

## Anxiety and Depression Prevalence in Essential Hypertensive Patients is there an Association with Arterial Stiffness?

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### Abstract

**Background:** The aim of the present study was to assess the prevalence of anxiety and depression among essential hypertensive patients in different stages of hypertension compared to normotensives. Subjects were free of any psychiatric illness. Further evaluation of arterial stiffness was carried out and attempt to correlate with anxiety and depression was made.

**Materials and Methods:** The study comprised of 127 participants who were divided in three groups based on the stage of hypertension; Group 1 (n=33 patients with stage 1 HTN), group 2 (n=30 patients with stage 2 HTN) and group 3 (n=30 patients with stage 3 HTN). The assessment of depression was made by means of the Becks Depression Inventory, BDI scale. Patients were further evaluated for anxiety and depression symptoms using the Hospital Anxiety and Depression, HADS scale. The cardio-ankle vascular index (CAVI) was used to assess arterial stiffness in all participants, whereas stage 1, 2 and 3 hypertensives were all subjected to 24 h ambulatory blood pressure monitoring.

**Results:** There was a significant ( $p<0.001$ ) increase in prevalence of depression as assessed by the BDI scale as the stages of hypertension evolved. Similarly, an increase ( $p<0.001$ ) in both anxiety and depression, assessed by means of HADS scale, among the 3 stages of hypertension was noted. Finally, assessment of the arterial stiffness indices CAVIR and CAVIL was performed and demonstrated that there was a significant increase ( $p<0.001$ ) in their values as HADS-A, HADS-D and BDI score increased.

**Conclusion:** This prospective study demonstrated a clear burden of both anxiety and depression in higher levels of hypertension compared to normotensives. Furthermore, anxiety and depression are both linked to higher arterial stiffness levels among essential hypertensive patients irrespectively of the blood pressure levels.

**Keywords:** Essential hypertension; Anxiety; Depression; Arterial stiffness

### Introduction

Physical health and psychological status have a rather intricate relationship. Since cardiovascular system is regulated by the autonomic nervous system, conditions like anxiety and depression can have a profound influence including the levels of blood pressure. So far numerous studies have investigated the links between anxiety, depression and arterial hypertension with controversial results.

Hypertension has a multifactorial etiology with genetic, psychosocial and environmental factors being of great importance [1,2]. The complexity of the mechanisms involved however makes this link difficult to interpret. Anxiety is one of the commonest psychiatric disorders with high prevalence among adults in many countries, affecting patient's quality of life [3,4]. On the other hand depression has a prevalence of 4.8% to 8.6% in primary care settings, and it is estimated that it will be the second leading cause of disability worldwide in the next 20 years [5].

Several studies [6-8] suggest that individuals experiencing anxiety and depression are at high risk for developing hypertension, as well as being predisposed to stroke and ischemic heart disease. However some researchers do not support the role of anxiety and depression in the development of hypertension [9,10] reporting even a reduction in blood pressure levels on these patients [11,12].

The present prospective study aimed at assessing the prevalence of anxiety and depression in essential hypertensive patients compared with normotensive controls and sub analyze the difference in the prevalence among different stages of hypertension. Further

evaluation of arterial stiffness was carried out and attempt to correlate with anxiety and depression was made.

### Materials and Methods

The study comprised of 127 participants, who signed an informed consent form prior to participation. The study started on 2013 and finished on 2016. Of the 127 participants 34 were normotensives. The rest of the patients were divided in three groups based on the stage of hypertension. Group 1 (n=33 patients with stage 1 HTN), group 2 (n=30 patients with stage 2 HTN) and group 3 (n=30 patients with stage 3 HTN).

Full clinical and laboratory evaluation was carried out to exclude patients with acute or chronic inflammatory diseases, endocrine disorders, chronic obstructive pulmonary disease, malignancy, renal failure (creatinine >1.3 mg/dL), heart failure, recent (<6 months) cerebrovascular event, coronary artery disease (history of stable or

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unstable angina), ventricular arrhythmia, sinus bradycardia (<55 beats/min), sinus tachycardia (>100 beats/min) or atrioventricular conduction disturbance and severe hypercholesterolemia (TC levels >220 mg/dl). Patients with known anxiety or depression and any other psychiatric illness with or without active treatment, as well as patients receiving beta-blockers or central acting agents were also excluded from the study.

