Multidimensional psychological examination of fatigue and physical functioning in cardiovascular patients

Ph.D. Thesis

Alexandra Nagy

Department of Behavioral Sciences

Leader of Doctoral School: Prof. Dr. Júlia Szekeres

Program leader: Prof. Dr. János Kállai

Supervisor: Dr. Árpád Csathó

University of Pécs

Medical School

2017

I.study

Associations of subjective fatigue with exercise capacity in patients with coronary artery disease

I.A. Association of Exercise Capacity with Physical Functionality and Various Aspects of Fatigue in Patients with Coronary Artery Disease

I.A. Introduction

Cardiovascular patients often report unexplained fatigue during common everyday tasks. Everyday subjective fatigue has been found to be a predictor of negative cardiovascular events, and it also strongly affects patients' quality of life. It is well documented that exercise capacity indexed as metabolic equivalent of the task (MET) shows strong association with subjective physical exhaustion reported by coronary artery disease patients after an exercise stress testing protocol. By definition, it is also highly probable that MET predicts not only the physical exhaustion in clinical exercise testing but also patients' everyday functionality in various aspects. More specifically, MET expresses an individual's capacity to increase and maintain exercise intensity, and from this one would predict that MET would be related to the level of *subjective fatigue* experienced by patients with coronary artery disease.

Fatigue, however, is a multidimensional construct and it can be indexed in many different ways. For example, numerous questionnaires have been developed to monitor the impact of fatigue on everyday activities with separate subscales for the *physical*, *social* and *cognitive* aspects of fatigue. Alternatively, fatigue could be characterized as a state of *vital exhaustion* (*VE*).

The specific aims of the study were (*1*) to compare the predictability of exercise capacity (i.e. MET) for the different fatigue dimensions (i.e. physical, social, mental scales of the Fatigue Impact Scale); (*2*) to examine the association between exercise capacity and vital exhaustion; (*3*) finally, it was aimed at investigating how self-reported sleep complaints and sleep duration affect the association of exercise capacity with fatigue.

I.A. Methods

Two-hundred and forty patients with stable coronary artery disease were recruited from outpatient visits (men: 145; women: 95; M= 63.32, SD= 8.05) at 1st Department of Medicine, University of Pécs. Patients were eligible to participate if they did not have any acute disease, and had no changes in medication during the three months prior to the study. In addition, patients were included if they did not receive psychotherapy within the three months before the study.

All patients underwent a maximal exercise stress test and were asked to complete a set of questionnaires referring to their experience over the previous 4 weeks: The 9-item form of the Beck Depression Inventory (BDI-9), Physical functioning subscale (PF-10) of the SF-36

Health Survey Questionnaire, The Fatigue Impact Scale (FIS), Shortened Maastricht Exhaustion Questionnaire (SMEQ).

All patients performed a maximal exercise stress test (Bruce protocol). Peak exercise capacity was estimated from exercise time and expressed as MET.

I.A. Data analysis

Non-parametric Spearman's correlations were computed to test the associations between MET and the self-reported scales.

We also conducted a series of multiple linear regressions to evaluate the unique contribution of MET to physical functionality, the different aspects of fatigue and depression. In the *first regression model* scores on all the self-report scales were separately regressed on one block of predictors comprising age, BMI, gender, education, diabetes, and MET.

To analyze the modulatory effect of self-reported sleep quality, in a *second analysis*, two sleep related variables (average sleep duration, and the sleep complaints scores of VE) were entered into the model as a second block of predictors. In this analysis, subjective measurements without sleep related items were used as dependent variables only (i.e. the cognitive, social, and physical subscales of FIS, SF-10, VE-fatigue, and VE-irritability dimensions).

I.A. Results

In *the first analysis* MET remained a significant independent predictor of physical functionality (SF-10), physical fatigue, and social fatigue. The strongest association was found with the physical fatigue subscale of FIS. The analysis also yielded a significant independent predictability of MET for the total scores of vital exhaustion, as well as for the fatigue, and irritability dimensions of VE. For the depression scores, the predictability of MET reached only a marginal significance (p= 0.054).

The *second regression analysis* showed that unlike average sleep duration, patients' self-reported sleep complaint was an independent predictor of the dependent variables. Second, the analysis also implied that the significant predictability of MET on the dependent variables remained unchanged by controlling for the sleep related factors.

The analyses also showed very strong associations between *physical* fatigue and the other, *non-physical* fatigue dimensions. These findings suggest that physical fatigue might mediate the observed associations between MET and the non-physical fatigue variables: social fatigue, VE-total and VE-fatigue. This assumption was investigated by controlling for physical fatigue in a final regression model. The control for physical fatigue eliminated the significant associations of MET with social fatigue [b = 0.05, t = 1.65, *n.s.*] and VE-total scores [b = -.06, t = -1.43, *n.s.*]. This suggests that the significant associations found by the previous analyses might be partially indirect and those can also be derived through the associations with physical fatigue. Interestingly, MET remained a significant predictor of VE-fatigue scores suggesting that MET predicts patients' feelings of loss of energy and malaise independently from the impact of fatigue on their physical activities [b = -.12, t = -2.09, $p <$ 0.05] (Figure 1.).

