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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Cardiovascular autonomic dysfunction in patients with multiple sclerosis

Promotor :
dr. Inez WENS

Copromotor :
Prof. dr. Paul DENDALE

Lotte Bylois , Ilse Drenth

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Research framework

This cohort study, situated within the neurological rehabilitation, was conducted in association with the Rehabilitation Research Center REVAL. The research team at REVAL has great expertise in the research of neurodegenerative diseases, especially multiple sclerosis (MS). MS is a demyelinating auto-immune disease, which affects the central nervous system and causes great disability in various activities of daily living. The study is part of the doctoral research of Charly Keytsman; 'MS: associated cardio-metabolic risks and impact of exercise therapy'. Within this PhD research, several researchers are examining cardio-metabolic parameters, like glucose intolerance, hypertension, fat percentage, echocardiographic parameters, autonomic regulation of the heart rate and blood pressure,… . These factors may be altered in MS patients compared to healthy controls.

Cardiovascular autonomic dysfunction (CAD) is seen as a possible undesirable factor in the cardio-metabolic risk profile. From this perspective, this study describes the prevalence of CAD in patients with MS, compared to healthy controls.

Two students from the University of Hasselt performed this study, supervised by promotor dr. ir. Inez Wens.

Abstract

Objectives Multiple sclerosis (MS) is a highly investigated neurologic disorder, creating dysfunction and disability. The demyelination of the central nervous system can cause disturbances in the autonomic regulation. The existence of cardiovascular autonomic dysfunction (CAD) within this population remains uncertain. The aim of this study was to examine the existence of CAD in the MS population, compared to the healthy population.

Methods Seventy-five participants were included in this screening study, including 51 MS patients and 24 age- and sex matched healthy controls. The participants were subjected to five different autonomic tests: sustained handgrip test, valsalva maneuver, deep breathing test, cold pressure test and passive tilt test. Heart rate and/or blood pressure responses were continuously measured.

Results There were no differences in age and sex between the MS and the control group. There was no significant difference in the prevalence of CAD in the MS group (38.78%) and the control group (30.43%). During the deep breathing test the variation in heart rate was significantly lower in MS patients compared to the healthy controls. Other autonomic tests failed to show a significant difference between both groups. Regarding the MS group, small but significant correlations were discovered between the EDSS/disease duration and the results from the deep breathing test.

Conclusion The results of this study did not indicate CAD in MS in comparison to the healthy population.

Introduction

MS is a degenerative auto-immune disease affecting the central nervous system. Due to diffuse demyelination of white matter, central nerve conduction is compromised, which may lead to dysfunction and disability. Various symptoms may occur, including sensory disturbances, visual impairments, motoric and coordinative disorders, fatigue and bladder and bowel dysfunction [1, 2]. Some disease characteristics of MS patients are linked to autonomic dysfunction. This dysfunction is caused by demyelination of certain parts of the autonomic nervous system. The autonomic nervous system, consisting of a parasympathetic and sympathetic part, is responsible for maintaining the homeostasis of the human body. For example, the sympathetic nervous system is responsible for the regulation of the fight- or flight response, which occurs during perceived stress [3]. Using a complex system of nerve pathways, the autonomic control signals travel from the brain centers to various organs, like the heart, the gut and the bladder. In MS, a disturbance in this conduction can have a major impact on disability levels and quality of life, for example due to constipation or incontinence [4, 5].

In the general population CAD is expressed by a reduced heart rate variability. This is proven to be a major predictor of coronary artery disease and mortality [6]. Several studies have shown a correlation between autonomic dysfunction and exercise intolerance as well as decreased quality of life [7, 8].

Autonomic disturbances in the bladder, the gastro-intestinal system and thermoregulation are well described within the MS population. Less consistent evidence is found regarding CAD. In a meta-analysis of Racosta, Sposato [9] several studies on CAD in the MS population were included. After data pooling 42.1% (prevalence ranging from sixteen – 76%) of the MS population appeared to have CAD. Correlations between MS duration, EDSS, type of MS and CAD are not yet determined.

The aim of this study is to examine the prevalence of CAD in the MS population, compared to the healthy population, and to clear out the current inconsistencies regarding this prevalence. Important correlations between CAD and disease characteristics will be explored.

