DOI:10.14753/SE.2020.2300

SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2300.

LÁSZLÓ ANDREA

Experimentális és klinikai farmakológia
című program

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DOI:10.14753/SE.2020.2300

Associations of affective temperaments with arterial stiffness and Brain-derived Neurotrophic Factor in hypertension

Ph.D. Thesis

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Budapest

2019

DOI:10.14753/SE.2020.2300

DOI:10.14753/SE.2020.2300

DOI:10.14753/SE.2020.2300

DOI:10.14753/SE.2020.2300

ABBREVIATIONS

CCTA	Coronary computed tomography angiography
5-HTTLPR	Serotonin-transporter-linked polymorphic region
AC	Abdominal circumference
ACE	Angiotensin-converting enzyme
AIx	Augmentation index
Alp	Patients regularly using alprazolam;
AP	Augmentation pressure
ARB	Angiotensin II receptor blocker
AT	Angiotensin
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
cDBP	Central diastolic blood pressure
CHD	Coronary heart disease
cMBP	Central mean blood pressure
CONT	Controls
cPP	Central pulse pressure
CREB	cAMP response element binding protein
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
cSBP	Central systolic blood pressure
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DBPB	Diastolic brachial blood pressure
DOM	Patients with dominant affective temperaments
DT	Diastolic time
ECG	Electrocardiography
ESBP	End-systolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension

ESRD	End-stage renal disease
GABA	Gamma-Aminobutyric acid
GFR-EPI	Glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation
HDL	High-density lipoprotein
HP	Heart periode
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HT	Hypertensive patients
ICAM-1	Intercellular Adhesion Molecule 1
IL	Interleukin
IMT	Intima media thickness
LDL	Low-density lipoprotein
LPR	LDL receptor-related protein
LV	Left ventricular
LVET	Left ventricular ejection time
MAP	Mean arterial pressure
MDBP	Mean diastolic blood pressure
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
MSBP	Mean systolic blood pressure
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B
NGF	Nerve growth factor
NO	Nitric oxide
NT	Neurotrophin
NT-3	Neurotrophin 3
NT-4	Neurotrophin 4
p75Ntr	Neurotrophin receptor p75
Partial R^a	Partial correlation coefficient
PP	Pulse pressure
PPAmp	Pulse pressure amplification
PPB	Brachial pulse pressure

PWV	Pulse Wave Velocity
QOL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
Rpm	Revolutions per minute
SBP	Systolic blood pressure
SBPAmp	Systolic blood pressure amplification
SBPB	Systolic brachial blood pressure
SD	Standard deviation
SE	Standard error
seBDNF	Serum Brain-derived neurotrophic factor
SEM	Standard error of the mean
TEMPS-A	Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire
TIA	Transient ischemic attack
TNF	Tumour necrosis factor
Trk	Tropomyosin receptor kinase
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

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1. BACKGROUND

1.1. Cardiovascular diseases, hypertension and mood disorders: incidence and connections

1.1.1. Cardiovascular diseases in the XXIst century

Cardiovascular diseases (CVDs) are leading causes of death, major causes of health loss worldwide and therefore major barriers to sustainable human development (1). In 2011, the United Nations formally recognized noncommunicable diseases, including CVDs – among cancer, chronic respiratory disease, and diabetes – as major concerns for global health. According to the World Health Statistics, an estimated 17.9 million deaths occurred due to CVDs, accounting for 31.4% of the overall total of 57 million deaths in the year 2016 (2). Ischemic heart disease was the leading cause of CVD health lost globally and also in each world region, followed by stroke. Even though over the past 25 years sociodemographic changes have been associated with dramatic declines in CVDs, at present there is only a gradual decrease or no change in most regions. So, the trends in CVD mortality have plateaued and are no longer declining in high-income regions (3).

1.1.2. The importance of hypertension

Among the risk factors of CVDs hypertension has a major role affecting 1 billion adults globally (4): it is the leading cause of death and disability-adjusted life years (5) having an excessive impact on mortality worldwide. In the United States hypertension accounted for more cardiovascular (CV) deaths than any other modifiable CVD risk factor and was second only to cigarette smoking as a preventable cause of death for any reason (6, 7). In Europe the prevalence of high blood pressure among adults is between 30 and 45%, rising with aging (8). In Hungary, the number of subjects with hypertension is approximately 3.5 million and this high prevalence contributes markedly to the poor Hungarian CV morbidity and mortality figures (9): in 2014, 51.7% of all-cause mortality was due to CVDs (10).

There are modifiable (e.g. smoking, obesity, unhealthy diet) and non-modifiable (e.g. positive family history, age, male sex) risk factors of CVD which have a complex and interdependent relationship with hypertension. CVD risk factors can influence those

pathophysiological pathways which are also involved in the development of hypertension, such as the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, cardiac natriuretic peptide system or the endothelial function (11-13). Consequently, hypertension can also be considered as an outcome of different harmful processes, not only a simple disease. On the other hand, the development of high blood pressure can lead in longer term to adverse CV outcomes (14).

Hypertension is the most prevalent modifiable risk factor for global disease burden in both sexes, regardless of ancestry, geographic region or income (5), thus early diagnosis and treatment of this condition is essential. Among the healthy population it would be required to find subpopulations, in which the risk of the onset of this disease is higher. Furthermore, among the hypertensive subjects the recognition of patients with elevated CV risk would help reach more effective primary and secondary prevention. Hypertension prevention receives a great attention, but the role of personality in the development of high blood pressure has not been fully clarified yet.

1.1.3. Mood disorders: a common public health problem in the Western world

According to the World Health Organisation (WHO) depression is a common disease worldwide, involving up to 15% of the general population, with more than 350 million people affected in 2018 (15). According to WHO's estimation, by 2020 depression will be already the second leading cause of world disability (16) and by 2030 it is expected to be the largest contributor to disease burden (17). Major depressive disorder (MDD) accounts for 12.3% of the global burden of disease (18). Based on the fact that depressive disorders often start at a young age – reducing the person's functioning and oftentimes recurring – it is not surprising, that depression is the leading cause of disability for both men and women worldwide in terms of total years lost due to disability (19). While in 1990 depressive disorders were listed as the fourth leading cause of burden in the Global Burden of Disease (20), in 2000 they reached the third place (21).

1.1.4. Well-known connections between CVDs and depression

There is growing evidence, that physical and psychological diseases are not independent from each other. Between 9.3% and 23% of individuals with one or more chronic physical disease suffer from co-morbid depression (22). It is also known, that there is a

complex reciprocal interrelationship between depression and coronary heart disease (CHD) (23, 24). Depression is associated with a 3- to 4-fold increase in the risk of recurrent cardiac events and death (25). In addition, among people with CHD, depression increases the risk of future cardiac mortality and morbidity (26, 27). On the other hand, patients with CHD have a depression prevalence of about 300% than healthy subjects (28). In patients after an acute myocardial infarction, major depression is three times more common than in the general population (29).

There are multiple mechanisms by which depression could increase the probability of vascular diseases. These include increased platelet activation (30), endothelial dysfunction (31), elevation of inflammatory markers (32), as well as reduced heart rate variability (33). Dysregulation of metabolic, immune-inflammatory and autonomic systems, as well as the hypothalamic-pituitary axis, also seem to build a link between MDD and CVDs (34). Furthermore neurohormonal factors, and genetic linkages – such as with the serotonin transporter mechanism (35, 36) –, and also behaviour mechanisms are part of the pathophysiological background connecting both diseases (37).

1.2. Affective temperaments: risk factors for psychiatric disorders and CVDs

Parallel to depression, well-established biomarkers of inflammation were also found to be elevated in subjects in states of anger or hostility (38, 39), while a reduced function of the autonomic nervous system was observed in subjects in states of anxiety (40), and interpersonal antagonism was connected with carotid arterial intima-media thickening (41). These findings suggest that there are also psychological conditions in the range of normality which could influence CV risk. These data suggest that besides the evaluation of depression, analysing people's characteristics based on their individual nature would lead us to a better understanding and prevention of CV risk.

1.2.1. Background, definition and assessing of affective temperaments

The concept of human personality dates back to Hippocrates (ca. 460 BC - ca. 370 BC) and Aristotle (384-322 BC). Four temperamental types were differentiated based on body fluids (called "humors"): melancholic, choleric, sanguine and phlegmatic (42). Not only the ancient Greeks, but much later Luois XIV was delighted by the theory of the four temperament types, as clearly illustrated by his "grande commande" of statues

DOI:10.14753/SE.2020.2300

ordered to decorate the gardens of the Palace of Versailles in 1674. Among the 24 statues, the "The Four Humors of Man" were also included (Figure 1).

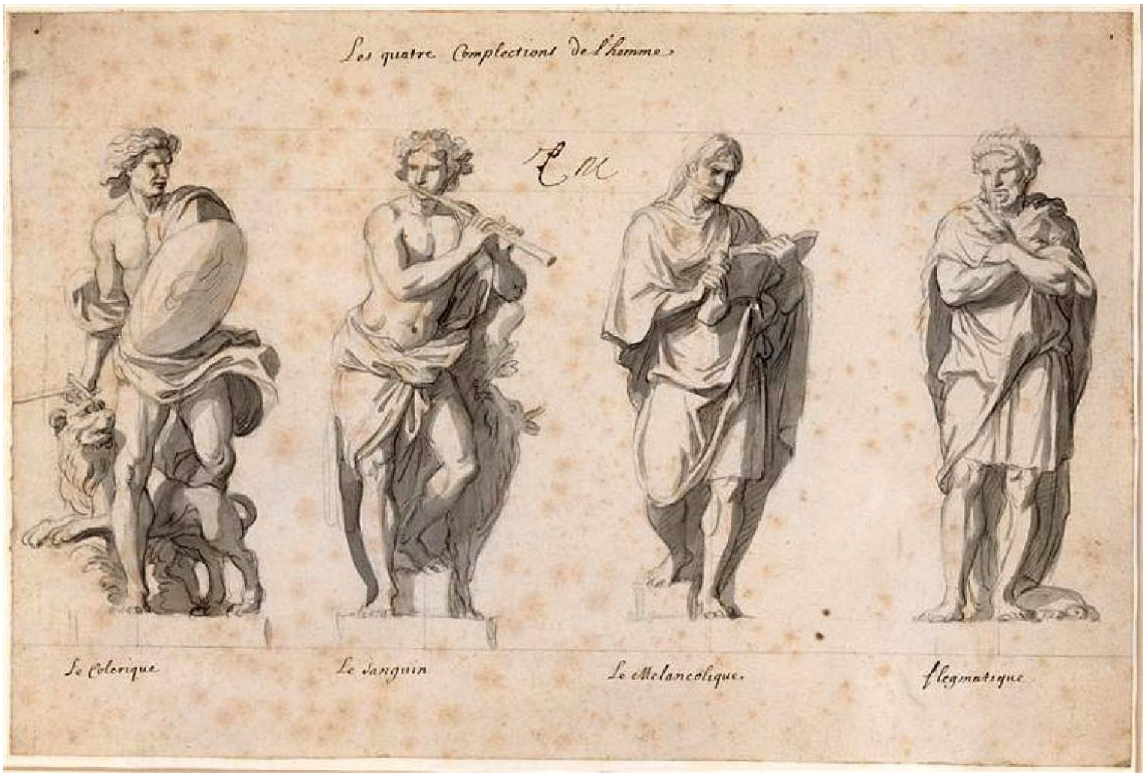

Figure 1. Charles Le Brun: The Four Humors of Man.
From left to right: choleric, melancholic, sanguine and phlegmatic.

Building on such classical theory and on Kraepelin's four distinct basic temperament types from 1913, professor Hagop S. Akiskal formulated the modern concept of affective temperaments and completed them with another one. Since then, we speak about five affective temperaments: depressive, irritable, hyperthymic, cyclothymic and anxious (43). Furthermore, Akiskal gave a new point of view on the definition of temperament and widened the term "temperament" to include healthy personality. Thus temperament – like personality – does not by itself necessarily constitute a pathology (44). All of us have our own characteristic temperamental profile determining our emotional response to environmental stimuli. In their natural mixture affective temperaments are responsible for cultural characteristics on a national level and can be associated with desirable outcomes such as adaptation and achievement (44-46).

The presence of these affective temperaments can be evaluated with the autoquestionnaire version of Temperament Evaluation of Memphis, Pisa, Paris and San

Diego (TEMPS-A). The questionnaire was developed by Akiskal and his co-workers (47, 48), and since 2005 it has been translated and/or validated in more than 30 languages, including such diverse cultures as the USA, Egypt, Japan, Lebanon, Portugal, Italy, Turkey, Germany, France, China, Korea, Russia, Tunis, Argentina, Brazil, Armenia, Hungary and many others (49). The questionnaire consists of 5 subscales – according to the 5 affective temperaments, requiring only simple "yes" (score 1) or "no" (score 0) answers.

1.2.2. Five types of affective temperaments

As mentioned above, according to Akiskal's concept, 5 affective temperament types can be distinguished: depressive, cyclothymic, irritable, anxious and hyperthymic. A person with a *depressive* temperament can be described as pessimistic, highly self-critical, gloomy, excessively worrying, preoccupied with personal failure, lacking assertiveness, self-denying, and striving to please others (48). In *cyclothymic* temperament, a person shows abrupt biphasic alterations in mood between highs and lows in energy, self-confidence and agility of mind with a frequency of several days each (50). A person with an *irritable* temperament reacts to negative events with negative emotions, presents fluctuations in mood and complaints, and shows close linkages to the cyclothymic temperament (51). People with *anxious* temperaments show uncontrolled worry even about their routine, an unfounded sense of danger, a real fear of unhappiness and an overalertness. They are unable to relax, stressed, restless and anxious (52). The difference between the *hyperthymic* temperament and the other four is that it proves to be more adaptive and beneficial for the patient, since it involves potentially positive characteristics: inter alia higher scores in sociability, energy and mood. On the other hand, such characteristics come in excess, and the flip side of this temperament is that it can involve maladaptive behavior, e.g. overconfidence, over-socialization, irresponsibility and ruthlessness, which can all result in undesirable outcomes of a person's actions (50).

It is important to note that sex differences are present in relation with affective temperaments. Vázquez et al. – and also other studies – found in the general population significantly higher irritable and hyperthymic temperament scores in men, and significantly higher anxious, depressive and cyclothymic temperament scores in women

(43, 53-55). On the other hand, each person scores differently in the different temperament directions and these are not fully independent form each other: positive associations were described between depressive and anxious, and cyclothymic and irritable temperaments (43).

1.2.3. Dominant affective temperaments and their relation to affective disorders – a spectrum concept

Dominant affective temperaments are defined with a cut-off point of z-scores above +2 standard deviation (SD) in the TEMPS-A questionnaire. Investigating the different countries, 13 to 20% of the population has some kind of dominant affective temperaments; in Hungary this value is 16.8 % (54). Temperaments can also be so extreme that they could be considered abnormal in a statistical sense – even with the absence of mental disorder (44).

It is unclear whether Aristotle discovered the concept of the bipolar spectrum, but he seems to have placed the query on exceptional greatness within the dimensional space between temperament and affective disease. At the beginning of the twentieth century, Kraepelin believed that the temperaments are subclinical forms and many times the precursors of major affective psychoses (56). According to Akiskal's theory of dominant affective temperaments – temperaments in their extreme forms, these are regarded as the subclinical/trait-related manifestations or phenotypes of bipolar or unipolar mood disorders (49). They often present an increased inclination towards these diseases and are located at the end of the continuum, close to affective illness (45, 49, 57, 58). Based on these facts, Akiskal visualized the spectrum concept of temperament and bipolar disease on the basis of Kretschmer’s work (1936) (42). In a Gaussian curve Figure 2 shows the normal population, the 13-20% of people having dominant affective temperaments and the remaining small part of the population with bipolar diseases – depending on the genetic loading.

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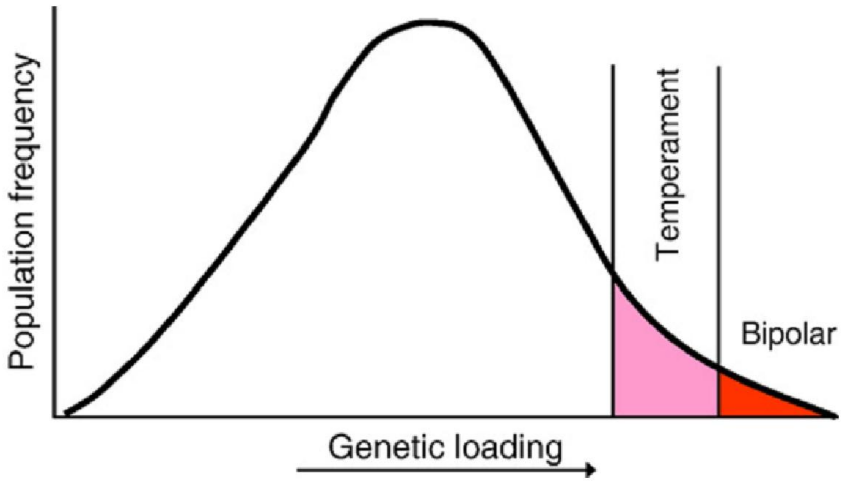

Figure 2. Temperament and bipolar disease in a spectrum concept.

Adopted from: (42).

1.2.4. Affective temperaments: molecular genetic backgrounds

Since different affective temperaments are predominant in the population in different geographic regions and cultures, a connection to genetic causes appears logical. Temperament in general (59) and affective temperaments in particular are biological in nature and are strongly determined by genetic factors (60-62). Molecular genetic studies show a strong connection to the central serotonergic regulation in depressive, cyclothymic, irritable and anxious temperaments, while the involvement of dopaminergic regulation seems to be significant in hyperthymic temperament (49). Gonda et al. found a significant association between the "s" allele of serotonin-transporter-linked polymorphic region (5-HTTLPR) gene and the TEMPS-A scores of depressive, anxious, irritable, and particularly of cyclothymic temperaments – like in depression (63). While people with one or two short alleles of the 5-HTT serotonin transporter gene become more often depressed after stressful events, subjects with two long alleles of this gene are less prone to such mood changes. No such association emerged with respect to the hyperthymic temperament (64). However, the same findings could not be demonstrated in South Korea. This may be due to the very different genotype distribution of 5-HTTLPR in the populations of the two mentioned countries (64-66). On the other hand, Kang et al. found a significant association

between the dopamine receptor 4 polymorphism and cyclothymic and irritable temperaments in men (65).

1.2.5. Affective temperaments are, in healthy populations, part of the bipolar and unipolar mood disorder spectrum

Not only in cases of affective temperaments, but also in unipolar and bipolar major mood disorders, the role of genetic modulation related to the disturbance of central serotonin and dopamine/noradrenaline neurotransmission is proven. The "s" allele of the HTTLPR gene shows a strong association with major depression (67), as well as with subthreshold forms of depression (66). So, these findings show that the genetic potential of major mood disorder episodes is based on affective temperaments (49).

It is already known that there is a continuum between dysthymia, subsyndromal depression, minor depression and unipolar major depression (68-72). Such a continuum could be demonstrated between cyclothymic disorder, bipolar I, and bipolar II disorders (73-75). Other studies on affective temperaments in healthy controls without affective family history showed the lowest, and in recovered bipolar I patients the highest mean hyperthymic and cyclothymic scores (60-62). In line with these findings, a pronounced onset of hyperthymic and cyclothymic temperaments was demonstrated in nonaffected first-degree relatives of bipolar I disorder patients. However, this does not mean that cyclothymic temperament itself is necessarily a good genetic marker for bipolar disorders in general (61). It is possible however, that it is relevant for bipolar II disorder (76).

1.2.6. The role of affective temperaments in the psychopathology: bipolar and unipolar mood disorders

According to data in literature, the relationship between affective temperaments and major mood episodes is quite complex. It is already known that hyperthymic and – to a lesser degree of magnitude – cyclothymic temperament are characteristic for bipolar I disorders, while the depressive temperament dominates in unipolar major depression (47).

Among bipolar I patients with higher frequency of maniac episodes, hyperthymic temperament is more pronounced, whereas among those with predominant depressive polarity, the characteristic temperament type is the depressive one (77).

However, cyclothymic temperament is the most common affective temperament type among patients with bipolar II disorder (47, 76, 78, 79). It is the precursor of bipolar disorder often with earlier onset, atypical features, more relapses and worse prognosis (49, 80). This temperament is 88% sensitive in identifying bipolar II disorder (81) and it has high predictive power for bipolar, especially for bipolar II transformation (82). Interestingly, in a smaller number of "unipolar" depressive patients – especially with a positive family history of bipolar disorder – the core feature of cyclothymic temperament can also be detected because it is typically accompanied by mood and energy alterations (83). On the other hand, cyclothymic temperament was also shown to be associated with atypical depression (49, 84).

1.2.7. Affective temperaments and cardiovascular risk

According to the European Guidelines on CVD prevention in clinical practice, personality can also affect vulnerability to and prognosis of CV disorders (85). Hostility, anxiety, and type D personality promote the development, clinical course and prognosis of CVD. The reasons are behavioral risk factors, such as unhealthy lifestyle, low adherence to behavior-change recommendations or to cardiac medications, which are preponderant in CV disorders (85). Thus, personality patterns and possibly temperaments can also be considered moderators, and not causes of specific diseases (86, 87).

We had limited knowledge about the association between affective temperaments and hypertension. Előry et al. demonstrated that dominant cyclothymic temperament is associated with the presence of chronic hypertension – independently of age, diabetes mellitus and obesity; suggesting an additional risk factor in CV morbidity (88). Unfortunately, in this study, the patients' blood pressure was not measured, only the diagnosis of high blood pressure was present in their medical history. In another study of Előry et al., cyclothymic temperament was also associated with the history of coronary events in chronic hypertensive patients, independently of depression or

depressive symptoms, age, gender and smoking, but in this cross sectional study only a very low number of patients (n=16) had CV events in their history (89).

Based on these results, it was reasonable to study in more depth the associations between affective temperaments and hypertension, including hemodynamic parameters, as well as to evaluate the differences between men and women.

1.3. Arterial stiffening as a risk factor for CVDs

1.3.1. Definition and pathophysiology of arterial stiffness

Arterial stiffness is a generic term describing the rigidity of the arterial wall. Vascular stiffening develops from a complex interaction between stable and dynamic changes including structural and cellular elements of the vessel wall (90). Interestingly, stiffness is not uniformly disseminated throughout the vascular tree (91-93) occurring in elastic arteries, while mostly sparing peripheral arteries (94, 95).

The pathophysiological background of arterial stiffening is complex. The chronic cyclical stress on the walls of large arteries leads to irreversible elastin fracturing and thinning (96). The activation of RAAS also enhances arterial stiffening through stimulating multiple inflammatory pathways such as tissue growth factor-β and nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), promoting reactive oxygen species production with reduction in nitric oxide bioavailability (97-99). Inflammatory processes disturb the balance between the production of proteases and their inhibitors and promote the synthesis of advanced glycation end-products (97). Sodium also plays an important role in the process of arterial stiffening: a high sodium level causes vascular smooth muscle cell hypertrophy (100), while in sodium sensitive patients it seems to lead to alterations in the viscoelastic properties of arterial wall characteristics (101).

Arterial stiffness and blood pressure are closely related. Although arterial stiffness was for a long time considered to be one of the complications of hypertension, there is now growing evidence that arterial stiffening itself can lead to an increase in systolic blood pressure (SBP); and in this vicious circle, this blood pressure elevation causes further arterial stiffening (102-104), suggesting that arterial stiffening is both a cause and a consequence of hypertension (105).

The result of the pathophysiological changes described above is the increased arterial stiffness in the aorta and in the carotid arteries, but not in the large peripheral muscular arteries. Thus, the peripheral impedance to the forward component of the arterial pulse-wave is reduced and the pulsatile energy transmission to the microcirculation is increased (106). The increase of blood flow and pressure pulsatility can lead to damage of high flow, low impedance organs, especially the kidneys and the brain (106). Additionally, aortic stiffening promotes left ventricular (LV) remodelling, hypertrophy and dysfunction (107, 108).

1.3.2. Methods for measuring arterial stiffness, focused on arterial tonometry

In clinical practice, non-invasive measurements of arterial stiffness using numerous devices are becoming more and more relevant. Regional methods are based on direct measurements of parameters strongly linked to wall stiffness. The most commonly applied non-invasive, "gold standard" method of evaluating arterial stiffness involves the use of a tonometer or a mechanotransducer to measure carotid and femoral pulse waves (109). Arterial tonometry is based on the applanation tonometry principle. The sensor must be placed on the skin above the artery, applying a moderate pressure. In this way the artery becomes slightly compressed with a balance of the circumferential forces inside the vessel, enabling the sensor to record the pressure in the middle of the compressed artery. However, these devices require a skilled operator to produce measurements of acceptable quality. With this method, the carotid-femoral pulse wave velocity (PWV) can be determined, which means the velocity of pulse wave as it travels from the heart to the carotid and then to the femoral artery. The pulse waves are usually registered on the right common carotid and the right femoral arteries (105). There are also other possibilities for regional arterial stiffness measurements: new and less operator-dependent methods are available. Some of these oscillometric methods are accompanied by ambulatory blood pressure monitoring and are able to determine the 24-hour profile of arterial stiffness and central blood pressure. Although clinical data are accumulating, questions remain as to the real relevance of these new devices, which cannot replace the use of the "gold standard" direct measurement of PWV (110).

1.3.3. Parameters of arterial stiffness

Various parameters can be measured and calculated in order to evaluate arterial stiffness and wave reflections in a non-invasive manner. Central SBP (cSBP), central pulse pressure (cPP), augmentation index (AIx) and PWV all show an increase with age and in association with CV risk factors, like hypertension, diabetes mellitus, and hypercholesterolemia. Although all of them are associated with target organ damage – like LV hypertrophy, increased carotid intima media thickness (IMT), microalbuminuria, endothelial dysfunction – and clinical outcomes, these are not replaceable indexes of arterial stiffness.

1.3.4. Pulse wave velocity

PWV is defined as the speed of the pulse pressure wave travelling along the arterial system. Arterial pressure waves are recorded on both proximal and distal arteries. The length of the arterial segment (ΔL) between the two measured points with surface tape must be determined, as well. The wave transit time (Δt) is obtained either by using the QRS complex of a simultaneously recorded electrocardiography (ECG) in order to have a reference frame, or by using two probes above the femoral and the carotid arteries at the same time (Figure 3) (109).

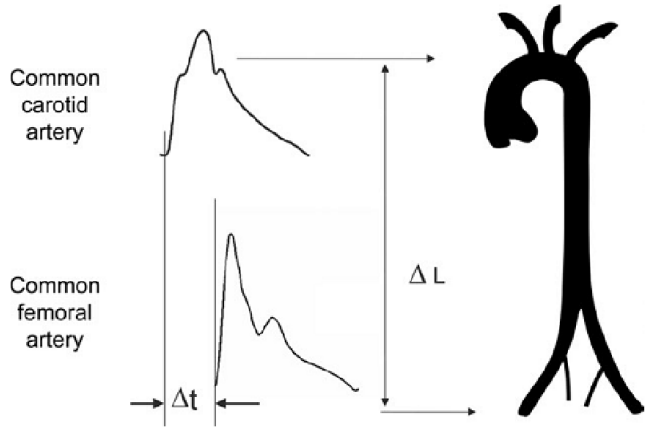

Figure 3. Measurement of carotid-femoral PWV with the foot-to-foot method.

Adopted from: (109).

Arterial wall properties are also important in determining PWV. These factors are described by the Moens-Kroteweg equation (105):

$$\text{PWV}=\sqrt{Einc * \frac{h}{\rho} * D}.$$

Here, PWV is the pulse wave velocity, *Einc* is the Young's elastic modulus of arterial wall describing the intrinsic elastic properties of the vessel walls, *h* is the arterial wall thickness, *ρ* is the blood density and *D* is the vessel diameter. An increase of *Einc*, and of arterial wall thickness results in elevated PWV, while the arterial calibre is inversely proportional to PWV. Taken together, arterial stiffness can be modulated directly by arterial wall mechanical properties, thickness and changes in vascular tone, but also indirectly, by changes in blood pressure (97).