The diagnosis of arterial hypertension was based upon elevations of either systolic (>140 mmHg) or diastolic (>90 mmHg) blood pressure on three visits, one week apart, and mean values were calculated. A two week washout period preceded the measurements for every patient already receiving antihypertensive treatment. In each visit, blood pressure was measured three times at one-minute intervals and with the patient resting comfortably, back supported in the sitting position after a 10-15 minute relaxation period. A mercury sphygmomanometer was used for all measurements, with a medium or a large size cuff according to the patient's arm circumference.

A 24 h ambulatory blood pressure monitoring (24 h ABPM, Spacelabs®) was carried out in all participants and based on the results the patients were stratified in the 4 different groups; normotensives where clinic BP is <140/90 mmHg and subsequently 24 h ABPM is <135/85 mmHg, stage 1 HTN where clinic blood pressure is 140/90 mmHg or higher and subsequently 24 h ABPM daytime average is 135/85 mmHg or higher, stage 2 HTN where clinic blood pressure is 160/100 mmHg or higher and subsequently 24 h ABPM daytime average is 150/95 mmHg or higher and stage 3 HTN where clinic systolic blood pressure is 180 mmHg or higher or clinic diastolic blood pressure is 110 mmHg or higher [13].

The assessment of depression was made by means of the Becks Depression Inventory, BDI scale. The BDI was developed as an interviewer-administered measure of the intensity of depression in psychiatric patients, but has come to be used widely also for detecting depression in general populations and been revised and modified several times and is commonly used in self-completed questionnaire format. The scale comprises 21 items reflecting particular aspects of depression (symptoms and attitudes). For each, the respondent selects one of four statements, rated in severity from 0 to 3, and the total is calculated; score ranges indicate whether depression is absent/minimal, mild, moderate, or severe. Cut-off score guidelines for the BDI-II are given with the recommendation that thresholds be adjusted based on the characteristics of the sample, and the purpose for use of the BDI. Items scored 0 (best) to 3 (worst); 0-14=minor symptoms, 14-19=mild symptoms of anxiety, 20-28= moderate symptoms of anxiety and >29=severe anxiety/cause of concern [14].

Patients were further evaluated for anxiety and depression symptoms using the Hospital Anxiety and Depression, HADS scale. The HADS was developed as a screening instrument for use in hospital outpatient departments; it has subsequently been validated for use with primary care patients and the general population and has shown good psychometric properties [15]. Its aim is to detect the presence and severity of depression and anxiety in non-psychiatric settings. The scale comprises of 14 items divided equally between the two mood states, 7 items for depression HADS-D and 7 items for anxiety HADS-A, with 4-point verbal rating scales for each item. HADS-D mainly covers the core depressive symptoms anhedonia and loss of interest and HADS-A covers the core anxiety features worry and tension. Both sub-scales exclude somatic components of depression and anxiety. A cut-off was set at 8 points for both subscales: symptoms of depression were defined as HADS-D ≥ 8 and HADS-A <8, anxiety HADS-A ≥ 8 and HADS-D <8 and mixed anxiety and depression by both HADS-D and HADS-A ≥ 8.

## Arterial stiffness measurement

The cardio-ankle vascular index (CAVI) has recently been developed to evaluate arterial stiffness similarly to pulse wave velocity (PWV), but theoretically, this index is less influenced by blood pressure. Arterial stiffness indexed by CAVI was examined using the system VaSera 1500N (Fukuda Denshi, Japan) between 8.00 and 10.00 a.m. under standard conditions after 15 minutes of rest in supine position. To take the measurement, cuffs were applied to the four extremities of the subject, and electrocardiographic electrodes were attached to the upper arm. A microphone was placed on the sternal angle for phonocardiography. The subject then rested in the supine position for 5 min. The PWV was calculated by dividing the distance from the subjects' aortic valve to their ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same wave was detected at the ankle, and the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse wave [16,17]. To minimize the effect of cuff inflation on blood flow dynamics, pulse waves were measured with cuffs that were inflated to less than diastolic BP (50 mm Hg), and extremity BP was measured by oscillometry. The systolic and diastolic BP and the pulse pressure were obtained by measurements taken at the right brachial artery.