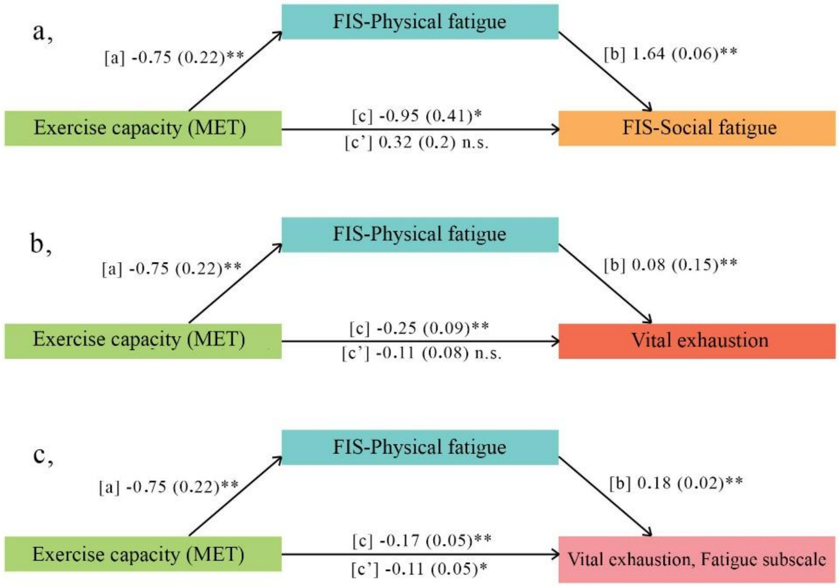

Figure 1, The mediator role of Physical fatigue between Exercise capacity and non-physical fatigue dimensions (a, Social fatigue; b, Vital exhaustion; c, Vital exhaustion-Fatigue subscale).

I.A. Discussion

This study investigated potential associations of exercise capacity indexed as MET, and the various dimensions of subjective fatigue and depression in patients with coronary artery disease. Patients with lower MET reported greater VE and find that fatigue has more impact on their physical and social functioning, and slightly more impact on their cognitive functioning. In addition, exercise capacity was associated with patients' everyday physical limitations.

MET independently predicted subjective physical limitations indexed by the PF-10 scores and three aspects of fatigue as vital exhaustion (SMEQ), physical fatigue (physical subscale of FIS) and social fatigue (the social subscale of FIS). Our analyses also indicated that physical fatigue strongly mediates the associations between exercise capacity and the non-physical fatigue dimensions as, social fatigue. High social fatigue has been shown to increase withdrawal from social relationships, which may be associated with the increase in risk of severe depression. Our results suggest that exercise-based interventions might reduce social fatigue and thus enhance their social functioning.

Previous studies found that Vital exhaustion is one of the best psychosocial predictors of adverse cardiovascular events, and poor health-related quality of life. An important finding from the current study is that VE is associated with energy cost of physical activities and MET was most strongly related to the fatigue dimension of VE.

Finally, patients' sleep complaints, but not their average sleep duration, were significant predictors of each of the fatigue dimensions. Importantly, however, the predictability of exercise capacity for fatigue and physical functionality was found to be unaffected by these complaints.

I.B. The effects of change in exercise capacity on subjective fatigue

I.B. Introduction

Due to the cross-sectional design in the first part of the study, we could not draw causal conclusions. Therefore, in the second part of our study we investigated whether the exercise training-related changes in exercise capacity were related to the magnitude of improvement in subjective fatigue.

I.B. Methods

Seventy patients with stable coronary artery disease participated in an ambulatory cardiac rehabilitation training program (men: 27, women: 43; age: M= 65.13; SD= 5.8).

In addition to the baseline measurements, patients underwent an exercise stress test (Bruce protocol was used) and completed a self-report assessment of fatigue after the first *12* weeks of the program. Patients did not receive any psychological intervention or therapy during this period. All patients had an ejection fraction higher than 40%, a MET value higher than 5, and had no significant ST depression.

I.B. Data analysis

First, we used Wilcoxon-test to compare the baseline measures with the 12-weeks data. Second, multiple linear regression was conducted to evaluate the associations of the training-related changes in exercise capacity with the changes in subjective fatigue variables.

I.B. Results

Comparison of baseline and follow-up scores showed that all aspects of subjective fatigue improved whilst patients were following the exercise training program (VE: $Z= -2.52$, $p < 0.05$; VE-sleep: $Z= -1.10$, $p < 0.05$; VE-mood: $Z= -3.13$, $p < 0.05$; VE-fatigue: $Z= -0.75$, $p < 0.05$; Cognitive fatigue: $Z= -3.08$, $p < 0.01$; Physical fatigue: $Z= -3.78$, $p < 0.001$; Social fatigue: $Z= -4.11$, $p < 0.001$). The physical functioning did not change (PF-10: $Z= -0.72$, *n.s.*). Exercise capacity also improved significantly during the follow-up: $Z= -5.76$, $p < 0.001$. However, this improvement in exercise capacity was not associated with the magnitude of improvement in any of the fatigue variables according to the multiple linear regressions.

