CARDIOVASCULAR IMPLICATIONS OF AFFECTIVE TEMPERAMENTS

Ph.D. thesis

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1. INTRODUCTION

Affective temperament is considered the inherited biological core of personality. Temperaments can be conceived as biological predispositions toward certain patterns of emotions, cognitions and behaviors that characterize emotional reactivity to environmental stimuli and they comprise of five distinct dimensions: cyclothymic, hyperthymic, irritable, anxious and depressive. The 110 self-reported items of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) were formulated to quantify affective temperaments along these five subscales. Affective temperaments not only demonstrate a pathoplastic effect on the initiation, clinical course and core characteristics of major affective disorders but they are widely considered as the subclinical manifestations of these clinical conditions. Besides psychopathology, a growing body of evidence suggest the impact of affective temperaments on somatic diseases but limited attention has been paid to temperaments as potential risk factors of cardiovascular (CV) pathology.

CV disease remains the leading cause of morbidity and mortality in the majority of developed countries worldwide. In spite of substantial declines in CV disease mortality over the past four decades in Europe, it remains the most frequent cause of death on the continent, with coronary artery disease (CAD) accounting for 43 % of all CV deaths. Aging, in particular, contributes to a large proportion of overall personal CV risk, however, individuals do not age at the same pace. This observation eventually led to the introduction of the concept of vascular age that describes the gradual deterioration of vascular structure and function, as opposed to chronological age that solely refers to the passage of time. Furthermore, hypertension remains a major contributing factor to CV morbidity and mortality in patients with ischemic heart disease, recently emerging as the single leading risk factor for the overall global burden of the disease. High blood pressure (BP) is still accountable for more CV deaths than any other modifiable CV risk factor. Left ventricular hypertrophy (LVH) has proven to be an independent predictor of CV morbidity and mortality in chronic hypertensive patients.

2. OBJECTIVES

2.1. Assessing the link between temperaments and accelerated vascular aging

We sought to estimate the arterial age of participants based on non-enhanced cardiac scans using coronary artery calcium score (CACS) measures calculated by the Agatston's method and to assess the potential link between affective temperaments and accelerated vascular aging.

2.2. Establishing associations between temperament scores and the presence of severe CAD

Furthermore, we intended to assess the association of affective temperaments and the presence of significant coronary artery stenosis in low to intermediate CV risk patients with stable angina by analyzing the coronary CT angiography (CCTA) images performed at our institution.

2.3. Evaluating the relationship of affective temperaments and left ventricular hypertrophy

The final aim of our studies was to evaluate the relationship of affective temperaments and LVH in chronic hypertensive patients, as assessed by CCTA.

3. METHODS

3.1. Affective temperaments and accelerated vascular aging

Overall, we enrolled a total of 209 patients in the current cross-sectional sub-study consisting of subjects with stable anginal symptoms referred to clinically indicated CCTA. The arterial age assigned to each patient was the age that has the same expected CHD risk as the observed CACS. A documented mathematical equation was used for the conversion: arterial age = $39.1 + 7.25 * \log_{10}(CACS + 1)$. The difference between vascular and chronological age was calculated. Uni- and multivariate linear regression analysis was used to assess the determinants of accelerated vascular aging in the whole cohort, and then in men and in women, separately.

3.2. TEMPERAMENT SCORES AND THE PRESENCE OF SEVERE CAD

Images were evaluated by experienced readers with 5-10 years of experience in cardiac CT. Severe CAD was defined as the presence of significant luminal diameter stenosis (≥ 70 % or ≥ 50 % in case of left main coronary artery) in ≥ 1 major coronary artery. Major coronary arteries included the left main, the left anterior descending, the left circumflex and the right coronary artery, as well as major side branches with a > 2 mm luminal diameter. Logistic regression analyses were used to assess the determinants of severe CAD. Given that age and sex are documented and widely accepted predictors of CAD, our first model was primarily adjusted for these factors.