To obtain the CAVI, the stiffness parameter  $\beta$  was substituted into the equation for determining vascular elasticity and PWV, as described below. The stiffness parameter  $\beta$  indicates patient-specific, BP-independent vascular stiffness as measured by arterial ultrasound [18] and is calculated as follows:

$$\text{Stiffness parameter } \beta = [\ln(Ps/Pd)] \times (D + \Delta D) / \Delta D \quad (1)$$

Where Ps and Pd are the systolic and diastolic BP in mm Hg, respectively. D is the diameter of the blood vessel and  $\Delta D$  is the change in D. PWV can then be estimated by the Bramwell-Hill equation as follows:

$$(D + \Delta D) / \Delta D = 2\rho \times 1 / (Ps - Pd) \times PWV^2 \quad (2)$$

Where  $\rho$  is the density of blood.

If we substitute equation 2 into equation 1, we obtain the following:

$$\text{Stiffness parameter } \beta = 2\rho \times 1 / (Ps - Pd) \times \ln(Ps/Pd) \times PWV^2 = \text{CAVI.}$$

## Statistical analysis

Statistical analysis was performed using the SPSS package for windows version 13.0 (SPSS, Chicago, IL, USA). Values were expressed as mean  $\pm$  S.D. or as percentages. Means were compared using the independent samples Student's *t*-test or after analysis of variance when appropriate. Analysis of categorical data was carried out with the  $\chi^2$ -test. Values without normal distribution were analyzed with the Kruskal-Wallis test. A post hoc test (Bonferroni) was also used to correct for multiple comparisons when normotensives and stage 1 hypertensive were combined in one group. Pearson's correlation coefficients were calculated to examine the univariate relation of HADS-A, HADS-D and BDI scores to continuous variables. Exact *p* values <0.05 were considered as statistically significant.

## Results

Patient baseline characteristics are summarized in Table 1. BDI score and HADS-A, HADS-D as well as a combined HADS score are presented in Table 2.

Univariate analysis was performed and showed significant increase occurrence of anxiety and depression with increasing

Variables	Normotensives (n=34)	Stage 1 (n=33)	Stage 2 (n=30)	Resistant Hypertension (n=30)
Age	58 ± 11	43 ± 15	50 ± 8	65 ± 13
BMI (kg/m <sup>2</sup> )	32 ± 6	24 ± 4	26 ± 3	26 ± 4
SBP (mmHg)	117 ± 13	146 ± 3	159 ± 3	161 ± 22
DBP (mmHg)	73.3 ± 8.2	90 ± 8	91.8 ± 16	88 ± 10
24h SBP (mmHg)	*	142.9 ± 2.9	143.9 ± 16.7	154 ± 3.8
24hDBP (mmHg)	*	81.8 ± 10	88.5 ± 9.5	91.3 ± 7.6
Gender (M/F)	27/7	12/21	18/12	18/12
Smoking (%)	9	3	13	50

BMI: Body Mass Index, SBP: Systolic Blood pressure, DBP: Diastolic Blood Pressure, \* 24h Blood pressure monitor not performed.

Table 1: Patients baseline characteristics.

BDI Score	Minor <14		Mild 14-19		Moderate 20-28		Severe 29-63	
	N	%	N	%	N	%	N	%
Normotensive	27	79	4	12	3	9	0	0
Stage 1 HTN	23	70	2	6	4	12	4	12
Stage 2 HTN	0	0	2	7	16	53	12	40
Resistant HTN	0	0	0	0	6	20	24	80
HADS-A	HADS-D				HADS			
Normotensive	6.4 ± 5		2.6 ± 4.3				10.2 ± 7.2	
Stage 1 HTN	3.5 ± 5		3.3 ± 5.4				9.7 ± 7.0	
Stage 2 HTN	9.0 ± 3		8.2 ± 4.1				16 ± 4.7	
Resistant HTN	12.0 ± 3.7		14 ± 5.5				27 ± 5.1	

Table 2: BDI score, HADS-A, HADS-D and combined HADS score among the four groups of participants.