I.B. Discussion

The follow-up analysis supported that even a 12-week long physical training decreased the subjective fatigue of patients with coronary artery disease in all dimensions. The improvement in psychological well-being is a valuable effect of physical rehabilitation, however, this improvement is not necessarily related to the changes in objective physical parameters (e.g. MET). According to our results, the improvement in subjective fatigue during physical rehabilitation did not relate to the improvement in exercise capacity. The reduction of fatigue during training might be caused by other factors too (e.g. changes in mood). There is also the question, whether the amount of improvement in exercise capacity during the follow-up was enough to reach a subjective level of experience. The average improvement in MET was 1.3 units (SD: 1.45), that might be under the threshold of recognition. The absence of subjective experience might be due to the average MET value of the patients (M= 8.26) that supports convenient everyday functioning.

Further studies are needed to test which level of improvement is enough to reach the threshold of subjective experience and to evaluate whether a higher level of functionality is related to decreased subjective fatigue and better overall well-being.

I.C. The changes in subjective fatigue of patients with coronary artery disease after inpatient cardiac rehabilitation

I.C. Introduction

Although, outpatient cardiac rehabilitation has many indications, it is not available for all patients (e.g. the distance of the rehabilitation centre, the cardiovascular status of the patient). After a cardiovascular event, however, all patients have the possibility to attend an inpatient cardiac rehabilitation. A Hungarian study found both forms of rehabilitation similarly effective but the improvement in cardiovascular parameters of those who gave up systematic training was not long-lasting and during the follow-up it significantly decreased.

Therefore, in the third part of the study we followed a group of coronary artery disease patients for 12 weeks after a period of an inpatient cardiac rehabilitation.

I.C. Methods

Forty patients (age: M= 61.62; SD= 9.03) with stable coronary artery disease were recruited for the study. The patients attended a classical inpatient rehabilitation programme at 1st Department of Internal Medicine, University of Pécs. The patients completed a set of questionnaires (similar to the first part of the study) at baseline and at the end of the 12-weeks follow-up. The follow-up questionnaires were returned by post. We also checked whether patients had any acute disease or positive/negative life event that could effect the results. After the rehabilitation programme patients did not receive any physical or psychological interventions, except for their medical therapy.

I.C. Data analysis

Thirty-nine patients returned the questionnaires. One-Way Anova was used to compare the baseline and follow-up data.

I.C. Results

Neither of the subjective fatigue dimensions (FIS Cognitive: $F(1, 76) < 0,01$; *n.s.*, FIS Physical: $F(1,76) = 0,21$; *n.s.*, FIS Social: $F(1,76) = 0,38$; *n.s.*, VE: $F(1,76) = 0,013$; *n.s.*) changed during the 12-weeks. There was no change in patients' depression level ($F(1,76) = 0,19$; *n.s.*) and physical functioning ($F(1,76) = 1,08$; *n.s.*) either.

I.C. Discussion

In our study, inpatient cardiac rehabilitation was not enough to cause a long-lasting change in the dimensions of subjective fatigue. There was no change in patients subjective fatigue and VE during the follow-up. One of the possible causes might be that patients often reduce their physical activities at their homes. Previous studies support that a high amount of patients give up physical activity after cardiac rehabilitation. After a cardiac arrest patients show willingness to change behavior but this change is often not permanent.

Our results support that an organized cardiac rehabilitation program can facilitate permanent behavior change so systematic intervention programs should be used widespread.

II.study

Cardiac patients' heart drawings reflect exercise capacity and the time elapsed since coronary intervention procedures

II. Introduction

Cardiac patients' perception about their illness has been shown to strongly influence their recovery and return to prevoiusly valued activities: a slower recovery pattern has been associated with negatively perceived illness conditions. A recently established method to assess illness perception is the analysis of patients' drawings about their heart. The size of the heart drawings or the amount of heart failures drawn were found to be associated with patients' activity level, severity of the illness and the speed of return to work. In sum, heart drawings might provide a good opportunity for clinicians to assess how patients model their heart conditions and how this model directs their everyday functioning.

The present study was aimed at contributing to the evaluation of heart drawings in three aspects that have not been addressed by previous studies. *First*, we examined how coronary artery disease patients' heart drawings associate with self-reported physical functionality and fatigue. We also compared the predictability of heart drawings for the different fatigue dimensions. We expected that the heart drawings might be stronger predictors of physical fatigue than of the non-physical fatigue dimensions.

Second, previous studies have demonstrated that exercise capacity is associated with illness perceptions, suggesting the prediction that exercise capacity is associated with the appearance of heart drawings. We predicted to find CAD patients with lower MET tend to draw larger hearts with more details referring to heart damages than patients with higher capacity.

Third, we also examined whether heart drawings show associations with the time elapsed since some of the important events of the disease history, myocardial infarction and coronary intervention procedures (CABG, PCI).

