8 minutes.

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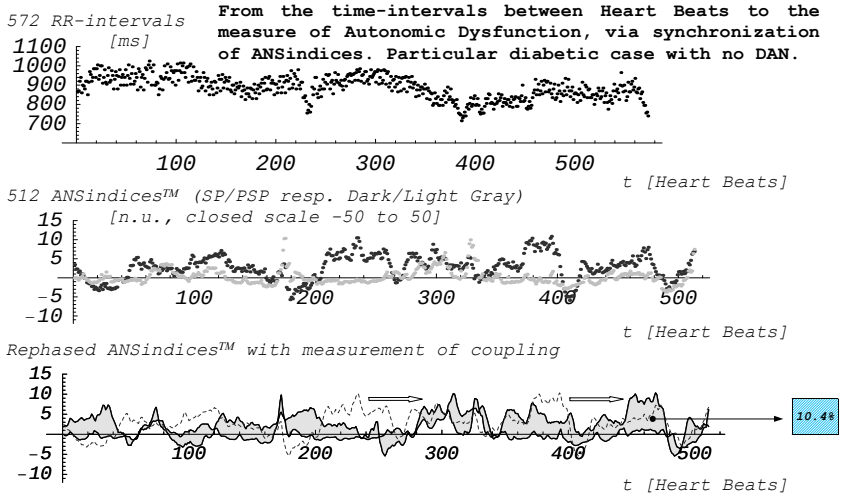
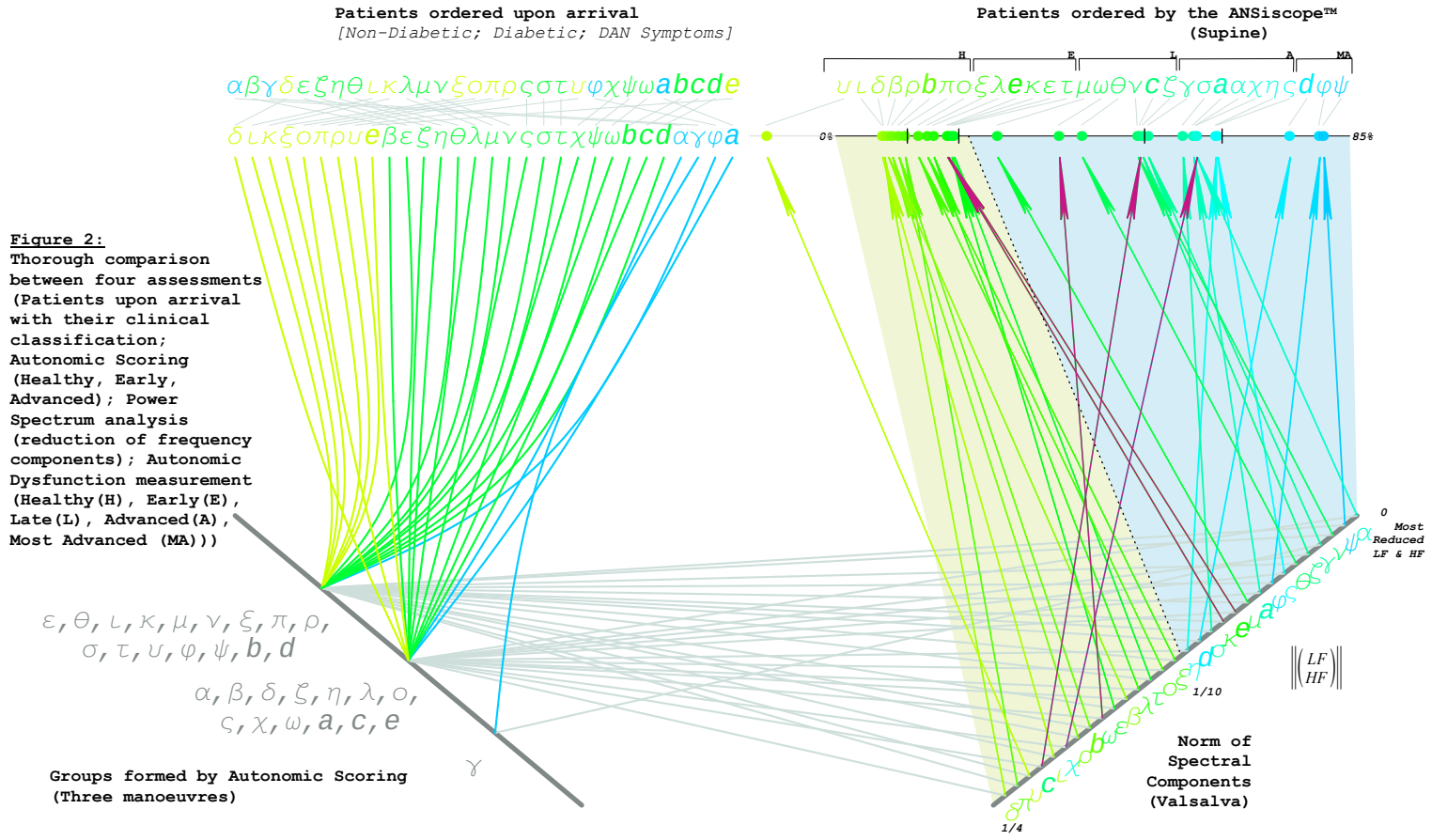
Figure 1:
From the time-intervals between Heart Beats to the measure of Autonomic Dysfunction, via synchronization of ANSindices. Particular diabetic case with no DAN.





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