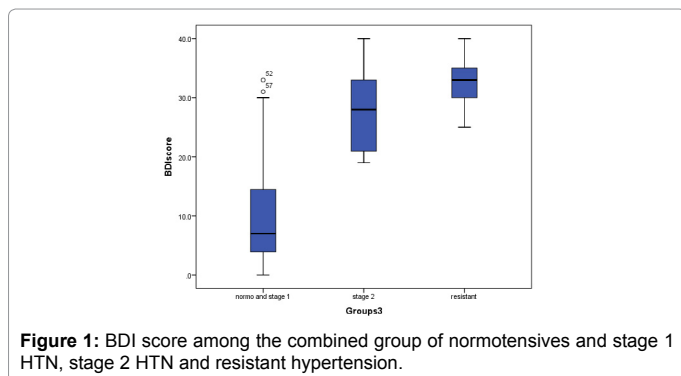


Figure 1: BDI score among the combined group of normotensives and stage 1 HTN, stage 2 HTN and resistant hypertension.

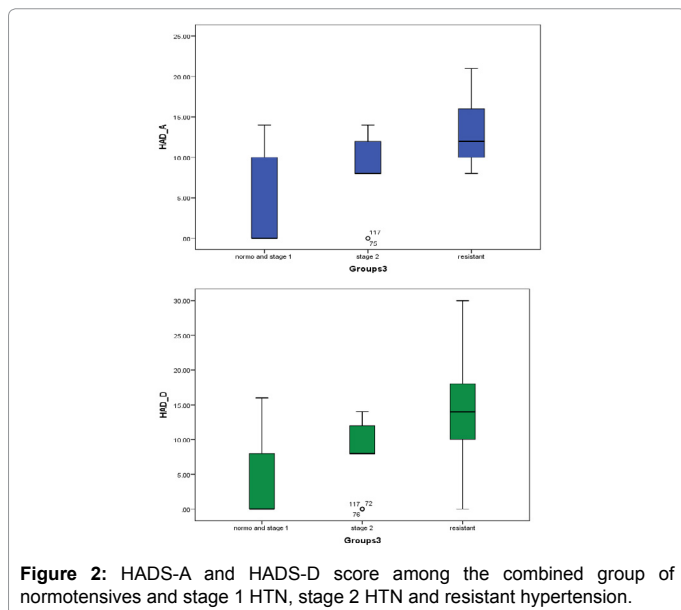


Figure 2: HADS-A and HADS-D score among the combined group of normotensives and stage 1 HTN, stage 2 HTN and resistant hypertension.

hypertension group. Comparing HADS-A, HADS-D and BDI among normotensives, stage 1, stage 2 and resistant hypertension patients there was a significant increase in score [6.4 ± 5 vs. 3.5 ± 5.2 vs. 9.0 ± 3.0 vs. 12.9 ± 3.7, p<0.001 respectively], [2.6 ± 4.3 vs. 3.3 ± 5.4 vs. 8.2 ± 4.1 vs. 14.4 ± 5.5, p<0.0001 respectively] and [8.6 ± 7.0 vs. 11.6 ± 10.4 vs. 27.1 ± 5.8 vs. 32.4 ± 3.9, p<0.0001 respectively]. Due to small numbers in each group the normotensive and stage 1 patients were combined into one group which had significant lower BDI (p=0.021, ANOVA with Bonferroni correction), HADS-A and HADS-D score (p<0.0001, ANOVA with Bonferroni correction) compared to stage 2 and resistant hypertensive patients (Figures 1 and 2).

There was no significant difference in HADS-A, HADS-D or BDI according to gender, (Chi square, p>0.05) or alcohol consumption (p>0.05) for each comparison. There was a significant correlation between HADS-A, HADS-D and BDI with age [Pearson r=0.341, r=0.29, p<0.001, respectively].

Further assessment of the arterial stiffness indices CAVIR and CAVIL was performed and demonstrated that there was a significant increase (p<0.001) in their values as HADS-A, HADS-D and BDI score increased. For the purposes of the comparison HADS score was divided in 4 groups (no depression or anxiety, depression alone, anxiety alone, both depression and anxiety) and BDI score on four groups (score <14, 14-19, 20-28 and 29-63) (Table 3).

## Discussion

The present prospective study aimed at investigating the occurrence of anxiety and depression among patients in different stages of arterial hypertension. Additionally, the association between arterial stiffness indices with the severity of anxiety and depression was also exploited. Up to date the results from previous studies have been controversial mainly because of small cohort size and different diagnostic tools used not easily allowing the generalization of the results.