II. Methods

One-hundred and twenty patients with stable CAD were recruited from outpatient visits during a 2-month-long period at 1st Department of Medicine, University of Pécs (men: 69, women: 51; age: M= 63.85, SD= 6.73).

Patients completed *5 questionnaires* referring to their experience over the previous 4 weeks: The 9-item form of the Beck Depression Inventory (BDI-9), Physical functioning subscale (PF-10) of the SF-36 Health Survey Questionnaire, The Fatigue Impact Scale (FIS), Shortened Maastricht Exhaustion Questionnaire (SMEQ), Spielberger State-Trait Anxiety Inventory (STAI-S, STAI-T).

Patients' illness perceptions were assessed by a *heart drawing task*. For the task we adopted a method used in previous studies (Broadbent et al.). The participants were given a blank box size of 9.5x12 cm, and they were asked to draw a heart picture into the box following the instruction: 'Please draw a picture of what you think your heart now looks like.'

All patients performed a *maximal exercise stress test* (Bruce protocol). Peak exercise capacity was estimated from exercise time and expressed as MET.

III. Data analysis

To analyze patients' drawings *five* measures were assessed: the width and height of the heart, the area of the heart, as well as the indication of vessels and damages. Width, height and area were assessed by the ImageJ software (*Figure 2*).

To analyse the associations of the drawing variables with MET, the questionnaire and the time variables data, *first*, bivariate correlations were performed. *Second*, independent sample t-tests were conducted to determine whether the questionnaire and the MET data of those patients who indicated vessels or heart damages were different to those who did not draw such details. *Third*, we performed a series of multiple linear regressions to evaluate the unique contribution of patients' heart drawing to MET, the questionnaire and the time variables data. The MET, the questionnaire and the time variable data as dependent variables were separately regressed on each of the three drawing variables separately.

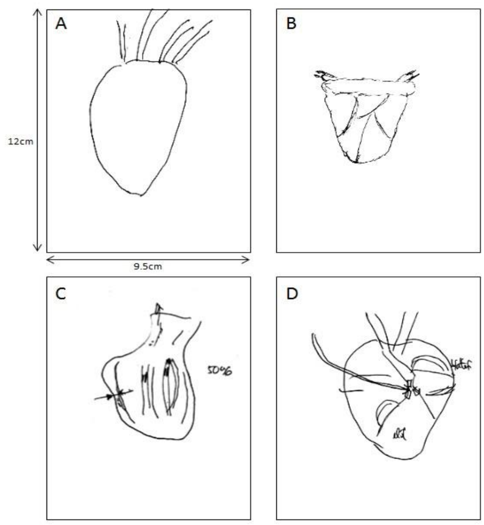

Figure 2. Some examples of CAD patients' heart drawings from simple ones to more complex drawings depicted closed arteries (A-D).

III. Results

The analysis of the category variables yielded no significant difference between those who drew vessels or damages and those who did not. The area of the heart drawing was found to show significant associations with MET: Patients with lower values of MET tend to draw hearts with larger area. The heart area was also negatively associated with PF-10 scores. However, in contrast to PF-10, the physical scale of FIS did not show significant association with any of the drawing variables. Similarly, the associations of heart drawing variables with the non-physical fatigue dimensions (social and cognitive fatigue), vital exhaustion and depression did not reach significance. Only state anxiety was associated with hearts of less height and width.

The covariate controlled multivariate analyses revealed that the area of the drawn heart became an independent predictor of both MET values and PF-10 scores. The correlation analysis showed a strong association between MET and PF-10 (r= -0.37, $p < 0.001$) that might predict that MET might mediate the association between heart drawings and PF-10. The potential mediator role of MET was tested by a mediator model. After controlling for MET, the association between PF-10 and heart area vanished (b= 0.13, t= 1.38, *n.s.*), therefore this association might be indirect through patients' exercise capacity.

Covariate controlled analyses revealed significant associations of heart area with AMI and the time elapsed since the diagnosis of CAD. The heart area drawn by the patients significantly and independently predicted the time elapsed since CABG and it remained significant even after controlling for MET (b= -0.43, t= -3.06, $p < 0.01$). This proves that MET doesn't mediate the relation of the heart area and the time elapsed since CAB.

II. Discussion

We found that the area of the hearts drawn by CAD patients increased with decreasing physical functionality. Interestingly, however, the dimensions of fatigue including the physical dimension were not found to be associated with heart drawings. Conceptually, compared to physical functionality, FIS Physical fatigue subscale consists of general, situation-independent statements about fatigue, while PF-10 asks patients to indicate their capacity to perform everyday physical activities. The results, therefore, suggest that the situation specific functionality assessed by the PF-10 might be reflected by heart drawings, but a more general fatigue level is not.

The heart area was a significant predictor of MET. MET can predict fatal and non-fatal cardiovascular events, therefore our result that patients' representation of their heart reflects on MET might prove the clinical relevance of drawing techniques.