Methods

Sampling

MS patients were recruited in association with the 'Rehabilitation and MS centrum' in Overpelt and by distributing informational flyers to local physiotherapist and several local hospitals. Age and sex matched healthy controls were gathered by using informational flyers. Only participants older than eighteen were included. All MS participants had a confirmed diagnosis of MS by the criteria of Poser [2] . Exclusion followed in MS patients with an EDSS > 6 or relevant comorbidities, like known heart diseases. Control participants with known chronic diseases were excluded. All participants signed the informed consent. The study was approved by the Ethics Committee of the Jessa Hospital and by the Ethics Committee of the University of Hasselt (12/12/2014, 14.84/cardio14.11).

Procedure

All participants were subjected to five standardized non-invasive cardiovascular autonomic tests, carried out in a previously set order in Jessa Hospital Hasselt. Participants refrained from food, coffee and nicotine for at least three hours before testing. Irregularities were noted. Medication use of the participants could be continued, but was extensively described. During testing, the participants were in a supine position, fixed to a tilt table with belts, in a quiet and slightly darkened room. Continuous monitoring of heart rate and blood pressure was provided by an ECG monitor and a continuous blood pressure monitor (CNAP® finger sensor). All data were recorded by the Task Force® Monitor.

(1) Isometric hand grip test

First, the participants were asked to generate a single maximal force output on a handgrip dynamometer (maximal voluntary contraction). Subsequently, the participants were instructed to produce a submaximal constant force (30% of the maximal voluntary contraction) for three minutes. The test instructor continuously monitored the force output and motivated the participant to maintain this submaximal contraction. The test was repeated, with a pause of one minute between both executions. Change in diastolic blood pressure was evaluated as a measurement of sympathetic function [10, 11].

(2) Valsalva maneuver

During the Valsalva maneuver, the participants were instructed to blow for fifteen seconds into a mouthpiece, connected to a pressure measuring device, creating a constant force output of 40 mmHg. The test instructor continuously monitored the pressure generated and provided the participant with feedback. This test was repeated twice, with a pause of 30 seconds between each execution. The Valsalva ratio was calculated dividing the maximum reached heart rate by the minimum heart rate, representing parasympathetic function [12, 13].

(3) Deep breathing test

During the deep breathing test, participants were asked to inhale and exhale at a rate of six complete breathing cycles per minute dictated by the test instructor. They were instructed to do this three times, with a pause of one minute where the participants resumed normal breathing. Fluctuation of heart rate was the parameter of interest, resulting in a deep breathing ratio (I/E index: maximal reached heart rate during inspiration divided by the minimal reached heart rate during expiration) and a deep breathing difference (I-E index : maximal reached heart rate during inspiration minus the minimal reached heart rate during expiration), expressing the function of the parasympathetic nervous system [13, 14].

(4) Cold-pressor test

The participant's hand was submerged into a bucket of ice-cold water (4-6°C) for 90 seconds. Change in diastolic blood pressure was evaluated as a measurement of sympathetic activation [15-17].

(5) Passive tilt test

The participants were tilted passively to 70° using the tilt-table. After ten minutes in upright position, they were returned to the previous supine position. The change in systolic and diastolic blood pressure was noted, representing the sympathetic function [13, 18].

Outcomes

(1) Primary outcome measurement

Prevalence - CAD was diagnosed by having abnormal results on three cardiovascular autonomic tests. Norm values for the different autonomic tests are described in table 1. Regarding the deep breathing ratio, no accurate norm values were found. Therefore, only the deep breathing difference could be analyzed using norm values. A comparison between the prevalence rates of the MS group and the control group was made.

Mean group comparison - The mean group responses (in heart rate and blood pressure) to the cardiovascular autonomic tests of the MS patients and the healthy controls were compared.

(2) Secondary outcome measurement

Correlations between various subject characteristics and cardiovascular autonomic test parameters were examined, as well as possible correlations between the different autonomic tests.

Data-analysis

Statistical analysis was performed using the statistical software program JMP. Normality of data was controlled with the Shapiro-Wilk test. Statistical differences between the MS and control group were calculated using one-way ANOVA for parametric data or Wilcoxon test for non-parametric data. Correlations were examined using Chi-squared test for categorical data, linear regression analysis for continuous data and one-way ANOVA for mixed data. The effect size was not derivable from previous reported studies. Consequently, the number of people necessary to reach an adequate power (= 0.80) was estimated based on other exploratory studies. Results with a p-value lower than 0.05 were considered to be significant.

