# An Ignored Factor in Depression Pathogenesis: Chronic Co-morbidity of Low Blood Pressure and Cervical Spine Symptoms

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## Summary

Worldwide, the incidence of depression is on the increase. Today, depression is considered one of the most common diseases, second only to infectious diseases. Only half the estimated 4 to 5 million depressed patients in Germany are properly diagnosed and treated. The successful treatment of depressed patients is considered difficult. According to the latest findings, most antidepressants have more side effects than real therapeutic effects. Obviously, the pathophysiological mechanisms of this disease have not yet been sufficiently understood in order to develop those appropriate therapeutic approaches so urgently needed in the day to day life of medical practice. Observations of many years in medical practice indicate a co-morbidity of low blood pressure and cervical spine disorders (cervical spine syndrome) on the one hand and symptoms of depression on the other hand. This aspect has not received much attention. In systematic studies in patients with a resting systolic blood pressure of <10mmHg we have been able to verify the triad of low blood pressure, cervical spine syndrome, and depressive disorders. Symptoms in these patients were partially or fully relieved after 2 to 4 weeks in which they followed a special Asclepian treatment aimed at a healthy life style. It is assumed that low blood pressure and cervical spine syndrome cause temporary or permanently recurring cerebral microhypoxias which in turn produce nitrosative and oxidative stress, causing an imbalance in neurotransmitter function and brain metabolisms. Should this hypothesis be confirmed, it would offer new therapeutic approaches for the treatment of chronic depression.

Five years of experience with a naturopathic, not drug-based Asclepian treatment confirm the possibility of the effective treatment of patients with these disorders and demonstrate that a holistic life-style containing chronopsychophysiological elements may assist in this treatment. According to this view, depression would be characterized as a psychosomatic disorder.

**Keywords** Depression, cervical spine syndrome, hypotension as concomitant symptom, nitrosative and oxidative stress, Asclepian treatment, healthy life-style, psychosomatics.

# Introduction

With a lifetime prevalence of 10-18% and a point prevalence of 7%, depressive disorders are among the most common diseases in Germany (Rudolf et al. 2006, p 3 – Guideline 2009). Women are reported to complain about these symptoms twice as often as men. According to the literature, 50% of patients with depressive disorders experience the first onset of symptoms before their 32nd year of life (Kessler et al. 2005, Rudolf et al. 2006).

At a crisis conference of the European Section of the WHO, held in Brussels in June, 1999, and dedicated to psychosocial health, the alarming development of mental disorders, in particular that of depression, was discussed. Worldwide, 350 million people are reported to be suffering from depression (Huber, 1999).

According to the literature,12,000 depressed patients in Germany commit suicide each year, most of them male and older. Reports on depressed children and youths are also increasing (Birmater et al. 1996, Wittchen and Pittrov 2002, Arieti and Bemporad 1998). In Germany, the societal cost associated with depressive disorders was 4 billion euros in 2002. It has been calculated that 157,000 man years of work have been lost (Weber 2006, Wittchen et al. 1999). In Germany, only half of the estimated 4 to 5 million patients with depressive disorders are properly diagnosed and treated by general practitioners (Weber 2006). The successful treatment of depressive disorders is often considered difficult (Rudolf et al. 2006, Wittchen et al. 1999).

The therapeutic effectiveness of antidepressants is currently being criticized. In the Medical Drug Prescription Report (Arzneiverordnungsreport) 2009, edited by Schwabe and Pfaffrath, Lohse and Müller-Oerlinghausen provide the following assessment (p. 774):

“There is no need to treat all cases of depression with drugs, because there are well validated non drug treatment options available (cf. Bschor and Adli 2009). For mild depression, according to the latest guidelines, antidepressants are no longer considered the preferred agent in primary therapy (Arzneimittelkommission der deutschen Ärzteschaft 2006a, Hegerl and Schönknecht 2009). Their efficacy is limited and also relatively unspecific (Leon et al. 1993). On average, the absolute