3.3. AFFECTIVE TEMPERAMENTS AND LEFT VENTRICULAR HYPERTROPHY

Among a series of 382 consecutive patients who underwent CCTA in the inclusion period, we excluded 1) 27 patients because of prior AMI/PCI, 2) 19 patients due to severe comorbidity, 3) 2 patients because of inadequate CTA image quality, and 4) 38 patients due to the presence of severe coronary artery stenosis. Overall, 296 patients met the inclusion criteria of the current study. LV measurements were performed by an experienced reader with 4 years of experience in CCTA, while a second CV radiologist (with 6 years of experience in CCTA) subsequently re-evaluated 10 datasets to measure reproducibility. Myocardial mass was quantified in a semi-automated fashion (Simpson method) and LVM was indexed by the body surface area to acquire LVMi. Previously documented CTA-derived reference values were used to define LVH (men: ≥ 67.2 g/m^2, women: ≥ 54.7 g/m^2). Logistic regression analyses determined the independent predictors of LVH.

4. RESULTS

4.1. AFFECTIVE TEMPERAMENTS AND ACCELERATED VASCULAR AGING

Univariate regression model demonstrated that female sex was protective against vascular aging, while alcohol consumption, diabetes, dyslipidemia and irritable temperament

correlated with advanced vascular aging. Female sex [β = -10.82 (95 % CI: -15.30 – -6.33), p < 0.001], diabetes [β = 7.16 (95 % CI: 1.20 – 13.12), p = 0.02] and dyslipidemia [β = 8.28 (95 % CI: 3.94 – 12.62), p < 0.001] maintained their significant independent association with accelerated aging in a multivariate setting. Table 1 provides the results of the multiple linear regression analyses in the whole cohort.

Table 1. Uni- and multivariate linear regression analysis of cardiovascular risk factors, affective temperaments, BDI-scores and the difference between vascular and chronological age.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
Female sex	***-11.39***	***-15.67***	***-7.11***	***<0.001***	***-10.82***	***-15.30***	***-6.33***	***<0.001***
BMI (kg/m^2)	0.12	-0.30	0.54	0.58	-0.10	-0.52	0.31	0.63
Current smoker	3.33	-3.56	10.20	0.34	3.73	-2.57	10.03	0.24
Alcohol consumption	***5.06***	***0.56***	***9.56***	***0.03***	1.10	-3.33	5.52	0.63
Hypertension	1.58	-3.30	6.44	0.52	-1.90	-6.76	2.97	0.44
Diabetes	***7.56***	***1.41***	***13.71***	***0.02***	***7.16***	***1.20***	***13.12***	***0.02***
Dyslipidemia	***7.18***	***2.73***	***11.62***	***0.002***	***8.28***	***3.94***	***12.62***	***<0.001***
Depressive	0.18	-0.56	0.93	0.62				
Cyclothymic	0.48	-0.12	1.07	0.12				
Hyperthymic	0.19	-0.33	0.70	0.47				
Irritable	***0.07***	***0.05***	***1.39***	***0.04***	0.45	-0.19	1.08	0.17
Anxious	-0.07	-0.49	0.35	0.75				
BDI	0.18	-0.20	0.56	0.35				

Given that substantial sex differences have previously been proposed, potential associations were assessed separately in men and women, as well. No association was found regarding traditional risk factors for women, on the other hand, cyclothymic temperament independently predicted accelerated vascular aging in multivariate analysis [β = 0.89 (95 % CI: 0.04 – 1.75), p = 0.04]. Detailed results of the multiple regression analyses in the female cohort is provided in Table 2.

Table 2. Results of the multiple linear regression analyses in female population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
BMI (kg/m^2)	-0.01	-0.55	0.53	0.96	-0.18	-0.76	0.41	0.55
Current smoker	4.88	-4.40	14.15	0.30	1.90	-7.52	11.33	0.69
Alcohol consumption	-0.94	-7.73	5.85	0.79	-1.98	-9.07	5.10	0.58
Hypertension	2.96	-3.91	9.84	0.40	0.18	-7.38	7.75	0.96
Diabetes	8.66	-0.23	17.56	0.06	7.95	-1.51	17.41	0.10
Dyslipidemia	3.65	-2.71	10.02	0.26	3.23	-3.43	9.89	0.34
Depressive	0.60	-0.46	1.67	0.26				
Cyclothymic	***0.94***	***0.12***	***1.76***	***0.03***	***0.89***	***0.04***	***1.75***	***0.04***
Hyperthymic	-0.20	-0.89	0.50	0.58				
Irritable	0.80	-0.22	1.82	0.12				
Anxious	0.27	-0.32	0.86	0.37				
BDI	0.23	-0.30	0.76	0.39				