The "gold standard" PWV measurement is usually evaluated using the "foot-to-foot" velocity method, as mentioned above, from a number of waveforms using the following formula expressed in the unit of meter/second (m/s):

$$PWV = \frac{D}{Dt}.$$

D is the distance between the two recording sites and *Dt* is the time delay between the "foot" of the carotid and the femoral waveforms. The "foot" of the wave is defined at the end of the diastole, when the steep rise of the waveform begins (111). In order to reach a proper result, the correct measurement of the covered distance is essential: according to a consensus document from 2012, 80 % of the direct carotid to femoral distance shall be used (112). The more elasticity the great arteries show, the lower is the PWV value; while a higher PWV value indicates increased arterial stiffness.

1.3.4.1. Central systolic blood pressure

Brachial blood pressure is only a surrogate marker of central, i.e., aortic blood pressure. Recalculation of the artery tonometer pressure wave that was measured on the carotid artery is based on the observation that diastolic and mean arterial pressures are relatively constant throughout the large artery tree. However, systolic blood pressure may be up to 40 mmHg higher in the brachial artery compared to the aorta due to an increase in arterial stiffness moving away from the heart (113-115). This phenomenon is called the systolic blood pressure amplification (SBPAmp). As the pressure wave travels from the elastic central arteries to the stiffer peripheral (brachial) artery, the upper portion of the wave becomes narrower, the systolic peak turns to be more

prominent, and systolic pressure increases (116). In practice, blood pressure is measured at the reference (brachial) artery with a validated blood pressure device. From the direct measured peripheral diastolic blood pressure (DBP) and SBP mean arterial pressure (MAP) can be calculated. Using brachial DBP and MAP carotid SBP can be determined (Figure 4).

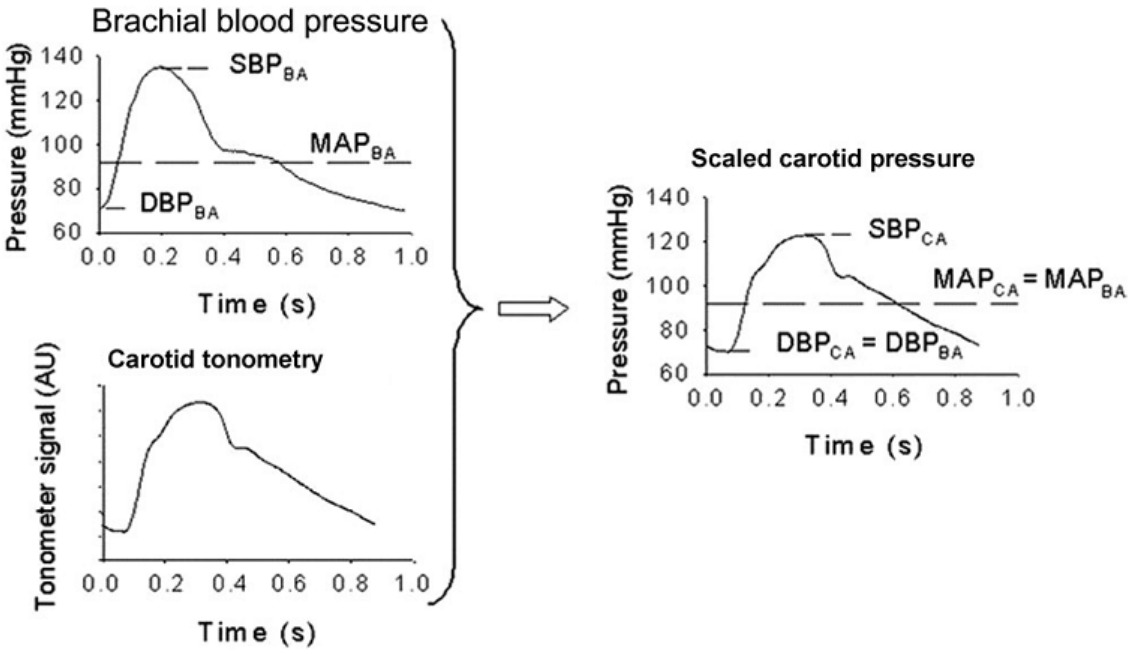

Figure 4. Calibration method for central pulse pressure.

Adapted from Kelly and Fitchett and Verbekeet al. (117, 118). SBPBA: systolic brachial blood pressure; DBPBA: diastolic brachial blood pressure; MAPBA: mean brachial blood pressure; SBPCA: systolic carotid blood pressure; DBPCA: diastolic carotid blood pressure; MAPCA: mean carotid blood pressure.

1.3.4.2. Central pulse pressure

Arterial blood pressure and flow waves are generated by LV contraction and its interaction with the elastic arterial walls. In order to provide a steady flow distribution to the tissues and organs, arteries distend while accommodating the sudden increase in blood volume caused by cardiac contraction, and contract in the diastole, when the elastic energy generated during distension is released. As a result of this phenomenon, arteries present a regular beating, the pulse, which follows the heartbeat and propagates in the form of pulse waves (119). The arterial pressure waveform itself is a mixture of the forward wave (pressure wave spreading away from the heart) and the late arriving

reflected wave from the periphery, mainly at branch points or sites of impedance mismatch (pressure wave running towards the heart) (109). Therefore, pulse pressure and pulse wave shape are determined by the physical properties of the CV system, like the arterial geometry and distensibility, the LV ejection, and the impedance due to the smallest blood vessels (119). A schematic representation of central pulse pressure is shown in Figure 5.

1.3.4.3. Augmentation index

From the central diastolic to the systolic pressure the inflection point (Pi) can be determined, where the pressure indicates the beginning upstroke of the reflected wave. The time (Ti) – belonging to the inflection point – defines the timing of the reflection. Augmentation pressure (AP) is the pressure above the inflection point – the point in time which coincides with the peak of the flow wave in the artery. AIx is defined as the ratio between the second and first systolic peaks, the AP and pulse pressure (PP), usually expressed in percentage (Figure 5) (120, 121).

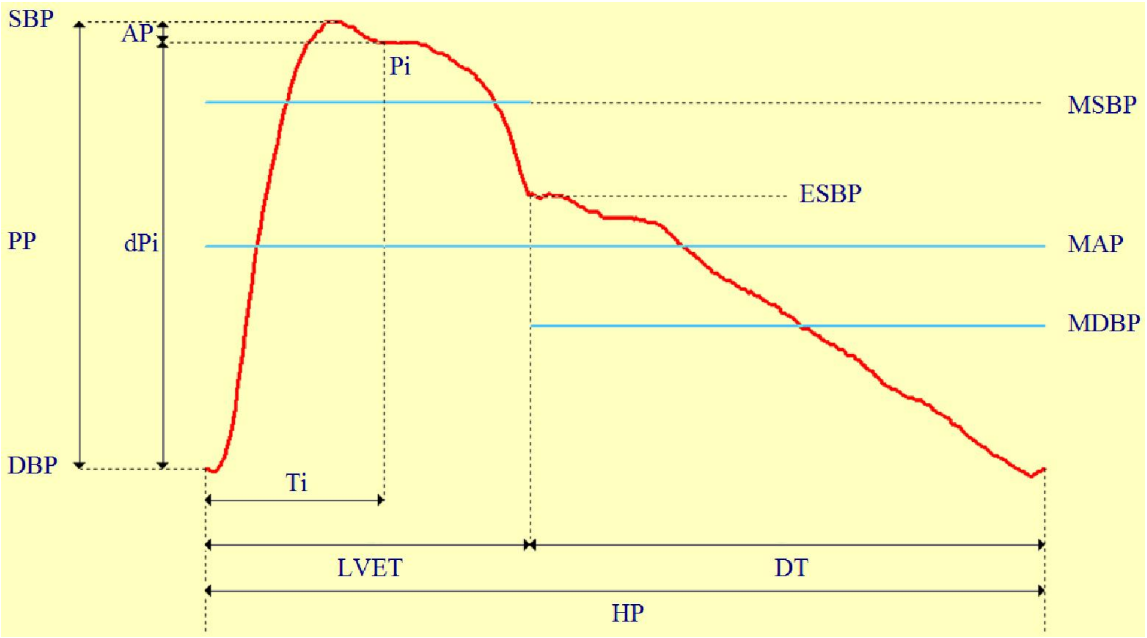

Figure 5. Pulse wave of the carotid artery.

AP: augmentation pressure; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure, MAP: mean arterial blood pressure; MSBP: mean systolic blood pressure; MDBP: diastolic blood pressure; ESBP: end-systolic blood pressure; PP: pulse pressure; Ti: rise time of the reflected wave; Pi: arterial pressure at the Ti; dPi: pulse pressure at the Ti; LVET: left ventricular ejection time; DT: diastolic time; HP: heart period.

In elastic vessels the reflected wave tends to arrive back at the central arteries during diastole. If the arteries are stiff, the reflected wave arrives back at the aortic root earlier, adding to the forward wave and augmenting the systolic pressure (Figure 6) (109). Thus, for young patients the AIx value tends to be negative, while it will almost certainly be positive in elderly patients (Figure 6, left graph AIx=-5%; right graph AIx=+10%).

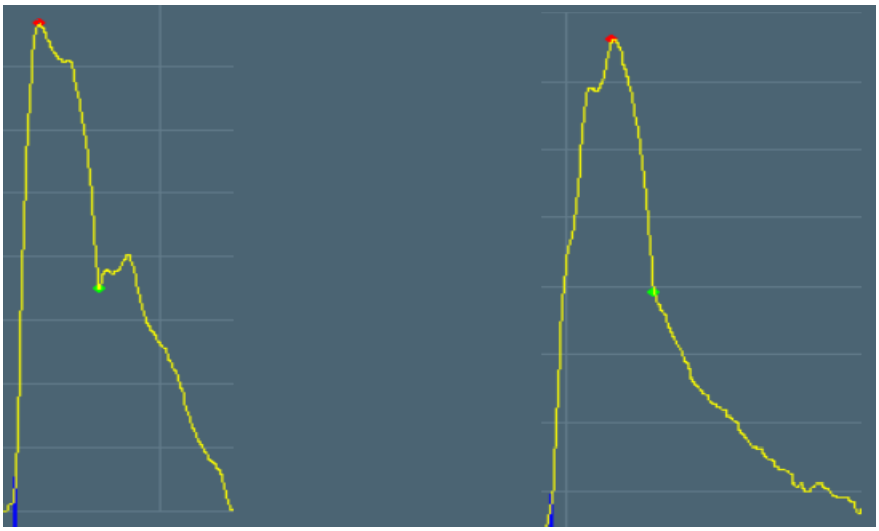

Figure 6. Changes of the carotid pulse curve with ageing: on the left side of a young patient (29 years), on the right side of an aged patient (84 years).

The red points indicate the systolic peak, the green points the end-systolic blood pressure. (The curves are selected from our own patients.)

1.3.5. Arterial stiffness parameters and CV risk estimation, according to actual guidelines

The association of the above mentioned arterial stiffness parameters with different CV risk factors as well as their role in the recent European Society of Cardiology (ESC) and the European Society of hypertension (ESH) (122) is summarized in Table 1.

Table 1. The association of pulse wave velocity, Augmentation index, central systolic and pulse pressure with different CV risk factors and their role in the actual guidelines.

PWV: pulse wave velocity; AIx: augmentation index; ESDR: end-stage renal disease; IMT: intima-media thickness; CV: cardiovascular; cSBP: central systolic blood pressure; cPP: central pulse pressure; CAD: coronary artery disease; LVH: left ventricular hypertrophy; CVD: cardiovascular disease; CRP: C-reactive protein.

Arterial stiffness parameters	**Association with CV risk factors**	**Predictive value**	**Actual guidelines**
PWV	Hypertension (123-126), ESRD (127), ischemic stroke (128), metabolic syndrome (129), echogenic plaques and increased IMT of the carotid artery (130, 131), endothelial dysfunction (132)	CV events and mortality (133-136).	class IIb, level of evidence B method (122)
cSBP	LVH, carotid atherosclerosis, carotid IMT (137-139)	CV events (138-141)	class IIb, level of evidence C methods (122)
cPP	carotid IMT (142), severity of CAD and endothelial dysfunction (143) vascular hypertrophy, the extent of atherosclerosis, incident CVD (138)	CV events and mortality (140, 144-148)	class IIb, level of evidence C methods (122)
AIx	hypercholesterolemia (149), heavy alcohol intake and smoking (150), type 1 diabetes mellitus (151, 152), endothelial function (132), high sensitivity CRP (153), premature CAD (154)	CV mortality in ESRD (140, 148) and CAD (155) and CV events in hypertension (147)	None

Patients at intermediate risk could be reclassified into a lower or higher CV risk category based on PWV measurements (136, 156, 157). In the Framingham follow-up study of 7.8 years for individuals at intermediate CV risk, higher aortic PWV was associated with a 48% increase in CVD risk. After adding PWV to a standard risk factor model, a result of an integrated discrimination improvement of 0.7% was achieved. Consequently, PWV resulted in upward reclassification of 14.3 % of subjects who suffered a CV event and downward reclassification of 1.4 % of participants who did not experience any CV events, meaning a reclassification altogether of 15.7 % (156). A recent meta-analysis demonstrated clearly the independent predictive value of PWV in CV risk. Ben-Shlomo et al. found that after the adjustment of additional risk factors an increase of 1 SD in log PWV is related to a 30% increase in CV events, a 28% increase in CV mortality and a 17% increase in all-cause mortality (133). In other words it means that for a 60-year-old non-smoker, non-diabetic, normotensive and normolipemic man, an increase of 1 m/s of PWV leads to a 7% growth of the hazard for CV events (133, 158). Reference values for PWV are available in healthy populations and also in patients with increased CV risk (159). The recent cut-off value of PWV>10 m/s is considered a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients (112). Whereas such cut-off value is set for PWV, indicating target organ damage and an increased CV risk, the other arterial stiffness parameters are showing less evidence.

In summary, the measurement of arterial stiffness can be considered to assess CV risk. As depression is connected to CV risk, it is not surprising, that depression was found to be associated with elevated arterial stiffness as well. Tiermeier et al found in their population-based, cross-sectional study including 3704 elderly subjects that patients with increased arterial stiffness were more likely to have depressive symptoms. The association was stronger in cases with diagnosed depressive disorders. The authors concluded that arterial stiffness may partly cause the proposed relationship between vascular factors and depression (160). Since dominant affective temperaments can be the precursors of depression, a question arises: is it possible that increased blood pressure values and elevated arterial stiffness can be detected in hypertensive patients with dominant affective temperaments, indicating an increased CV risk compared with hypertensive patients without dominant temperaments? Additionally, as temperaments

can be described as continuous variables, it would be important to ascertain the continuous association between affective temperament scores and blood pressure or arterial stiffness parameters.

1.4. New psychosomatic connections: the possible role of the brain-derived neurotrophic factor (BDNF) in psychopathology and cardiovascular diseases

Neurortophic factors or neurotrophins (NTs) consist a family of trophic factors of secreted proteins that promote growth, survival and differentiation of neurons both in the central and peripheral nervous system (161). We summarized the role of NTs in psychopathology and CV diseases in a recent review paper (162).

1.4.1. Brain-derived neurotrophic factor (BDNF)

BDNF is the most frequently studied NT. It is initially synthesized in the endoplasmic reticulum as its precursor protein, preproBDNF. After the cleavage of the signal peptide this form becomes proBDNF, and proBDNF is converted by extracellular proteases to mature BDNF (163, 164).

Mature BDNF binds with higher-affinity Trk family receptors (165) – especially TrkB – increasing cell survival and differentiation, dendritic spine complexity, long-term potentiation (166, 167), synaptic plasticity (168), and the resculpting of neuronal networks (169). ProBDNF is also biologically active, it mediates its actions through binding to low-affinity p75Ntr, having antagonistic effect compared to matured BDNF: reducing spine complexity and density (170) and promoting neuronal cell death (171).

1.4.2. BDNF in mood disorders

Although NTs themselves do not control mood directly, they are fundamental in the activity-dependent modulation of networks and changes in plasticity can affect mood as well (172). Numerous clinical studies confirm the involvement of BDNF in the pathophysiology of depression (173). Reductions in serum and plasma mature BDNF have been demonstrated in patients suffering from depression (164, 174) and in those who committed suicide (175, 176). Significantly lower levels of serum BDNF were found in antidepressant-free patients with major depressive disorder compared with healthy controls (177), which findings were confirmed by a large cohort study (178) and by three meta-analyses as well (179-181).

1.4.3. BDNF and CV pathology

BDNF plays an important role during development of the CV system: the activated TrkB receptor leads to the survival of endothelial cells and the formation of the cardiac vasculature (182). Embryonic BDNF deficiency impairs the development of intramyocardial vessels and can also lead to cardiac hypercontractility (183). This NT functions as an angiogenic regulator, promoting angiogenesis (184). It is expressed in a greater amount in the peripheral vessels, where it could influence vasoreactivity (185, 186). BDNF is able to enhance vascular flow and can regulate the revascularization of ischemic tissues (184). It was shown to be vasorelaxant on pulmonary arteries (187) and on rat aortic rings (185). Furthermore, it improves left-ventricular function in ischemic myocardium (188).

Numerous data are available about the association between BDNF and CV health. In the general population a significant positive correlation was observed between plasma BDNF and diastolic blood pressure and sex differences were demonstrated in relation with different serum lipids (189). As it was a cross-sectional study, it is unclear whether the associations observed are casual or elevated plasma BDNF represents a compensatory response for the disrupted lipid metabolism and hypertension.

Increased BDNF expression was found in atherosclerotic coronary arteries in humans (190), and decreased plasma BDNF level was observed in metabolic syndrome (191), in acute coronary syndrome (192, 193) and in type 2 diabetes mellitus (194). In patients with angina pectoris Jiang at al. found that plasma BDNF was inversely associated with triglyceride and low-density lipoprotein (LDL)-cholesterol, male sex and age, while it was correlated positively with (HDL)-cholesterol. In this cohort, during the 4-year follow-up period, low plasma BDNF was an independent predictor of future coronary events and mortality (195). The predictive role of BDNF for future CV events and mortality was confirmed by other studies as well: higher serum BDNF (seBDNF) was found to be associated with decreased risk of CV morbidity and mortality (196). On the contrary, decreased serum BDNF was found to be associated with increased risk of incident stroke/transient ischemic attack (TIA) (197).

1.4.4. BDNF polymorphism

A functional polymorphism Val66Met in the BDNF gene – an amino acid substitution valine to methionine at codon 66 in the precursor BDNF peptidesequence (198) – was

found to influence BDNF's secretion and function. Moreover, it is also associated with mood and cognitive-related phenotypes. There is ample biological evidence that the BDNF gene is an attractive candidate gene for MDDs (199). Nevertheless, a recent meta-analysis of Li et al. showed that the Val66Met polymorphism was significantly associated with bipolar disorder in Europeans, but not with MDD (200). Regarding to affective temperaments, the variant of BDNF polymorphism has already been studied. However, no significant difference in the frequency of alleles between subjects with and without affective temperaments was shown (201).

Taken together, the role of BDNF is already proven in psychiatric disorders, and it seems to have an influence on CV risk. In different animal models BDNF was shown to be vasorelaxant, also on aortic rings. Based on these data, a possible association between the seBDNF level and different arterial stiffness parameters in hypertension can also be supposed in humans. On the other hand, BDNF polymorphism has already been investigated in MDDs and in affective temperaments, but in hypertension the association between affective temperaments and the serum level of BDNF has not been studied yet.

DOI:10.14753/SE.2020.2300

2. OBJECTIVES

1. In the first study, our aim was to measure arterial stiffness and serum BDNF levels in hypertensive patients with and without dominant affective temperaments. We hypothesised that hypertensive patients with dominant affective temperaments score higher depression and anxiety values and have impaired arterial stiffness, central blood pressure or serum BDNF compared with hypertensive patients without dominant affective temperaments, forming a high-risk subgroup patient population.

2. In the second study, our aim was to explore the associations of affective temperaments with blood pressure and arterial stiffness in hypertensive patients. We hypothesized that individual affective temperament scores may be related to brachial blood pressure as well as arterial stiffness in chronic hypertensive patients. We speculated a positive association in instances of depressive, cyclothymic, irritable or anxious temperaments and an inverse association in instances of hyperthymic temperament. We also hypothesized the presence of sex differences in relation to these studied associations.

3. In our third study, our aim was to measure BDNF serum levels in hypertensive patients and in healthy controls to discover the associations of BDNF with affective temperaments, depression, anxiety and arterial stiffness. We hypothesized that as hypertension is a risk factor for cardiovascular diseases and BDNF is protective in cardiovascular pathology, seBDNF can be altered in hypertension. We also presumed that seBDNF is associated with different affective temperaments, depression, anxiety, and arterial stiffness parameters providing a new bridge of psychosomatic processes.

3. PATIENTS AND METHODS

3.1. Study 1: patients and methods in the study measuring arterial stiffness and serum BDNF level in patients with and without dominant affective temperaments

Caucasian patients were selected from two primary care practices in Budapest, Hungary. Out of the 183 patients 175 completed the TEMPS-A, Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) questionnaires in order to evaluate the presence of affective temperaments, or the depression and anxiety, respectively. Exclusion criteria were the history or ongoing treatment of depression or anxiety (as with arterial stiffening the associations are clarified (160)), bipolar disorders, schizophrenia, dementia posing an obstacle to completing questionnaires or denial of consent, the presence of atrial fibrillation or uncontrolled hypertension (>145/95 mmHg in repeated office measurements). In patients with an average blood pressure between 140/90 and 145/95 mmHg in repeated office blood pressure measurements, ambulatory 24-hour blood pressure monitoring or home blood pressure monitoring was performed and only well-controlled patients were admitted into the study. Prior to the participation, all patients gave their written informed consent. All the studies were approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health and carried out in accordance with the tenets of the Declaration of Helsinki.

Following the initial screening, 29 hypertensive patients with dominant affective temperaments (reaching the mean+2 SD point scores or higher in each affective temperament subscale, DOM) were identified, and 24 were investigated in our study. 24 hypertensive controls without DOM, matched in age, gender and presence of diabetes, were selected from the initial hypertensive patient cohort and included in the arterial stiffness and seBDNF measurements. As blood pressure medication can highly influence arterial stiffness, it was further analyzed, but patients were not matched in this aspect.

During the initial visit patients completed the questionnaires. Physical examination (blood pressure, heart rate, height, weight and waist circumference) were completed and

data on medical history (with special attention to CV risk factors, complications and depression) as well as on current medication was collected.

3.1.1. Questionnaires

3.1.1.1. Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire

The TEMPS-A was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales, requiring "yes" (score 1) or "no" (score 0) answers [17]. TEMPS-A contains 110 items (109 in the version for males) and the questions of the various temperament types are grouped together as follows:

- depressive temperament: questions 1 to 21 (21 points)
- cyclothymic temperament: questions 22 to 42 (21 points)
- hyperthymic temperament: questions 23 to 63 (21 points)
- irritable temperament: questions 64 to 84 (21 points in women, 20 in the men's version)
- anxious temperament: questions 85 to 110 (26 points).

TEMPS-A is used to assess the point scores of each subscale and also to measure the presence of the dominant form of affective temperaments by taking the mean of the subscale and adding up two standard deviations to it. Those reaching the mean+2 SD level or higher in each subscale are considered to have dominant affective temperaments.

3.1.1.2. The Beck Depression Inventory

The BDI, created by Aaron T. Beck, is a 21-question multiple-choice self-report questionnaire, one of the widely used instruments for measuring the severity of depression. This questionnaire is designed as a measure of severity of depressive symptoms, not as a diagnostic instrument. In the 21 items the most common depressive symptoms (e.g. sad mood, pessimism, failure, dissatisfaction, guilt, crying, irritability, social withdrawal, inability to resolve, insomnia, appetite loss, etc.) are evaluated. Participants are asked to make ratings on a four-point scale, where a higher score correlates with more severe depression. The total value of the BDI can range from 0 to 63 points. The cut-off values might differ in various populations, but there are generally

accepted thresholds. Values below 11 points are considered normal. Values between 11 and 17 points are regarded as a mild to moderate expression of depressive symptoms. Values of 18 and more are considered as a clinically relevant depression (202).

3.1.1.3. Hamilton Anxiety Scale

HAM-A was evaluated by the examiner. This questionnaire was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe (203).

3.1.2. Clinical measurements

3.1.2.1.Arterial stiffness recordings

Measurements were performed in a temperature-controlled room in supine position, on the day of blood sampling, prior to it, between 7:00 and 8:00 a.m. Patients were asked to refrain from eating, smoking, and caffeine containing drinks in the morning of the procedure, but to take their regular antihypertensive medication. Upon arrival after 5 minutes rest, two brachial blood pressure measurements were taken on each arm in the sitting position with a validated oscillometric blood pressure device (Omron M3). The mean value of the higher side was further taken into calculation as brachial systolic and diastolic blood pressures (SBPB and DBPB) and heart rate. Brachial pulse pressure (PPB) was also calculated from these data. Next, subjects were equipped with arterial stiffness measurement device and then rested in the supine position for approximately 15 minutes before being measured. Arterial stiffness parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy) (204). This method provides estimates of PWV and in which cSBP, cPP and pulse pressure amplification (PPAmp) can be calculated. Aix, a widely used wave reflection parameter, can also be measured by automatic identification of the “first shoulder” (inflection point) of the averaged carotid pulse signal by the PulsePen software. This index is provided by the pressure amplitude following this point divided by the pulse pressure

and calculated as a percentage. In these calculations, brachial blood pressure values measured in the supine position were used, which were required for calibration after each (carotid or femoral) pulse wave detection. In each subject, two sequences of arterial stiffness measurements were performed and their mean used for statistical analysis. In the PWV calculations, 80 % of the carotid-femoral distance was used, according the most recent recommendation guideline (112). The intra- and interobserver variability of PWV measurements obtained by the PulsePen device in hypertensive patients was 4.6 and 6.3 %, respectively. Since PulsePen calculates pressures based on brachial diastolic blood pressure calibration, the calculated central diastolic blood pressure is identical to the brachial diastolic blood pressure assessed in the supine position (204).

3.1.2.2. Measurement of serum BDNF concentrations

Peripheral blood samples of patients were collected in anticoagulant-free tubes, right after the measurement of arterial stiffness. After centrifugation at 3600 revolutions per minute (rpm) for 6 minutes, the serum was stored at -20 °C. SeBDNF was measured using commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis MN, USA) according to the manufacturer's protocol, and seBDNF level was determined in pg/ml.

3.1.3. Statistical analysis

Differences in variables between controls and DOM patients were analyzed using unpaired Student's t-tests or Mann-Whitney rank-sum tests for data failing tests of normality. Blood pressure medications were calculated and compared using equivalent doses, differences were analysed with unpaired Student's t-tests or Mann-Whitney rank-sum tests. Data were expressed as mean±SEM and medians, significance was accepted at $p<0.05$. Statistical analysis was performed using the SigmaStat for Windows Version 3.5 (SPSS) program package.

3.2. Study 2: patients and methods in the study exploring the association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients

The difference in patient selection compared to the first study was that in the second cross-sectional study patients with well-controlled or grade 1 chronic (on medication for

more than 3 months) hypertension were investigated from three primary care practices in Budapest. In this study a total of 173 subjects were included. Moderate use of the anxiolytic alprazolam (less than 0.5 mg/day) was not a restrictive criterion. All of the patients of Study 1 were also involved.

The methods regarding to the questionnaires and arterial stiffness measurement were the same like in the first study, but seBDNF was not investigated.

