Heart rate variability is lower in patients with intermittent claudication: a preliminary study

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Summary

Introduction: Peripheral arterial disease is a chronic disorder affecting blood flow to lower limbs and many patients can develop intermittent claudication (IC). They suffer a blood flow decrease to lower limbs, making impossible to walk short distances without feeling pain or stopping the gait. Heart Rate Variability (HRV) is a non-invasive tool based on the calculation of time variations along consecutive heartbeats. It is reasonable to think that, since HRV assess the autonomic balance through the cardiovascular system, it could be useful in the assessment of patients with IC.
Objectives: The aim of this study was to assess if there are differences in resting HRV between patients with IC and age matched controls, both with linear and non-linear analysis, and its possible relation with the gait capacity.
Methods: 14 control male subjects (60±5 years) and 14 male IC patients (64±6 years) underwent 10 minutes of HRV analysis. The study calculated Time Domain variables, Poincaré Plot analysis and nonlinear parameters (Entropy and slopes of Detrend Fluctuation Analysis).
Results: The main finding of this study is the presence of a clear sympathetic predominance at rest in the IC patients and a significant correlation between the parasympathetic rest tone and the distance covered in the 6MWT when all subjects are included.
Conclusions: HRV seems to be an accurate method to detect the sympathetic misbalance present in patients with IC but as a nonspecific finding that could be present in other cardiovascular pathologies. Complex structure of the heartbeat signal is not affected by IC.

Key words:
Peripheral arterial disease.
Walking ability.
Intermittent claudication.
Autonomic balance.

La variabilidad de la frecuencia cardiaca es menor en pacientes con claudicación intermitente: un estudio preliminar

Resumen

Introducción: La enfermedad arterial periférica es un trastorno crónico que afecta al flujo sanguíneo de los miembros inferiores y muchos pacientes desarrollan claudicación intermitente (CI), sufriendo una reducción del flujo sanguíneo que les hace imposible caminar cortas distancias sin sufrir dolor o tener que detenerse. La variabilidad de la frecuencia cardiaca (VFC) es una herramienta no invasiva basada en el cálculo de las variaciones de tiempo entre latidos sucesivos. Es razonable pensar que, puesto que la VFC evalúa el balance autonómico a través del sistema cardiovascular, podría ser útil en la valoración de pacientes con CI.
Objetivos: Evaluar si hay diferencias en la VFC de reposo entre pacientes con CI y controles de la misma edad (tanto con análisis lineal como no lineal) y su posible relación con la capacidad de marcha.
Métodos: Se realiza un análisis de VFC de 10 min a 14 controles (60±5 años) y 14 pacientes con CI (64±6 años). Se calcularon variables del dominio de tiempo, gráfico de Poincaré y parámetros no lineales. Todos los sujetos realizaron a continuación un test de 6 min.
Resultados: El principal hallazgo de este estudio es la presencia de un claro predominio simpático en reposo en los pacientes con CI y una correlación significativa entre el tono parasimpático de reposo y la distancia recorrida en el test de 6 min.
Conclusiones: La VFC parece ser un método adecuado para detectar la disfunción simpática presente en pacientes con CI pero como un hallazgo inespecífico que puede estar presente en otras patologías vasculares. La estructura compleja de la señal cardiaca no se ve afectada en la CI.

Palabras clave:
Enfermedad arterial periférica.
Capacidad de marcha.
Claudicación intermitente.
Balance autonómico.

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Introduction

Peripheral Arterial Disease (PAD) is an atherosclerotic occlusive disorder of arteries distal to the aortic bifurcation[1]. Due to the arterial occlusion, lower limb muscles do not receive the oxygen required while exercising provoking pain and necessity of stop walking. This phenomenon is called intermittent claudication (IC) and it affects around 12 million people in the United States of America[2]. The estimated overall prevalence of the disease is 3-10% at all ages and 15-20% in patients over 70 years[3]. Thus, one in five patients over 65 years has either symptomatic or asymptomatic PAD[4].