While dyslipidemia proved to be an independent predictor of advanced vascular aging for men in multivariate regression analyses [β = 12.77 (95 % CI: 7.05 – 1.75), p < 0.001], no association could be noted, however, with affective temperaments and BDI scores, as presented in Table 3.

Table 3. Results of the multivariate linear regression analyses in male population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
BMI (kg/m^2)	0.04	-0.57	0.65	0.89	-0.10	-0.70	0.50	0.74
Current smoker	2.84	-6.34	12.03	0.54	4.63	-4.00	13.26	0.29
Alcohol consumption	3.93	-2,14	10.00	0.20	2.03	-3.72	7.78	0.48
Hypertension	0.76	-5.44	6.96	0.81	-3.78	-10.06	2.49	0.24
Diabetes	5.66	-2.03	13.35	0.15	5.16	-2.41	12.73	0.18
Dyslipidemia	***11.82***	***6.45***	***17.18***	***<0.001***	***12.77***	***7.05***	***18.48***	***<0.001***
Depressive	0.56	-0.40	1.52	0.25				
Cyclothymic	0.17	-0.60	0.93	0.67				
Hyperthymic	-0.03	-0.77	0.71	0.94				
Irritable	0.04	-0.80	0.88	0.93				
Anxious	0.04	-0.80	0.88	0.93				
BDI	0.38	-0.11	0.86	0.12				

4.2. Affective temperaments and the presence of significant coronary stenosis

In our logistic regression model, the traditional risk factor dyslipidemia and cyclothymic temperament were both associated with the presence of significant luminal stenosis. Multivariate analysis confirmed the independently predictive nature of both dyslipidemia [odds ratio (OR) = 4.73 CI: 1.95–11.49, p < 0.001] and cyclothymic affective temperament (OR = 1.12 CI: 1.02–1.23, p = 0.02), while hyperthymic temperament (OR = 0.91 CI: 0.83–0.96, p = 0.04) was associated with a significantly decreased odds of severe CAD. Table 4 details the results of the multivariate logistic regression analyses.

Table 4. Uni- and multivariate logistic regression analysis of affective temperaments, cardiovascular risk factors and severe coronary artery disease, adjusted for age and sex.

	Model I.			Model II.			Model III.		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
BMI (kg/m^2)	1.01	0.95-1.08	0.75	0.99	0.91-1.07	0.75	0.96	0.92-1.08	0.91
Current smoker	1.62	0.59-4.47	0.35	2.03	0.67-6.11	0.21	2.19	0.72-6.60	0.17
Hypertension	0.89	0.38-2.06	0.79	0.59	0.21-1.64	0.31	0.59	0.21-1.66	0.32
Diabetes	1.95	0.85-4.47	0.10	1.50	0.57-3.95	0.41	1.57	0.61-4.06	0.35
Dyslipidemia	***3.81***	***1.69-8.58***	***0.001***	***5.36***	***2.16-13.28***	***<0.001***	***4.73***	***1.95-11.49***	***<0.001***
PTP	***1.08***	***1.00-1.16***	***0.045***	***1.10***	***1.01-1.19***	***0.03***	***1.09***	***1.00-1.18***	***0.04***
Depressive	1.08	0.96-1.22	0.18						
Cyclothymic	***1.10***	***1.01-1.20***	***0.03***	***1.12***	***1.02-1.23***	***0.02***			

Hyperthymic	0.92	0.85-1.00	0.053	***0.91***	***0.83-0.96***	***0.04***
Irritable	1.06	0.96-1.18	0.26			
Anxious	1.03	0.97-1.11	0.32			
BDI	1.03	0.97-1.09	0.31			

4.3. Affective temperaments and the presence of left ventricular hypertrophy

Inter-observer variability of LVM measurements was currently characterized by intraclass correlation coefficient (ICC), which demonstrated excellent reproducibility (ICC: 0.91) based on the re-evaluation of 10 CTA datasets.