Finally, we found strong associations of the area of the hearts and the time elapsed since CABG. This association was not find between heart drawings and PCI. The finding that heart drawings reflect better on CABG, might be explained by the difference in the effectiveness of the two procedures: previous studies found that CABG decreased angina symptoms better than PCI did and it improved physical and emotional state of patients many years after the intervention.

As a conclusion, heart drawings, especially the area of the hearts drawn, reflected on what patients thought about what happened to their hearts and the medical knowledge about their heart disease. Worse functional capacity was associated with bigger drawings- decreased functionality referred to "*bigger heart problem*".

III.study

The effect of asymptomatic carotid artery stenosis on attention

III. Introduction

Carotid stenosis (CS) is the narrowing of the carotid arteries around or above 50%. When the carotid artery stenosis is determined, the examination of cognitive functions is often not taken into consideration. Most studies involved symptomatic patients, who showed ischemic symptoms (stroke or TIA) at the section of the carotid stenosis. In the past few years, however, some studies appeared involving asymptomatic (ACS) patient polulations, who are free of ischemic events.

Studies using general neuropsychological test batteries found cognitive deficits in many areas, like attention, memory, spatial, visual and language skills of asymptomatic patients. Due to the laterality of these cognitive functions the degree of cognitive deficits might depend on the side of the carotid stenosis, too.

The effect of carotid stenosis on attentional functioning was neglected so far. It was only measured as a part of the test batteries. The Attentional Network Task is becoming a useful measurement of attention, which is designed to assess the three attentional networks (alerting, orienting and executive function) at the same time.

In the *first part* of the study we examined the effect of asymptomatic carotid stenosis on attentional networks, then in the *second part* we also analysed the effects of the side of the carotid stenosis on the attentional networks.

III. Methods

25 patients with ACS and 25 healthy volunteers entered the study. The 25 patients (age: M= 65..64; SD= 4.06) were recruited from the Deparment of Neurology, University of Pécs. The stenosis was proven by Carotid Duplex Doppler Ultrasound. The degree of the stenosis was between 50-70%. The control group consisted of 25 healthy volunteers who had neither carotid stenosis (proven by carotid doppler ultrasound), nor other serious illness.

All participants attended a Carotid Duplex Doppler Ultrasound examination and fulfilled a package of questionnaires (The 9-item form of the Beck Depression Inventory (BDI-9), Physical functioning subscale (PF-10) of the SF-36 Health Survey Questionnaire, The Fatigue Impact Scale (FIS), Shortened Maastricht Exhaustion Questionnaire (SMEQ), Spielberger State-Trait Anxiety Inventory (STAI-S, STAI-T)). To measure the severity of cognitive impairment the Mini-Mental State Examination was used.

The Attentional Network Task (ANT) was used to measure the three attentional networks at the same time: alerting, orienting and executive function.

The participants' task was to identify the direction (left or right) of the centrally presented arrow. The target was flanked on either side by two arrows in the same direction (congruent condition) or in the opposite direction (incongruent condition). The appearance of the target arrow was determined by spatial cues, so the subjects had to shift spatial attention from the fixation point to the target stimulus on each trial in order to determine the proper response.

We also measured the *flicker fusion frequency* of all participants. This method is used to estimate the activation level of the central nervous system and to diagnose different ophthalmological problems.

III. Data analysis

To compare the questionnaire variables of the patient and control group we used Mann-Whitney test. To analyze the ANT data we used Repeated Measures Anova and Mann-Whitney test.

III. Results

The analysis of the questionnaire variables revealed, that the control and patient group did not differ from each other in any of the subjective fatigue dimensions (Cognitive fatigue: U = 271, *n.s.*; Physical fatigue: U = 278,5, *n.s.*; Social fatigue: U = 282, *n.s.*), nor anxiety (STAI-S: U= 300,5, *n.s.*; STAI-T: U= 272,5, *n.s.*). The patient group, however, showed greater Vital exhaustion than the control group (U= 202, $p < 0.05$). This increase was caused by the depressed mood of VE (U= 199.5, $p < 0.05$). In the case of subjective physical functioning the patient group rated their physical functioning worse than the control group (U= 162.5, $p < 0.01$).

There was no difference between the two groups in the results of the flicker fusion frequency: the speed of the visual processing and the level of cortical arousal was similar in the two groups (Fusion frequency: U= 297, *n.s.*; Flicker frequency: U= 235, *n.s.*).

Analysing the ANT reaction time data, there was no difference in the general reaction time (the mean reaction time of all trials) between the two groups, more specifically, the mean speed of performing the test was similar in the control and patient groups (U= 306, *n.s.*). In contrast, the analysis of the reaction times reflecting on the operation of the attentional networks varied in the two groups. The effectiveness of the orientation (U= 273, *n.s.*) and executive (U= 291, *n.s.*) networks was similar but the activity level of the alerting function was significantly lower in the patient group (U= 189, $p < 0.05$).

Finally, we also tested the difference between left (N=13) and right (N=11) sided carotid stenosis in the functioning of the attentional networks. The analysis yielded no significant difference between the two groups (alerting: U= 59, *n.s.*; orienting: U= 61, *n.s.*; executive: U= 54, *n.s.*). However, the reaction time calculated from all trials was significantly slower in those patients who had right sided carotid stenosis (U= 24, $p < 0.01$).