Table 1: Norm values cardiovascular autonomic tests

Autonomic test	**Outcome measurement**	**Norm values**	
Isometric hand grip test	Δ DBP	>10 mmHg	
Valsalva maneuver	Valsalva ratio	20-29 year	1,22
		30-34 year	1,21
		35-39 year	1,20
		40-49 year	1,19
		50-54 year	1,18
		55-64 year	1,17
		≥65 year	1,16
Deep breathing test	I-E index	10-29 year	≥ 14
		30-39 year	≥ 12
		40-49 year	≥ 10
		50-59 year	≥ 9
		≥ 60 year	≥ 7
Cold-pressor test	Δ DBP	>15 mmHg	
Passive tilt-table test	Δ SBP	>30 mmHg	
	Δ DBP	>10mmHg	

DBP: Diastolic Blood Pressure; I-E index: maximal reached heart rate during inspiration minus the minimal reached heart rate during expiration; SBP: Systolic Blood Pressure

Results

Subject characteristics

Subject characteristics are displayed in table 2. Seventy-five participants were recruited, including 51 MS patients (18 men, 33 women; mean age 51 ± 10.72) and 24 age-and sex matched healthy controls (8 men, 16 women; mean age 49 ± 11.20). At the start of the study, there were no statistical differences between both groups regarding age and sex ($p > 0.05$). The MS patients had a mean Expanded Disability Status Scale of 2,97 ± 1,39 (n = 48) and a mean disease duration of 13,41 ± 9,44 (n = 49). Thirty-three MS patient had relapse-remitting MS, thirteen primary-progressive MS and two secondary-progressive MS (n=48). Detailed information about medication use is also covered in appendix 'Medication use'.

Table 2: Subject characteristics

	MS patients	**Control**
Number	51	24
Mean age [in years]*	51 (± 10.72, range 29 - 75)	49 (± 11.20, range 31 - 64)
Sex [male]*	18	8
Mean EDSS (n = 48)	2,97 ± 1,39	
Mean disease duration [in years] (n = 49)	13,41 ± 9,44	
MS type		
RR-MS	33 (n=48)	
PP-MS	13 (n=48)	
SP-MS	2 (n=48)	
Medication use		
- **MS-related drugs**	84%	
- **Hypertension treatment**	27%	
- **Cholesterol-lowering treatment**	18%	
- **Anti-coagulation treatment**	2%	
- **Beta-blockers**	6%	
- **Anti-depressants**	35%	
- **Muscle-relaxing drugs**	12%	
- **Analgesics**	2%	
- **Somnifacient**	22%	
- **Anticonvulsant**	25%	
- **Diabetic treatment**	6%	
- **Others°**	49%	

EDSS: Expanded Disability Status Scale; RR-MS: relapse-remitting MS; PP-MS: primary progressive MS; SP-MS: secondary progressive MS. * No significant difference (p>0,05) ° like stomach protecting medication, vitamin supplements, medication for urinary tract infection, thyroid modulating medication

Test results

Only one of the seven performed autonomic tests showed a statistical significant difference between the MS and the control group (Table 3). During the deep breathing test, the MS patients had a significant lower I/E index (p=0,0057). However, there was no significant difference in the mean I-E index between both groups. Likewise, the mean Valsalva ratio did not differ between the MS and the control group. The response of diastolic blood pressure during both handgrip and cold pressure test was not significantly different. Furthermore, the

blood pressure response during the head-up tilt test also turned out to be similar in both groups.

Table 3: Mean group comparison results of autonomic tests

Test	MS patients	Control	p-waarde
Mean response DBP handgrip	9.12	6.04	0.0698
Mean valsalva ratio	1.34	1.37	0.2421
Mean I-E index	8.89	11.14	0.0597
Mean I/E index	1.14	1.21	0.0057*
Response DBP cold pressure	12.16	15.75	0.0711
Response SBP tilt	-11.59	-16.79	0.2978
Response DBP tilt	-12.61	-16.29	0.4220

SBP: Systolic Blood Pressure; I-E index: maximal reached heart rate during inspiration minus the minimal reached heart rate during expiration; I/E index: maximal reached heart rate during inspiration divided by the minimal reached heart rate during expiration; DBP: Diastolic Blood Pressure; * Significant difference ($p<0.05$)

The diagnosis of CAD depends on the required number of abnormal test results. Table 4 resumes the number of abnormal tests in both groups. In this study, CAD was defined by having three or more abnormal autonomic tests. Subsequently, 38.78% of the MS group were diagnosed with CAD, compared with 30.43% in the control group. There was no significant difference between the prevalence rates of the MS group and the healthy control group. In other previous performed studies, CAD was defined by having two or more abnormal tests [17, 19]. A detailed description is visualized in table 5.