3.2.1. Statistical analysis

Normality of continuous parameters was tested with the Kolmogorov-Smirnov test. Pearson correlation coefficients were calculated to study the relationship between affective temperament scores and demographic, hemodynamic or arterial stiffness parameters. Multiple linear regression analysis was used to study the determinants of these hemodynamic or arterial stiffness parameters which were associated in univariate analysis with affective temperaments. Based on literature data, sex differences in the association between affective temperaments and the studied hemodynamic or arterial stiffness parameters (43) were expected, and therefore sex and its interaction with the given affective parameter was included into all regression models and where an interaction was found, such interaction was further studied. Descriptive data were expressed as mean±SD or median with interquartile ranges or percentages. A two-sided $p<0.05$ was considered to be significant. SPSS 13.0 for Windows was used for all calculations.

3.3. Study 3: patients and methods in the study measuring serum BDNF levels in a hypertensive and a control population to discover the associations of BDNF with affective temperaments, depression, anxiety and arterial stiffness

The difference in patient selection compared to the first study was that in the third cross-sectional study chronic (>12 months medication) well-controlled or grade 1 consecutive hypertensive patients (HT) and age-matched healthy controls (CONT) were involved from three primary care practices in Budapest. In this study a total number of 183 patients were investigated: 151 HT and 32 CONT. Moderate use of the anxiolytic alprazolam (less than 0.5 mg/day) was not a restrictive criterion. All of the chronic hypertensive patients of Study 1 were involved as well. In the case of CONT, the denial

of consent was the only exclusion criterion. Data of the subjects were analysed for the relationship between the seBDNF level, routine laboratory parameters, affective temperaments, anxiety, depression, and arterial stiffness parameters.

The methods were the same like in Study 1.

3.3.1. Statistical analysis

Normality of the parameters was tested with the Kolmogorov–Smirnov test. Descriptive characteristics, laboratory, arterial stiffness parameters and TEMPS-A, BDI, HAM-A scores were compared between CONT and HT groups using unpaired Student's t-tests or Mann-Whitney rank sum test for data failing tests of normality. The equality of variances was studied with Levene's test. Pearson correlation coefficients were calculated to study the relationship between seBDNF and all other factors measured. Hierarchic linear regression analysis was used to study the determinants of seBDNF in the whole population with a stepwise entry of variables with either previously described association with seBDNF or with a significant univariate correlation with seBDNF in the present data set. As a bidirectional association can be hypothesized between affective temperaments and hypertension (88), predetermined interaction analysis was performed to investigate moderation between hypertension and affective temperament scores on seBDNF level. Data were expressed as mean±SD or mean with interquartile ranges, and $p<0.05$ was considered to be significant. SPSS 13.0 for Windows was used in calculations.

4. RESULTS

4.1. Study 1: results of hemodynamic, arterial stiffness and serum BDNF levels in hypertensive patients with or without dominant affective temperaments

In this cross-sectional case-control study well-treated chronic (>12 months medication) hypertensive patients were investigated. Out of the 29 DOM four patients declined to further participate in our study and one died 3 days prior to the planned arterial stiffness measurement. The arterial stiffness and BDNF of altogether 48 hypertensive patients was evaluated: 24 DOM and 24 control subjects matched in age, gender and presence of diabetes. Among the DOM patients, six subjects were found to have a depressive, five an irritable and four an anxious dominant temperament. In the other patients, combinations of dominant temperaments were present: three patients had cyclothymic and depressive, two had cyclothymic and irritable, two had cyclothymic, depressive and anxious, one had cyclothymic, irritable and anxious temperaments and one patient was dominant for cyclothymic, irritable, anxious and depressive affective temperaments. No patient with a dominant hyperthymic temperament was found in our cohort.

Comparing the control and DOM patients for statistical differences baseline demographic, anthropometric and laboratory parameters and the used CV medications of the patients are presented in Table 2.

Table 2. Baseline demographic, anthropometric and laboratory parameters and the used cardiovascular medication of the patients.

*The values are means±SEM or medians (quartiles). DOM: patients with dominant affective temperament; AC: abdominal circumference; BMI: body mass index; CKD-EPI GFR: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; BDNF: brain-derived neurotrophic factor; ARBs: angiotensin II receptor blockers. The groups were compared for differences by using Student's t-test or the Mann–Whitney rank-sum for data failing tests of normality. *p<0.05 compared with controls.*

	Control	DOM
N (male:female)	24 (9:15)	24 (9:15)
Age (year)	63.7±2.54	64.3±2.52
Body height [cm]	164.5±1.51	166±2,06
Body weight [kg]	76.3±2.66	81±3.34
AC [cm]	101.5±4.1	102±5.5
BMI [kg/m^2]	28.2 (26-31.2)	29.8 (24.4-34.6)
Glucose [mmol/l]	5.36 (5.03-6.07)	5.7 (4.94-6.63)
CKD-EPI GFR [mmol/l]	77.5 (62.5-86)	78.5 (60.8-90)
Uric acid [μmol/l]	309.3±15.26	321.6±16.82
Cholesterol [mmol/l]	5.48±0.22	5±0.35
Triglyceride [mmol/l]	1.36 (1.08-2.18)	1.82 (0.99-2,15)
BDNF [pg/ml]	27290 (24200-30350)	**20100 (14740-27110)***
ACE-inhibitors [n (%)]	13 (54.2)	13 (54.2)
ARBs	9 (37.5)	5 (20.8)
Calcium-channel blockers	11 (45.8)	11 (45.8)
Beta-blockers	12 (50)	**18 (75)***
Diuretics	11 (45.8)	11 (45.8)
Antiplatelet medication	8 (33.3)	11 (45.8)

SeBDNF levels were lower in DOM patients. Compared with controls, beta-blockers were prescribed more frequently and in higher dose in the DOM group [0.63 (0-5) vs. 5

(0.63-6.88) mg, calculated for bisoprolol, respectively, $p<0.05$]. No differences were found in the mean duration of hypertension among controls and DOM patients [10.5 (4-15.8) vs. 12 (6.5-17.8), $p=0.238$, respectively]. No differences were found among the groups studied in smoking habits and in the frequency of physical training (data are not shown).

Table 3 represents the differences in the five affective temperaments and in the BDI and HAM-A scores. Compared with controls, in DOM patients depressive, cyclothymic, irritable and anxious scores were higher, while hyperthymic scores were equal. Both BDI and HAM-A scores were markedly higher in DOM patients than in the controls.

Table 3. TEMPS-A scores of affective temperaments, BDI and HAM-A scores.

*DOM: patients with dominant affective temperament; TEMPS-A: The Temperament Evaluation of Memphis Pisa, Paris and San Diego questionnaire; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale. The values are means±SEM and medians (quartiles). The groups were compared for differences by using Student's t-test or the Mann-Whitney rank-sum for data failing tests of normality. *p<0.05 compared with controls.*

	Control N=24	DOM N=24
Depressive	6 (4.25-8.75)	**12.5 (7-13.75)***
Cyclothymic	3 (1-5)	**9.5 (7-13.75)***
Hyperthymic	12.13±0.73	10.46±0.99
Irritable	2 (1-4.75)	**9.5 (5-11)***
Anxious	5.08±0.81	**14.67±0.88***
BDI	5 (2-7.75)	**14.5 (8.5-19.75)***
HAM-A	7±1.27	**16.67±1.68***

Brachial and central hemodynamic and arterial stiffness parameters are shown in Table 4. Brachial systolic and both brachial and central diastolic and mean blood pressures were lower in DOM patients. PWV and AIx did not differ when compared with controls.

Table 4. Brachial and central hemodynamic and arterial stiffness parameters.

*The values are means±SEM and medians (quartiles). DOM: patients with dominant affective temperament; HR: heart rate; SBPB: systolic brachial blood pressure; DBPB: diastolic brachial blood pressure; MBPB: mean brachial blood pressure; PPB: brachial pulse pressure; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cMBP: central mean blood pressure; cPP: central pulse pressure; PWV: pulse wave velocity; AIx: augmentation index. The groups were compared for differences by using Student's t-test or the Mann-Whitney rank-sum for data failing tests of normality. *p<0.05 compared with controls.*

	Control N=24	DOM N=24
HR [1/min]	66±1.25	63.1±1.17
SBPB [mmHg]	130.8 (122-137.1)	**122.6 (116.4-129.7)***
DBPB [mmHg]	71.2±1.5	**66.6±1.71***
MBPB [mmHg]	91.9±1.53	**86.6±1.94***
PPB [mmHg]	59.3 (49.4-67.5)	54.3 (50.1-61.9)
cSBP [mmHg]	124.3 (113.5-136.4)	117 (112.6-131.7)
cDBP [mmHg]	71.2±1.5	**66.5±1.71***
cMBP [mmHg]	94.1±1.55	**88.9±1.96***
cPP [mmHg]	50.6 (44.5-66.6)	52.3 (48.8-1.72)
PWV [m/sec]	9.32 (8.02-11.25)	8.74 (8.32-9.87)
AIx (%)	16.04±2.24	14.54±2.66

4.2. Study 2: results of affective temperaments' association with blood pressure and arterial stiffness in hypertensive patients

Baseline demographic and laboratory parameters, current medication, TEMPS-A, BDI and HAM-A scores, central blood pressure and arterial stiffness parameters are summarized in Table 5. The median number of antihypertensive drugs taken was 2 (IQR: 2-3).

Table 5. Baseline demographic, laboratory, hemodynamic and arterial stiffness parameters and the scores of the different questionnaires.

Data are presented as mean±SD or mean (interquartile range). Categorical parameters are presented as n (%).CV diseases: cardiovascular diseases; BMI: body mass index; GFR-EPI: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; TEMPS-A: Temperament Evaluation of Memphis Pisa, Paris and San Diego questionnaire; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale; SBPB: systolic brachial blood pressure; DBPB: diastolic brachial blood pressure; PPB: brachial pulse pressure; cSBP: central systolic pressure; cPP: central pulse pressure; PPAmp: pulse pressure amplification; PWV: carotid-femoral pulse wave velocity; AIx: augmentation index.

N (male/female)	173 (68/105)
Age (years)	63 (53-70)
Duration of hypertension (year)	9 (3-16)
Diabetes [n (%)]	38 (22)
CV disease [n (%)]	26 (15)
Current smokers [n (%)]	33 (19.1)
Body height [cm]	168 (160-174)
Body weight [kg]	80 (70-90)
BMI [kg/m^2]	27.8 (25.3-31.2)
Blood glucose [mmol/l]	5.6 (5.1-6.6)
GFR-EPI [ml/min/1.73m^2]	81.9 (67.9-90)
Uric acid [µmol/l]	324.2±79.6
Cholesterol [mmol/l]	5.2±1.1
Triglyceride [mmol/l]	1.4 (1.1-2.1)
Medications	
ACE-inhibitors	116 (67.1)
ARBs	35 (20.2)
Calcium channel blockers	88 (50.9)
Beta-blockers	98 (56.6)
Diuretics	72 (41.6)
Antiplatelet drugs	52 (30.1)

Statins	57 (33.4)
Alprazolam	23 (13.3)
TEMPS-A, BDI, HAM-A scores	
Depressive	6 (4-9)
Cyclothymic	3 (1-5)
Hyperthymic	12 (9-14)
Irritable	3 (2-6)
Anxious	4 (2-9)
BDI	5 (2-9)
HAM-A	5 (2-10)
Hemodynamic and arterial stiffness parameters	
Heart rate [1/min]	70.8 (64.8-78)
SBPB [mmHg]	133.5±12
DBPB [mmHg]	75.6±9.2
PPB [mmHg]	54.2 (47.1-62.4)
cSBP [mmHg]	123 (113.2-130.8)
cDBP [mmHg]	70.5±8
cPP [mmHg]	51 (43.5-60.4)
PPAmp	1.07 (1.00-1.13)
PWV	8.7 (7.7-9.9)
AIx	15.5 (8.5-25.2)

Table 6 lists the hemodynamic or arterial stiffness parameters and their significant correlations for which affective temperaments were also significantly associated. Table 6 also shows those variables which were not significantly correlated with outcome variables, but were entered into the final multiple regression models. Partial correlations corrected for age and sex are also demonstrated. Although, in univariate models, affective temperament scores were associated with hemodynamic or arterial stiffness parameters in many cases, however, upon further correction for age and sex, certain temperaments failed to be independent covariables of these parameters, notably irritable temperament score of brachial systolic blood pressure (p=0.056) and depressive temperament score of AIx (p=0.595).

DOI:10.14753/SE.2020.2300

Table 6. Variables with significant Pearson correlations and variables entered in the final multiple linear regression model showing the independent predictors of brachial systolic blood pressure, pulse wave velocity and augmentation index.

Partial Ra: partial correlation coefficient, corrected for age and sex; SBPAmp: systolic blood pressure amplification. See Table 5 for the rest of abbreviations.

Variable	**R**	**P**	**Partial R[a]**	**P**
Brachial systolic blood pressure				
Sex	-0.155	0.048	-	-
Cholesterol [mmol/l]	-0.179	0.022	-0.072	0.365
DBPB [mmHg]	0.428	<0.001	0.474	<0.001
PPB [mmHg]	0.484	<0.001	0.489	<0.001
cSBP [mmHg]	0.591	<0.001	0.598	<0.001
cDBP [mmHg]	0.284	<0.001	0.329	<0.001
cPP [mmHg]	0.461	<0.001	0.471	<0.001
SBPAmp [mmHg]	0.281	<0.001	0.300	<0.001
PWV [m/s]	0.261	<0.001	0.265	0.001
TEMPS-A Irritable	0.171	0.030	0.151	0.056
TEMPS-A Cyclothymic	0.167	0.032	0.171	0.030
Age	0.037	0.630	-	-
BDI	0.006	0.932	0.026	0.738
HAM-A	0.062	0.430	0.082	0.299
Alprazolam	0.007	0.932	0.018	0.820
Pulse wave velocity				
Age [year]	0.544	<0.001	-	-
Duration of hypertension [year]	0.250	<0.001	-0.019	0.808
CV disease	0.241	0.001	0.095	0.218
Blood glucose [mmol/l]	0.213	0.005	0.128	0.097
GFR-EPI [ml/min/1.73m^2]	- 0.308	<0.001	-0.112	0.154
SBPB [mmHg]	0.260	<0.001	0.265	0.001
PPB [mmHg]	0.507	<0.001	0.408	<0.001
cSBP [mmHg]	0.410	<0.001	0.369	<0.001

cPP [mmHg]	0.478	<0.001	0.338	<0.001
TEMPS-A Irritable	0.156	0.040	0.173	0.025
TEMPS-A Anxious	0.157	0.039	0.156	0.043
BDI	0.164	0.031	0.104	0.176
HAM-A	0.173	0.024	0.179	0.021
Sex	-0.143	0.059	-	-
Alprazolam	0.121	0.111	0.078	0.308
Augmentation index				
Age [year]	0.203	<0.001	-	-
Sex	0.347	<0.001	-	-
Current smoking [p/y]	0.159	0.038	0.175	0.023
Body height [cm]	0.247	0.001	-0.021	0.791
Heart rate [1/min]	-0.195	0.013	-0.151	0.058
Uric acid [µmol/l]	-0.255	<0.001	-0.163	0.035
TEMPS-A Depressive	0.168	0.027	0.041	0.595
TEMPS-A Hyperthymic	-0.215	0.004	-0.158	0.034
BDI	0.054	0.478	-0.097	0.210
HAM-A	0.040	0.605	-0.057	0.467
Alprazolam	0.048	0.525	-0.023	0.768

Table 7 demonstrates that cyclothymic temperament score was an independent covariate of brachial systolic blood pressure and hyperthymic temperament of AIx after adjustment for further relevant confounders. In the final model adjusted for all potential confounders, a one-unit increase in cyclothymic score was associated with 0.529 (95% CI: 0.019-1.040) mmHg higher brachial systolic blood pressure while a one-unit increase in hyperthymic score was associated with -0.612 (95% CI: -1.092–0.132) % lower AIx.

Table 7. Predictive value of cyclothymic affective temperament scores on brachial systolic blood pressure and of hyperthymic affective temperament scores on augmentation index in the various models.

The progressive involvement of variables into models and other significant predictors in the final models are also demonstrated. B: Beta; SE: standard error; Std. Beta: Standardized Beta; Adj. R2: adjusted R2; Cyclothymic temp. score: cyclothymic affective temperament score; DBPB: brachial diastolic blood pressure; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale; Alp: patients regularly using alprazolam; Hyperthymic temp. score: hyperthymic affective temperament score

Model	B	SE	Std. Beta	P	R^2
Brachial systolic blood pressure					
Model 1					0.029
Cyclothymic temp. score	0.539	0.247	0.171	0.030	
Model 2: Model 1+Age+Sex					0.059
Cyclothymic temp. score	0.568	0.245	0.180	0.0216	
Model 3: Model 2+DBPB					0.264
Cyclothymic temp. score	0.464	0.218	0.147	0.034	
Model 4: Model 3+Triglyceride+Cholesterol					0.302
Cyclothymic temp. score	0.431	0.214	0.137	0.045	
Model 5: Model 4+ BDI+HAMA-A+Alp					0.310
Cyclothymic temp. score	0.529	0.258	0.167	0.042	
Age	0.177	0.076	0.181	0.021	
DBPB	0.629	0.094	0.482	<0.001	
Triglyceride	-1.981	0.987	-0.141	0.047	
Augmentation index					
Model 1					0.052
Hyperthymic temp. score	-0.733	0.255	-0.227	0.004	
Model 2: Model 1+Age+Sex					0.203
Hyperthymic temp. score	-0.509	0.239	-0.158	0.034	
Model 3: Model 2+Smoking					0.230
Hyperthymic temp. score	-0.562	0.237	-0.174	0.019	

Model 4: Model 3+Heart rate					0.256
Hyperthymic temp. score	-0.555	0.234	-0.172	0.019	
Model 5: Model 4+Uric acid					0.272
Hyperthymic temp. Score	-0.523	0.232	-0.162	0.026	
Model 6: Model 5+BDI+HAM-A+Alp					0.288
Hyperthymic temp. score	-0.612	0.243	-0.189	0.013	
Age	0.297	0.087	0.258	0.001	
Sex	7.445	2.189	0.264	0.001	
Smoking	6.159	2.610	0.176	0.020	
Heart rate	-0.209	0.098	-0.152	0.035	

With regard to the association between PWV and irritable temperament score, the correlation still remained significant (p=0.012) after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension, although became nonsignificant after further adjustment for BDI and HAM-A scores and the use of alprazolam (p=0.078). The same results were also found for anxious temperament score and PWV: the significant association (p=0.043) that was present after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension disappeared after further adjustment for BDI and HAM-A scores and the use of alprazolam (p=0.475).

When studying the interaction between cyclothymic temperament score and sex in predicting brachial systolic blood pressure, a significant association was found (p=0.025, Fig. 7a). There was a positive association between cyclothymic temperament score and brachial systolic blood pressure in men (B=1.012, SE=0.392, p=0.011) which was absent in women (B=0.294, SE=0.311, p=0.346). After adjustment for age, brachial diastolic blood pressure, cholesterol and triglycerides, this interaction became nonsignificant (p=0.090; in men B=0.680, SE=0.347, p=0.052 and in women B=0.279, SE=0.272, p=0.307).

There was also a significant interaction between irritable temperament score and sex in predicting PWV (p=0.021). There was a positive association between irritable temperament score and PWV in men (B=0.154, SE=0.060, p=0.012) which was absent

in women (B=0.076, SE=0.064, p=0.235) (Fig. 7b). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p=0.037), however the strength of the association remained similar (in men B=0.104, SE=0.050, p=0.039 and in women B=0.082, SE=0.052, p=0.116). The interaction became nonsignificant (p=0.168) after further adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B=0.091, SE=0.051, p=0.078 and in women B=0.054, SE=0.061, p=0.375).

Similarly to irritable temperament, there was also a significant interaction between the anxious temperament score and sex in predicting PWV (p=0.023). There was a positive association between anxious temperament score and PWV in men (B=0.106, SE=0.043, p=0.015) which was absent in women (B=0.047, SE=0.036, p=0.189) (Fig. 7c). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p=0.046), however the strength of the association remained similar in men (in men B=0.088, SE=0.036, p=0.017 and in women B=0.021, SE=0.030, p=0.484). The interaction became nonsignificant (p=0.135) after further adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B=0.070, SE=0.039, p=0.075 and in women B=-0.017, SE=0.037, p=0.656). An interaction with borderline significance (p=0.052) was found between sex and hyperthymic affective temperament in predicting Aix. An inverse association was found in women (B=-0.754, SE=0.326, p=0.022) which was absent in men (B=-0.305, SE=0.370, p=0.411) (Fig. 7d). This interaction became weaker (p=0.064) after further adjustment for age, smoking, heart rate and uric acid (in women B=-0.678, SE=0.312, p=0.032 and in men B=-0.327, SE=0.352, p=0.325).

DOI:10.14753/SE.2020.2300

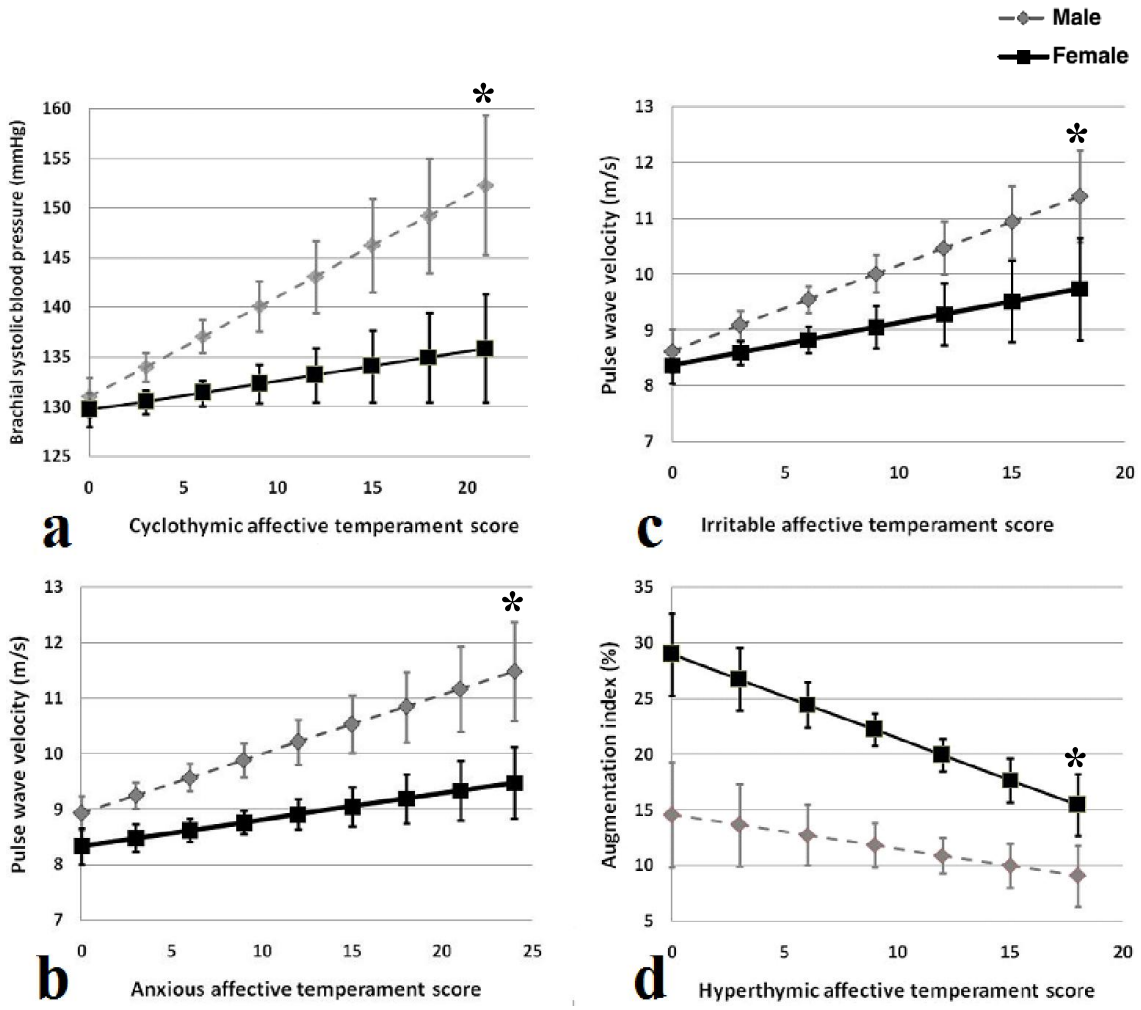

Fig. 7. The interaction between sex and different affective temperaments in the prediction of the studied variables.

*a: cyclothymic temperament score and brachial systolic blood pressure; b: irritable temperament score and pulse wave velocity; c: anxious temperament score and pulse wave velocity; d: hyperthymic temperament score and augmentation index. Continuous lines with squares represents females, while broken lines with rhombs represent males. Error bars represent±1 standard errors. *p<0.05*

4.3.Study 3: results of serum BDNF levels in hypertensive patients and healthy controls; associations of serum BDNF with affective temperaments, depression, anxiety and arterial stiffness

Baseline demographic and laboratory parameters, current medication, TEMPS-A, BDI, and HAM-A scores, central blood pressure, and arterial stiffness parameters as well as seBDNF levels are shown in Table 7. The median number of the used antihypertensive

compounds was 2 (IQR: 2–3). Differences between CONT and HT were found in body weight and BMI, serum glucose, cholesterol, LDL and HDL, BDI and HAM-A scores, in the brachial and central systolic blood pressure and the brachial pulse pressure. SeBDNF was elevated in HT (Table 8).

Table 8. Demographic, laboratory, hemodynamic and arterial stiffness parameters; subjects' autoquestionnaires scores.

