Heart Rate Recovery in the Diagnosis of Diabetic Cardiovascular Autonomic Neuropathy

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Abstract

Cardiovascular Autonomic Neuropath(CAN) is a poorly understood chronic complication of Diabetes Mellitus (DM). A single instrument to evaluate CAN is not available yet, because of the complex balance between both sympathetic and parasympathetic drives. Heart Rate Recovery (HRR) is a promising parameter for clinicians to use, which is the difference between the maximal heart rate achieved at the end of the exercise phase and the heart rate at different stages of the recovery. The objective of this study was to characterize parameters obtained from RR trends during the recovery phase of the Exercise ECG. Our preliminary analysis is performed with 23 patients enrolled in the DM group and 6 patients in the control group. It showed that both HRR1 after the first minute of recovery and HRR2 after the second minute of recovery are able to discriminate between groups. These results are encouraging and more trends analysis within a different window period is still needed.

1. Introduction

Autonomic imbalance and decreased parasympathetic activity may be the common feature to numerous diseases, many of them highly associated to increased mortality [1]. A poorly understood chronic complication of Diabetes mellitus (DM) is Cardiovascular Autonomic Neuropathy (CAN). CAN presents with damage to anatomic substrates such as autonomic nerve fibers that innervate and regulate the cardiovascular dynamic, among other disturbances [2].

Diabetes remains a consistent model to assess Autonomic Dysfunction since it has been found in this condition regardless of age or type although type 1 and type 2 Diabetes may have different progression paths. It is also an ideal model to assess progression of disease and additional complications such as diabetic nephropathy. Autonomic dysfunction impairs exercise tolerance, orthostatic changes, which is associated with perioperative cardiovascular instability, sensitivity to pain related to Cardiac Denervation Syndrome and represents an independent predictor of acute cerebrovascular disease and all-cause mortality. Moreover, blunted vagal tone has been associated with coronary artery occlusion, plaque rupture and increased markers of inflammation [3]. A single instrument to evaluate CAN is not available yet, because of the complex balance between both sympathetic and parasympathetic drives. Most of the clinical instruments used to assess autonomic dysfunction are time-consuming and require a long list of devices to measure changes in heart rate, blood pressure, skin galvanic response and cutaneous blood flow while exposing the patient to a battery of non-standardized maneuvers [2].

The ECG is one of the easily accessible windows into autonomic activity in humans. Moreover, the Exercise ECG one of the most powerful, inexpensive and non-invasive instruments available in a wide range of clinical settings that can be used for this purpose. During the first minutes after maximum exercise, heart rate decreases and its behaviour responds to several mechanism such as sympathetic withdrawal, parasympathetic reactivation, baseline resting heart rate and age among others. Recently, a growing literature has become available to address these findings and its real clinical significance.

There is an increase number of work that advocates the usage of Exercise ECG as a valuable instrument for diagnostic and prognosis purposes in diabetic patients [4-6]. Heart Rate Recovery (HRR), defined as the absolute change of heart rate after a maximal heart rate during the recovery phase in different periods of time in the Exercise ECG, has been recently studied as a potential instrument to assess Autonomic Dysfunction in patients with Diabetes. However, it has shown in diverse settings, controversial results in the assessment of autonomic balance probably due to limited standardization in different centers.

The objective of this study was to establish the level of association between parameters obtained from RR trends during the recovery phase of the Exercise ECG in patients with and without Diabetes. Autonomic physiology in exercise and rest is a very complex system.

It is assumed that during the recovery phase, sympathetic withdrawal and parasympathetic reactivation take place but their dynamics are not well understood. It is hypothesized that the heart rate as a consequence of this complex autonomic regulation would behave different in patients with longstanding Diabetes.

2. Material and methods

23 Patients from the Diabetes Mellitus (DM) outpatient clinic in the "Fundación Venezolana de Cardiologia" were invited to participate after reading exhaustively and signing informed consent forms. A group of subjects with no relevant past medical history and a normal resting ECG was enrolled to build the control group. In figure 1, the methodology used for this work is shown.