Table 4: Number of abnormal results

	MS	Control
Hand grip	31/51 (60.78%)	22/24 (91.67%)
Valsalva maneuver	15/50 (30.00%)	4/23 (17.39%)
Deep breathing	30/50 (60.00%)	9/24 (37.50%)
Cold pressure	32/50 (64.00%)	10/24 (41.67%)
Tilt test	8/51 (15.69%)	7/24 (29.17%)

Table 5: prevalence of CAD according to number of abnormal tests

	MS	Control	p-value
2 or more abnormal tests*	75.51%	69.57%	0.5819
3 or more abnormal tests*	38.78%	30.43%	0.6022

* No significant difference (p>0,05)

Correlations

(1) Correlations between different autonomic tests

The results of the Valsalva maneuver was significantly correlated with the results of the deep breathing test. Like expected, the I-E index of the deep breathing test was highly correlated with the I/E – index ($r^2 = 0.91$) and the systolic BP was strongly correlated with the diastolic BP during the tilt test ($r^2 = 0.77$). No other correlations between the different autonomic tests were found.

(2) Correlations between autonomic tests and subject characteristics

Age was significantly correlated with the I-E index and the I/E index measured during the deep breathing test (respectively $r^2 = 0.22$; $p < 0.0001$ and $r^2 = 0.24$, $p < 0.0001$): higher age was related to lower heart rate responses to the deep breathing test. However, there was no correlation between age and other autonomic test results. In the MS population, EDSS was significantly correlated with the I-E index ($r^2 = 0.12$; $p = 0.0142$) and the I/E index ($r^2 = 0.09$; $p = 0.0299$). Disease duration was only significantly correlated to the I-E index ($r^2 = 0.10$; $p = 0.0226$) and the diastolic blood pressure during the hand grip test ($r^2 = 0.09$; $p = 0.0281$).

(3) Correlations between subject characteristics

MS type was significantly correlated with the EDSS ($r^2 = 0.29$; $p = 0.0003$) and disease duration ($r^2 = 0.36$; $p < 0.0001$). Finally, EDSS was significantly correlated with the disease duration ($r^2 = 0.18$; $p = 0.0002$).

Missing values

Not all test results could be included in the data for the statistical analysis. Some patients were not able to perform a certain test or the system did not record the results correctly. In the MS group, the valsalva maneuver of one participant could not be analyzed. Similarly, the data processing of one deep breathing test and one cold pressure test failed. In the control group, only one test result of the valsalva maneuver could not be used.

Discussion

Prevalence of CAD

Considering the results from this study, CAD appears to be prevalent in MS: 38.78% of the MS participants showed abnormal responses on at least three autonomic tests. However, in the healthy control group, CAD is, with a prevalence rate of 30.43%, not rare either. There was no significant difference in prevalence between both groups. The high prevalence in the healthy control group is consistent with other studies. For example, Flachenecker, Wolf [20] described a prevalence rate of only 17% within the control group. Acevedo, Nava [19] found a prevalence of 12.5% in the control group. These results question studies who used the responses of their own healthy control group as norm values [21]. Using the control group as a norm value in such small samples might influence the results, because these small group might not be representative for the total healthy population.

In this study, three or more abnormal tests were necessary to be defined as CAD, which is quiet strict compared to other studies [11, 19, 22]. Therefore, the prevalence rates of this study and the previous mentioned studies cannot be compared. Although norm values for this study were obtained from high quality studies [13, 14], several studies used different norm values which makes it even more difficult to compare.

Group comparison MS and healthy controls

From the five performed autonomic tests, only the deep breathing test showed a statistical significant difference between the MS sample and the healthy control group. This is consistent with other studies, which might indicate that parasympathetic tests are more sensitive compared to sympathetic tests.