Uni- and multivariate logistic regression analyses were used to determine predictors of elevated LVM. Assessment of patient baseline data demonstrated that BMI increased the odds of hypertrophy (OR = 1.07 CI: 1.02–1.13, p = 0.01), while age was inversely associated with the presence of LVH (OR = 0.97 CI: 0.94–0.99, p = 0.01). Antihypertensive agents and variables with $p < 0.10$ in univariate analysis were entered into the multivariate model.

While BMI remained independently predictive in a multivariate setting (OR = 1.04 CI: 1.01–1.10, p = 0.04), none of the regularly prescribed antihypertensive agents correlated significantly with the presence of LVH. Moreover, cyclothymic affective temperament was a further independent predictor of LVH in the multivariate analysis (OR = 1.06 CI: 1.00–1.12, p = 0.04). Overall, a 1-point higher cyclothymic affective temperament score resulted in a 6 % increase in the odds of LVH. Table 5 summarizes the results of the multiple regression analyses.

Table 5. Uni- and multivariate logistic regression analysis of the association of cardiovascular risk factors, affective temperaments, and left ventricular hypertrophy.

	Univariate			Multivariate		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
Age (years)	***0.97***	***0.94 – 0.99***	***0.01***	1.00	0.95 – 1.01	0.11
Female sex	0.61	0.36 – 1.03	0.07	0.77	0.41 – 1.35	0.38
BMI (kg/m^2)	***1.07***	***1.02 – 1.13***	***0.01***	***1.04***	***1.01 – 1.10***	***0.04***
Duration of hypertension, (years)	1.00	0.98 – 1.03	0.86			
Number of antihypertensive agents, n (%)	1.23	0.92 – 1.63	0.16			
ACE/ARB	2.50	0.73 – 8.63	0.15	2.12	0.60 – 7.50	0.24
Beta blocker	1.03	0.48 – 2.18	0.63	1.01	0.46 – 2.18	0.99
Calcium channel blocker	0.83	0.39 – 1.75	0.83	0.76	0.35 – 1.65	0.50
Diuretic	1.81	0.89 – 3.69	0.10	1.62	0.77 – 3.39	0.20
Alpha-adrenergic receptor blocker	2.08	0.80 – 5.36	0.13	1.77	0.67 – 4.68	0.25
Current smoker	0.67	0.29 – 1.52	0.33			
Diabetes	1.50	0.76 – 2.96	0.24			
Dyslipidemia	0.83	0.49 – 1.40	0.48			
SSS	0.99	0.93 – 1.05	0.68			
SIS	0.97	0.89 – 1.07	0.59			
Depressive	0.97	0.89 – 1.06	0.54			

Cyclothymic	1.06	0.99 – 1.12	0.09	***1.06***	***1.00 – 1.12***	***0.04***
Hyperthymic	1.06	1.00 – 1.13	0.07	1.04	0.98 – 1.15	0.12
Irritable	1.04	0.96 – 1.13	0.33			
Anxious	0.96	0.91 – 1.01	0.10			

5. CONCLUSIONS

Our findings demonstrated that aside from conventional CV risk factors, affective temperaments independently predict a number of cardiovascular diseases. Temperaments yield implications in both accelerated vascular aging and the presence of severe CAD, as well as having a significant association with presence of LVH in chronic hypertensive patients. Our results provide further evidence on the detrimental role of psychometric parameters on CV disease and establish novel potential risk factors for CV pathologies. Provided that prospective investigations confirm their utility in clinical practice, affective temperaments might add incremental value to the CV risk stratification of patients and emerge as novel tools that aid the identification of patients with elevated CV risk as potential targets for earlier and more aggressive primary intervention. The delineation of the pathophysiological background of the current findings remains a topic of focus and identifying the factors potentially mediating the effect of affective temperaments in CV pathology requires further prospective studies.

6. BIBILIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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