III. Discussion

This study investigated the influence of ACS on attentional networks. The ACS group and the control group did not differ in the subjective fatigue dimensions, but the patient group reported greater VE and lower physical functioning. Depressed mood and hopelessness that appear in VE might influence the progression of atherosclerosis by affecting arterial stiffness that causes plaque rupture. Greater VE though might increase the risk of carotid stenosis.

Testing the effectiveness of attentional networks, we found that the orienting and executive networks were both effective in the two groups. The alerting network, however, showed worse functioning in the patient group. The Attentional Network Task is useful to measure how the alertness of the study participants increases from a tonal to a phasic level. According to our results this phasic attentional alerting is sensitive to the changes in blood flow at the area of the carotid stenosis.

When the side of the stenosis was included, we found no difference in the functioning of the attentional networks. Though, the slower completion of the task in the case of right sided ACS supports that the right sided ACS might cause a general decline in the speed of cognitive processing but this slowering does not affect higher attentional systems.

In sum, ACS plays an important role in the worsening of the alerting processes through haemodynamic changes, like chronic hypoperfusion and embolisation. Our results support that these changes appear at an early phase of CS, so even asymptomatic carotid stenosis, on its own can decrease the functioning of the alerting system of attention. The decline in attention might lead to the worsening of patients' quality of life: Problems with sustaining attention or ignoring target cues might cause difficulties during everyday activities. These findings make the early testing of attentional functions clinically relevant.

IV.study

Associations of exercise capacity with psychomotor vigilance in patients with coronary artery disease: The role of rheological factors in behavioral regulation

I. Introduction

The results of the *I.A. study* revealed a strong and independent association of exercise capacity with physical fatigue in cardiovascular patients, while the association of exercise capacity with mental fatigue was found to be weak. The cognitive fatigue, measured by FIS refers to a higher level of cognitive functioning, while exercise capacity refers to a lower level, more specifically the energetization of the organic system. However, cognitive fatigue also has a lower level of functioning that is in connection with a more general energetization that can be measured by instruments sensitive to the implicit level of fatigue. Such an instrument is the *Psychomotor Vigilance Test (PVT)* that measures psychophysical data, like reaction time. From the performance on the PVT (the reaction time of the research subjects) we can get information about alerting and sustained attention.

The aim of the present study was to (*1*) test whether the exercise capacity of coronary artery disease patients predicts their psychomotor speed. Furthermore, (*2*) we also examined the associations of psychomotor functioning with subjective fatigue. Finally, (*3*) we analyzed rheological processes, as common biological mechanisms that might refer to both a lower level of fatigue, measured by the PVT, both to exercise capacity (MET). Previous studies found a lower level of blood flow in patients with cognitive decline. Some of these studies could reveal relationship between Vital exhaustion and altered fibrinolytic processes. According to these findings, someone can hypothesize that other dimensions of fatigue might be related to fibrinogen level of patients. The associations of exercise capacity with fibrinogen is also supported by observations, where physical rehabilitation had a positive effect on rheological factors (e.g. the level of C-reactive protein and fibrinogen decreased, the deformability of red blood cells increased during rehabilitation).

IV. Methods

Sixty-seven patients with stable coronary artery disease were recruited for the study (35 men, 32 women, age: M= 65.72, SD= 5,71). Patients were eligible to participate if they did not have any acute disease, and had no changes in medication during the three months prior to the study. In addition, patients were included if they did not receive psychotherapy within the three months before the study and their BDI-9 was under 15 points.

Patients completed *4 questionnaires* referring to their experience over the previous 4 weeks: The 9-item form of the Beck Depression Inventory (BDI-9), Physical functioning subscale (PF-10) of the SF-36 Health Survey Questionnaire, The Fatigue Impact Scale (FIS), Shortened Maastricht Exhaustion Questionnaire (SMEQ).

All patients performed a *maximal exercise stress test* (Bruce protocol). Peak exercise capacity was estimated from exercise time and expressed as MET.

Blood samples were also taken from the patients: routine laboratory (hemoglobin, total protein, albumin, C-reactive protein, fibrinogen) and hemorheological measurements were then performed (whole and plasma viscosity, Red Blood Cell deformability).

To measure patients' *psychomotor vigilance*, we used a visual reaction time task (PEBL Psychological Test Battery). Participants were asked to respond to a visual stimulus (red light) appeared on the screen by pushing a response button as quickly as possible.

IV. Data analysis

To analyze the associations of PVT with MET we used multiple linear regressions (*1*). MET was the independent variable and the dependent variables were the PVT dimensions. We controlled for age, BMI, gender, diabetes mellitus and BDI-9 in our model. (*2*) We also used multiple linear regressions to test the relations of PVT variables (as independent factors) to the questionnaire variables (as dependent factors) and to (*3*) analyze the rheological factors contributed in psychomotor vigilance and exercise capacity. Rheological factors were entered separately as independent variables.