difference in response rate for antidepressants and placebo, usually based on the Hamilton Depression Scale, is 20% (Walsh et al. 2002). This makes it difficult to prove efficacy and even more to demonstrate valid differences in the efficacy of different antidepressants. Accordingly, critical voices have been saying for a while now that the efficacy of antidepressants is overrated (Moncrieff 2001, Oeljeschläger und Müller-Oerlinghausen 2004, Bschor 2008). A meta analysis of the safety and efficacy of antidepressants in general medical practice found response rates of 56-59% for the active ingredient vs. 42-47% for placebo."[1] ... "More recent meta analyses indicate that in case of mild or moderate depression, the placebo part of the total effect is predominant (Kirsch et al. 2008, Arzneimittelkommission der deutschen Ärzteschaft 2008). Also, if one includes in the evaluation those studies that have not been published by the manufacturers, dramatically lower efficacies result for almost all antidepressants. (Turner et al. 2008). In the meantime, the EMEA has responded to these problems in a defensive manner, however, with weak arguments (Broich 2009). Finally, there is no proof that antidepressants reduce the suicide-related excess mortality of depressed patients (Anonym 2005a, Moncrieff and Kirsch 2005, Bschor 2008)."

In an assessment of reboxetine published on Nov 24, 2009 by the German Institute for Quality and Efficiency in Health Care (IQWiG) it is stated: "The lack of proof of a benefit of reboxetine on the one hand is countered by proof of harm on the other hand." It is a well-known fact that undesirable side effects of various antidepressants are not insignificant, as is stated in their packaging information. In the packaging inserts of tricyclic and tetracyclic antidepressants, for example, fatigue, changes in liver parameters, changes in EKG, weight gain, and restless legs syndrome are listed as undesirable side effects.

These reports on the low efficacy of various antidepressants suggest that representatives of pharmaceutical science are pursuing a false therapeutic approach that is founded on and incomplete understanding of the pathophysiology of depression.

[1] Translator's note: All quotes have been translated from German for this paper.

Officially, depressive disorders today are classified as mood disorders (ICD-10, Chapter V, Section F (F30-F39)) and are considered to be the responsibility of psychiatry and psychotherapy. And this is the case although there are numerous studies as well as practical experience showing that while psychotherapy may be effective (Arieti and Bemporad 1998) there continue to be apparent unsolved problems in psychotherapy for depression (Rudolf et al. 2006, Wittchen et al. 1999). The 12,000 annual deaths from suicide in Germany may be considered proof of this.

Therefore, it is understandable that the search for new approaches in the treatment of those affected by depression has become an extreme necessity. It is quite obvious that efforts to this end are being made. Numerous authors see stress, in particular unresolved chronic emotional distress that has become uncontrollable, or post-traumatic stress disorder (PTSD) as “early stages” of depressive disorders. In some cases, PTSD can be traced back to the patient’s childhood and may be the main cause of depression (Rüegg 2006, Seligman 1979, Jung and Irwin 1999, Irwin 1996, Manji et al. 2001, Sapolsky 1996). These authors are of the documented opinion that in the presence of unresolved emotional distress patients feel helpless and hopeless, which in turn presents as melancholia (depression). This is reflected by an excessive increase in stress hormones such as corticotropine releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. In 1996, Birbaumer and Schmidt described helplessness syndrome as a consequence of the flooding of tissues with endogenous opiates. At the same time, this neurohormonal dysbalance leads to an inhibition of the activity of natural killer cells (NK cells) associated with a weakening of the immune system (Jung and Irwin 1999, Irwin 1996). Based on this, depression is seen as a psychosomatic disorder with a psychoneuroimmunological component (Rüegg 2006, Seligman 1979, Irwin 1996, Jung and Irwin 1999).

Rüegg (2006) in this context is of the opinion that, as the decisive therapeutic factor, the depressive patient requires the “skill of an emphatic physician” who is able to “give hope to psychosomatically ill patients and to present them with an optimistic look to the future” in order to cope with the unresolved distress the patients are suffering from. Psychoneuroimmunology also views chronic unresolved emotional distress or post-traumatic stress as the cause of depression (Irwin 1996, Irwin et al. 1991, Waltman et al. 1992). These processes are associated with an inhibition of the activity of natural killer cells (NK cells). Psychoneuroimmunologists also point out that

sleep disturbances in the depressively ill and their limited physical activity caused by a lack of motivation may significantly weaken the various processes and symptoms of the immune system (Lötzerich et al. 1996, 1993, 1994, Lötzerich and Uhlenbruck 1991 (review)). The results of these studies not only demonstrate the psychosomatic character of depressive disorders, but also provide, from a psychoneuroimmunological viewpoint, important clues for an extended range of treatments for the depressively ill, which need to include the natural normalization of sleep and the sleeping-waking cycle as well as physical activity. More and more often there also are reports of concomitant somatic disorders in depressive patients, such as myocardial infarction (Ojlschläger and Müller-Oerlinghausen 2004), diabetes mellitus (Kruse 2004 and Bornstein 2008) and carcinoma (Pedrosa 2004, Linke 2008). These, too, point to the somatic character of secondary depressive disorders.