*Continuous data are presented as mean (SD) or mean (interquartile range). *p<0.05. Categorical parameters are presented as % (n). BMI: body mass index; ARBs: angiotensin II receptor blockers; CCBs: calcium channel blockers; SBPB: systolic brachial blood pressure; DBPB: diastolic brachial blood pressure; PPB: brachial pulse pressure; cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, cPP: central pulse pressure, PWV: pulse wave velocity; AIx: augmentation index; TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale.*

	CONT	HT
N (male:female)	32 (12:20)	151 (58:93)
Age [year]	61.1 (55.9-70.5)	63.7 (57-71)
Duration of hypertension [year]	-	11 (5-18)
Diabetes [n (%)]	-	38 (25.2)
Cardiovascular disease [n (%)]	-	21 (13.9)
Current smoker [n (%)]	3 (9.4)	22 (14.6)
Body height [cm]	168.8±8.6	166.8±8.6
Body weight [kg]	72.4±12.1	**79.7±14***
BMI [kg/m^2]	24.5±5.4	**28.6±4.5***
Platelet count [G/l]	239.6 (215-277)	257 (209.7-303.2)
Glucose [mmol/l]	5.36 (4.88-5.81)	**6.15 (5.11-6.7)***
GFR-EPI [ml/min/1.73m^2]	79.7 (69.5-82.2)	77.9 (67-90)
Uric acid [µmol/l]	313.7±11.6	318.4±6.3
Cholesterol [mmol/l]	5.57 (4.97-6.05)	**5.18 (4.37-5.98)***
LDL [mmol/l]	3.46±0.91	**3.07±1.04***
HDL [mmol/l]	1.68 (1.31-1.98)	**1.40 (1.15-1.61)***

Triglyceride [mmol/l]	1.16 (0.75-1.43)	**1.67 (1.08-2.06)***
Regular medication [n (%)]:		
ACE inhibitors	-	93 (61.5)
ARBs	-	34 (22.5)
CCBs	-	67 (44.4)
Beta blockers	-	87 (57.6)
Diuretics	-	68 (45)
Antiplatelet drugs	-	44 (29.1)
Statins	5 (15.7)	54 (35.7)
Alprazolam	-	23 (15.2)
TEMPS-A:		
Depressive	5.9 (4-7)	7.1 (5-9)
Cyclothymic	2.9 (0-4)	3.9 (1-6)
Hyperthymic	11.2±4	11 (4.2)
Irritable	3.2 (2-4)	4.3 (2-6)
Anxious	4.1 (1-6)	6.3 (2-9)
BDI	2.8 (1-4)	**6.3 (3-9)***
HAM-A	3.9 (1-6)	**7.4 (2-10)***
Heart rate [1/min]	72.1 (66.6-78.2)	72.7 (64.1-77.2)
SBPB [mmHg]	125.5±9.3	**133.0±12.3***
DBPB [mmHg]	72±6.4	75±9
PPB [mmHg]	51.5 (46.4-56.7)	**56.7 (46.4-63)***
cSBP [mmHg]	117 (111.2-122.3)	**124.1 (113.4-131.6)***
cDBP [mmHg]	67.1±7	69.8±8.2
cPP [mmHg]	49.9 (43.2-54.5)	54.3 (45.2-61)
Pulse pressure amplification	1.08 (1.03-1.14)	1.07 (0.98-1.12)
PWV [m/sec]	8.6 (7.4-9.2)	9.3 (7.8-10)
AIx (%)	13.2 (5.75-23)	17.8 (8.5-25.1)
Serum BDNF (pg/ml)	21202.6±6045.5	**24880±8279***

In the analysis of simple correlations, the following parameters were found to be associated significantly with seBDNF: hypertension (r=0.174, p=0.018), serum

cholesterol (r=0.194, p=0.009), LDL (r=0.208, p=0.015) and HDL level (r=0.204, p=0.006), platelet count (r=0.188, p=0.011), pulse pressure amplification (r=0.157, p=0.037), and hyperthymic temperament score (r=0.189, p=0.010). Tendencies of inverse correlations were found with the presence of diabetes or the use of alprazolam, but these were not significant (r=-0.114, p=0.12 and r=-0.103, p=0.16, respectively).

Table 9 demonstrates the results of hierarchical linear regression models. In the final model adjusted for all potential confounders, one unit increase in the hyperthymic score was associated with a 405.8 pg/ml higher seBDNF and the presence of hypertension with a 6121.2 pg/ml higher seBDNF. We found an interaction (p=0.002) between hypertension and hyperthymic temperament score on seBDNF in the whole study population: there was no significant association between hyperthymic score and seBDNF in CONT (p=0.545) and a unit increase in hyperthymic score was associated with a 533.3 (95 %CI 241.3–825.3) pg/ml higher seBDNF level in HT (p<0.001). The different impact of hyperthymic score in seBDNF in HT and CONT is shown in Fig. 8.

Table 9. The predictive values of hypertension and hyperthymic affective temperament score on serum BDNF level in different models evaluated with linear regression analysis in the whole study population (n=183).

B: Beta; Hyperthymic temp. score: hyperthymic affective temperament score; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale; Alp: patients regularly using alprazolam; PPamp: pulse pressure amplification.

Models	B	Std. Error	Std. Beta	p	R^2
Model 1					0.036
Hypertension	4149.6	1681.8	0.190	0.015	
Model 2					0.050
Hyperthymic temp. score	410.7	140	0.225	0.004	
Model 3					
Hypertension+ Hyperthymic temp. score					0.089
Hypertension	4310.3	1640.6	0.198	0.009	
Hyperthymic temp. score	422.2	137.6	0.231	0.003	
Model 4: Model 3+age+sex					0.107

Hypertension	4365.1	1636.7	0.200	0.008	
Hyperthymic temp. score	449.8	138.1	0.246	0.001	
Model 5: Model 4+diabetes					0.132
Hypertension	5161.4	1661.2	0.237	0.002	
Hyperthymic temp. score	459.4	136.6	0.251	0.001	
Model 6: Model 5+cholesterol+HDL					0.158
Hypertension	5954.7	1685.5	0.273	0.001	
Hyp. temp. score	430.6	136.8	0.235	0.002	
Model 7: Model 6+platelet number					0.176
Hypertension	5540	1688.4	0.254	0.001	
Hyperthymic temp. score	431.9	135.8	0.236	0.002	
Model 8: Model 7+BDI+HAMA-A+Alp					0.191
Hypertension	6167	1748.4	0.283	0.001	
Hyperthymic temp. score	408	140.9	0.223	0.004	
Model 9: Model 8+PPamp.					0.202
Hypertension	6121.2	1742.3	0.281	0.001	
Hyperthymic temp. score	405.8	140.4	0.222	0.004	

DOI:10.14753/SE.2020.2300

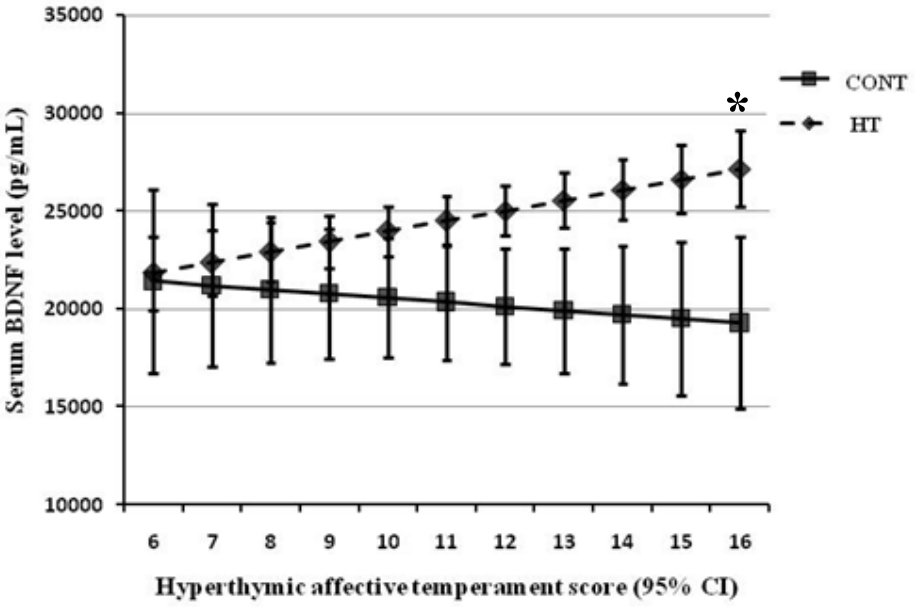

Figure 8. Association between serum BDNF level and hyperthymic affective temperament score in hypertensive patients (HT) and in controls (CONT).

Continuous line with squares represents CONT, while broken line with rhombs represents HT.

**p<0.05*

5. DISCUSSION

5.1. Study 1: arterial stiffness and serum BDNF levels in hypertensive patients with or without dominant affective temperaments

Our study was performed on hypertensive patients with dominant cyclothymic, irritable, depressive or anxious affective temperaments without the history or any present psychiatric medications. We found that DOM patients had higher anxiety and depression scores and lower seBDNF level. DOM patients had similar levels of arterial stiffening with a lower peripheral and central blood pressure compared with hypertensive controls.

As affective temperaments are tightly related to affective disorders, it is not surprising, that in our cohort DOM patients also had higher depression and anxiety scores. These results suggest the importance of a joint evaluation of affective temperaments together with depression and anxiety even in those hypertensive patients who have no records of previous psychiatric diseases or any present antidepressant or anxiolytic medication.

Although the presence of dominant affective temperaments frequently precedes the onset of minor and major affective illness which are related with CVD (49), and therefore screening for their presence would be an important target in the prevention and early intervention of CV disorders as well, only few studies are available which aim to investigate the role of affective temperaments in the development and risk of different CV risk factors or CVDs. Patients with depressive temperament were found to have worse metabolic control in type-2 diabetes (205), cyclothymic, irritable and anxious temperaments showed affinity to obesity (206), while anxious temperament was associated with an increased likelihood for the presence of prediabetic condition (207). As already mentioned above, recently Előry et al., evaluating the role of affective temperaments in primary hypertension, found a significant association with the dominant cyclothymic temperament (88), and showed a connection between cyclothymic temperament and the history of acute coronary events (89).

In our first study, patients with dominant affective temperaments had lower brachial and central diastolic and mean blood pressure values compared with controls. It is well known that decreased diastolic blood pressure is associated with increased mortality

(208). In the study of Staessen et al. 15693 patients with isolated systolic hypertension in eight trials were followed up for 3.8 years. Independently of systolic blood pressure, diastolic blood pressure was found to be inversely correlated with total mortality, focusing on the role of pulse pressure as a risk factor (208). Parallel to the findings of Előry et al. (88, 89), this phenomenon of decreased blood pressure values might be more expressed in cyclothymic patients and would in this case suggest their increased susceptibility to CV complications. However, the clarification of this hypothesis requires further studies.

As our DOM patients had higher depression score compared with control patients, one explanation of the decreased blood pressure might reflect the fact that lower blood pressure levels are often accompanied with a pronounced presence of depressive symptoms, and in follow-up studies symptoms of anxiety and depression predicted the development of lower blood pressure (209, 210). In case of a co-occurring onset of depression and hypotension, the pathophysiological mechanisms are considered to be the alterations in neurohormonal, immune and autonomic regulations (211). Whether only the increased depression per se caused the decreased blood pressure in our DOM patients, or another independent factor is also involved, is a question still to be answered.

Most of the studies support the idea that antagonistic traits, depression and anxiety increase the probability of the development of CVDs (41, 212, 213), and data are also available with respect to arterial stiffness. In contrast to the findings of Tiemeier at al – that depression is associated with elevated arterial stiffness (160) – we found no difference in PWV or augmentation index between our DOM and control hypertensive patients. An explanation to this phenomenon can be that in the study of Tiermeier et al. the patients' arterial stiffness was much higher, as the border of the lowest PWV quartile was 11.4 m/s. This suggests a very poor vascular status of those patients, while in our patients PWV values were much lower.

In a study of Seldenrijk et al., depression and anxiety sensitivity and their association with arterial stiffening were evaluated. The authors found that out of these, only anxiety sensitivity was associated with arterial stiffness; however, they studied only the AIx, which is a more variable parameter compared to PWV and is influenced by resistance

vessels, that can be dysfunctional in patients with anxiety (214, 215). It is also worth mentioning that the population of Seldenrijk et al. was much younger (46 years) compared with ours and only 18% of the patients regularly took antihypertensive medication which suggests their better general resistance vessel function. Considering all these results we suppose that in older patients besides optimal vascular therapy, the deleterious effects of depression and anxiety for arterial stiffening can be attenuated, but in younger population without vascular medication the deleterious effects of anxiety can lead to detectable dysfunction of resistance vessels in comparison to healthy controls.

In Study 1 seBDNF was also measured and we observed its decreased level in our DOM patients. As already mentioned, seBDNF was found to be lower in patients suffering from major depressive disorder (177), and also in increased CV risk, such as acute coronary syndrome and type 2 diabetes (193, 194). Taking these into consideration and the fact, that seBDNF is also decreased in some types of anxiety disorders (216), and in animal models the regulation of BDNF was suggested to contribute both to anxiety-like behavior and hypertension (217), a common background of BDNF level changes in psychopathology and CVDs might be assumed. Whether the decreased seBDNF in our hypertensive DOM patients is correlated with their higher depression and anxiety and bears any clinical relevance with respect to the CV outcome or not, further studies need to clarify.

One explanation of our results can be described with the theory of “allostatic load”. The term allostatic load refers to a cumulative, multisystem view of the physiologic toll that is required for adaptation to stress. In mood disorders, especially in bipolar disorder allostatic load increases progressively as mood episodes occur over time (218). Among many mediators, neurotrophic factors such as decreased level of BDNF indicates allostatic load (219). Seeman et al. found in their longitudinal, community-based study that allostatic load may play a role in CV disorders (220) and there is evidence that reduction in allostatic load is associated with lower all-cause mortality, even in geriatric patients (221). As affective temperaments are the subclinical manifestations of minor and major mood disorders and we found decreased BDNF level in patients with dominant temperaments, it can indicate an increased allostatic load among them, as

well. According to this theory the increased CV risk could also be explained with the phenomenon of allostatic load.

In our first study the depressive, cyclothymic, irritable and anxious temperaments or their combinations were investigated together. The neurobiological background of these temperaments seems to be at least partly common, as all were found to be associated with the 5-HTTLPR polymorphism of the serotonin transporter gene, namely the presence of the s allele, which is connected with decreased serotonin uptake of cells – mentioned already in chapter 1.2.4. (64). Moreover, the scales of depressive, anxious, cyclothymic and irritable temperaments were found to be closely associated in different populations suggesting real phenotypical connections beyond the similarities in the neurobiological background (54, 222). Whether the clustering of dominant temperaments has any pronounced clinical relevance above single dominant temperaments is another question to be answered.

5.2. Study 2: association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients

In our second study we demonstrated for the first time that in chronic hypertensive patients cyclothymic temperament score is associated with brachial systolic blood pressure, while hyperthymic temperament score is independently related to the augmentation index after adjustment for potential confounders including severity of depression and anxiety and the use of alprazolam. Sex differences were also found in relation with brachial systolic blood pressure and cyclothymic temperament score, pulse wave velocity and irritable and anxious temperament scores and augmentation index and hyperthymic temperament score.

Previous findings support our observations in our Study 2, that affective temperaments are associated with CV pathology (205-207). Our result regarding to cyclothymic temperament is in line with the previous findings in which dominant cyclothymic temperament demonstrated a significant association with the presence of hypertension (88) and with acute coronary events in a hypertensive patient population (89).

An increasing cyclothymic temperament score was found herein to be associated with a higher brachial systolic blood pressure. This temperament shows such alterations, which

can span from lethargy to eutonia, from pessimistic brooding to optimism, from hypersomnia to decreased need for sleep or from introverted self-absorption to uninhibited people-seeking (223). In contrast, subjects with hyperthymic temperament are cheerful, overoptimistic, overconfident as well as over-talkative and vigorous (223). While the hyperthymic temperament is associated with better quality of life (QOL), the cyclothymic temperament is conversely associated with worse QOL (223). Moreover, people with hyperthymic temperament can better cope with somatic problems (224), while cyclothymic disposition is related to a high somatic risk (225). Based on these results, we hypothesize that there is a likely differential impact of these two temperaments on vascular pathology, although prospective studies are required to confirm this hypothesis.

There are existing data in the literature regarding the association between personality traits and arterial stiffening. In a study by Midei and Matthews, higher trait anxiety and hostility were associated with a higher PWV (226). In the Baltimore Longitudinal study of Aging, middle-aged adults with suppressed anger had elevated carotid arterial stiffness (227). In keeping with these studies, irritable and anxious affective temperament scores were found herein to be covariates of PWV after adjustment for age, sex, brachial systolic blood pressure, blood glucose, GFR-EPI and duration of hypertension. However, these associations became nonsignificant after further adjustment with severity of depression and anxiety and the use of alprazolam. Given that arterial stiffness is associated with depression and anxiety (160, 214), we can hypothesize that, similarly to the relationship between life stress and arterial stiffness (228), the association between anxious and irritable affective temperaments and PWV is partly mediated by severity of depressive and anxiety symptoms.

Augmentation index is an accepted parameter of pulse wave analysis and a predictor of mortality in various pathological conditions (148, 155). AIx is associated with age, sex, body height, smoking and heart rate (229, 230), associations which were also reproduced in the present study. Furthermore, its predictive value was also confirmed by a meta-analysis: a 10% increase of AIx was associated with a relative risk of almost 1.4 for all-cause mortality (231). On the other hand, Seldenrijk et al. also found that anxiety-related symptoms were associated with AIx (see above) (214). Our present

results of our second study indicate that hyperthymic affective temperament score is an independent covariable of AIx with higher scores being associated with better wave reflection and thus a preserved elasticity of the arteries. This suggests a protective role of hyperthymic temperament on CV pathology and emphasizes the potential of further evaluation of affective temperaments with wave reflection parameters.

Significant interactions were also found in our second study between sex and cyclothymic temperament score in predicting brachial systolic blood pressure, between sex and irritable temperament as well as between sex and anxious temperament scores in predicting PWV, while the interaction between sex and hyperthymic temperament score in predicting AIx had borderline significance. These findings are consistent with the study of Williams et al., where trait anger was associated with elevated arterial stiffness in men, while in women the association was marginally significant (232). These results suggest that, similarly to the presence of sex differences in scoring in different affective temperament directions (43), sex differences are also present in the associations between affective temperament scores and brachial systolic blood pressure and arterial stiffness parameters. Additional studies are likely needed to specify these observed sex differences, including taking into consideration menopausal status or the use of hormone replacement therapy.

Based on these findings we tried to deepen our knowledge about affective temperaments and CV risk. While Előry et al. found that cyclothymic affective temperament showed a correlation with the diagnosis of chronic hypertension (88) and with the history of acute coronary events in hypertensive patients (89), we managed to find a more demonstrative association: brachial systolic blood pressure values and cyclothymic temperament score, as well as arterial stiffness and hyperthymic score are correlated in chronic hypertensive patients. In order to prove the role of affective temperaments in CV risk more objectively, we decided to evaluate the associations between different affective temperaments and the presence of coronary atherosclerosis among 200 patients, who were examined due to suspected coronary artery disease by coronary computed tomography angiography (CCTA). In this study, 39 subjects were found free of any coronary atherosclerosis (CCTA-), while the other 161 had coronary atherosclerosis (CCTA+). Among them hyperthymic affective temperament score was higher in CCTA-

subjects as compared to CCTA+ (13.1±3.0 vs. 11.5±4.6, p=0.010, respectively). Hyperthymic affective temperament score showed a significant independent, inverse relationship with coronary atherosclerosis (OR: 0.91 CI: 0.82–0.99, p=0.04). These results suggest that hyperthymic affective temperament is independently associated with the absence of coronary artery disease (CAD). It requires further research to delineate the mechanism mediating the effect of hyperthymia on better coronary artery health and establishing potential biochemical or behavioral factors, both of which could be exploited for prevention and treatment purposes (233).

Based on our studies, another question arises: if affective temperaments have a role in the development of hypertension, is there a possible association between these temperaments and the age of hypertension onset? In our next cross-sectional study on 353 hypertensive patients, the independent predictors of the age of hypertension onset were male sex (B=-4.57 [95%CI=-1.40–-7.74], p=0.005), smoking (B=-4.31 [-7.41–-1.22], p=0.006) and positive family history (B=-6.84 [-10.22–-3.45], p<0.001). In women cyclothymic temperament score was an independent predictor of the initiation of hypertension (B=-0.83 [-1.54–-0.12], p=0.023), while this association was absent in men (B=0.26 [-0.71-1.23], p=0.595). So, besides traditional factors, cyclothymic affective temperament might also contribute to the earlier initiation of hypertension in women (234).

As affective temperaments can be associated with the time of onset of hypertension, blood pressure values, arterial stiffness and CV risk, it can be hypothesized, that they influence the severity of hypertension. In order to prove it, we evaluated affective temperament scores hemodynamic and arterial stiffness parameters in healthy subjects (Cont), as well as in chronic well-treated (Chr), chronic resistant (Res) and white-coat (Wh) hypertensive patient populations. Among the 261 patients (148 Chr, 29 Res, 17 Wh and 67 Cont subjects) as far as cyclothymic affective temperament scores was concerned, we found significant differences between the Cont, Chr and Res groups (2 (0–4), 3 (1–5), 4 (3–8), respectively) with the highest score in Res (p<0.05 compared with Cont and Chr). Therefore, the evaluation of affective temperaments might be helpful in identifying high-risk subgroups of hypertensive patients, but of course, prospective studies are required to confirm these observations (235).

5.3. Study 3: serum BDNF levels in a hypertensive and a control population; associations of serum BDNF with affective temperaments, depression, anxiety and arterial stiffness.

In our third study we demonstrated for the first time in the literature that in chronic hypertensive patients seBDNF is elevated, and hyperthymic affective temperament score, and the presence of hypertension are independent determinants of seBDNF level. In hypertensive patients the elevation of hyperthymic temperament score is associated with the elevation of seBDNF; however, this association is not present in healthy subjects.

As the association between seBDNF level and CV morbidity and mortality have been proven (195, 196), we suppose that the observed BDNF elevation in hypertension can be part of a protective compensatory mechanism targeting peripheral neurons and vascular cells. BDNF has beneficial effects on the regulation of blood pressure, as it is involved not only in the development, but also in the survival of arterial baroreceptor system (236), and this NT is produced by vascular endothelial cells (186). In our study, the positive correlation with HDL and also with pulse pressure amplification, where higher values refer to better vascular conditions (237), also supports the plausible beneficial effect of BDNF in hypertension.

Some of the findings of our study were already described in the literature, such as the seBDNF correlation with cholesterol and LDL (189), as well as with platelets (238). As stored BDNF is released from platelets during clotting (238) and in essential hypertension increased platelet activation is a trigger of hypercoagulable state (239), our finding, that platelet count is positively correlated with seBDNF may refer to a chief source of seBDNF in this pathological condition.

If elevated BDNF is associated with hypertension, what could be the common background in the psychopathology? How can BDNF influence blood pressure, potentially playing an important role in the development of hypertension? We aimed to address these questions in our recent review paper analysing the psychosomatic connections of BDNF (162).

Axonal guidance is among the top pathways explaining the association between mood disorders and cardio-metabolic-disease risk (240). Mutant axonal guidance genes – including BDNF – followed by abnormal axonal guidance and connectivity can cause disorders primarily in the brain and subsequently in peripheral organs (241). During embryonic development, BDNF is found to be not only a target-derived survival factor for a large subset of nodose ganglion neurons, such as arterial baroreceptors (236) but is also involved in the development of chemoafferent sensory neurons innervating the carotid body (242, 243). Furthermore, postnatally BDNF is expressed by the nodose ganglion neurons themselves (244, 245) and can be also released from these neurons by activity (246). BDNF is expressed in arterial baroreceptors and their central terminals in medial nucleus tractus solitarius in vivo. BDNF release from cultured nodose ganglion neurons is increased by electrical stimulation with patterns that mimic the in vivo activity of baroreceptor afferents (247). So it seems, that BDNF is involved not only in the development and survival of baroreceptors, but also in their normal functioning in adulthood.

During normal conditions when blood pressure increases, the activated baroreflex reduces heart rate and blood pressure by a negative feedback loop. In addition, elevated blood pressure activates inhibitory GABAergic (Gamma-Aminobutyric acid) neurons in the hypothalamus, reducing the secretion of the blood pressure-elevating hormone vasopressin (248). But different pathophysiological changes can influence the mechanism of the baroreflex loop. It is already shown that high dietary salt intake can affect blood pressure through NT-mediated changes of the central homeostatic circuit. Choe et al. proved in an animal study, that chronic high salt intake is able to decrease the baroreceptor-mediated inhibition of vasopressin neurons through a BDNF-dependent activation of TrkB receptors and through the downregulation of potassium/chloride co-transporter 2 expression, which prevents inhibitory of GABAergic signalling (249). Furthermore, reduced BDNF level in mice results in elevated heart rate, and infusion of this NT into the cerebral ventricles can restore this effect (250). In the same study Wan et al. showed that GABAergic responses are increased in brainstem cardiovagal neurons of BDNF+/- mice, suggesting that BDNF increases the activity of the parasympathetic neurons to reduce heart rate (250). In summary, BDNF is required for normal carotid body innervation, baroreceptor function

and heart rate regulation and these effects can be blunted in pathological conditions, like high salt intake, which can lead to the development of hypertension.

Another pathway explaining the association between BDNF, CV function and susceptibility to mental diseases as well is the RAS. Increased central RAS activation is an indicator of many CVDs, like hypertension and heart failure (251, 252). On the other hand, data are accumulating about the newly discovered effects of the RAS related to neuroprotection, cognition and cerebral vasodilation. Angiotensin (AT) 1-7 also affects non-CV functions in the brain, such as learning, memory, and neuroprotection (253). Clinical studies have shown that AT II receptor type 1 (AT1R) blockers – independent of blood pressure-lowering effect – improve cognitive function in elderly hypertensive patients (254, 255). The background mechanism of this phenomenon was investigated in animal studies. Goel et al. showed the evidence that chronic neuroinflammation and memory impairment in hypertension – associated with increased apoptotic cell death and with amyloid beta deposition – can be prevented with candesartan treatment, suggesting partly to be explained by an increase of BDNF/CREB (cAMP response element binding protein) expression (256). Furthermore, the connection between RAS and TrkB signaling is proven in vitro (257) and in vivo as well, as Becker et al demonstrated the mediator role of BDNF-TrkB signaling on Ang II-induced mean blood pressure and renal sympathetic nerve activity elevation in male rats (258).

Cumulating data suggest the connection between endothelial dysfunction and BDNF as well. In an animal study the protecting effect of the AT1R blocker candesartan after stroke was mediated by endothelial nitric oxide (NO) synthase and it was positively associated with BDNF expression (259). BDNF is probably indirectly associated with the NO-system as BDNF is secreted by endothelial cells (260), it increases vascular endothelial growth factor (VEGF) expression, which induces angiogenesis (261, 262) and VEGF also enhances the NO production of endothelial cells (263). The connection with endothelial dysfunction is also supported by the observation, that circulating BDNF level inversely correlates with vascular cell adhesion molecule-1 (264), which is an accepted biomarker of endothelial dysfunction (265). Taken together, RAS and NO production are also associated with BDNF, forming a possible bridge in the understanding of the connections between hypertension, CV risk, mood disorders.

Another main finding of our study is that hyperthymic affective temperament is an independent determinant of seBDNF. In contrast to the other four temperaments (depressive, irritable, cyclothymic and anxious), which tend to have a mainly negative impact on life, hyperthymic temperament seems to have rather optimistic components. We suppose that patients with higher hyperthymic temperament scores might have reduced inclination to CV complications, thanks to the beneficial effect of elevated seBDNF and also through its association with AIx as was demonstrated in Study 2, hypotheses that need to be confirmed in follow-up studies. As the observed association between hyperthymic temperament score and seBDNF was only present in our hypertensive patients, we suppose an active role of affective temperaments not only in psychiatric but also in CV pathophysiology.

Considering that BDNF is involved in CV physiology and through enhancing the neuroplasticity and neurogenesis it increases the resistance of neurons to metabolic and excitotoxic stress (266) a new therapeutic target of mood and CV disorders could be the restoration of BDNF level. Lifestyle changes like physical activity, such as running and other types of aerobic exercise (267, 268) or calorie restriction (266) could be cardioprotective through BDNF mediation. Long-term treatment with various antidepressants can also normalize serum BDNF level (181, 269). In animal studies antidepressants, including selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors elevate BDNF mRNA level in hippocampus (270). In psychiatry practice BDNF level improvement can be evoked not only through medication, but also through electroconvulsive therapy (271). In relation with the CV pharmacology the AT1R blocker candesartan is proven to restore BDNF (259) and the ACE-inhibitor perindopril has beneficial effects as well (272), but interestingly in case of ramipril this feature seems to be missing (273). As we previously mentioned, RAS blockers probably restore BDNF through TrkB signaling pathway. In the future a possibility of BDNF restoration could be the inhibition of its degradation. The mechanism of BDNF degradation is not well investigated, in the literature there are only few studies about this process. More than 25% of synthesized BDNF is depredated by lysosomes. Soluble sortilin is a main protein, which directs the trafficking of BDNF. Sortilin binds to sorting motif of BDNF and facilitates BDNF allocation to the late endosome; hereby sortilin rescues BDNF from lysosomal

degradation. Until now no pharmacological option exists to inhibit the degradation of BDNF. Modifying sortilin either with increasing its level or its binding action would be options to increase total BDNF levels through its decreased targeting to the lysosome (274). As there is no agent that would reduce BDNF degradation, direct receptor (TrkB) activation via ligands/agonists or mechanisms of increasing the BDNF level would be also appropriate therapeutic applications. Based on the listed psychopathological and CV effects of BDNF, such a medication can potentially be beneficial for both systems.