IV. Results

First, we found significant associations of PVT with MET: lower functionality was associated with lower psychomotor vigilance. Furthermore, MET was a significant predictor of some of the PVT variables.

Second, none of the PVT variables were associated with the questionnaire variables (*b*: -0.25 and 0.22, *n.s.*). This finding supports that the results of objective psychomotor tests do not reflect on the subjective fatigue experienced by the patients.

Third, the fibrinogen level of the patients significantly associated with MET (b= -0.13, t= -1.08, $p < 0.05$): lower exercise capacity was related to higher fibrinogen level. Fibrinogen also predicted some of the PVT variables and lower psychomotor vigilance was always associated with higher fibrinogen level.

Finally, in a separate analysis we tested whether fibrinogen could be a mediator between MET and PVT. After controlling for fibrinogen, MET remained an independent predictor of performance on PVT. When controlling for MET, fibrinogen became an independent predictor of psychomotor vigilance. These results support that fibrinogen has no significant mediator role in the relation of PVT to exercise capacity. These two were independently related even without the influence of fibrinogen.

IV. Discussion

Our aim was to analyze further the relation of cognitive fatigue to exercise capacity: beside measuring cognitive fatigue with subjective scales, we also used the Psychomotor Vigilance Test to measure a behavior component of fatigue.

MET found to be an independent predictor of the PVT variables, that might refer to the fact, that MET and PVT can both reflect on the energy level of the individual.

There was no relation between PVT and subjective cognitive fatigue, more specifically psychomotor vigilance of patients did not predict the subjective fatigue dimensions. The fatigue measured by reaction time tasks might reflect rather on an implicit level of experience that do not manifest in explicit ways.

In our study, fibrinogen level was associated with both MET and PVT but it did not mediate the relation between them. Declined fibrinolytic processes might support the progression of cardiovascular disease, so it can be hypothesized that a lower level of fibrinogen leads to an increase in exercise capacity. Fibrinogen might have a key role in cognitive functioning, as well: insufficient blood flow leads to cerebral hypoperfusion that might increase the risk of cognitive disfunctions.

General discussion

In our **first study**, we analyzed the associations of exercise capacity (MET) with subjective fatigue in coronary artery disease patients. Lower MET was associated with greater Vital exhaustion, physical and social fatigue and with more limitations in everyday physical functioning. MET also predicted these subjective variables independently. In the relations of MET-Vital exhaustion and MET-Social fatigue, physical fatigue played an important mediator role. We also tested whether a physical improvement during an outpatient cardiac rehabilitation program was associated with the changes in subjective fatigue of the patients. Our results supported that the improvement in subjective, psychological variables was not associated with the improvement in objective physical parameters (e.g. MET). We also found, that subjective fatigue does not necessarily change after an inpatient cardiac rehabilitation program.

In the **second study**, our aim was to analyze the heart drawings of coronary artery disease patients, more specifically, to test the associations of heart drawings with subjective fatigue and with some of the important events of disease history: myocardial infarction and coronary intervention procedures (CABG, PCI). Heart drawings with bigger area were associated with lower exercise capacity and the size of the drawings also reflected on the time elapsed since CABG.

In the **third study**, we tested the effects of asymptomatic carotid stenosis (ACS) on subjective fatigue and its effect on the three attentional networks: alerting, orienting and executive function. The ACS patient group showed worse functioning of the alerting network than the healthy control group. The patients also reported greater Vital exhaustion and worse physical functioning. Furthermore, patients with right-sided carotid stenosis showed a general slowness during testing.

In the **fourth study**, we analyzed further the relations of cognitive fatigue to exercise capacity by testing the behavioral component of fatigue. MET independently predicted the psychomotor vigilance of coronary artery disease patients: patients with lower MET showed lower psychomotor vigilance. Subjective fatigue, however was not associated with psychomotor vigilance. From the rheological variables, only fibrinogen was related to both MET and psychomotor vigilance, but importantly, it did not mediate their relation.

List of publications

Publications related to the thesis

1. Nagy, A., Szabados, E., Simon, A., Mezey, B., Sándor, B., Tiringer, I., Tóth, K., Bencsik, K., Csathó, Á. (2016). Association of Exercise Capacity with Physical Functionality and Various Aspects of Fatigue in Patients with Coronary Artery Disease. ***BEHAVIORAL MEDICINE***, e-pub: 25 May, 2016, pp 1-8. (*IF: 1,73*)

2. Sándor, B., Nagy, A., Tóth, A., Rábai, M., Mezey, B., Csathó, Á., Czuriga, I., Tóth, K., Szabados, E. (2014). Effects of moderate aerobic exercise training on hemorheological and laboratory parameters in ischemic heart disease patients. ***PLOS ONE***, 9, (10), Paper e110751. 8 p. (*IF: 4,17*)

Cumulative IF: 5,86; Number of independent citations: 6

Publications unrelated to the thesis

1. Tótsimon, K., Nagy, A., Sándor, B., Bíró, K., Csathó, Á., Szapáry, L., Tóth, K., Márton, Zs., Kenyeres, P. (2016). Hemorheological alterations in carotid artery stenosis. ***CLINICAL HEMORHEOLOGY AND MICROCIRCULATION***, e-pub: 17 February 2016 *(IF: 1,81)*

2. Nagy A., Tiringer I., Szabados E. (2016). Integrált egészségpszichológiai edukációs program alkalmazása koszorúérbetegek rehabilitációjában. ***KARDIOVASZKULÁRIS PREVENCIÓ ÉS REHABILITÁCIÓ***, 6 (2), 20-22.