Atherosclerosis, and thereby PAD, are especially found in elderly and it is associated to diabetes mellitus and other cardiovascular risk factors such as hypertension, high body mass index and dyslipidemia[1,4]. Being current smoker or having smoked in the past increases also the possibilities of developing PAD[1].

PAD is asymptomatic in the first stages of the disease and people may be affected without knowing it[4]. In more advanced stages PAD turns symptomatic appearing IC and claudicating patients tend to reduce their mobility due to pain[2]. Moreover, the loss of work capacity affect not only to the ischemic limb but also to the healthy one[5].

Since the nineties, several qualitative and quantitative methods have been proposed to assess the state of the disease in IC patients[6-12] including studies of gait variability[13].

The analysis of Heart Rate Variability (HRV) is a non-invasive tool based on the calculation of time variations along consecutive heartbeats. It reflects cardiovascular (CV) response to autonomic activity in such a way that a reduced HRV is related to CV risk[14].

HRV analysis comprises different methods for its calculation[14]: A) The Frequency-domain analysis includes the determination of the frequency spectrum using the Fast Fourier Transform (FFT): high-frequency (HF), low-frequency (LF), very low frequency (VLF) and ultra-low frequency (ULF)[14,15]. B) The Time-domain analysis includes statistical measures which basically reflect parasympathetic activity, such as the Mean RR Interval, the Root-Mean-Square differences of successive heartbeat Intervals (rMSSD) or the percentage of RR intervals >50ms (PNN50)[14,15]. C) The Poincaré Plot analysis[16] provides an ellipse-shaped graph of RR intervals in which transverse (SD1) and longitudinal (SD2) diameters can be measured. SD1 reflects parasympathetic activity while SD2 is inverse to sympathetic activity. Recently, a new index based in Poincaré Plot has been proposed[17,18]. It is the Stress Score and it reflects in a direct way the sympathetic activity. D) The nonlinear analysis of HRV studies the complexity of the signal and it includes the fractal characteristics of the series[19].

It is reasonable to think that, since HRV assess the behavior of the autonomic system through the cardiovascular system, it could be useful in the assessment of patients with IC. To our knowlege, only four studies have analyzed HRV in patients with IC[20-23]. Two of them[20,21] did not find relation between HRV and the improvement in patients' walking ability. The third one[22] found significant differences in the HRV between patients and healthy subjects and suggested its use in the risk stratification. The fourth one[23] reported that time domain and non-linear indices of HRV were positively associated with maximal walking distance, but not with claudication distance, in symptomatic PAD patients.

The aim of our study was to assess if there are differences in resting HRV between patients with IC and age matched controls, both with linear and non-linear analysis, and its possible relation with the gait capacity.

Material and method

14 control male subjects (60±5 years, 90±12 kg, 174±7 cm) and 14 male PAD patients with IC (age 64±6 years, 83±17 kg, 168±7 cm) were recruited from two Hospitals in the town of Sevilla (Spain). The inclusion criteria for controls were not suffering from cardiovascular disease, not following any medical treatment and having an Ankle Brachial Index (ABI) >1. On the other hand, the inclusion criterion for the patients was to be referred by the Vascular Surgery Service of one of the two hospitals participating in the study, where they had to have a history with the diagnosis of PAD without surgery and an ABI <0.9[24,25]. All subjects included in the study (patients and controls) were non-smokers and none of them were taking any medications that had a relationship with the cardiovascular system in the past three months.

Subjects came to the Lab in the morning, 2 hours after breakfast, without drinking caffeine or exercising one day prior data collection. HRV was recorded for 15 minutes at rest in supine position using a Firstbeat Bodyguard recorder (Firstbeat Technologies Ltd, Jyväskylä, Finland). The first five minutes of every record were excluded assuming this time for relaxing. After the HRV record, each subject underwent a 6-minutes walking test (6MWT) in a closed hallway 50 m long.

All RR intervals were analyzed with the software Kubios HRV v2.0 (Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland). All time series were visually examined to detect possible artifacts and to apply, if necessary, any of the filters available in the program.