On the other hand, we cannot exclude the possible influence of antihypertensive medication on seBDNF levels, on affective temperaments, on BDI and HAMA-A scores, or even on personality. Therefore in our next study we, investigated the psychometric, haemodynamic, arterial stiffness and laboratory parameters before as well as 3 months after the initiation of antihypertensive medication in untreated hypertensive patients (HT, n=31), and once in healthy controls (CONT, n=22). The used antihypertensive medication was mainly perindopril and amlodipin, which are known to penetrate into the central nervous system (275). Furthermore, cumulating data in animal models suggest their neuroprotective role (276, 277), and both of them were found to modify BDNF in a beneficial way on cellular level (272, 278). As we expected, brachial systolic blood pressure, as well as pulse wave velocity were significantly improved in the HT group over the 3-month follow-up (153.3±15.9 mmHg vs. 129.5±10.0 mmHg and 8.2±1.4 m/s vs. 7.5±1.6 m/s, respectively). Expectedly, no significant changes in affective temperaments were found after the initiation of antihypertensive medication, suggesting that these agents do not influence the measures of these personality constructs. However, we found improvements in BDI score (0.73 points) and in several Symptom Checklist 90 Revised (SCL-90) subscales. Interestingly, contrary to our third study, seBDNF did not differ between CONT and HT and did not evolve significantly during therapy – although an upward trend was observed. This phenomenon can be explained with the difference in the average duration of hypertension (in Study 3, it was 11 years); it is plausible, that seBDNF elevation is not an acute event, but might be a part of a long-term compensatory process. Longer follow-up and a higher number of untreated hypertensive patients would be required to clarify this issue and the possible impact of specific antihypertensive agent groups on seBDNF. On the other hand, these results indicate that the initiation of currently recommended antihypertensive

medications in newly diagnosed patients may have a significant impact on the psychological well-being of patients and could influence their quality of life as well.(279).

To understand how NT-s can have a connective role between psychopathology and cardiovascular diseases it must be noted, that they can cross the blood-brain barrier. NT pathways are supposed to mediate psychosomatic processes: its physiological background is based on the shared signalling pathways descending from Trk receptors and p75Ntr to both psychopathological and CV directions. Figure 9 summarizes our knowledge in this field, how these different diseases, such as mood disorders, hypertension and CVDs can have common background based on the activity of NTs (162).

DOI:10.14753/SE.2020.2300

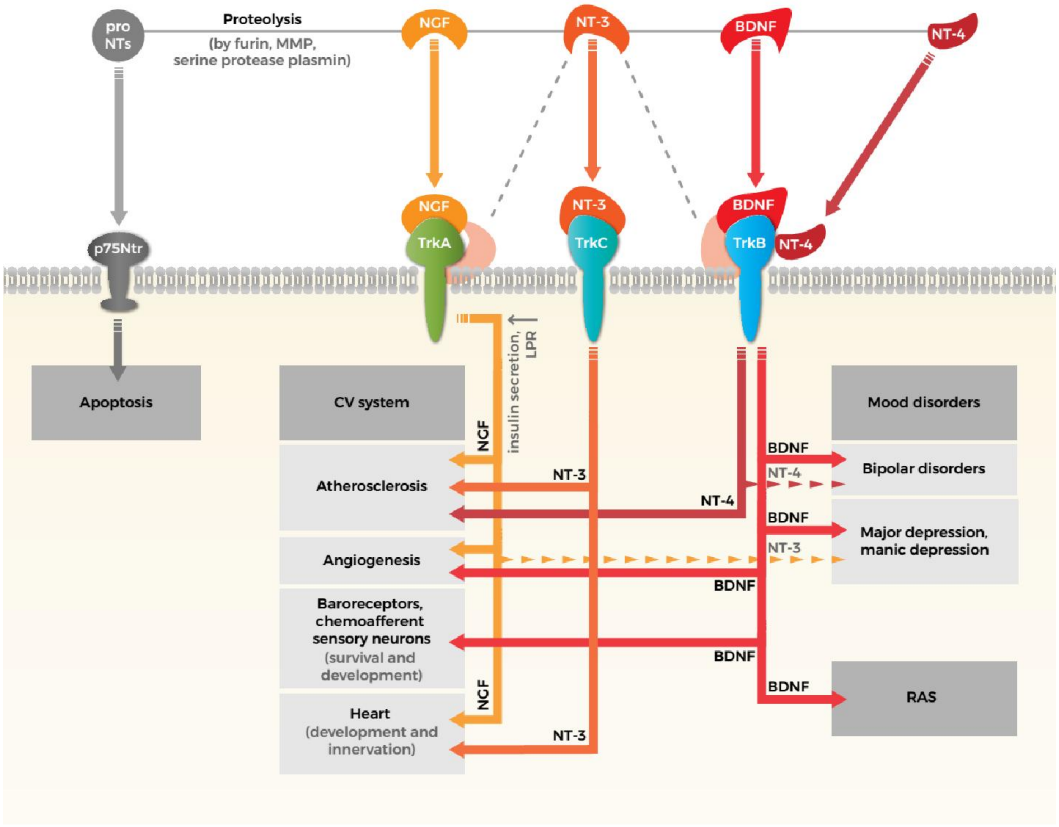

Figure 9. Crossroads of neurotrophins in cardiovascular system and psychopathology.

Neurotrophin family consist of four types of neurotrophins (NTs): nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4). NTs are synthesized as proforms that can be cleaved to release mature NTs. Both pro and mature forms of NTs are biologically active and eliciting opposite effects. ProNTs typically activate apoptotic down-stream pathways via neurotrophin receptor p75 (p75Ntr). The effects of mature NTs are mediated by three tyrosine kinase receptors: NGF interacts with tropomyosin receptor kinase (Trk) A, BDNF binds to TrkB, NT3 binds to TrkC and lower affinity to TrkA and TrkB (illustrated by the grey dashed line). Finally NT4 also interacts with TrkB.

The effects of NTs on the cardiovascular (CV) system: (i) NGF may have a protective role in atherosclerosis by upregulating LDL receptor-related protein (LPR) and increasing glucose-induced insulin secretion, while NT-4 and NT-3 seem to be a profibrotic mediator in the aortic valve. (ii) Both BDNF and NGF promote angiogenesis through vascular endothelial cells directly or by influencing the action of other endogenous factors indirectly. (iii) BDNF is required for the survival of arterial baroreceptors. NT-3 is involved in the development of chemoafferent sensory neurons' innervations of the carotid body. (iv) NGF promotes the survival of sympathetic and sensory neurons that innervate the heart. NT-3 promotes the development of the arteries and of the ventricles of the heart.

The effects of NTs on mood disorders: (i) BDNF and NGF participate in the pathophysiology of depression: reduced levels of NGF and BDNF in serum and also in plasma have been demonstrated in patients suffering from depression. (ii) Association between mood disorders and NT-3, NT-4 is plausible, but results are still controversial (illustrated by the dashed narrows).

Renin-angiotensin system (RAS) is one of the possible pathways which might explain the association between BDNF and CV function and the susceptibility to mental disorders.

Interestingly, in our study, no association between seBDNF and anxiety or depression was found. We suppose that this phenomenon can be explained by the patients' mild anxiety and depression severity. In contrast to the literature, the presence of diabetes or the use of the benzodiazepine alprazolam was not found to be significantly correlated with seBDNF; however, the direction of correlations was as expected. We think that in both cases, the lack of significance was caused by the low proportion of patients suffering from diabetes or using alprazolam in our cohort.

The associations between seBDNF level and arterial stiffness parameters have never been evaluated in any patient population yet. Since BDNF has a relaxant effect on pulmonary arterial and aortic rings in different animal models (185, 187), we supposed a possible link between BDNF and arterial stiffness parameters. In contrast to this, in our study, seBDNF showed an association only with pulse pressure amplification, but even this failed to be an independent predictor in regression analysis. Based on these findings, we suppose that seBDNF may exert its protective role rather on the level of the endothelium and perivascular nerves rather on the level of large arteries.

5.4. Limitation of the studies

In all studies although we used standardized questionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by patients is impossible.

5.4.1. Limitations of Study 1

The main limitation of our study is the relatively low number of patients involved. Out of 183 invited hypertensive patients, the arterial stiffness parameters of only 24 subjects

with dominant affective temperament and 24 controls were analysed. The low number of patients limits the generalisability of our data and type I and type II errors cannot be excluded. As the detailed analysis of the impact of unique dominant affective temperaments on arterial stiffness, central blood pressure or seBDNF require higher number of involved patients, we defined this study as a "pilot". Another limitation comes from the cross-sectional design of the study which precludes causal inference.

5.4.2. Limitations of Study 2

One of the limitations of the present analysis is the relatively low number of chronic hypertensive patients used to study the associations between affective temperaments and blood pressure or arterial stiffness parameters, which limits the generalizability of our results, as well as the number of entered confounders into regression analyses. Another main limitation stems from its cross-sectional design which precludes causal inference.

5.4.3. Limitations of Study 3

The main limitation of our third study also comes from its cross-sectional design which precludes causal inference. In addition, the number of the subjects involved into the study limited the number of potential confounding variables that were involved in the final regression model. Consequently, the presence of sleeping disorder, the amount of alcohol intake or the habit of regular exercise, variables with documented influence on BDNF level, were not involved into the final analysis (these were not significantly correlated with seBDNF in univariate models, data were not shown). Moreover, other potential confounders, like childhood trauma, stress or sunlight exposition were not evaluated.

5.5. Future perspectives

The main advantage of primary care practices is the possibility to follow the patients. Therefore, besides extending our patient population and investigating not only the static arterial stiffness, but also 24-hour arterial stiffness parameters, our aim is to carry out follow-up studies. These could show the role of affective temperaments in the development of diseases and their predictive value in already existing diseases. These could help us to find the factors mediating the effects of affective temperaments (perhaps smoking or alcohol consumption), and inter alia analyzing (CV) endpoints could improve our better knowledge of this topic.

DOI:10.14753/SE.2020.2300

6. CONCLUSIONS

Although similar arterial stiffness parameters were found in hypertensive patients with depressive, cyclothymic, anxious and irritable dominant affective temperaments, their increased depression and anxiety scores, the decreased brachial and central diastolic blood pressures as well as the decreased seBDNF might refer to their higher vulnerability regarding the development not only of major mood disorders, but also of CV complications.

On the other hand, since the ratio of those subjects who score high on different temperament directions while having a dominant affective temperament is relatively low, the evaluation of the continuous association between affective temperament scores and blood pressure or arterial stiffness parameters are meaningful. We have found elevated blood pressure among subjects (analysing also sex differences) with high cyclothymic temperament as well as an increased level of arterial stiffening in subjects with low hyperthymic scores, suggesting that affective temperaments scores are associated with hypertension and arterial stiffening and may thus represent markers of CV risk.

Since the pathophysiological background of our findings is complex we tried to clarify the possible role of BDNF, as a potential psychosomatic connection between affective temperaments and CV risk. We have found significantly higher seBDNF levels in hypertensive patients compared to controls. Hyperthymic temperament score and the presence of hypertension were independent determinants of seBDNF.

DOI:10.14753/SE.2020.2300

7. SUMMARY

In our pilot study, we demonstrated that hypertensive patients with dominant cyclothymic, irritable, depressive or anxious affective temperaments without previous or present psychiatric medication had higher anxiety and depression scores, and lower seBDNF levels. They showed similar levels of arterial stiffening rates with a lower peripheral and central blood pressure as their hypertensive controls (László et al, Ann Gen Psychiatry, 14: 33, 2015).

In our second study, we found for the first time in literature that in chronic hypertensive patients, cyclothymic temperament score is associated with brachial systolic blood pressure, while hyperthymic temperament scores are independently related to the augmentation index – after adjustment for potential confounders, including severity of depression and anxiety, and the use of alprazolam. We also demonstrated sex differences in relation to brachial systolic blood pressure and cyclothymic temperament score, to pulse wave velocity and irritable and anxious temperament scores, and to the augmentation index and hyperthymic temperament score (László at al, BMC Cardiovasc Disord, 16: 158, 2016).

In our third study, we described for the first time in literature that in chronic hypertensive patients, seBDNF is elevated, and that a hyperthymic affective temperament score and the presence of hypertension are independent determinants of seBDNF levels. While in hypertensive patients the hyperthymic temperament score elevation is associated with a seBDNF elevation, this association could not be observed in healthy subjects (Nemcsik at al, Ann Gen Psychiatry, 15: 17, 2016).

To summarize our findings, affective temperaments play a role not only in psychopathology, but also in CVDs. Hence, with further supporting studies, they can receive more attention both in regard to psychopathology and to CV health management. Since affective temperaments are easy to measure, constitute the core of a personality and are stable from young adulthood on, it would be possible to identify a subpopulation with a higher vulnerability towards psychopathological and CV diseases.

Even if BDNF is not likely to have an effect on large arteries, it is elevated in cases of hypertension; furthermore, it is linked to the hyperthymic affective temperament. Our findings may suggest its complex psychosomatic mediator role in linking mood disorders, hypertension and CVDs.

DOI:10.14753/SE.2020.2300

ÖSSZEFOGLALÁS

Az első vizsgálatunkban kimutattuk, hogy pszichiátriai anamnézissel, és ilyen irányú medikációval nem rendelkező ciklotím, irritábilis, depresszív vagy szorongó domináns affektív temperamentumú hipertóniás betegeknek magasabbak a szorongásos és depresszív pontszámuk és alacsonyabb a seBDNF szintjük. Hipertóniás kontrollokkal összehasonlítva az artériás érfalmerevségük nem emelkedett, perifériás és centrális vérnyomásuk alacsonyabb (László et al, Ann Gen Psychiatry, 14: 33, 2015).

Második vizsgálatunkban elsőként mutattuk ki, hogy krónikus hipertóniás betegeknél a depresszió és a szorongás súlyosságára, valamint az alprazolam használatára vonatkozó korrekció után is a ciklotím temperamentum pontszám a brachiális szisztolés vérnyomás, míg a hipertím temperamentum pontszám az augmentációs index független prediktora. Nemek közötti különbségeket mutattunk ki a brachiális szisztolés vérnyomás és a ciklotím; a pulzushullám terjedési sebesség és az irritábilis és a szorongó; valamint az augmentációs index és a hipertím temperamentum pontszám között (László at al, BMC Cardiovasc Disord, 16: 158, 2016).

Harmadik vizsgálatunkban elsőként írtuk le, hogy krónikus hipertóniás betegek seBDNF szintje emelkedett, valamint a hipertím affektív temperamentum pontszám és a hipertónia jelenléte a seBDNF szint független meghatározói. A hipertóniában megfigyelt hipertím temperamentum pontszám emelkedésének összefüggése a seBDNF szint emelkedéssel az egészséges kontrolloknál nem volt kimutatható (Nemcsik at al, Ann Gen Psychiatry, 15: 17, 2016).

Összefoglalásul az affektív temperamentumoknak nem csak pszichopatológiai, hanem kardiovaszkuláris szerepük is lehet. Így több figyelmet érdemelnének mind a pszichipatológiai, mind a kardiovaszkuláris ellátásban. További megerősítő vizsgálatok birtokában egyszerű mérésüknek köszönhetően a személyiség stabil magját képező affektív temperamentumok megállapításának segítségével már fiatal felnőttkortól meghatározható lenne egy magasabb pszichoptalógiai és kardiovaszkuláris rizikóval rendelkező szubpopuláció, mely a rizikóbecslés részét képezhetné.

Bár a BDNF úgy tűnik, nem hat a nagyereken, hipertóniában való emelkedése, valamint ezen belül a hipertim affektiv temperamentummal való kapcsolata komplex pszichoszomatikus mediátorszerepre utalhat: részben megmagyarázva a hiprtónia és a kardiovaszkuláris betegségek közötti összefüggést.

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DOI:10.14753/SE.2020.2300

9. PUBLICATION SUMMARY

9.1. Publications related to the thesis

László A, Babos L, Kiss-Igari Z, Pálfy A, Torzsa P, Előry A, Kalabay L, Gonda X, Rihmer Z, Cseprekál O, Tislér A, Lénárt L, Hodrea J, Fekete A, Nemcsik J: Identification of hypertensive patients with dominant affective temperaments might improve the psychopathological and cardiovascular risk stratification: a pilot, case-control study. Annals of General Psychiatry 14: 33, 8 p. (2015) *IF: 1.411*

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9.2. Publications not directly related to the thesis

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DOI:10.14753/SE.2020.2300

10. ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. János Nemcsik, for giving me the opportunity to work on such a fascinating topic. During the time of my medical specialization as a GP and during our common research he had always trust in me. I learned a lot during the time I spent in his office. He led my way by providing the base for our research, investing much time in reading my articles' drafts, helping me to improve my scientific writing skills. He was constantly available consulting about my questions (my e-mails get answered within 10 minutes, usually). I want to thank him for his helpful comments and his constructive criticism.

I would like to thank Dr. Ajándék Előry and Dr. Péter Torzsa who started their research on affective temperaments in Semmelweis University's Department of Family Medicine. I am thankful for the opportunity to participate in their studies in my sixth year at the Semmelweis University with many other students of whom one is to be mentioned explicitly: Dr. Zsóka Kis-Igari. I would like to thank Professor Zoltán Rihmer and Dr. Xénia Gonda for contributing their thoughts and ideas on which part of our research based.

Dr. András Tislér from the Semmelweis University's 1st Department of Medicine provided us with the PulsePen device. Dr. Orsolya Cseprekál made this cooperation possible and taught us with high professionalism how to operate this device and how to evaluate the measurement results being always a conscientious contact. My thanks go to Dr. Levente Babos helping me with the measurements in the beginning and encouraging me not to give up – even when their amount seemed to be sheerly endless.

I would like to thank Dr. Lilla Lénárt, Dr. Judit Hodrea and Dr. Andrea Fekete for the collaboration that enabled us studying the role of BDNF in our patient population. Furthermore, I am thankful to all the members of the Pediatrics and Nephrology Research Group for donating their time and blood to our research.

Dr. Dániel Eörsi provided us access to his patient pool by allowing us to invite the subjects to our study and thus increased our cohort's size. Dr. Ádám Tabák completed our statistical knowledge with his deep experience in this field.

Dr. Beáta Kőrösi and Dr. Dóra Batta, Ph.D. students working in our team, continue the research I begun completing it and always giving me mental and emotional

support. Zsófia Nemcsik-Bencze helped us by digitalizing the filled questionnaires and therefore reducing my workload.

The kind help of the office's assistants was crucial to reach our goals. Many thanks to Lászlóné Hárshegyi and Ágnes Polyák.

Also, I have to thank all the members of my previous research group for inspiring me and in this way to get my goal to write my thesis. Even it did not happen in that exceptional laboratory, I am still thankful to professor Dr. Márk Kollai, Dr. Péter Studinger, Dr. Alexandra Pintér, Dr. Tamás Horváth and Dr. Beatrix Mersich helping me to start my "research career". Specifically, I would like to mention Ibolya Balogh, who always supported my research activity during my years as a medical student at the Semmelweis University's Institute of Human Physiology and Clinical Experimental Research.

Not as closely related to my thesis are my therapists who nevertheless played a key role in my research – they held my health stable enough so I was able to carry out the physically challenging field and computer work: Dr. Gellért Kovács and his team, Kinga Gartai, Judith Förster, Susanne Hoyer and Jeon Son Jung.

I also have to mention my long-time friends who bear with me and support me, no matter when I need their help.

I also acknowledge the contribution of Anne-Sophie Dubrux for her linguistic and for Oleg Pogrebnyak for his technical and linguistic support.

And not least I would like to thank my family for their support.

DOI:10.14753/SE.2020.2300

APPENDIX

Tempermant Scale of Memphis, Pisa, Paris and San Diego – Autoquestionnaire Version (TEMPS-A)

Circle T (True) for all items that are true about you for much of your life.
Circle F (False) for all the rest that don't apply to you for much of your life.

1. T F I'm a sad, unhappy person.
2. T F People tell me I am unable to see the lighter side of things.
3. T F I have suffered a lot in life
4. T F I think things often turn out for the worst.
5. T F I give up easily.
6. T F For as long as I can remember, I've felt like a failure.
7. T F I have always blamed myself for what others might consider no big deal.
8. T F I don't seem to have as much energy as other people.
9. T F I'm the kind of person who doesn't like change very much.
10. T F In a group, I would rather hear others talk.
11. T F I often give in to others.
12. T F I feel very uneasy meeting new people.
13. T F My feelings are easily hurt by criticism or rejection.
14. T F I am the kind of person you can always depend on.
15. T F I put the needs of others above my own.
16. T F I am a hard working person.
17. T F I would rather work for someone else than be the boss.
18. T F It is natural for me to be neat and organized.
19. T F I'm the kind of person who doubts everything.
20. T F My sex drive has always been low.
21. T F I normally need more than 9 hours of sleep.
22. T F I often feel tired for no reason.
23. T F I get sudden shifts in mood and energy.
24. T F My moods and energy are either high or low, rarely in between.
25. T F My ability to think varies greatly from sharp to dull for no apparent reason.

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26. T F I can really like someone a lot, and then completely lose interest in them.
27. T F I often blow up at people and then feel guilty about it.
28. T F I often start things and then lose interest before finishing them.
29. T F My mood often changes for no reason.
30. T F I constantly switch between being lively and sluggish.
31. T F I sometimes go to bed feeling down, but wake up in the morning feeling terrific.
32. T F I sometimes go to bed feeling great, and wake up in the morning feeling life is not worth living.
33. T F I am told that I often get pessimistic about things, and forget previous happy times.
34. T F I go back and forth between feeling overconfident and feeling unsure of myself.
35. T F I go back and forth between being outgoing and being withdrawn from others.
36. T F I feel all emotions intensely.
37. T F My need for sleep varies a lot from just a few hours to more than 9 hours.
38. T F The way I see things is sometimes vivid, but at other times lifeless.
39. T F I am the kind of person who can be sad and happy at the same time.
40. T F I daydream a great deal about things that other people consider impossible to achieve.
41. T F I often have a strong urge to do outrageous things.
42. T F I am the kind of person who falls in and out of love easily.
43. T F I'm usually in an upbeat or cheerful mood.
44. T F Life is a feast which I enjoy to the fullest.
45. T F I like telling jokes, people tell me I'm humorous.
46. T F I'm the kind of person who believes everything will eventually turn out all right.
47. T F I have great confidence in myself.
48. T F I often get many great ideas.
49. T F I am always on the go.

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50. T F I can accomplish many tasks without even getting tired.
51. T F I have a gift for speech, convincing and inspiring to others.
52. T F I love to tackle new projects, even if risky.
53. T F Once I decide to accomplish something, nothing can stop me.
54. T F I am totally comfortable, even with people I hardly know.
55. T F I love to be with a lot of people.
56. T F People tell me that I often get my nose into others' business.
57. T F I am known to be generous, and spend a lot of money on other people.
58. T F I have abilities and expertise in many areas.
59. T F I feel I have the right and privilege to do as I please.
60. T F I am the kind of person who likes to be the boss.
61. T F When I disagree with someone, I can get into a heated argument.
62. T F My sex drive is always high.
63. T F Normally I can get by with less than 6 hours of sleep.
64. T F I am a grouchy (irritable) person.
65. T F I am by nature a dissatisfied person.
66. T F I complain a lot.
67. T F I am highly critical of others.
68. T F I often feel on edge.
69. T F I often feel wound up.
70. T F I am driven by an unpleasant restlessness that I don't understand.
71. T F I often get so mad that I will just trash everything.
72. T F When crossed, I could get into a fight.
73. T F People tell me I blow up out of nowhere.
74. T F When angry, I snap at people.
75. T F I like to tease people, even those I hardly know.
76. T F My biting humor has gotten me into trouble.
77. T F I can get so furious I could hurt someone.
78. T F I am so jealous of my spouse (or lover), that I cannot stand it.
79. T F I am known to swear a lot.
80. T F I have been told that I become violent with just a few drinks.
81. T F I am a very skeptical person.

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82. T F I could be a revolutionary.

83. T F My sex drive is often so intense that it is truly unpleasant.

84. T F (Women only): I have attacks of uncontrollable rage right before my period.

85. T F I have been a worrier for as long as I can remember.

86. T F I'm always worrying about one thing or another.

87. T F I keep on worrying about daily matters that others consider minor.

88. T F I cannot help worrying.

89. T F Many people have told me not to worry so much.

90. T F When stressed, my mind often goes blank.

91. T F I am unable to relax.

92. T F I often feel jittery inside.

93. T F When stressed, my hands often tremble.

94. T F I often have an upset stomach.

95. T F When I'm nervous, I may have diarrhea.

96. T F When I'm nervous, I often feel nauseous.

97. T F When I'm nervous, I have to go to the bathroom more often.

98. T F When someone is late coming home, I fear they have had an accident.

99. T F I am often fearful of someone in my family coming down with a serious disease.

100. T F I'm always thinking someone might break bad news to me about a family member.

101. T F My sleep is not restful.

102. T F I frequently have difficulty falling asleep.

103. T F I am, by nature, a very cautious person.

104. T F I often wake up at night afraid that burglars are in the house.

105. T F I easily get headaches when stressed.

106. T F When stressed, I get an uncomfortable feeling in my chest.

107. T F I'm an insecure person.

108. T F Even minor changes in routine, stress me highly.

109. T F While driving, even when I haven't done anything wrong, I fear that the police may stop me.

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110. T F Sudden noises startle me easily.

Interpreting the TEMPS-A

depressive temperament: questions 1 to 21 (21 points)
cyclothymic temperament: questions 22 to 42 (21 points)
hyperthymic temperament: questions 23 to 63 (21 points)
irritable temperament: questions 64 to 84 (21 points in women, 20 in the men's version)
anxious temperament: questions 85 to 110 (26 points).

Those reaching the mean+2 SD level or higher in each subscale are considered to have dominant affective temperaments.

Beck's Depression Inventory

This depression inventory can be self-scored. Select one of the four responses for each of the 21 points.

1.

0 I do not feel sad.

1 I feel sad

2 I am sad all the time and I can't snap out of it.

3 I am so sad and unhappy that I can't stand it.

2.

0 I am not particularly discouraged about the future.

1 I feel discouraged about the future.

2 I feel I have nothing to look forward to.

3 I feel the future is hopeless and that things cannot improve.

3.

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0 I do not feel like a failure.

1 I feel I have failed more than the average person.

2 As I look back on my life, all I can see is a lot of failures.

3 I feel I am a complete failure as a person.

4.

0 I get as much satisfaction out of things as I used to.

1 I don't enjoy things the way I used to.

2 I don't get realsatisfaction out ofanything anymore.

3 I am dissatisfied or bored with everything.

5.

0 I don't feel particularly guilty

1 I feel guilty a good part of the time.

2 I feel quite guilty most of the time.

3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7.

0 I don't feel disappointed in myself.

1 I am disappointed in myself.

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2 I am disgusted with myself.

3 I hate myself.

8.

0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.

1 I am slightly more irritated now than usual.

2 I am quite annoyed or irritated a good deal of the time.

3 I feel irritated all the time.

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12.

0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions more than I used to.

3 I can't make decisions at all anymore.

14.

0 I don't feel thatI look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel there are permanent changes in my appearance that make me look unattractive

3 I believe that I look ugly.

15.

0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16.

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0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.

1 I am worried about physical problems like aches, pains, upset stomach, or

constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I have almost no interest in sex.

3 I have lost interest in sex completely.

Interpreting the Beck Depression Inventory

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).