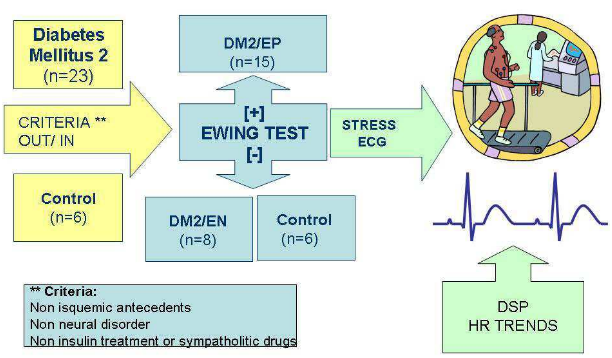

Figure 1. Methodology Schema to evaluate each DM group and Control group.

All subjects underwent Ewing tests:

i) HR response during deep breathing,
ii) BP and HR response to standing and supine
iii) BP and HR changes during Valsalva maneuver.

Sustained Handgrip was not tested in this work. DM group were split into two groups: DM2/EP, with positive Ewing tests and DM2/EN with negative Ewing tests. All control subjects were negative for Ewing test. Then all subjects underwent Exercise ECG test following Bruce Protocol performed on a treadmill and "The American Heart Association" guidelines [7], until linear estimation of maximum heart rate was reached based on age and gender. ECG was acquired with a 300 Hz sampling rate using commercial equipment Cardio Control® 1.3.3.240. HR sequences were obtained using the Gritzali QRS detector [8]. For assuring the detection of normal sinus beats, artifacts and ectopic beats were removed from the HR signal using a 10-beat sliding window algorithm.

Heart Rate Recovery (HRR) for 1 minute and 2 minute after maximum HR are given by:

$$HRR_1 = HR\max - HR_{1\min\, after} \quad (1)$$

$$HRR_2 = HR\max - HR_{2\min\, after} \quad (2)$$

Also, a regression analysis using non parametric estimation based en the Spearman correlation method was performed to obtain the β parameters for $y = A + \beta x$ by minimizing mean quadratic error. These parameters were calculated for each recovery interval (1 minute and 2 minutes).

Figure 2 shows an example of the procedure In the top panel, Heart Rate is filtered and HR point is localized. In the bottom panel, the two simple parameters are calculated for both intervals.

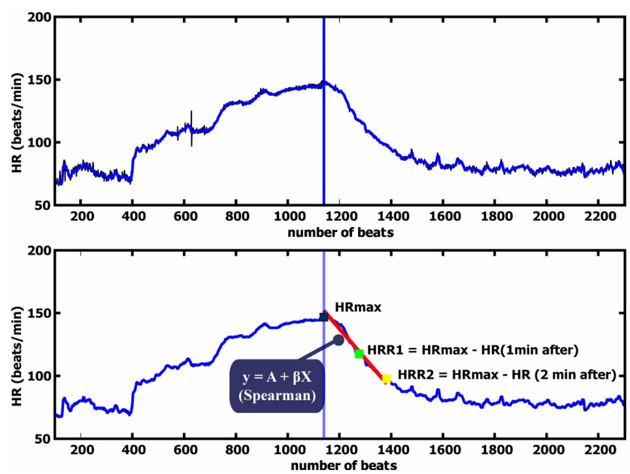

Figure 2. Example Heart Rate Recovery phase analysis after a maximum reached heart rate according to age and gender.

3. Results

Continuous data are presented as mean ± standard deviation (σ), nominal parameters are presented as frequency. The Wilcoxon signed rank test was used to compare the differences between groups.

Table 1. Characteristics of the groups

	CRT (n=6)	DM2/EN (n=8)	DM2/EP (n=15)	*p*
Age (years ± σ)	60.4 ± 11.8	62.2 ± 12.6	68.2 ± 9.6	*NS*
Women	2	2	9	*NS*
Years with DM (years ± σ)	0	19.8 ± 12.2	18.3 ± 6.6	---
BMI ([Kg x mt-2] ± σ)	24.8 ± 5.4	27.39 ± 6.4	24.3 ± 7.8	*NS*
Random Glucose (mg x dl-1 ± σ)	78 ± 8	128 ± 66	165 ± 56	---
HbA1C (%± σ)	----	10.2 ± 6.6	12 ± 4.2	---
Chronotropic Reserve (ν± σ)	0.96 ± 0.2	0.98 ± 0.1	0.90 ± 0.21	*NS*

Characteristics of the populations recorded are shown in table 1. Age, sex, body mass index (BMI) and chronotropic reserve did not revealed significant differences between diabetic patients and control group. HRR and β values are shown in tables 2 and 3 respectively. Differences between groups were performed using Mann-Whitney test that are shown in table 4.