The variables analysed were rMSSD and pNN50 in the Time Domine and SD1, SD2 and SS in the Poincaré Plot. The Sample Entropy (SampEn) and the slopes $\alpha 1$ and $\alpha 2$ of Detrend Fluctuation Analysis (DFA) were calculated as complexity indexes.

The normality of distribution was assessed through the Shapiro Wilk test. For the contrast of hypothesis between two distributions, the Student t-Test was applied for those variables with normal distribution (SD2, SampEn and DFA $\alpha 1$ and $\alpha 2$ for both groups) and the Mann–Witney U-Test for the non-normal (Mean RR, rMSSD, pNN50, and SS for both groups).

To assess de magnitude of the changes, the Effect Size was determined and interpreted according to the Hopkins criteria: 0.2 small; 0.6 moderate; 1.2 large; 2.0 very large; 4.0 extremely large[26].

A Pearson correlation analysis was performed between the distances covered in the 6MWT and all HRV variables.

The statistical analysis was performed using the SPSS Statistics Software version 18 (SPSS Inc, Chicago, IL, USA).

The study was approved by the Ethics Board of the University and all the subjects signed an informed written consent in accordance with the Declaration of Helsinki.

Results

Table 1 shows the results for the variables in the Time Domine and the Poincaré Plot. A significantly lower parasympathetic activity (lower rMSSD, pNN50 and SD1) is observed in patients as well as a significantly higher sympathetic activity (lower SD2 and higher SS). In both cases the difference not only was significant but also had an effect size large or very large.

Table 2 shows the results for the complex variables. Any significant difference is observed between patients and control subjects and the effect size was moderate or small.

The distance covered in the 6MWT was 518.77±61.51 m for controls and 326.82±87.76 for patients (p = 0.00001; Effect Size 2.57, very large). Four patients could not complete the 6 minutes of the walking test, stopping at 4 and 5 minutes. The distance covered at the time of stopping was counted.

Table 3 shows the correlations between distances and HRV parameters. There was no correlation in the groups separately, but when considering the total of subjects a significant correlation appears between the distance covered and rMSSD, pNN50, SD1 and SD2.

Table 1. Data for HRV variables in the Time Domine and Poincaré Plot.

		rMSSD	pNN50	SD1	SD2	SS
Control	Mean	22.73	3.85	15.83	62.9	20.16
	SD	8.19	3.87	5.67	24.92	14.22
Patients	Mean	10.19	0.33	7.21	25.25	45.55
	SD	5.27	0.39	3.73	9.13	19.51
	% change	-55.2%	-91.5%	-54.5%	-59.9%	125.9%
	P Value	0.005	0.013	0.006	0.0001	0.0002
	Effect size	1.86	1.65	1.83	2.21	-1.51
		Large	Large	Large	Very large	Large

rMSSD: Root-Mean-Square differences of successive heartbeat Intervals; pNN50: percentage of RR intervals >50ms; SD1: transverse diameter of Poincaré Plot analysis; SD2: longitudinal diameter of Poincaré Plot analysis; SS: stress score.

Table 2. Data for non-linear variables.

		DFA. α 1	DFA. α 2	SampEn
Control	Mean	1.31	1	1.28
	SD	0.14	0.12	0.3
Patients	Mean	1.22	1.07	1.36
	SD	0.12	0.1	0.13
	% change	-6.8%	6.2%	6.2%
	P Value	0.198	0.11	0.292
	Effect size	0.69	-0.64	-0.37
		Moderate	Moderate	Small

DFA: Detrend Fluctuation Analysis with slopes α1 and α2; SampEn: Sample Entropy.

Table 3. Correlation between HRV variables and distance covered in the 6 minutes walking test.