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	Not present	Mild	Moderate	Severe	Very Severe
1. **Anxious Mood** Worries, anticipation of the worst, fearful anticipation, irritability.					
2. **Tension** Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.					
3. **Fears** Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.					
4. **Insomnia** Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.					
5. **Intellectual** Difficulty in concentration, poor memory.					
6. **Depressed Mood** Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.					
7. **Somatic (muscular)** Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.					
8. **Somatic (sensory)** Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking					

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sensation.					
9. **Cardiovascular Symptoms** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.					
10. **Respiratory Symptoms** Pressure or constriction in chest, choking feelings, sighing, dyspnea.					
11. **Gastrointestinal Symptoms** Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.					
12. **Genitourinary Symptoms** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of rigidity, premature ejaculation, loss of libido, impotence.					
13. **Autonomic Symptoms** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.					
14. **Behavior at Interview** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.					

DOI:10.14753/SE.2020.2300

Interpreting HAMA-A

Sum the scores from all 14 parameters.

14-17=Mild Anxiety

18-24=Moderate Anxiety

25-30=Severe Anxiety

László et al. Ann Gen Psychiatry (2015) 14:33
DOI 10.1186/s12991-015-0072-0

DOI:10.14753/SE.2020.2300

ANNALS OF GENERAL PSYCHIATRY

PRIMARY RESEARCH

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Identification of hypertensive patients with dominant affective temperaments might improve the psychopathological and cardiovascular risk stratification: a pilot, case–control study

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Abstract

Background: Although mood disorders and cardiovascular diseases have widely studied psychosomatic connections, data concerning the influence of the psychopathologically important affective temperaments in hypertension are scarce. To define a possibly higher cardiovascular risk subpopulation we investigated in well-treated hypertensive patients with dominant affective temperaments (DOM) and in well-treated hypertensive patients without dominant temperaments the level of depression and anxiety, arterial stiffness and serum Brain-derived Neurotrophic Factor (seBDNF).

Methods: 175 hypertensive patients, free of the history of psychiatric diseases, completed the TEMPS-A, Beck Depression Inventory and Hamilton Anxiety Scale questionnaires in two primary care practices. Of those 175 patients, 24 DOM patients and 24 hypertensive controls (matched in age, sex and the presence of diabetes) were selected for measurements of arterial stiffness and seBDNF level.

Results: Beck and Hamilton scores in DOM patients were higher compared with controls. Pulse wave velocity and augmentation index did not differ between the groups while in the DOM patients decreased brachial systolic and diastolic and central diastolic blood pressures were found compared with controls. SeBDNF was lower in the DOM group than in the controls (22.4 ± 7.2 vs. 27.3 ± 7.8 ng/mL, $p < 0.05$).

Conclusions: Although similar arterial stiffness parameters were found in DOM patients, their increased depression and anxiety scores, the decreased brachial and central diastolic blood pressures as well as the decreased seBDNF might refer to their higher vulnerability regarding the development not only of major mood disorders, but also of cardiovascular complications. These data suggest that the evaluation of affective temperaments should get more attention both with regard to psychopathology and cardiovascular health management.

Keywords: Hypertension, Affective temperaments, Depression, Anxiety, Arterial stiffness, Brain-derived neurotrophic factor, Cardiovascular risk

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Background

Mood disorders are common public health problem in the Western world and their strong connection to cardiovascular diseases (CVD) is well known [1]. Moreover, the negative impact of adverse individual psychological traits and characteristics, like anger, hostility and anxiety is also well-documented in connection to the development and progression of coronary heart disease [2, 3], while individual differences in antagonism-related traits seem to predict a variety of cardiovascular outcomes [4, 5].

There are multiple mechanisms by which depression could increase the probability of vascular diseases, such as increased platelet activation [6], inflammatory markers [7] as well as reduced heart rate variability [8]. Parallel to this, well-established biomarkers of inflammation were also found to be elevated in persons in states of anger or hostility [9, 10], while a reduced function of the autonomic nervous system was observed in states of anxiety [11] and interpersonal antagonism was connected with carotid arterial intima-media thickening [12].

Another possible link might be the brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, which is not only associated with major depressive disorder [13], but its higher serum level is also connected to a decreased risk of cardiovascular disease and mortality [14].

The independent continuous relationship between elevated blood pressure and several cardiovascular events is well-known for patients in all ages and ethnic groups [15]. Besides elevated blood pressure, arterial stiffening is increasingly recognised as a risk factor for CVD. The determination of decreased arterial elasticity helps to identify the patient's higher risk of cardiovascular morbidity and mortality [16]. In Europe, the measurement of arterial stiffness is already a recommended method for cardiovascular risk assessment among hypertensive patients [17]. Previously, depressive symptoms, especially in diagnosed depressive disorders were found to be associated with increased arterial stiffening [18].

According to our recent findings, specific affective temperament types (depressive, cyclothymic, hyperthymic, irritable and anxious) are the subclinical, trait-related manifestations and commonly the antecedents of minor and major mood disorders [19]. Recently, in a study of primary care patients we also demonstrated a strong connection between dominant cyclothymic temperament and hypertension [20]. Moreover, we also showed that cyclothymic temperament is connected to acute coronary events in hypertensive patients [21].

We hypothesised that hypertensive patients with dominant affective temperaments (DOM) score higher depression and anxiety values and have impaired arterial stiffness, central blood pressure or serum BDNF compared with hypertensive patients without dominant affective temperaments, forming a high-risk subgroup patient population.

Methods

Patients

In our cross-sectional case–control study well-treated chronic (>12 months medication) hypertensive Caucasian patients were investigated in two primary care practices. All patients completed the TEMPS-A, Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) questionnaires in order to evaluate the presence of affective temperaments, depression and anxiety, respectively. Following this initial screening, patients with dominant affective temperaments (reaching the mean + 2 SD point scores or higher in each affective temperament subscale, DOM) were identified. Hypertensive controls without DOM, matched in age, gender and presence of diabetes, were selected from the initial hypertensive patient cohort and included in the arterial stiffness and seBDNF measurements. As blood pressure medication can highly influence arterial stiffness, it was further analysed, but patients were not matched in this aspect.

Exclusion criteria were the history or ongoing treatment of depression or anxiety (as with arterial stiffening the associations are clarified [18]), and the presence of atrial fibrillation or uncontrolled hypertension (>145/95 mmHg in repeated office measurements). In patients with an average blood pressure between 140/90 and 145/95 mmHg in repeated office blood pressure measurements, ambulatory 24-h blood pressure monitoring or home blood pressure monitoring was performed and only well-controlled patients were admitted to the study. Prior to the participation, all patients gave their written informed consent. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and carried out in accordance with the tenets of the Declaration of Helsinki.

Procedures

During the initial visit patients completed the questionnaires. Physical examination (blood pressure, heart rate, height, weight and waist circumference) were completed and data on medical history (with special attention to cardiovascular risk factors, complications and depression) as well as on current medication was collected.

After the analysis of the questionnaires, patients meeting the criteria of dominant temperament and their controls were invited for arterial stiffness and seBDNF measurements, which took place within 1 month after the initial visit.

Questionnaires

*The temperament evaluation of Memphis Pisa, Paris and San Diego (*TEMPS-A) questionnaire is an 110-item, self-report instrument, developed to measure affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales and requiring the answers 'yes' (score 1) or 'no' (score 0) [22]. TEMPS-A is used to assess the point scores of each subscale and also to measure the presence of the dominant form of affective temperaments by taking the mean of the subscale and adding up two standard deviations to it. Those reaching the mean + 2 SD level or higher in each subscale are considered to have dominant affective temperaments.

The *beck depression inventory* (BDI), created by Aaron T. Beck, is a 21-question multiple-choice self-report questionnaire, one of the widely used instruments for measuring the severity of depression. Participants are asked to make ratings on a four-point scale, where a higher score correlates with more severe depression.

Hamilton Anxiety Scale (HAM-A) was evaluated by the examiner to study the severity of anxiety. The scale consists of 14 items, each item is scored on a scale of 0 (not present) to 4 (severe anxiety).

Arterial stiffness recordings

Measurements were performed in a temperature-controlled room in supine position, on the day of blood sampling, before it, between 7.00 and 8.00 a.m. Patients were required to fast overnight and refrain from smoking and caffeine-containing beverages before the procedure, but to take the usual blood pressure regulating medication. Upon arrival at the investigation unit, the subjects were equipped with measurement devices, and then rested in supine position for approximately 15 min before being measured. Arterial stiffness parameters were evaluated using the validated, gold-standard PulsePen tonometer (DiaTecne, Milan, Italy, [23]). With this method the pulse wave velocity (PWV) augmentation index (AI), as well as the central systolic blood pressure (central SBP) and central pulse pressure (central PP) can be calculated. In each subject two sequences of measurements were performed and their mean was used for statistical analysis. ECG was recorded continuously from the limb lead with the largest R wave.

In the PWV calculations 80 % of the carotid-femoral distance was used, following the recent guideline [24]. Previously we evaluated the intra- and interobserver variabilities of PWV measurements obtained by the PulsePen device on hypertensive patients and found them to be 4.6 and 6.3 % high, respectively. As PulsePen calculates pressure values using brachial diastolic blood pressure calibration, the calculated central and brachial diastolic blood pressure values were identical [23].

Measurement of seBDNF concentration

Peripheral blood samples of patients were collected in anticoagulant-free tubes, right after the measurement of arterial stiffness. After centrifugation (3600 rpm for 6 min) the serum was stored at −20 °C. SeBDNF was measured using commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis MN, USA) according to the manufacturer's protocol and serum BDNF level was determined in ng/mL.

Data analysis

Data were expressed as mean ± SEM and medians. Differences in variables between controls and DOM patients were analysed using unpaired Student's *t* tests or Mann–Whitney rank-sum tests for data failing tests of normality. Blood pressure medications were calculated and compared using equivalent doses, differences were analysed with unpaired Student's *t* tests or Mann–Whitney rank-sum tests. Significance was accepted at $p < 0.05$. Statistical analysis was performed using the SigmaStat for Windows Version 3.5 (SPSS) program package.

Results and discussion

Characteristics of the patients

183 hypertensive patients were recruited to participate in the study and 175 of them completed the questionnaires. 29 of the patients had dominant affective temperaments (DOM). Out of the 29 DOM patients one died 3 days prior to the planned arterial stiffness measurement and four declined to further participate in arterial stiffness measurements. The arterial stiffness and BDNF of altogether 48 hypertensive patients was evaluated: 24 DOM and 24 control subjects matched in age, gender and presence of diabetes.

Among the DOM patients six subjects with depressive, five irritable and four anxious dominant temperaments were found. In the other patients, combinations of dominant temperaments were present: three patients had cyclothymic and depressive, two had cyclothymic and irritable, two had cyclothymic, depressive and anxious, one had cyclothymic, irritable and anxious temperaments and one patient was dominant for cyclothymic, irritable, anxious and depressive affective temperaments. No patient with a dominant hyperthymic temperament was found in our cohort.

Comparing the control and DOM patients for statistical differences

Baseline demographic, anthropometric and laboratory parameters and the used cardiovascular medications of the patients are presented in Table 1. SeBDNF levels were lower in DOM patients. Compared with controls, beta-blockers

Table 1 Baseline demographic, anthropometric and laboratory parameters and the used cardiovascular medication of the patients

	Control	DOM
N (male:female)	24 (9:15)	24 (9:15)
Age (year)	63.7 ± 2.54	64.3 ± 2.52
Body height (cm)	164.5 ± 1.51	166 ± 2.06
Body weight (kg)	76.3 ± 2.66	81 ± 3.34
AC (cm)	101.5 ± 4.1	102 ± 5.5
BMI (kg/m^2)	28.2 (26–31.2)	29.8 (24.4–34.6)
Glucose (mmol/l)	5.36 (5.03–6.07)	5.7 (4.94–6.63)
CKD-EPI GFR (mmol/l)	77.5 (62.5–86)	78.5 (60.8–90)
Uric acid (μmol/l)	309.3 ± 15.26	321.6 ± 16.82
Cholesterol (mmol/l)	5.48 ± 0.22	5 ± 0.35
Triglyceride (mmol/l)	1.36 (1.08–2.18)	1.82 (0.99–2.15)
BDNF (ng/ml)	27.29 (24.2–30.35)	20.10 (14.74–27.11)*
ACE-inhibitors [n (%)]	13 (54.2)	13 (54.2)
ARBs	9 (37.5)	5 (20.8)
Calcium-channel blockers	11 (45.8)	11 (45.8)
Beta-blockers	12 (50)	18 (75)*
Diuretics	11 (45.8)	11 (45.8)
Antiplatelet medication	8 (33.3)	11 (45.8)

The values are mean ± SEM or medians (quartiles)

The groups were compared for differences by using Student's *t* test or the Mann–Whitney rank-sum for data failing tests of normality

DOM patients with dominant affective temperament, *AC* abdominal circumference, *BMI* body mass index, *CKD-EPI GFR* glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; BDNF: brain-derived neurotrophic factor, *ARBs* angiotensin II receptor blockers

* $p < 0.05$ compared with controls

were prescribed more frequently and in higher dose in the DOM group [0.63 (0–5) vs. 5 (0.63–6.88) mg, calculated for bisoprolol, respectively, $p < 0.05$]. No differences were found in the mean duration of hypertension among controls and DOM patients [10.5 (4–15.8) vs. 12 (6.5–17.8) $p = 0.238$, respectively]. No differences were found among the groups studied in smoking habits and in the frequency of physical training (data are not shown).

Table 2 represents the differences in the five affective temperaments and in the BDI and HAM-A scores. Compared with controls, in DOM patients depressive, cyclothymic, irritable and anxious scores were higher, while hyperthymic scores were equal. Both BDI and HAM-A scores were markedly higher in DOM patients than in the controls.

Brachial and central hemodynamic and arterial stiffness parameters are shown in Table 3. Brachial systolic and both brachial and central diastolic and mean blood pressures were lower in DOM patients. PWV and AI, the two main arterial stiffness parameters, did not differ when compared with controls.

Table 2 TEMPS-A scores of affective temperaments, BDI and HAM-A scores

	Control *N* = 24	DOM *N* = 24
Depressive	6 (4.25–8.75)	12.5 (7–13.75)*
Cyclothymic	3 (1–5)	9.5 (7–13.75)*
Hyperthymic	12.13 ± 0.73	10.46 ± 0.99
Irritable	2 (1–4.75)	9.5 (5–11)*
Anxious	5.08 ± 0.81	14.67 ± 0.88*
BDI	5 (2–7.75)	14.5 (8.5–19.75)*
HAM-A	7 ± 1.27	16.67 ± 1.68*

The values are mean ± SEM and medians (quartiles). The groups were compared for differences by using Student's *t* test or the Mann–Whitney rank-sum for data failing tests of normality

DOM patients with dominant affective temperament, *TEMPS-A* the temperament evaluation of Memphis Pisa, Paris and San Diego questionnaire, *BDI* beck depression inventory, *HAM-A* Hamilton Anxiety Scale

* $p < 0.05$ compared with controls

Table 3 Brachial and central hemodynamic and arterial stiffness parameters

	Control *N* = 24	DOM *N* = 24
HR (1/min)	66 ± 1.25	63.1 ± 1.17
SBPB (Hgmm)	130.8 (122–137.1)	122.6 (116.4–129.7)*
DBPB (Hgmm)	71.2 ± 1.5	66.6 ± 1.71*
MBPB (Hgmm)	91.9 ± 1.53	86.6 ± 1.94*
PPB (Hgmm)	59.3 (49.4–67.5)	54.3 (50.1–61.9)
Central SBP (Hgmm)	124.3 (113.5–136.4)	117 (112.6–131.7)
Central DBP (Hgmm)	71.2 ± 1.5	66.5 ± 1.71*
Central MBP (Hgmm)	94.1 ± 1.55	88.9 ± 1.96*
Central PP (Hgmm)	50.6 (44.5–66.6)	52.3 (48.8–1.72)
PWV (m/s)	9.32 (8.02–11.25)	8.74 (8.32–9.87)
AI (%)	16.04 ± 2.24	14.54 ± 2.66

The values are mean ± SEM and medians (quartiles). The groups were compared for differences by using Student's t test or the Mann–Whitney rank-sum for data failing tests of normality

DOM patients with dominant affective temperament, *HR* heart rate, *SBPB* systolic brachial blood pressure, *DBPB* diastolic brachial blood pressure, *MBPB* mean brachial blood pressure, *PPB* brachial pulse pressure, *Central SBP* central systolic blood pressure, *Central DBP* central diastolic blood pressure, *Central MBP* central mean blood pressure, *Central PP* central pulse pressure, *PWV* pulse wave velocity, *AI* Augmentation index

* $p < 0.05$ compared with controls

Our pilot study was performed on hypertensive patients with dominant cyclothymic, irritable, depressive or anxious affective temperaments without the history or any present psychiatric medications. We found that DOM patients had higher anxiety and depression scores and lower seBDNF level. DOM patients had similar levels of arterial stiffening with a lower peripheral and central blood pressure compared with hypertensive controls.

Affective temperaments are associated with depression and anxiety

Affective temperaments are tightly related to affective disorders. Hyperthymic temperament was found to be associated with type-I and cyclothymic with type-II bipolar disease [25] and atypical depression [19, 26], depressive temperament, in contrast to this, with unipolar major depression [19, 27]. In our cohort DOM patients also had higher depression and anxiety scores suggesting the importance of a joint evaluation of affective temperaments together with depression and anxiety even in those hypertensive patients who have no records of previous psychiatric diseases or any present antidepressant or anxiolytic medication.

Affective temperaments and cardiovascular risk

Although the presence of dominant affective temperaments frequently precedes the onset of minor and major affective illness [19], and therefore screening for their presence would be an important target in the prevention and early intervention of cardiovascular disorders as well, only few studies are available which aim to investigate the role of affective temperaments in the development and risk of different cardiovascular diseases. Patients with depressive temperament were found to have worse metabolic control in type-2 diabetes [28], while cyclothymic, irritable and anxious temperaments showed affinity to obesity [29]. Recently we evaluated the role of affective temperaments in primary hypertension and found a significant association with the dominant cyclothymic temperament [20]. Moreover, cyclothymic temperament was associated with acute coronary events in hypertensive patient population [21]. In our present study, patients with affective temperaments had lower brachial and central diastolic and mean blood pressure values than controls. It is well known that decreased diastolic blood pressure is associated with increased mortality [30]. Parallel to our previous findings in hypertensive patients mentioned above [20, 21], this phenomenon of decreased blood pressure values might be more expressed in cyclothymic patients and would in this case suggest their increased susceptibility to cardiovascular complications. However, the clarification of this hypothesis requires further studies.

As our DOM patients had higher depression score compared with control patients, one explanation of the decreased blood pressure might reflect the fact that lower blood pressure levels are often accompanied by a pronounced presence of depressive symptoms and in follow-up studies symptoms of anxiety and depression predicted the development of lower blood pressure [31, 32]. In case of a co-occurring onset of depression and hypotension, the pathophysiological mechanisms are considered to be the alterations in neurohormonal, immune and autonomic regulations [33]. Whether only the increased depression per se caused the decreased blood pressure in our DOM patients, or another independent factor is also involved, is a question still to be answered.

Most of the studies support the idea that antagonistic traits, depression and anxiety increase the probability of the development of cardiovascular diseases [12, 34, 35], and data are also available with respect to arterial stiffness. In their population-based, cross-sectional study including 3704 elderly patients, Tiermeier et al. found that patients with increased arterial stiffness were more likely to have depressive symptoms. The association was stronger in cases with diagnosed depressive disorders. The authors concluded that arterial stiffness may partly cause the proposed relationship between vascular factors and depression [18]. In contrast to this we found no difference in PWV or augmentation index between our DOM and control hypertensive patients. An explanation to this phenomenon can be that in the study of Tiermeier et al. the patients' arterial stiffness was much higher, as the border of the lowest PWV quartile was 11.4 m/s. This suggests a very poor vascular status of those patients, while in our patients PWV values were much lower.

In a recent study of Seldenrijk et al., depression and anxiety sensitivity and their association with arterial stiffening were evaluated. The authors found that out of these only anxiety sensitivity was associated with arterial stiffness; however, they studied only the augmentation index, which is a more variable parameter compared to PWV and is influenced by resistance vessels, that can be dysfunctional in patients with anxiety [36, 37]. It is also worth mentioning that the population of Seldenrijk et al. was much younger (46 years) compared with ours and only 18 % of the patients regularly took antihypertensive medication which suggests their better general resistance vessel function. Considering all these results we suppose that in older patients besides optimal vascular therapy, the deleterious effects of depression and anxiety for arterial stiffening can be attenuated, but in younger population without vascular medication the deleterious effects of anxiety can lead to detectable dysfunction of resistance vessels in comparison to healthy controls.

Serum BDNF level, affective temperaments and allostatic load

In our study seBDNF, too, was measured and we observed its decreased level in our DOM patients. SeBDNF was found to be lower in patients suffering from major depressive disorder and some types of anxiety disorders, while in animal models the regulation of BDNF was suggested to contribute both to anxiety-like behaviour and hypertension [38–40]. BDNF was found

to be decreased also in such pathological conditions as acute coronary syndrome and type 2 diabetes [41, 42]. Whether the decreased seBDNF in our hypertensive DOM patients is correlated with their higher depression and anxiety and bears any clinical relevance with respect to the cardiovascular outcome or not, further studies need to clarify.

The term "allostatic load" refers to a cumulative, multisystem view of the physiologic toll that is required for adaptation to stress. In mood disorders, especially in bipolar disorder allostatic load increases progressively as mood episodes occur over time [43]. Among many mediators, neurotrophic factors such as decreased level of BDNF indicates allostatic load [44]. Seeman et al. found in their longitudinal, community-based study that allostatic load may play a role in cardiovascular disorders [45] and there is evidence that reduction in allostatic load is associated with lower all-cause mortality, even in geriatric patients [46]. As affective temperaments are the subclinical manifestations of minor and major mood disorders and we found decreased BDNF level in patients with dominant temperaments, it can indicate an increased allostatic load among them, as well. According to this theory the increased cardiovascular risk could also be explained with the phenomenon of allostatic load.

In our study the depressive, cyclothymic, irritable and anxious temperaments or their combinations were investigated together. The neurobiological background of these temperaments seems to be at least partly common, as all were found to be associated with the 5-HTTLPR polymorphism of the serotonin transporter gene, namely the presence of the s allele, which is connected with decreased serotonin uptake of cells [47]. Moreover, the scales of depressive, anxious, cyclothymic and irritable temperaments were found to be closely associated in different populations suggesting real phenotypical connections beyond the similarities in the neurobiological background [48, 49]. Whether the clustering of dominant temperaments has any pronounced clinical relevance above single dominant temperaments is another question to be answered.

Risk stratification of hypertensive patients

The calculation of total cardiovascular risk of hypertensive patients is a very important task of hypertension care [17]. Our results support the possibility that in the future the evaluation of affective temperaments might be the part of the risk stratification procedure of hypertensive patients as besides the obvious connection with mood disorders, the identification of DOM patients could determine a higher cardiovascular risk patient population as well.

Limitations

The main limitation of our study is the relatively low number of patients involved. Out of 183 invited hypertensive patients, the arterial stiffness parameters of only 24 subjects with dominant affective temperament and 24 controls were analysed. The low number of patients limits the generalisability of our data and type I and type II errors cannot be excluded. As the detailed analysis of the impact of unique dominant affective temperaments on arterial stiffness, central blood pressure or seBDNF require higher number of involved patients, we defined this study as a "pilot". Another limitation comes from the cross-sectional design of the study which precludes causal inference.

Conclusions

In conclusion, although arterial stiffness parameters did not differ between the DOM subgroup of well-treated hypertensive patients and their hypertensive controls, their higher depressive and anxious scores and lower seBDNF might reflect their higher susceptibility for cardiovascular complications. Furthermore, DOM patients might bear a higher risk, as they have lower brachial and central diastolic blood pressure values in comparison to patients without dominant temperaments. The clinical significance of our findings with respect to the cardiovascular outcome of these patients needs further examinations on higher number of patients involved, but the cumulating data suggest that the evaluation of affective temperaments might improve both psychopathological and cardiovascular risk stratification.

Abbreviations

AC: abdominal circumference; AI: augmentation index; ARBs: angiotensin II receptor blockers; BDI: beck depression inventory; BDNF: brain-derived neurotrophic factor; BMI: body mass index; Central DBP: central diastolic blood pressure; Central MBP: central mean blood pressure; Central PP: central pulse pressure; Central SBP: central systolic blood pressure; CKD-EPI GFR: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; DBPB: diastolic brachial blood pressure; DOM: patients with dominant affective temperament; HAM-A: Hamilton Anxiety Scale; HR: heart rate; MBPB: mean brachial blood pressure; PPB: brachial pulse pressure; PWV: pulse wave velocity; SBPB: systolic brachial blood pressure; seBDNF: serum brain-derived neurotrophic factor; TEMPS-A: the temperament evaluation of Memphis Pisa, Paris and San Diego questionnaire.

Authors' contributions

AL participated by data collection and analysis, arterial stiffness measurement and by the composition of the paper. LB participated by arterial stiffness measuring. Zs K-I, AP, PT and AE participated by patient recruitment and data acquisition and management. LK participated by data analysis and the critical review of the manuscript. XG and ZR helped by conceiving and designing the study and by critically reviewing the manuscript. OC participated by the analysis of the pulse wave curves and in the training of the examiners of arterial stiffness. AT designed and supervised the arterial stiffness part of the study and helped with the writing of the manuscript. JH, LL and AF participated by laboratory measurements and contributed to writing the manuscript. JN planned and supervised the study, helped by patient recruitment and completed the manuscript. All authors read and approved the final manuscript.

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Acknowledgements
The authors acknowledge the contribution of Lászlóné Hárshegyi and Zoltánné Reisz, who helped by medically assisting the patients and by data acquisition. We also acknowledge the contribution of Oleg Pogrebnyak for his technical and linguistic support. Xenia Gonda is recipient of the János Bolyai Research Fellowship of the Hungarian Academy of Sciences. This study was supported by the Hungarian Society of Hypertension and by the "Lendület" Research Grant: LP008/2014.

Competing interests
Xenia Gonda is a recipient of the János Bolyai Research Fellowship of the Hungarian Academy of Sciences. This study was supported by the Hungarian Society of Hypertension and by the "Lendület" Research Grant: LP008/2014.

Received: 22 June 2015 Accepted: 14 October 2015
Published online: 26 October 2015

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László et al. BMC Cardiovascular Disorders (2016) 16:158
DOI 10.1186/s12872-016-0337-9

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study

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Abstract

Background: Affective temperaments (anxious, depressive, cyclothymic, irritable and hyperthymic) measure subclinical manifestations of major mood disorders. Furthermore, cumulating evidence suggests their involvement in somatic disorders as well. We aimed to assess associations between affective temperament scores and blood pressure and arterial stiffness parameters in hypertensive patients.

Methods: In this cross-sectional study, 173 patients with well-controlled or grade 1 chronic hypertension, with no history of depression, completed the TEMPS-A, Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) questionnaires in three GP practices. Arterial stiffness was measured with tonometry (PulsePen).

Results: According to multiple linear regression analysis, cyclothymic temperament score was positively associated with brachial systolic blood pressure independently of age, sex, total cholesterol, brachial diastolic blood pressure, BDI, HAM-A and the use of alprazolam ($\beta = 0.529$, $p = 0.042$), while hyperthymic temperament score was negatively related to augmentation index independent of age, sex, smoking, heart rate, BDI, HAM-A and the use of alprazolam ($\beta = -0.612$, $p = 0.013$). A significant interaction was found between cyclothymic temperament score and sex in predicting brachial systolic blood pressure ($p = 0.025$), between irritable and anxious temperament scores and sex in predicting pulse wave velocity ($p = 0.021$, $p = 0.023$, respectively) and an interaction with borderline significance between hyperthymic temperament score and sex in predicting augmentation index ($p = 0.052$).