Research has shown that:

- Neuroplasticity is limited by the inhibition of cerebral neurogenesis as a consequence of unresolved long-term stress or post-traumatic stress and the subsequent cortisol flooding of the brain (Rüegg 2006, Manji et al. 2001, Bremner et al. 2000; Sheline et al. 1996, Sapolsky et al. 1996, Jacobs et al. 2000).
- Changes in energy metabolism and disruptions of the circulation in various areas of the brain, and in particular in the left hippocampus, cause depression (Rüegg 2006, Brody et al. 2001, Goldapple et al. 2004 und Leuchter et al. 2002).

Neuroplasticity refers to the ability of the brain to structurally change or regenerate itself via neurogenesis. Neuroplasticity is essential to human health (Rüegg 2006).

Stress-induced inhibition of neurogenesis may even result in a volume loss of brain substance in depressive patients, as shown in magnetic resonance imaging (MRI) studies (Sheline et al. 2003, Gurvits et al. 1996, Sapolsky 1996, Rüegg 2006). Such volume losses in the brain are reported to be reversible by stimulating neurogenesis, e.g., by means of placebo application, imagery, psychotherapy, or certain pharmaceuticals (Rüegg 2006).

Rüegg (2006) prefers “talking medicine” for stimulating neurogenesis and sees it as a major opportunity for the treatment of depressive patients.

In the following, we would like to add another, hitherto unnoticed factor to the previously described complex psychosomatic, psychoneuroimmunological, and neurobiological study of the pathogenesis and, therefore, the treatment of depressive patients.

## The Consequences of Chronic Co-morbidity of Low Blood Pressure and Cervical Spine Syndrome

In patients of the naturopathic-oriented NaturMed Hot Springs and Health Resort Davutlar (Western Turkey) who routinely received a relaxation blood pressure test (Scherf et al. 2007, Hecht et al. 1991, 2001, 2002, 2007) at least 6 times as part of their Asclepian treatment, we found that more than 40% of those tested had low blood pressure (resting systolic blood pressure of <100mmgHg). In these low blood pressure patients the predominant diagnosis on which their primary care physicians had based their referrals were burn-out syndrome, overstress syndrome, chronic fatigue syndrome, sleep disorders, and, mainly, depression, in some cases with a history of long-term antidepressant therapy that had not achieved the desired outcomes. During history taking upon admission to the NaturMed Health Resort, we determined in these patients, in addition to their measured low blood pressure, primarily depressive symptoms, cervical spine syndromes with major discomfort of the neck muscles, chronic fatigue, worsening of symptoms in the morning (“morning low”), head discomforts and vertigo.

Because little attention is paid to low blood pressure in medicine, the following short description is given to aid with understanding the described issues.

The opinion that “arterial hypertension is a stepchild of medicine" dates back to 1973 (Gross). Since then, there have been some new findings regarding arterial hypotension, but no major changes in general medicine. In previous studies (Hecht et al. 1991, 2001, 2007, Scherf et al. 2006) we have shown that the common one-time blood pressure measurements often will not detect low blood pressure, in particular due to a certain anxiety (and increase in blood pressure) that is associated with seeing a physician in many patients (“white-coat effect”). Using the relaxation blood pressure test (BET, Hecht et al. 1999, 2001, 2002, 2003, 2007, Scherf et al. 2006) it is, however, possible, to measure the true resting blood pressure after relaxation,

thus verifying low blood pressure where present. Patients with a low systolic blood pressure often exhibit multi-symptomatic concomitant clinical symptoms.

Huep (1973) described the symptoms of low blood pressure patients as follows (these observations have since been confirmed by many other authors, e.g., Hecht et al. 1991, 2001, 2007, Jorken 2001, Leibold 2002, Reiner and Hecht 2001, Vogt-Spychalla 2001, Sinz and Witzleb 1993):

Fatigue, low achievement, irritability, dampened or anxious exhaustion, depressive moods, narcoleptic-like bouts of sleeping during the day (in particular on monotonous or hot days), cold feet and hands, breaking out in sweats, anomia, occasionally also temporary impotence and fainting, palpitations, other sensations in the region of the heart, extrasystoles and feelings of fear related to the heart, feelings of choking, "inability to take a deep breath", sigh breath, forced yawning, hyperventilation up to hyperventilation tetany, food intolerances, feelings of fullness, diarrhea, constipation, undifferentiated head discomforts, as well as cervical spine syndrome associated with tension in the neck, pain in the back and the extremities.