Correlations

Correlations between the outcomes of both breathing tests - Valsalva and deep breathing - emphasizes the influence of the breathing pattern on heart rate. Nevertheless, it was not a strong relationship. Consistent with several other studies, age significantly influences the results of the deep breathing test [13, 21]. Higher age is correlated with a lower I/E index and I-E index. This highlights the need for all future studies to use age-related norm values in describing CAD. Although age was taken into account in determining the norm values, like described in Novak [13], there appeared to be no significant correlation between age and the heart rate response of the Valsalva maneuver in this study. There was no clear reason for this inconsistency. The disease duration of the MS patients showed a significant correlation with some of the autonomic testing (deep breathing and hand grip). This confirms to some extent the study of Mahovic and Lakusic [24], describing a higher rate of CAD MS patients with a longer disease duration. However, other autonomic tests failed to show a correlation with disease duration. This underlines the doubtful correlation between disease duration and CAD, as Tombul, Anlar [25] previously described. Comparable to the disease duration, EDSS was only significantly correlated with the results of the deep breathing tests. All other autonomic tests failed to show a significant correlation, consistent with other previously performed studies [20, 25].

Limitations

It is important to acknowledge the limitations of this research. The most important remark was the inclusion of MS patients using drugs other than MS related medication, for example beta-blockers. However, after statistical analysis, it could be concluded that the medication use in the MS group did not influence the prevalence of CAD. Although patients were asked to refrain from food, coffee and nicotine for at least three hours before testing, some patients might have (accidently) neglected those directives, which could have influenced the results [12]. Another limitation of this study was that the test order was not randomized. For practical reasons, all MS patients were tested in the winter (February - April), while all the control subjects were tested in summer (June - July). There is some evidence that this temperature difference might have a significant influence on the test results, more specifically blood pressure values [27]. During periods of cold temperature blood pressure

values might be higher. However in this research only change in blood pressure was recorded as an outcome measurement. No studies were found describing the seasonal effect on blood pressure variability. Finally, despite encouragement, the motivation of the patients could have influenced the test results. For example, during the hand grip test, there was no control whether the participants performed according to their absolute maximum during the test [12].

Despite limitations, the strength of this research can be confirmed by several illustrations. For example, small faults in data processing were prevented with a double check of two independent examiners. While other studies often used less than three autonomic tests [21, 23, 28], this study conducted a test battery of five highly sensitive and specific autonomic tests. Furthermore, in comparison with other studies [11, 17, 28-41] a larger number of MS patients was included in this study.

In conclusion, the results of this study did not indicate CAD in MS in comparison to the healthy population. Due to the possible tremendous effects of CAD on morbidity and mortality, it might be relevant to pay attention to the presence of CAD, specifically in the MS population.

Appendix: Medication use

Subjects	MS-related drugs	Hypertension treatment	Cholesterol-lowering treatment	Beta-blocker	Anti-coagulation treatment	Antidepressants	Muscle-relaxing drugs	Analgesics	Somnifacient	Anticonvulsant	Diabetic treatment	Others
1	x	X				x			x			
2		X	x				x	x		x	x	x
3	x			x					x	x		
4	x	X	x		x	x					x	
5	x	X	x			x			x			x
6	x		x	x		x			x		x	x
7	x					x			x	x		
8	x											x
9	x	X										
10									x			x
11	x					x						
12	x											
13	x											
14	x		x			x						x
15	x	X										x
16	x						x					x
17	x											x
18	x											x
19	x											
20	x											
21	x											x
22	x									x		
23	x											

24	X					X				X		
Subjects	**MS-related drugs**	**Hypertension treatment**	**Cholesterol-lowering treatment**	**Beta-blocker**	**Anti-coagulation treatment**	**Antidepressants**	**Muscle-relaxing drugs**	**Analgesics**	**Somnifacient**	**Anticonvulsant**	**Diabetic treatment**	**Others**
25	X	X				X						
26	X									X		X
27	X									X		X
28										X		X
29	X	X										X
30	X											
31	X	X	X						X			
32	X					X	X					X
33	X						X			X		X
34	X											
35		X	X	X		X			X			X
36	X											
37	X											
38	X											
39	X											
40	X	X	X			X	X			X		X
41	X					X			X	X		X
42	X	X	X									
43									X			X
44	X	X				X						X
45	X	X				X						X
46						X			X			X
47						X				X		X
48	X					X						

49	X									X		
Subjects	**MS-related drugs**	**Hypertension treatment**	**Cholesterol-lowering treatment**	**Beta-blocker**	**Anti-coagulation treatment**	**Antidepressants**	**Muscle-relaxing drugs**	**Analgesics**	**Somnifacient**	**Anticonvulsant**	**Diabetic treatment**	**Others**
50	X						X					
51												

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