Conclusions: The present findings highlight elevated blood pressure among subjects with high cyclothymic temperament as well as an increased level of arterial stiffening in subjects with low hyperthymic scores suggesting that affective temperaments may play a role in the development of hypertension and arterial stiffening and may thus represent markers of cardiovascular risk. Sex differences were also present in these associations.

Keywords: Affective temperament scores, Blood pressure, Arterial stiffness, Augmentation index, Hypertension

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Background

Cardiovascular diseases are the leading cause of morbidity and mortality in most industrialized countries worldwide, despite highly effective preventive treatments. A continuous linear relationship between elevated blood pressure and incident cardiovascular events is well known at all ages and in all ethnic groups [1–5]. In addition to elevated blood pressure, arterial stiffening – integrating the damage of risk factors on the aortic wall over a long period [6] – is increasingly recognized as a marker and mediator of cardiovascular diseases. Accordingly, carotid-femoral pulse wave velocity (PWV), an accepted non-invasive measure of arterial stiffness, is recommended for cardiovascular risk prediction among hypertensive patients in European Guidelines [7].

Depression is also a common public health problem in the Western world and its strong connection with cardiovascular diseases is broadly recognized [8]. The pathophysiologies of depression and cardiovascular diseases show several similarities that include the dysregulation of metabolic, immune-inflammatory and autonomic systems as well as the hypothalamic-pituitary axis [9]. In addition to depression, anger, hostility and anxiety – the negative impact of adverse individual psychological traits and characteristics – are also well-documented risk factors of coronary heart diseases [10, 11], while antagonism-related traits also appear to predict a variety of cardiovascular outcomes [12, 13].

Temperament is regarded as an inherited part of personality and represents the biologically stable core of emotional reactivity [14, 15]; however, there is ongoing discussion regarding the influence of age on depressive temperament with differences between man and women also being present [16]. Affective temperaments can be measured on five temperament scales by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) [17]. Hyperthymic temperament is characterized by upbeat, overconfident and over-energetic traits while depressive temperament is self-denying, striving to live in harmony with others and sensitive to suffering. Anxious temperament can best be explained by exaggerated worries especially toward family members. Cyclothymic temperament shows affective instability with rapid mood shifts and intense emotions, while irritable temperament incorporates skeptical and critical traits [15, 18, 19]. Affective temperaments are also associated with numerous other measures of psychopathology [20]. Specific affective temperament types are the subclinical, trait-related manifestations and commonly the antecedents of minor and major mood disorders [21], where hyperthymic affective temperament can inversely be related to depression [22]. Recently, we described an association between chronic hypertension and the dominant cyclothymic temperament [23]. Cyclothymic temperament was also associated with acute coronary events in hypertensive patients [24]. In a small matched case-control study comparing hypertensive patients with and without dominant affective temperaments, we found lower peripheral and central diastolic blood pressure values and decreased serum brain-derived neurotrophic factor levels in patients with dominant temperaments [25]. Since the ratio of those subjects who score high on different temperament directions while having a dominant affective temperament is relatively low (rarely does a subject have multiple dominant temperaments), as found in only 16.8 % of the general population [26], it would be important to ascertain the continuous association between affective temperament scores and blood pressure or arterial stiffness parameters.

We hypothesized that individual affective temperament scores may be related to brachial blood pressure as well as arterial stiffness in chronic hypertensive patients. We speculated a positive association in instances of depressive, cyclothymic, irritable or anxious temperaments and an inverse association in instances of hyperthymic temperament. We also hypothesized the presence of sex differences in relation to these studied associations.

Methods

Patients

In the present cross-sectional study, 173 Caucasian patients with well-controlled or grade 1 chronic (on medication for >3 months) hypertension were investigated in three primary care practices. Patients with atrial fibrillation and treated depression or with dementia potentially interfering with the completion of questionnaires were excluded. Patients on moderate doses of alprazolam (<0.5 mg/day) were not excluded. All of the 48 patients of our previous pilot study [25] were also involved in the present study.

Evaluation of affective temperaments, depression and anxiety

The *Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire* (TEMPS-A) was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales, requiring 'yes' (score 1) or 'no' (score 0) answers [17]. TEMPS-A contains 110 items (109 in the version for males) and the questions of the various temperament types are grouped together as follows:

1. depressive temperament: questions 1 to 21 (21 points)
2. cyclothymic temperament: questions 22 to 42 (21 points)
3. hyperthymic temperament: questions 23 to 63 (21 points)

4. irritable temperament: questions 64 to 84 (21 points in women, 20 in the men's version)
5. anxious temperament: questions 85 to 110 (26 points).

TEMPS-A has been extensively studied, translated into more than 25 languages and validated in several of the latter. Similarities and differences were also found in national samples which suggest that distribution of affective temperaments has both universal and cultural-specific characteristics [16].

The *Beck Depression Inventory* (BDI), created by Aaron T. Beck, is a 21-question multiple-choice self-report questionnaire and is one of the widely used instruments for measuring depression severity. Participants are asked to make ratings on a four point scale, where a higher score correlates with more severe depression [27].

The *Hamilton Anxiety Scale* (HAM-A) was used to study the severity of anxiety. The scale consists of 14 items, each item is scored on a scale of 0 (not present) to 4 (severe anxiety) [28].

Blood pressure and arterial stiffness measurements

Measurements were performed in a temperature-controlled room, between 7.00 and 8.00 a.m. prior to blood collection. Patients were required to fast overnight and refrain from smoking and drinking caffeine-containing beverages before the procedure, but to take their usual blood pressure medication. Upon arrival and after 5 min rest, two brachial blood pressure measurements were taken on each arm in the sitting position with a validated oscillometric blood pressure device (Omron M3). The mean value of the higher side of arms was further taken into calculation as brachial systolic (SBPbrach) and diastolic (DBPbrach) blood pressures and heart rate. Brachial pulse pressure (PPbrach) was also calculated from these data. The subjects were next fitted with arterial stiffness measurement device and were asked to rest in the supine position for approximately 15 min before being measured. Arterial stiffness parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy) [29]. This method provides estimates of pulse wave velocity (PWV) and in which central systolic blood pressure (SBPcentr), central pulse pressure (PPcentr) and pulse pressure amplification (PPAmp) can be calculated. Augmentation index (Aix), a widely used wave reflection parameter, can also be measured by automatic identification of the "first shoulder" (inflection point) of the averaged carotid pulse signal by the PulsePen software. This index is provided by the pressure amplitude following this point divided by the pulse pressure and calculated as a percentage. In these calculations, brachial blood pressure values measured in the supine position were used, which were required for calibration after each (carotid or femoral) pulse wave detection. In each subject, two sequences of arterial stiffness measurements were performed and their mean used for statistical analysis. In the PWV calculations, 80 % of the carotid-femoral distance was used, according the most recent recommendation [30]. The intra- and interobserver variability of PWV measurements obtained by the PulsePen device in hypertensive patients was 4.6 and 6.3 %, respectively. Since PulsePen calculates pressures based on brachial diastolic blood pressure calibration, the calculated central diastolic blood pressure is identical to the brachial diastolic blood pressure assessed in the supine position [29].

Statistical analysis

Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges or percentages. Normality of continuous parameters was tested with the Kolmogorov-Smirnov test. Pearson correlation coefficients were calculated to study the relationship between affective temperament scores and demographic, hemodynamic or arterial stiffness parameters. Multiple linear regression analysis was used to study the determinants of these hemodynamic or arterial stiffness parameters which were associated in univariate analysis with affective temperaments. Based on literature data, sex differences in the association between affective temperaments and the studied hemodynamic or arterial stiffness parameters [16] were expected, and therefore sex and its interaction with the given affective parameter was included into all regression models and where an interaction was found, such interaction was further studied. A two-sided $p < 0.05$ was considered to be significant. SPSS 13.0 for Windows was used for all calculations.

Results

A total of 173 subjects were included. Baseline demographic and laboratory parameters, current medication, TEMPS-A, BDI and HAM-A scores, central blood pressure and arterial stiffness parameters are summarized in Table 1. The median number of antihypertensive drugs taken was 2 (IQR: 2-3).

Table 2 lists the hemodynamic or arterial stiffness parameters and their significant correlations for which affective temperaments were also significantly associated. Table 2 also shows those variables which were not significantly correlated with outcome variables, but were entered into the final multiple regression models. Partial correlations corrected for age and sex are also demonstrated. Although, in univariate models, affective temperament scores were associated with hemodynamic or arterial stiffness parameters in many cases, however,

Table 1 Baseline characteristics of study participants

N (male/female)	173 (68/105)
Age (years)	63 (53-70)
Duration of hypertension (year)	9 (3-16)
Diabetes [*n* (%)]	38 (22)
CV disease [*n* (%)]	26 (15)
Current smoker [*n* (%)]	33 (19.1)
Body height [cm]	168 (160-174)
Body weight [kg]	80 (70-90)
BMI [kg/m^2]	27.8 (25.3-31.2)
Blood glucose [mmol/l]	5.6 (5.1-6.6)
GFR-EPI [ml/min/1.73 m^2]	81.9 (67.9-90)
Uric acid [μmol/l]	324.2 ± 79.6
Total cholesterol [mmol/l]	5.2 ± 1.1
Triglyceride [mmol/l]	1.4 (1.1-2.1)
Medications	
ACE-inhibitor [*n* (%)]	116 (67.1)
ARB [*n* (%)]	35 (20.2)
Calcium channel blocker [*n* (%)]	88 (50.9)
Beta-blocker [*n* (%)]	98 (56.6)
Diuretic [*n* (%)]	72 (41.6)
Antiplatelet drug [*n* (%)]	52 (30.1)
Statin [*n* (%)]	57 (33.4)
Alprazolam [*n* (%)]	23 (13.3)
TEMPS-A, BDI, HAM-A scores	
Depressive	6 (4-9)
Cyclothymic	3 (1-5)
Hyperthymic	12 (9-14)
Irritable	3 (2-6)
Anxious	4 (2-9)
BDI	5 (2-9)
HAM-A	5 (2-10)
Hemodynamic. arterial stiffness parameters	
Heart rate [1/min]	70.8 (64.8-78)
SBPbrach [mmHg]	133.5 ± 12
DBPbrach [mmHg]	75.6 ± 9.2
PPbrach [mmHg]	54.2 (47.1-62.4)
SBPcentr [mmHg]	123 (113.2-130.8)
PPcentr [mmHg]	51 (43.5-60.4)
PPAmp	1.07 (1.00-1.13)
PWV (m/sec)	8.7 (7.7-9.9)
Aix (%)	15.5 (8.5-25.2)

Data are presented as mean ± SD or median (interquartile range). Categorical parameters are presented as n (%). *CV diseases* cardiovascular diseases, *BMI* body mass index, *GFR-EPI* glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation, *ACE* Angiotensin converting enzyme, *ARB* angiotensin II receptor blocker, *TEMPS-A* Temperament Evaluation of Memphis Pisa, Paris and San Diego questionnaire, *BDI* Beck Depression Inventory, *HAM-A* Hamilton Anxiety Scale, *SBPbrach* brachial systolic pressure, *DBPbrach* brachial diastolic pressure, *PPbrach* brachial pulse pressure, *SBPcentr* central systolic pressure, *PPcentr* central pulse pressure, *PPAmp* pulse pressure amplification, *PWV* carotid-femoral pulse wave velocity, *Aix* augmentation index

upon further correction for age and sex, certain temperaments failed to be independent covariables of these parameters, notably irritable temperament score of brachial systolic blood pressure ($p = 0.056$) and depressive temperament score of Aix ($p = 0.595$). Table 3 demonstrates that cyclothymic temperament score was an independent covariate of brachial systolic blood pressure and hyperthymic temperament of Aix after adjustment for further relevant confounders. In the final model adjusted for all potential confounders, a one-unit increase in cyclothymic score was associated with 0.529 (95 % CI: 0.019-1.040) mmHg higher brachial systolic blood pressure while a one-unit increase in hyperthymic score was associated with -0.612 (95 % CI: -1.092–0.132) % lower Aix.

With regard to the association between PWV and irritable temperament score, the correlation still remained significant ($p = 0.012$) after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension, although became non-significant after further adjustment for BDI and HAM-A scores and the use of alprazolam ($p = 0.078$). The same results were also found for anxious temperament score and PWV: the significant association ($p = 0.043$) that was present after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension disappeared after further adjustment for BDI and HAM-A scores and the use of alprazolam ($p = 0.475$).

When studying the interaction between cyclothymic temperament score and sex in predicting brachial systolic blood pressure, a significant association was found ($p = 0.025$, Fig. 1a). There was a positive association between cyclothymic temperament score and brachial systolic blood pressure in men ($B = 1.012$, $SE = 0.392$, $p = 0.011$) which was absent in women ($B = 0.294$, $SE = 0.311$, $p = 0.346$). After adjustment for age, brachial diastolic blood pressure, cholesterol and triglycerides, this interaction became non-significant ($p = 0.090$; in men $B = 0.680$, $SE = 0.347$, $p = 0.052$ and in women $B = 0.279$, $SE = 0.272$, $p = 0.307$).

Table 2 Variables with significant Pearson correlations and variables entered in the final multiple linear regression model showing the independent predictors of brachial systolic blood pressure, pulse wave velocity and augmentation index

Variable	R	*p*	Partial R[a]	*p*
Brachial systolic blood pressure				
Sex	-0.155	0.048	-	-
Cholesterol [mmol/l]	-0.179	0.022	-0.072	0.365
DBPbrach [mmHg]	0.428	<0.001	0.474	<0.001
PPbrach [mmHg]	0.484	<0.001	0.489	<0.001
SBPcentr [mmHg]	0.591	<0.001	0.598	<0.001
DBPcetr [mmHg]	0.284	<0.001	0.329	<0.001
PPcentr [mmHg]	0.461	<0.001	0.471	<0.001
SBP amplification [mmHg]	0.281	<0.001	0.300	<0.001
PWV [m/s]	0.261	<0.001	0.265	0.001
TEMPS-A Irritable	0.171	0.030	0.151	0.056
TEMPS-A Cyclothymic	0.167	0.032	0.171	0.030
Age	0.037	0.630	-	-
BDI	0.006	0.932	0.026	0.738
HAM-A	0.062	0.430	0.082	0.299
Alprazolam	0.007	0.932	0.018	0.820
Pulse wave velocity				
Age [year]	0.544	<0.001	-	-
Duration of hypertension [year]	0.250	<0.001	-0.019	0.808
CV disease	0.241	0.001	0.095	0.218
Blood glucose [mmol/l]	0.213	0.005	0.128	0.097
GFR-EPI [ml/min/1.73 m^2]	- 0.308	<0.001	-0.112	0.154
SBPbrach [mmHg]	0.260	<0.001	0.265	0.001
PPbrach [mmHg]	0.507	<0.001	0.408	<0.001
SBPcentr [mmHg]	0.410	<0.001	0.369	<0.001
PPcentr [mmHg]	0.478	<0.001	0.338	<0.001
TEMPS-A Irritable	0.156	0.040	0.173	0.025
TEMPS-A Anxious	0.157	0.039	0.156	0.043
BDI	0.164	0.031	0.104	0.176
HAM-A	0.173	0.024	0.179	0.021
Sex	-0.143	0.059	-	-
Alprazolam	0.121	0.111	0.078	0.308
Augmentation index				
Age [year]	0.203	<0.001	-	-
Sex	0.347	<0.001	-	-
Current smoking [p/y]	0.159	0.038	0.175	0.023
Body height [cm]	0.247	0.001	-0.021	0.791
Heart rate [1/min]	-0.195	0.013	-0.151	0.058
Uric acid [μmol/l]	-0.255	<0.001	-0.163	0.035
TEMPS-A Depressive	0.168	0.027	0.041	0.595
TEMPS-A Hyperthymic	-0.215	0.004	-0.158	0.034
BDI	0.054	0.478	-0.097	0.210
HAM-A	0.040	0.605	-0.057	0.467
Alprazolam	0.048	0.525	-0.023	0.768

[a]Partial R: partial correlation coefficient, corrected for age and sex. See Table 1 for the rest of abbreviations

There was also a significant interaction between irritable temperament score and sex in predicting PWV (p = 0.021). There was a positive association between irritable temperament score and PWV in men (B = 0.154, SE = 0.060, p = 0.012) which was absent in women (B = 0.076, SE = 0.064, p = 0.235) (Fig. 1b). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p = 0.037), however the strength of the association remained similar (in men B = 0.104, SE = 0.050, p = 0.039 and in women B = 0.082, SE = 0.052, p = 0.116). The interaction became non-significant (p = 0.168) after further adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B = 0.091, SE = 0.051, p = 0.078 and in women B = 0.054, SE = 0.061, p = 0.375).

Similarly to irritable temperament, there was also a significant interaction between the anxious temperament score and sex in predicting PWV (p = 0.023). There was a positive association between anxious temperament score and PWV in men (B = 0.106, SE = 0.043, p = 0.015) which was absent in women (B = 0.047, SE = 0.036, p = 0.189) (Fig. 1c). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p = 0.046), however the strength of the association remained similar in men (in men B = 0.088, SE = 0.036, p = 0.017 and in women B = 0.021, SE = 0.030, p = 0.484). The interaction became non-significant (p = 0.135) after further adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B = 0.070, SE = 0.039, p = 0.075 and in women B = -0.017, SE = 0.037, p = 0.656).

An interaction with borderline significance (p = 0.052) was found between sex and hyperthymic affective temperament in predicting Aix. An inverse association was found in women (B = -0.754, SE = 0.326, p = 0.022) which was absent in men (B = -0.305, SE = 0.370, p = 0.411) (Fig. 1d). This interaction became weaker (p = 0.064) after further adjustment for age, smoking, heart rate and uric acid (in women B = -0.678, SE = 0.312, p = 0.032 and in men B = -0.327, SE = 0.352, p = 0.325).

Table 3 Predictive value of cyclothymic affective temperament scores on brachial systolic blood pressure and of hyperthymic affective temperament scores on augmentation index in the various models. The progressive involvement of variables into models and other significant predictors in the final models are also demonstrated

Model	B	Std. Error	Std. Beta	*P*	Adj. R^2
Brachial systolic blood pressure					
Model 1					0.023
Cyclothymic temp. score	0.539	0.247	0.171	0.030	
Model 2: Model 1 + Age + Sex					0.041
Cyclothymic temp. score	0.568	0.245	0.180	0.022	
Model 3: Model 2 + DBPbrach					0.245
Cyclothymic temp. score	0.464	0.218	0.147	0.034	
Model 4: Model 3 + Triglyceride + Cholesterol					0.275
Cyclothymic temp. score	0.431	0.214	0.137	0.045	
Model 5: Model 4 + BDI + HAM-A + Alp					0.269
Cyclothymic temp. score	0.529	0.258	0.167	0.042	
Age	0.177	0.076	0.181	0.021	
DBPbrach	0.629	0.094	0.482	<0.001	
Triglyceride	-1.981	0.987	-0.141	0.047	
Augmentation index					
Model 1					0.045
Hyperthymic temp. score	-0.733	0.255	-0.227	0.004	
Model 2: Model 1 + Age + Sex					0.187
Hyperthymic temp. score	-0.509	0.239	-0.158	0.034	
Model 3: Model 2 + Smoking					0.209
Hyperthymic temp. score	-0.562	0.237	-0.174	0.019	
Model 4: Model 3 + Heart rate					0.231
Hyperthymic temp. score	-0.555	0.234	-0.172	0.019	
Model 5: Model 4 + Uric acid					0.243
Hyperthymic temp. score	-0.523	0.232	-0.162	0.026	
Model 6: Model 5 + BDI + HAM-A + Alp					0.244
Hyperthymic temp. score	-0.612	0.243	-0.189	0.013	
Age	0.297	0.087	0.258	0.001	
Sex	7.445	2.189	0.264	0.001	
Smoking	6.159	2.610	0.176	0.020	
Heart rate	-0.209	0.098	-0.152	0.035	

Std. Error standard error, *Std. Beta* Standardized Beta, *Adj.* R^2 adjusted R^2, *Cyclothymic temp. score* cyclothymic affective temperament score, *DBPbrach* brachial diastolic blood pressure, *BDI* Beck Depression Inventory, *HAM-A* Hamilton Anxiety Scale, *Alp* patients regularly using alprazolam, *Hyperthymic temp. score* Hyperthymic affective temperament score

Discussion

To the best of our knowledge, this is the first study to demonstrate that, in chronic hypertensive patients, cyclothymic temperament score is associated with brachial systolic blood pressure while hyperthymic temperament score is independently related to the augmentation index after adjustment for potential confounders including severity of depression and anxiety and the use of alprazolam. Sex differences were also found in relation with brachial systolic blood pressure and cyclothymic temperament score, pulse wave velocity and irritable and anxious temperament scores and augmentation index and hyperthymic temperament score.

Previous findings support our present observations that affective temperaments are associated with cardiovascular pathology. For example, patients with cyclothymic, irritable and anxious temperaments were shown to have a tendency to obesity [31]. Depressive temperament was also found to be associated with worse metabolic control in type-2 diabetes [32], while anxious temperament

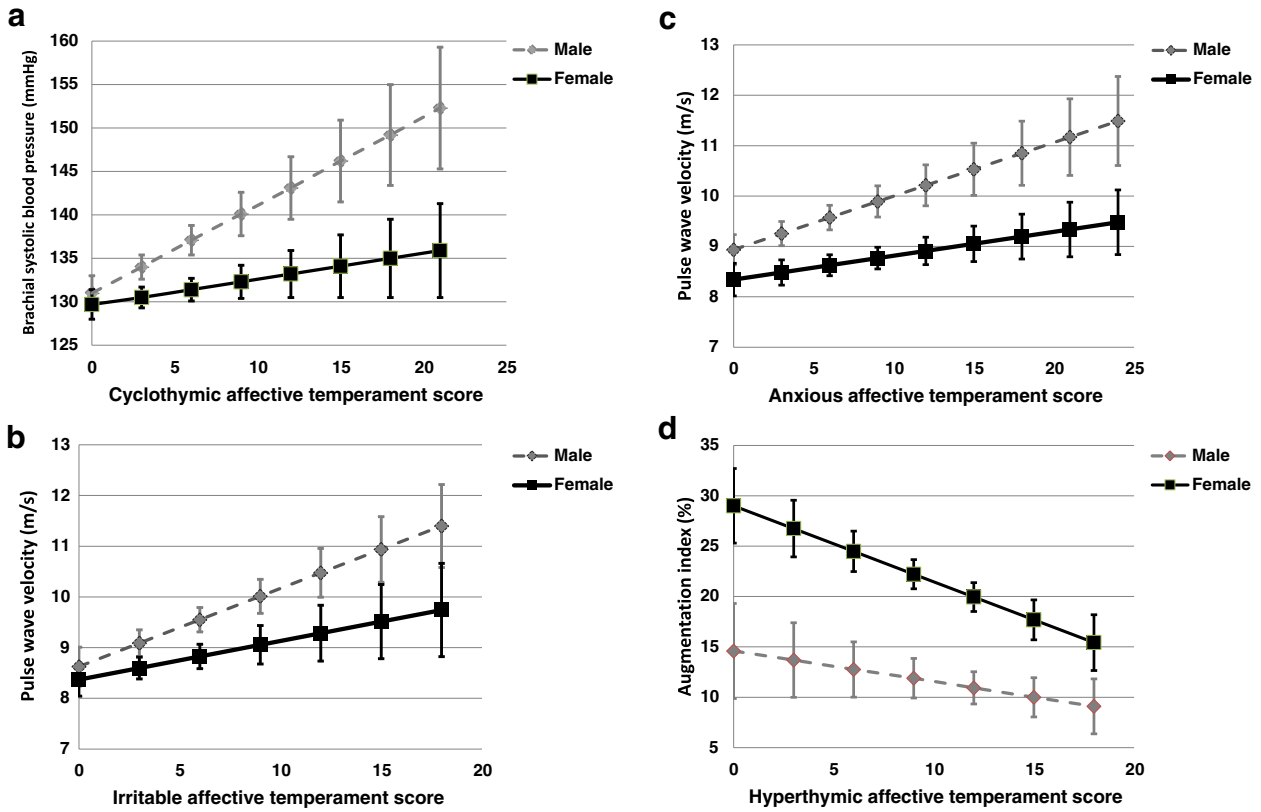

Fig. 1 The interaction between sex and different affective temperaments in the prediction of the studied variables. **a** cyclothymic temperament score and brachial systolic blood pressure; **b** irritable temperament score and pulse wave velocity; **c** anxious temperament score and pulse wave velocity; **d** hyperthymic temperament score and augmentation index. Error bars represent ± 1 standard errors

was associated with an increased likelihood for the presence of prediabetic condition [33]. Our result with regard to cyclothymic temperament is in line with our previous findings in which dominant cyclothymic temperament demonstrated a significant association with the presence of hypertension [23] and with acute coronary events in a hypertensive patient population [24].

An increasing cyclothymic temperament score was found herein to be associated with a higher brachial systolic blood pressure. This temperament shows a central dimension that includes rapid fluctuations in mood and emotional instability. Such alterations can span from lethargy to eutonia, from pessimistic brooding to optimistic, from hypersomnia to decreased need for sleep or from introverted self-absorption to uninhibited people-seeking [18]. In contrast, hyperthymic temperament, which was associated in our study with better wave reflection, can be described as a temperament that displays extroversion, emotional intensity, a high level of life-energy and little need for sleep. Subjects with hyperthymic temperament are cheerful, over-optimistic, overconfident as well as over-talkative and vigorous [18]. While the hyperthymic temperament is associated with better quality of life (QOL), the cyclothymic temperament is conversely associated with worse QOL [18]. Moreover, people with hyperthymic temperament can better cope with somatic problems [34], while cyclothymic disposition is related to a high somatic risk [35]. Based on these results, we hypothesize that there is a likely differential impact of these two temperaments on vascular pathology, although prospective studies are required to confirm this hypothesis.

There are existing data in the literature regarding the association between personality traits and arterial stiffening. In a study by Midei and Matthews, higher trait anxiety and hostility were associated with a higher PWV [36]. In the Baltimore Longitudinal study of Aging, middle-aged adults with suppressed anger had elevated carotid arterial stiffness [37]. In keeping with these studies, irritable and anxious affective temperament scores were found herein to be covariates of PWV after adjustment for age, sex, brachial systolic blood pressure, blood glucose, GFR-EPI and duration of hypertension. However, these associations became non-significant after further adjustment with severity of depression and anxiety and the use of alprazolam. Given that arterial stiffness is

associated with depression and anxiety [38, 39], we can hypothesize that, similarly to the relationship between life stress and arterial stiffness [40], the association between anxious and irritable affective temperaments and PWV is partly mediated by severity of depressive and anxiety symptoms.

Augmentation index is an accepted parameter of pulse wave analysis. Aix is associated with age, sex, body height, smoking and heart rate [41, 42], associations which were also reproduced in the present study. Aix is furthermore reported to be a predictor of mortality in various pathological conditions, such as end-stage renal disease [43] or coronary artery disease [44], and its predictive value was also confirmed by a meta-analysis [45]. In the study of Seldenrijk et al., anxiety-related symptoms were found to be associated with Aix [39]. Our present results indicate that hyperthymic affective temperament score is an independent covariable of Aix with higher scores being associated with better wave reflection and thus a preserved elasticity of the arteries. This suggests a protective role of hyperthymic temperament on cardiovascular pathology and emphasizes the potential of further evaluation of affective temperaments with wave reflection parameters.

Significant interactions were also found in the present study between sex and cyclothymic temperament score in predicting brachial systolic blood pressure, between sex and irritable temperament as well as between sex and anxious temperament scores in predicting PWV, while the interaction between sex and hyperthymic temperament score in predicting Aix had borderline significance. These findings are consistent with the study of Williams et al., where trait anger was associated with elevated arterial stiffness in men, while in women the association was marginally significant [46]. These results suggest that, similarly to the presence of sex differences in scoring in different affective temperament directions [16], sex differences are also present in the associations between affective temperament scores and brachial systolic blood pressure and arterial stiffness parameters. Additional studies are likely needed to specify these observed sex differences, including taking into consideration menopausal status or the use of hormone replacement therapy.