		Total distance	Control distance	Patients distance
rMSSD	r Pearson	0.47	-0.31	0.07
	p	0.02	0.31	0.84
pNN50	r Pearson	0.44	-0.01	0.28
	p	0.03	0.99	0.40
SD1	r Pearson	0.47	-0.30	0.07
	p	0.02	0.32	0.84
SD2	r Pearson	0.45	-0.56	0.11
	p	0.03	0.05	0.75
SS	r Pearson	-0.37	0.50	0.10
	p	0.08	0.08	0.77
alpha1	r Pearson	0.26	0.04	-0.15
	p	0.21	0.89	0.66
alpha2	r Pearson	-0.22	-0.20	0.18
	p	0.31	0.52	0.60
SampEn	r Pearson	-0.04	0.44	0.04
	p	0.85	0.13	0.91

rMSSD: Root-Mean-Square differences of successive heartbeat Intervals; pNN50: percentage of RR intervals >50ms; SD1: transverse diameter of Poincaré Plot analysis; SD2: longitudinal diameter of Poincaré Plot analysis; SS: stress score; SampEn: Sample Entropy.

Discussion

The main finding of this study is the presence of a clear sympathetic predominance at rest in the PAD patients and a significant correlation between the parasympathetic rest tone and the distance covered in the 6MWT when all subjects are included.

Parasympathetic HRV variables (rMSSD, pNN50 and SD1) were higher in controls indicating a healthier general state[27]. On the other hand, patients with IC had a higher sympathetic status showed by a lower SD2 and a much higher SS. Although the sample is not very large (as is usual in this type of study), the differences found between both groups present a very high level of significance for these variables together with a large or very large effect size. Therefore, there is no doubt about the existing differences.

Regarding nonlinear dynamics, no difference has been found between groups in the SampEn values and the alpha1 and alpha2 slopes of the DFA, indicating that, regardless of the existing autonomic imbalance, both groups retain the same complex structure in their heartbeat.

When comparing our data with the previously published works, we find that the Sandercock study[21] only analyzes HRV in the frequency domain using the Fast Fourier Transform, so it is not comparable with our results. The Leicht study[20] analyzes practically the same variables as we do, and in a very similar age range, but does not find differences between healthy subjects and patients with PAD. In our opinion, this may be due to the fact that this study includes men and women, which makes the variability of the data much greater (for example, rMSSD data provided by Leicht *et al* show a coefficient of variation of 77%). Regarding

the Goernig study[22], all subjects are patients with cardiovascular disease with and without PAD. They find significant differences in time domain variables between both groups and attribute it to the existence of PAD. In the study of Lima *et al*[23] there was no control group and they performed a treadmill test. They reported values of SDNN, rMSSD, pNN50, SD1 and SD2 much higher than ours.

As for the nonlinear variables, only the work of Leicht *et al*[20] reports data from SampEn, alpha1 and alpha2. The values referred by them are almost identical to ours and do not present differences between patients and healthy subjects, which seems to reinforce the idea that, whatever the changes in sympathetic-parasympathetic balance, the complex structure of the signal does not change.

Limitations

The main limitation of the current study was the small sample size. However, it is very difficult to achieve a greater number of subjects when the homogeneity of the groups is established with the criteria of this study. Thus, the work of Gornig *et al*[22] contains two groups of 26 and 27 subjects but including all kinds of basic cardiovascular pathologies. The Leicht *et al* study[20] is done with two groups of 24 and 25 subjects but mixing men and women. Finally, the Sandercock et al study[21] included 52 patients but with different concomitant pathologies and taking 11 different drug types (including statins, beta blockers, ACE inhibitors or diuretics).

In conclusion, HRV seems to be an accurate method to detect the sympathetic misbalance present in patients with PAD but as a nonspecific finding that could be present in other cardiovascular pathologies. Complex structure of the heartbeat signal is not affected by PAD.

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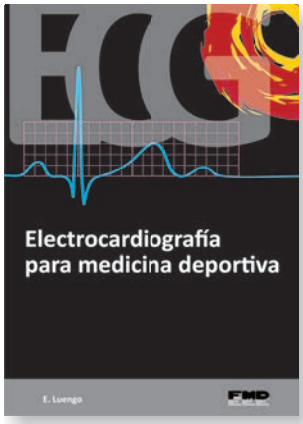

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