Table 2. HRR values for each tested groups where HRR is the decresed HR values obtained after maximum HR.

	Control	DM2/EN	DM2/EP
HRR1 (beats/min)	32.750 ± 2.63	28.500 ± 13.67	15.143 ± 3.38
HRR2 (beats/min)	62.500 ± 9.88	54.750 ± 20.04	37.857 ± 13.41

Table 3. β parameters for each tested groups.

	Control	DM2/EN	DM2/EP
β_1	-0.395 ± 0.132	-0.350 ± 0.039	-0.221 ± 0.028
β_2	-0.405 ± 0.072	-0.352 ± 0.254	-0.328 ± 0.308

Table 4. *p* values between each comparison groups

	HRR1	HRR2	β_1	β_2
DM2/EP vs Control	0.003	0.018	0.001	0.003
DM2/EP vs DM2EN	0.007	0.028	0.023	0.034

4. Discussion

Our preliminary analysis is performed with 23 patients enrolled in the DM group and 6 patients in the control group. It showed that both HRR1 after the first minute of recovery and HRR2 after the second minute of recovery are able to discriminate between groups. It is also shown how HRR1 is a better discriminator than HRR2.

These β parameters obtained from the regression estimates are consistent with HRR results. These parameters could be a potential instrument in the assessment of the recovery phase changes in the heart rate and probably less susceptible to changes due to baseline heart rates or heart rates achieved at peak exercise.

An interesting fact is that most protocols for Exercise ECG do not define recovery phase standards, if a patient is lying supine, sitting or standing during this phase, the heart rate changes might be susceptible of orthostatic effect. In our sample, these thresholds are not necessarily the same as some previous reports but are consistently found within each group.

More work in the recovery time windowing is still needed to define an ideal parameter. The rate of sympathetic withdrawal and parasympathetic reactivation during the recovery phase of an intense exercise is still not well understood. However, Goldberger et al. [9] has found that during the first 30 seconds of the recovery phase, most of the effects onto these changes in heart rate are due to sympathetic withdrawal subsequently overlapped with the effect of parasympathetic reactivation during the latter part of this phase.

As mentioned above, this complex interaction between both sympathetic and parasympathetic drives might need not necessarily one single ECG feature to improve the identification of autonomic dysfunction but perhaps a logical combination of findings. Nonetheless, it is always useful to define the least amount of parameters that could help the clinician identify this condition in his daily practice.

Several pharmacological and non-pharmacological strategies have been reported to improve progression in the setting of CAN and also decrease symptoms related to this chronic complication. Early diagnosis and intervention might provide ground for improvements in the lifestyle and mortality rate of these patients. More work in a more diverse population is needed to define a set of parameters that could improve the range of competence using the Exercise ECG. It is clear that associated diagnosis and the level of training of these sampling units could have caused an effect onto these results. The development of a diagnostic tool to achieve an early intervention, with an inexpensive and noninvasive stress ECG, would cause a great impact in the prevention of cardiovascular mortality within diabetic population.

5. Future works

An enlarged database is in the process of being acquired as part of a wider project named DICARDIA [10]. The goal of this database is to achieve a better understanding of the mechanisms underlying CAN and to develop methods for its early diagnoses and follow up. The database is composed by two populations: Type 2 Diabetes Mellitus group and a control group with no medical history of cardiovascular disease. At present, there are 62 records available from these two groups. Also, the database contains laboratory parameters, concurrent medical diagnoses reports verified by cardiologists and other clinicians for each patient. This database is being constructed on XML language using ecgML, a markup language for electrocardiogram data acquisition and analysis [10]. Automatic annotations and trend series from parameters extracted from the ECG signals such as RR intervals and ST segment measurements will be available. This database will give use a better understanding of DM patient with CAN and will be useful for evaluation of others procedures of analysis that are being developed.

Acknowledgements

This work was supported in part by the Fundación Venezolana de Cardiología and the Decanato de Investigación y Desarrollo of the Universidad Simón Bolívar.

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