3. Nagy A., Szabados E., Tiringer I., Csathó Á. (2014). A szívelégtelenség hatása a kognitív funkciókra. ***CARDIOLOGIA HUNGARICA,*** 44 (4), pp. 241-247.

4. Nagy A. (2015). Jakab Margó (szerk): Gyakorlati útmutató az autogén tréninghez: Könyvismertetés. ***PSZICHOTERÁPIA,*** 24 (4), pp. 348-349.

5. Nagy A. (2014). Kállai János, Kaszás Beáta, Tiringer István (szerk.): Az időskorúak egészségpszichológiája: Könyvismertetés. ***MAGYAR PSZICHOLÓGIAI SZEMLE,*** 69 (3/9.), pp. 627-629. (*IF: 0,13*)

6. Nagy A., Feldmann Á. (2014). Agyi plaszticitás gyermek- és felnőttkorbanIn: Komoly Sámuel (szerk.) Emberi életfolyamatok idegi szabályozása – a neurontól a viselkedésig. Interdiszciplináris tananyag az idegrendszer felépítése, működése és klinikuma témáiban orvostanhallgatók, egészség- és élettudományi képzésben résztvevők számára Magyarországon. 2299 p. Pécs: Dialóg Campus Kiadó, pp. 1369-1384.(ISBN:978-963-642-631-6). TÁMOP 4.1.2.A/1-11/1-2011-0094

7. Nagy, A., Feldmann, Á. (2014). Brain plasticity in the children and adults. In: Komoly Sámuel (Ed.) Neural regulation of human life processes – from the neuron to the behaviour. Interdisciplinary teaching material concerning the structure, function and clinic alaspects of the nervous system for students of medicine, health and life sciences in Hungary. 2270 p. Pécs: Dialóg Campus Kiadó, pp. 1354-1368.(ISBN:978-963-642-632-3).TÁMOP4.1.2.A/1-11/1-2011-0094

8. Nagy, A., Feldmann, Á. (2014). Neuronale Plastizität bei Kindern und Erwachsenen. In: Komoly Sámuel (Ed.) Neurologische Regulierung humaner Lebensprozesse – vom Neuron zumVerhalten. Interdisziplinärer Lernstoff zum Thema Aufbau, Funktion und Klinik des Nervensystems für Studierende der Medizin, Gesundheits- und Biowissenschaften in Ungarn. 2453 p. Pécs: Dialóg Campus Kiadó, pp. 1464-1480. (ISBN: 978-963-642-633-0). TÁMOP 4.1.2.A/1-11/1-2011-0094

Cumulative IF: 1,94

Acknowledgements

First, I wish to thank my supervisor, Dr. Árpád Csathó his continuous support and motiovation, useful ideas and irreplaceable help in my research and summarizing my thesis.

Special thanks to my program leader and the former principal of the Institute of Behavioral Sciences, Prof. Dr. János Kállai. He gave me the chance to join the program of the Doctoral School of Behavioral Sciences and with his professionism and advice he continuously helped my clinical work and contributed to my professional improvement.

I would like to thank Prof. Dr. Zsuzsanna Füzesi her support and all my collegues at the Deparment of Behavioral Sciences for working together.

Special thanks must go to Dr. Eszter Szabados for her cooperation and help in the implementation of our clinical research, her useful advice and ideas. I also thank Prof. Dr. Kálmán Tóth, who've given me the chance to participate in the clinical practice at the 1st Deparment of Medicine, Department of Cardiovascular Prevention and Rehabilitation. I would like to thank Dr. Béla Mezey for helping us with the clinical examinations and all the collegues of the rehabilitation team.

I also thank Dr. Attila Simon who coordinated the patients' examinations professionally at the Heart Clinic of Balatonfüred, and contributed to the increase of the sample size in our research data.

I wish to thank Dr. László Szapáry, who helped us with the patients' examinations at the Department of Neurology, and provided us with useful advice related to the details of our research.

I would like to thank Dr. István Hernádi and Dr. Attila Trunk, who helped us with the cognitive neuropsychological tests.

Here I thank the collegues of the Haemorheological Laboratory, namely Dr. Barbara Sándor and Dr. Kinga Tótsimon.

Special thanks go to Dr. István Tiringer for his continuous support, enthusiasm, professionism during our clinical work.

I also thank Boróka Gács and Márta Fürtös Frankovics for their endless motivation, support and encouragement.

I would like to express my gratitude to my family and friends. This thesis could not have been carried out without their emotional support, patience and encouragement through my whole life.