The pathophysiological background of our findings is complex and remains to be clarified. Subjects in states of anger or hostility show elevated levels of inflammation [47, 48] and those with anxiety show reduced autonomic nervous system function [49]. The involvement of neurotrophic molecules should also be considered since we recently demonstrated decreased serum brain-derived neurotrophic factor levels in chronic hypertensive patients with dominant cyclothymic, depressive, anxious or irritable affective temperament [25]. However, this area also requires further studies.

One of the limitations of the present analysis is the relatively low number of chronic hypertensive patients used to study the associations between affective temperaments and blood pressure or arterial stiffness parameters, which limits the generalizability of our results, as well as the number of entered confounders into regression analyses. Another main limitation stems from its cross-sectional design which precludes causal inference. Moreover, although our methodology used standardized questionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by patients is nevertheless impossible.

Conclusions

In conclusion, the elevated blood pressure among subjects with high cyclothymic temperament and the increased level of arterial stiffening in subjects with low hyperthymic scores suggest that affective temperaments might play a role in the development of hypertension and arterial stiffening and thus could represent potential markers of cardiovascular risk. The discovered sex differences in numerous studied associations may be the consequence of the known differences in affective temperaments between men and women. Cumulating data suggest that the identification of affective temperaments in the future can improve both the psychopathological and cardiovascular risk stratification of patients leading to a more accurate, personalized patient management.

Abbreviations

AIx, augmentation index; ARB, angiotensin II receptor blocker; BDI, Beck depression inventory; BMI, body mass index; Cyclothymic temp. score, cyclothymic affective temperament score; DBPbrach, brachial diastolic blood pressure; GFR-EPI, glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; HAM-A, Hamilton anxiety scale; HR, heart rate; Hyperthymic temp. score, hyperthymic affective temperament score; PPAmp, pulse pressure amplification; PPB, brachial pulse pressure; PPbrach, brachial pulse pressure; PPcentr, central pulse pressure; PWV, pulse wave velocity; SBPbrach, brachial systolic blood pressure; SBPcentr, central systolic blood pressure; TEMPS-A, the temperament evaluation of Memphis Pisa, Paris and San Diego questionnaire

Acknowledgements

The authors acknowledge the contribution of Lászlóné Hárshegyi, Ágnes Polyák and Zoltánné Reisz, who helped in medically assisting the patients and in data acquisition. We also acknowledge the contribution of Oleg Pogrebnyak for his technical and linguistic support.

Funding

Xenia Gonda is a recipient of the János Bolyai Research Fellowship of the Hungarian Academy of Sciences.
This study was supported by the Hungarian Society of Hypertension and the Hungarian Scientific Research Fund (OTKA K 100909, György Reusz). There has been no role of these grants in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The dataset supporting the results of this article are available in LabArchives, in the "Temp-BP-stiffness paper" repository, under the file name of "Patient_data_stiffness-temp", at http://dx.doi.org/10.6070/H4Q23X90.
No registration is required to view the dataset.

Authors' contributions

AL collected and analyzed the data, measured arterial stiffness and wrote the first version of the manuscript. BK helped in arterial stiffness measurements and clinical data collection. DE and PT helped in patient recruitment. OC helped in the analysis of the pulse wave curves and in the training of the examiners of arterial stiffness. AT supervised the arterial stiffness aspect of the study providing extensive intellectual input. ÁT helped in study planning and statistical analysis. GR supervised the data analysis and critically revised the manuscript. ZN-B uploaded the autoquestionnaires into Excel. XG helped in the psychiatric portion of the study in choosing the proper questionnaires and helped in their analysis as well as writing the paper. ZR supervised the psychiatric aspect of the study and critically reviewed the manuscript. JN planned and supervised the study, helped in patient recruitment and data analysis and completed the manuscript. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Prior to participation, all patients gave written informed consent. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and was carried out in accordance with the tenets of the Declaration of Helsinki.

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Received: 20 April 2016 Accepted: 29 July 2016
Published online: 08 August 2016

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DOI:10.14753/SE.2020.2300 Annals of General Psychiatry

PRIMARY RESEARCH

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Hyperthymic affective temperament and hypertension are independent determinants of serum brain-derived neurotrophic factor level

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) has neuroprotective, proangiogenic and myogenic effects and, therefore, possibly acts as a psychosomatic mediator. Here, we measured serum BDNF (seBDNF) level in hypertensive patients (HT) and healthy controls (CONT) and its relation to affective temperaments, depression and anxiety scales, and arterial stiffness parameters.

Methods: In this cross-sectional study, affective temperaments, anxiety, and depression were studied with questionnaires (TEMPS-A, HAM-A, and BDI, respectively). SeBDNF level and routine laboratory parameters were measured as well. Arterial stiffness was evaluated with a tonometric method.

Results: Allover, 151 HT, and 32 CONT subjects were involved in the study. SeBDNF level was significantly higher in HT compared to CONT (24880 ± 8279 vs 21202.6 ± 6045.5 pg/mL, $p < 0.05$). In the final model of regression analysis, hyperthymic temperament score (*Beta* = 405.8, $p = 0.004$) and the presence of hypertension (*Beta* = 6121.2, $p = 0.001$) were independent determinants of seBDNF. In interaction analysis, it was found that in HT, a unit increase in hyperthymic score was associated with a 533.3 (95 %CI 241.3–825.3) pg/mL higher seBDNF. This interaction was missing in CONT.

Conclusions: Our results suggest a complex psychosomatic involvement of BDNF in the pathophysiology of hypertension, where hyperthymic affective temperament may have a protective role. BDNF is not likely to have an effect on large arteries.

Keywords: Brain-derived neurotrophic factor, Hypertension, Affective temperaments, Arterial stiffness

Background

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family, playing a central role in the regulation of neuronal growth, maintenance, and survival [1]. Its involvement in psychiatric conditions is well described and was confirmed by a meta-analysis, as in major depressive disorder, the decreased serum BDNF (seBDNF) level was elevated following a course of antidepressant treatment [2]. In addition to its neurotrophic effects, BDNF has proangiogenic features as well. The importance of BDNF was suggested also in high cardiovascular risk conditions, such as obesity, metabolic syndrome, and coronary atherosclerosis [3–5]. It is hypothesized to play a protective role in cardiovascular pathophysiology as its higher serum level was found to be associated with decreased risk of cardiovascular disease

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and mortality [6]. It was demonstrated that circulating BDNF is influenced by age and gender [7], the presence of diabetes [8], and the use of benzodiazepines in different neurological diseases [9], correlates with total cholesterol [4], and BDNF is stored and released from platelets during activation [10]. Hypertension has widely studied psychosomatic connections [11, 12]; however, the role of BDNF in this condition has not been extensively evaluated yet.

Affective temperament types (depressive, cyclothymic, hyperthymic, irritable, and anxious) are subclinical, trait-related manifestations and commonly the antecedents of minor and major mood disorders [13]. Previously, we clarified an association between dominant cyclothymic affective temperament and hypertension [14]. Recently, we demonstrated decreased seBDNF level in chronic hypertensive patients with dominant anxious, irritable, depressive or cyclothymic temperaments compared with hypertensive controls without dominant temperaments [15]. However, the association between affective temperament scores, as continuous variables and seBDNF in chronic hypertension, has not been clarified yet.

Arterial stiffening is increasingly recognized as an independent risk factor for cardiovascular diseases. Carotid–femoral pulse wave velocity (PWV) is the most accepted non-invasive arterial stiffness parameter for cardiovascular risk assessment among hypertensive patients [16]. In different animal models, BDNF was shown to be vasorelaxant not only on pulmonary arteries [17] but also on rat aortic rings [18]. Based on these data, a possible association between the seBDNF level and different arterial stiffness parameters can also be supposed in humans.

We hypothesized that as hypertension is a risk factor for cardiovascular diseases and BDNF is protective in cardiovascular pathology, seBDNF can be altered in hypertension. We also presumed that seBDNF is associated with different affective temperaments, depression, anxiety, and arterial stiffness parameters providing a new bridge of psychosomatic processes.

Methods

In this cross-sectional study, chronic (>12 months medication) well-controlled or grade 1 consecutive hypertensive Caucasian patients (HT) and age-matched healthy controls (CONT) of three primary care practices were involved. All of the chronic hypertensive patients of our previous, pilot study [15] were involved into this study as well. Data of the involved subjects were analyzed for the relationship between the seBDNF level, routine laboratory parameters, affective temperaments, anxiety, depression, and arterial stiffness parameters. Exclusion criteria for HT were the presence of atrial fibrillation, treated depression, bipolar disorder or dementia posing an obstacle to completing questionnaires. Moderate use of the anxiolytic alprazolam (less than 0.5 mg/day) was not a restrictive criterion. In the case of CONT, the denial of consent was the only exclusion criterion.

Evaluation of affective temperaments, depression, and anxiety

The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable, and anxious subscales, requiring 'yes' (score 1) or 'no' (score 0) answers [19]. It contains 110 items (109 in the version for males), and the questions of the various temperament types are grouped together as follows:

1. depressive temperament: questions 1 to 21 (21 points);
2. cyclothymic temperament: questions 22 to 42 (21 points);
3. hyperthymic temperament: questions 23 to 63 (21 points);
4. irritable temperament: questions 64 to 84 (21 points in women and 20 points in men version);
5. anxious temperament: questions 85 to 110 (26 points).

The Beck depression inventory (BDI) is a 21-question multiple-choice self-report questionnaire, one of the widely used instruments for measuring the severity of depression. Participants are asked to make ratings on a four-point scale, where a higher score correlates with more severe depression [20].

Hamilton anxiety scale (HAM-A) was evaluated by the examiner to study the severity of anxiety. The scale consists of 14 items, and each item is scored on a scale of 0 (not present) to 4 (severe anxiety) [21].

Measures of blood pressure and arterial stiffness

Arterial stiffness parameters were evaluated with the validated tonometric PulsePen device (DiaTecne, Milan, Italy). Measurements were performed in a temperature-controlled room in supine position, on the day of blood sampling, prior to it, between 7:00 and 8:00 a.m. Patients were asked to refrain from eating, smoking, and caffeine-containing drinks in the morning of the procedure, but to take the regular blood pressure medication. Upon arrival after 5 min rest, two brachial blood pressure measurements were taken on each arm in the sitting position with a validated oscillometric blood pressure device (Omron M3). The mean value of the higher side was further taken into calculation as brachial systolic (brachial SBP) and diastolic (brachial DBP) blood pressures and heart rate.

Next, subjects were equipped with arterial stiffness measurement devices and then rested in the supine position for approximately 15 min before being measured. The mean of two successful measurements was used in the statistical calculations. In the PWV calculations, 80 % of the carotid–femoral distance was used following the recent guideline [22]. Augmentation index (AI), central systolic blood pressure (cSBP), central pulse pressure (cPP), and pulse pressure amplification (PPAmp) were also calculated. As PulsePen calculates pressure values using brachial diastolic blood pressure calibration, the calculated central and brachial diastolic blood pressure values were identical [23].

Measurement of seBDNF concentration

Peripheral blood samples of patients were collected in anticoagulant-free tubes, right after the measurement of arterial stiffness. After centrifugation (3600 rpm for 6 min), the serum was stored at −20 °C. SeBDNF was measured using commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis MN, USA) according to the manufacturer's protocol, and serum BDNF level was determined in pg/mL.

Statistical analysis

Normality of the parameters was tested with the Kolmogorov–Smirnov test. Descriptive characteristics, laboratory, arterial stiffness parameters and TEMPS-A, BDI, HAM-A scores were compared between CONT and HT groups using unpaired Student's *t* tests or Mann–Whitney rank sum test for data failing tests of normality. The equality of variances was studied with Levene's test. Pearson correlation coefficients were calculated to study the relationship between seBDNF and all other factors measured. Hierarchic linear regression analysis was used to study the determinants of seBDNF in the whole population with a stepwise entry of variables with either previously described association with seBDNF or with a significant univariate correlation with seBDNF in the present data set. As a bidirectional association can be hypothesized between affective temperaments and hypertension [14], predetermined interaction analysis was performed to investigate moderation between hypertension and affective temperament scores on seBDNF level.

Data were expressed as mean ± standard deviation or mean with interquartile ranges. $p < 0.05$ was considered to be significant. SPSS 13.0 for Windows was used in calculations.

Results

Altogether, 151 HT and 32 CONT subjects were involved. Eleven of the invited HT and four CONT did not give their informed consent and were excluded. Baseline demographic and laboratory parameters, current medication, TEMPS-A, BDI, and HAM-A scores, central blood pressure, and arterial stiffness parameters as well as seBDNF levels are shown in Table 1. The median number of the used antihypertensive compounds was 2 (IQR: 2–3). Differences between CONT and HT were found in body weight and BMI, serum glucose, cholesterol, LDL and HDL, BDI and HAM-A scores, in the brachial and central systolic blood pressure and the brachial pulse pressure. SeBDNF was elevated in HT (Table 1). In the analysis of simple correlations, the following parameters were found to be associated significantly with seBDNF: hypertension ($r = 0.174$, $p = 0.018$), serum cholesterol ($r = 0.194$, $p = 0.009$), LDL ($r = 0.208$, $p = 0.015$) and HDL level ($r = 0.204$, $p = 0.006$), platelet count ($r = 0.188$, $p = 0.011$), pulse pressure amplification ($r = 0.157$, $p = 0.037$), and hyperthymic temperament score ($r = 0.189$, $p = 0.010$). Tendencies of inverse correlations were found with the presence of diabetes or the use of alprazolam, but these were not significant ($r = -0.114$, $p = 0.12$ and $r = -0.103$, $p = 0.16$, respectively).

Table 2 demonstrates the results of hierarchical linear regression models. In the final model adjusted for all potential confounders, one unit increase in the hyperthymic score was associated with a 405.8 pg/mL higher seBDNF and the presence of hypertension with a 6121.2 pg/mL higher seBDNF. We found an interaction ($p = 0.002$) between hypertension and hyperthymic temperament score on seBDNF in the whole study population: there was no significant association between hyperthymic score and seBDNF in CONT ($p = 0.545$) and a unit increase in hyperthymic score was associated with a 533.3 (95 %CI 241.3–825.3) pg/mL higher seBDNF level in HT ($p < 0.001$). The different impact of hyperthymic score in seBDNF in HT and CONT is shown in Fig. 1.

Discussion

Here, we demonstrated for the first time in the literature that in chronic hypertensive patients, seBDNF is elevated, and hyperthymic affective temperament score and the presence of hypertension are independent determinants of seBDNF level. In hypertensive patients, the elevation of hyperthymic temperament score is associated with the elevation of seBDNF; however, this association is not present in healthy subjects.

We suppose that the observed BDNF elevation in HT can be part of a protective compensatory mechanism targeting peripheral neurons and vascular cells. BDNF has beneficial effects on the regulation of blood pressure, as it is involved not only in the development, but also in the survival of arterial baroreceptor system [24]. Vascular

Table 1 Demographic, laboratory, hemodynamic, and arterial stiffness parameters; subjects' questionnaire scores

	CONT	HT
N (male:female)	32 (12:20)	151 (58:93)
Age [year]	61.1 (55.9–70.5)	63.7 (57–71)
Duration of hypertension [year]	–	11 (5–18)
Diabetes [n (%)]	–	38 (25.2)
Cardiovascular disease [n (%)]	–	21 (13.9)
Current smoker [n (%)]	3 (9.4)	22 (14.6)
Body height [cm]	168.8 ± 8.6	166.8 ± 8.6
Body weight [kg]	72.4 ± 12.1	*79.7 ± 14**
BMI [kg/m^2]	24.5 ± 5.4	*28.6 ± 4.5**
Platelet count [G/l]	239.6 (215–277)	257 (209.7–303.2)
Glucose [mmol/l]	5.36 (4.88–5.81)	*6.15 (5.11–6.7)**
GFR-EPI [ml/min/1.73 m^2]	79.7 (69.5–82.2)	77.9 (67–90)
Uric acid [μmol/l]	313.7 ± 11.6	318.4 ± 6.3
Cholesterol [mmol/l]	5.57 (4.97-6.05)	*5.18 (4.37- 5.98)**
LDL [mmol/l]	3.46 ± 0.91	3.07 ± 1.04
HDL [mmol/l]	1.68 (1.31–1.98)	*1.40 (1.15–1.61)**
Triglyceride [mmol/l]	1.16 (0.75–1.43)	*1.67 (1.08–2.06)**
Regular medication [n (%)]		
ACE inhibitors	–	93 (61.5)
ARBs	–	34 (22.5)
CCBs	–	67 (44.4)
Beta blockers	–	87 (57.6)
Diuretics	–	68 (45)
Antiplatelet drugs	–	44 (29.1)
Statins	5 (15.7)	54 (35.7)
Alprazolam	–	23 (15.2)
TEMPS-A		
Depressive	5.9 (4–7)	7.1 (5–9)
Cyclothymic	2.9 (0–4)	3.9 (1–6)
Hyperthymic	11.2 ± 4	11 (4.2)
Irritable	3.2 (2–4)	4.3 (2–6)
Anxious	4.1 (1–6)	6.3 (2–9)
BDI	2.8 (1–4)	*6.3 (3–9)**
HAM-A	3.9 (1–6)	*7.4 (2–10)**
Heart rate [1/min]	72.1 (66.6–78.2)	72.7 (64.1–77.2)
Brachial SBP [Hgmm]	125.5 ± 9.3	*133.0 ± 12.3**
Brachial DBP [Hgmm]	72 ± 6.4	75 ± 9
Brachial PP [Hgmm]	51.5 (46.4–56.7)	*56.7 (46.4–63)**
Central SBP [Hgmm]	117 (111.2–122.3)	*124.1 (113.4–131.6)**
Central DBP [Hgmm]	67.1 ± 7	69.8 ± 8.2
Central PP [Hgmm]	49.9 (43.2–54.5)	54.3 (45.2–61)
PP amplification	1.08 (1.03–1.14)	1.07 (0.98–1.12)
PWV [m/sec]	8.6 (7.4–9.2)	9.3 (7.8–10)
AIx (%)	13.2 (5.75–23)	17.8 (8.5–25.1)
Serum BDNF (pg/ml)	21202.6 ± 6045.5	*24880 ± 8279**

Continuous data are presented as mean (SD) or mean (interquartile range)

Categorical parameters are presented as % (n)

BMI body mass index, *ARBs* angiotensin II receptor blockers, *CCBs* calcium channel blockers, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *PWV* pulse wave velocity, *AIx* augmentation index, *TEMPS-A* Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire, *BDI* Beck depression inventory, *HAM-A* Hamilton anxiety scale

* $p < 0.05$

endothelial cells are proved to produce BDNF [25]. In patients with angina pectoris, Jiang et al. demonstrated that low plasma BDNF level was associated with a higher probability of major cardiovascular events than a middle level or a high level during the 4-year follow-up period [26]. Moreover, in a recently published population-based study, higher seBDNF was found to be associated with decreased risk of cardiovascular morbidity and mortality [6]. On the contrary, decreased serum BDNF was found to be associated with increased risk of incident stroke/TIA [27]. In our study, the positive correlation with HDL and also with pulse pressure amplification, where higher values refer to better vascular conditions [28], also supports the plausible beneficial effect of BDNF in hypertension.

Some of the findings of our study were already described in the literature, such as the seBDNF correlation with cholesterol and LDL [4], as well as with platelets [10]. As stored BDNF is released from platelets during clotting [10] and in essential hypertension, increased platelet activation is a trigger of hypercoagulable state [29], our finding that platelet count is positively correlated with seBDNF may refer to a chief source of seBDNF in this pathological condition.

Another main finding of our study is that hyperthymic affective temperament is an independent determinant of seBDNF. This temperament is characterized by exuberant, upbeat, overenergetic, and overconfident lifelong traits [30]. We suppose that patients with higher hyperthymic temperament scores might have reduced inclination to cardiovascular complications, due to the beneficial effect of elevated seBDNF, a hypothesis that needs to be confirmed in follow-up studies. As the observed association between hyperthymic temperament score and seBDNF was only present in our hypertensive patients, we suppose an active role of affective temperaments not only in psychiatric but also in cardiovascular pathophysiology.

Interestingly, in our study, no association of seBDNF with anxiety or depression was found. We suppose that this phenomenon can be explained by the mild anxiety and depression severity of HT patients.

Table 2 The predictive values of hypertension and hyperthymic affective temperament score on serum BDNF level in different models evaluated with linear regression analysis in the whole study population ($n = 183$)

Models	Beta	Std. Error	Std. Beta	*p*	R^2
Model 1					0.036
Hypertension	4149.6	1681.8	0.190	0.015	
Model 2					0.050
Hyp. temp. score	410.7	140	0.225	0.004	
Model 3					
Hypertension + hyp. temp. score					0.089
Hypertension	4310.3	1640.6	0.198	0.009	
Hyp. temp. score	422.2	137.6	0.231	0.003	
Model 4: Model 3 + age + sex					0.107
Hypertension	4365.1	1636.7	0.200	0.008	
Hyp. temp. score	449.8	138.1	0.246	>0.001	
Model 5: Model 4 + diabetes					0.132
Hypertension	5161.4	1661.2	0.237	0.002	
Hyp. temp. score	459.4	136.6	0.251	>0.001	
Model 6: Model 5 + cholesterol + HDL					0.158
Hypertension	5954.7	1685.5	0.273	>0.001	
Hyp. temp. score	430.6	136.8	0.235	0.002	
Model 7: Model 6 + platelet number					0.176
Hypertension	5540	1688.4	0.254	>0.001	
Hyp. temp. score	431.9	135.8	0.236	0.002	
Model 8: Model 7 + BDI + HAM-A + Alp.					0.191
Hypertension	6167	1748.4	0.283	>0.001	
Hyp. temp. score	408	140.9	0.223	0.004	
Model 9: Model 8 + PPamp.					0.202
Hypertension	6121.2	1742.3	0.281	>0.001	
Hyp. temp. score	405.8	140.4	0.222	0.004	

Hyp. temp. score hyperthymic affective temperament score, *BDI* Beck depression inventory, *HAM-A* Hamilton anxiety scale, *Alp* patients regularly using alprazolam, *PPamp* pulse pressure amplification

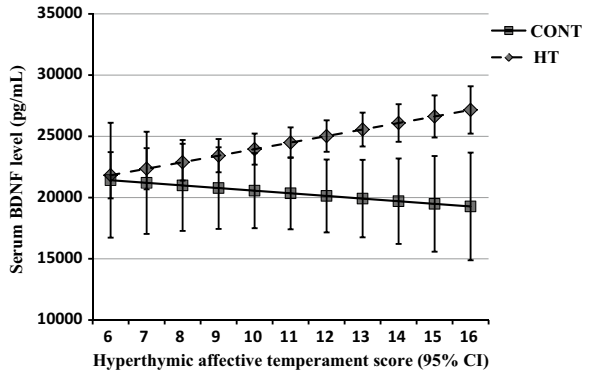

Fig. 1 Association between serum BDNF level and hyperthymic affective temperament score in hypertensive patients (HT) and in controls (CONT). *Continuous line* with *squares* represents CONT, while *broken line* with rhombs represents HT

In contrast to the literature, the presence of diabetes or the use of the benzodiazepine alprazolam was not significantly correlated with seBDNF; however, the direction of correlations was as expected. We think that in both cases, the lack of significance was caused by the low proportion of diabetic or alprazolam user patients in our cohort.

The associations between seBDNF level and arterial stiffness parameters have never been evaluated in any patient population yet. Since BDNF has a relaxant effect on pulmonary arterial and aortic rings in different animal models [17, 18], we supposed a possible link between BDNF and arterial stiffness parameters. In contrast to this, in our study seBDNF showed an association only with pulse pressure amplification, but even this failed to be an independent predictor in regression analysis. We

suppose from these findings that seBDNF may exert its protective role rather on the level of the endothelium and perivascular nerves than on the level of large arteries.

The main limitation of our study comes from its cross-sectional design which precludes causal inference. In addition, the number of the subjects involved into the study limited the number of potential confounding variables that were involved in the final regression model. Consequently, the presence of sleeping disorder, the amount of alcohol intake or the habit of regular exercise, variables with documented influence on BDNF level, were not involved into the final analysis (these were not significantly correlated with seBDNF in univariate models, data are not shown). Moreover, other potential confounders, like childhood trauma, stress or sunlight exposition were not evaluated. In addition to these limitations, although we used standardized questionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by the patients is impossible.

Conclusions

In conclusions, our results suggest a complex psychosomatic involvement of BDNF in the pathophysiology of hypertension, where hyperthymic affective temperament may have a protective role. The impact of this phenomenon for cardiovascular outcome has to be clarified in prospective studies, but its mechanism is probably not mediated by large arteries.

Abbreviations

AC: abdominal circumference; AI: augmentation index; ARBs: angiotensin II receptor blockers; BDI: Beck depression inventory; BDNF: brain-derived neurotrophic factor; BMI: body mass index; Brachial DBP: brachial diastolic blood pressure; Brachial PP: brachial pulse pressure; Brachial SBP: brachial systolic blood pressure; Central DBP: central diastolic blood pressure; Central MBP: central mean blood pressure; Central PP: central pulse pressure; Central SBP: central systolic blood pressure; CKD-EPI GFR: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; HAM-A: Hamilton anxiety scale; HR: heart rate; Hyp. temp. score: hyperthymic affective temperament score; PP amplification: pulse pressure amplification; PWV: carotid–femoral pulse wave velocity; seBDNF: serum brain-derived neurotrophic factor; TEMPS-A: the Temperament Evaluation of Memphis Pisa, Paris and San Diego questionnaire.

Authors' contributions

JN planned and supervised the study, helped in patient recruitment and completed the manuscript. AL collected and analyzed the data, measured arterial stiffness, and wrote the first version of the manuscript. LL assisted to BDNF measurements and other laboratory data collection. DE and PE helped in patient recruitment. BK helped in arterial stiffness measurements and clinical data collection. OCs helped in the analysis of the pulse wave curves and in the training of the examiners of arterial stiffness. AT supervised the arterial stiffness part of the study giving huge intellectual input. ÁT helped in study planning and statistical analysis. XG helped in the psychiatric part of the study with choosing the proper questionnaires and she helped in their analysis. ZR supervised the psychiatric part of the study and reviewed critically the manuscript. JH helped in BDNF measurements and other laboratory data collection. ZsN-B uploaded the questionnaires into Excel. AF supervised the BDNF measurement and other laboratory tests giving huge intellectual input. All authors read and approved the final manuscript.

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Acknowledgements

The authors acknowledge the contribution of Lászlóné Hárshegyi, Ágnes Polyák, and Zoltánné Reisz, who helped by medically assisting the patients and by data acquisition. We also acknowledge the contribution of Oleg Pogrebnyak for his technical and linguistic support. Xenia Gonda is a recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences. This study was supported by the Hungarian Society of Hypertension and by the "Lendület" Research Grant: LP008/2014.

Competing interest and funding

Xenia Gonda is a recipient of the János Bolyai Research Fellowship of the Hungarian Academy of Sciences. This study was supported by the Hungarian Society of Hypertension and by the "Lendület" Research Grant: LP008/2014. There has been no role of these grants in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of supporting data

The data set supporting the results of this article is available at LabArchives, in the "BDNF-Aff temp paper" repository, doi "10.6070/H4W093ZQ".

Ethics approval and consent to participate

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and carried out in accordance with the tenets of the Declaration of Helsinki. All patients gave written informed consent to their participation.

Received: 21 April 2016 Accepted: 30 June 2016
Published online: 29 July 2016

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