In the present study there was a significant increase in the occurrence

Variables	CAVIR	CAVIL
No depression or anxiety	17.1 ± 1.7	18.7 ± 2.0
Depression	23.3 ± 3.2	23.3 ± 3.6
Anxiety	24.4 ± 3.0	29.9 ± 3.1
Depression and anxiety	31.4 ± 0.9	31.9 ± 1.0
P	<0.001	<0.001
BDI <14	19.5 ± 1.7	23.2 ± 1.9
BDI 14-19	25.5 ± 4.5	22.1 ± 5.7
BDI 20-28	29.6 ± 1.3	29.7 ± 1.5
BDI 29-63	33.0 ± 1.0	33.4 ± 1.0
P	<0.001	<0.002

CAVIR: Cardio-Ankle Vascular Index Right, CAVIL: Cardio-Ankle Vascular Index Left, BDI: Becks Depression Inventory.

**Table 3:** CAVIR and CAVIL values according to HADS-A, HADS-D and BDI score.

of anxiety in higher stages of hypertension compared to normotensives and stage one hypertensive patients. The possible mechanisms involved include an increase in systemic vascular resistance, sympathetic activity, plasma renin activity, the homeostasis model, and blood lipids [19,20]. An ambulatory blood pressure monitoring study reported that anxiety disorder was associated with nocturnal and early morning hypertension in hypertensive outpatients [21]. The activation of the sympathetic system reduces renal blood flow, increases renal water and sodium retention, and elevates blood pressure, can also cause abnormal hemodynamic changes and abnormal lipid metabolism affecting the endothelial function [22,23].

On the other hand, there are studies confirming that patients with hypertension awareness are at higher risk of developing anxiety disorders [24], while anxiety can act as a barrier in patient compliance with antihypertensive treatment [25]. Further, the indirect association between anxiety and risk of hypertension could be secondary to sedentary lifestyle often seen in these patients including smoking, alcohol use, reduce exercise tolerance and erratic eating habits. Interestingly in our study there was no significant association between smoking, alcohol intake HADS and BDI scales. Thus, anxiety and hypertension may interact to affect human health.

In our study there was a significant increase in depression occurrence assessed by both BDI and HADS-D scales in patients with stage 2 and resistant hypertension compared to normotensives and stage 1 hypertensive patients. This finding is in line with previous studies suggesting a clear link between hypertension and depression [26,27], however there are studies reporting no association [28] or even lower blood pressure in patients with depression [29]. Depression and hypertension share common pathways mediated by an increased in sympathetic tone and a decrease in parasympathetic activity [30] as well as increased in secretion of adrenocorticotrophic hormone and cortisol. Despite its high prevalence, depression is often misdiagnosed by the primary physicians, which can lead to cardiovascular complications including hypertension. Therefore, the understanding of coexistence of these two modalities can improve patients' quality of life.

## Conclusion

Finally, the present study showed a clear increase in arterial stiffness, assessed by means of CAVI index, in hypertensive patients with anxiety, depression or both as well as an increase in the higher quartiles of BDI score. CAVI is an index eligible for widespread use due to its simplicity in measurement and the fact that it is relatively independent of blood pressure. To our knowledge this is the first study using CAVI to assess association of arterial stiffness with anxiety and depression. Previous studies suggested that patients with anxiety and

depression have higher levels of arterial stiffness [31,32], however the potential mechanisms involved are still vague. In our study CAVI levels independently of blood pressure were higher in patients with anxiety and depression allowing the assumption that the autonomic system balance may be the potential mechanism with sympathetic activation and parasympathetic withdrawal, leading to endothelial dysfunction and thus higher arterial stiffness levels. Moreover, increasing levels of the vaso-constrictive hormone norepinephrine is one of the sympathetic changes potentially responsible for stiffness as well as Inflammation could play a role because inflammatory cytokines have been associated with both mental stress and arterial stiffness [33,34].

The present study has the limitation of a small size cohort; however, its strength comes for its prospective design as well as the inclusion of the control group of normotensives. The reliability of our findings regarding the occurrence of anxiety, depression and higher arterial stiffness levels among patients with different levels of hypertension would require further large studies in the future to clarify the mechanisms involved.

In conclusion there is a higher occurrence of anxiety and depression as the hypertension burden rises. Equally, arterial stiffness independent of blood pressure levels is higher in patients with either anxiety or depression or both. These findings suggest the evaluation of mental health among hypertensive patients has important implications as it could affect patients' quality of life as well as vascular hemodynamics.

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