Hecht et al. (1991), Hecht and Balzer (1999), and Reiner and Hecht (2001) described a syndrome of “morning lows,” in which patients have difficulties getting up, do not feel rested, and have trouble starting their daytime activities. Also, specific sleep disorders were found in low blood pressure patients. However, one peculiarity was observed as well (Huep 1973, Reiner and Hecht 2001): Not all patients with low blood pressure show the symptoms described. Some do not experience these discomforts at all, others only experience them in the morning, and yet others experience them all day long (Maier 2003, Reiner und Hecht 2001). Why these differences are observed in persons with very low blood pressure has not yet been scientifically explained.

The associations of low systolic blood pressure with predominantly depressive symptoms and the presence of cervical spine syndrome with tension and pain in the neck region that we have observed for years in our medical practice were the reason for our studies as described hereafter.

# Methodology

All exams and tests were carried out during Asclepian treatments in the privately run NaturMed Hot Springs and Health Resort Davutlar (Western Turkey). This Asclepian treatment (not drug-based) consists of a chronopsychophysiological program, the main components of which are a regular sleeping-waking cycle, physical activity (hiking in the mountains and along the beach), a healthy diet, supplementation of micronutrients, relaxation, meditative breathing, different forms of massage, group dynamics, hot and cold baths, and imagery, and it offers essentially the same conditions for every patient. Every year about 800 to 900 patients from different countries are treated this way, most of them Turkish citizens. Since 2004, the relaxation blood pressure test has been routinely administered to each patient as a diagnostic and therapeutic measure at least six times. The relaxation blood pressure test has been developed by Hecht (1991, 2001, 2003) in order to eliminate the "white-coat effect" (Imai et al. 1996, Jorken 2001, Vogt-Spychalla 2001) and to avoid the masking of low blood pressure values as it occurs with the common one-time measurements of blood pressure.

The relaxation blood pressure test is done as follows: First, the patient is instructed to enter a state of relaxation by closing his or her eyes and mentally controlling his or her rhythmic breathing for 10 minutes. During this period of relaxation, the blood pressure is taken in the left upper arm in 1 minute intervals using a low noise automatic device (Omron comfort M8). (Figure 1)

Fig. 1: Relaxation blood pressure test

From these measurements over time the baseline and resting blood pressure (the lowest value of systolic pressure of the final five measurements) can be derived. In this way the true resting blood pressure without masked interferences (such as the "white-coat effect") is obtained.

The cuff used was an upper arm cuff for arm circumferences of 22 to 42 cm (Omron hard case cuff) that does not painfully squeeze the arm. (We are not pursuing any commercial interest in naming this equipment; it was simply chosen because we considered it the most appropriate for our purposes). Measurements were usually taken between 10 a.m. and 1 p.m., at least 90 minutes after breakfast. Patients who received blood pressure lowering medication or other medication were excluded. The exam room was sound proof, so that exogenous interferences such as noise were excluded as much as possible. From the group of patients we selected those having a resting systolic blood pressure of <110mgHg.

There were several variations of the exams.

## Variation 1

In patients with a resting systolic blood pressure of <110mmHg treated according to variation 1 a structured history was taken following the relaxation blood pressure test in order to record the following symptoms that in the previous 2.5 years had been observed most frequently in patients at the NaturMed Health Resort in association with low blood pressure:

1. “Morning low” syndrome: Problems in getting up, a need to sleep longer (which aggravates this state), feeling of never being fully rested, fatigue and exhaustion

2. Lack of drive, strongly diminished motivation, in particular after rising in the morning, chronic fatigue

3. Depressive symptoms of varying intensity, in part associated with world-weary thoughts. In some cases suicidal thoughts (“I don’t want to go on living like this”)

4. Vertigo, problems in maintaining balance, dizziness in association with high temperatures, low air pressure and monotony, and when changing position (in particular when getting up in the morning and after heavy meals)

5. Headaches of all types and feelings of emptiness in the head (“like cotton in my head”)
6. Symptoms 1-5 occurring in the morning only
7. Symptoms are occurring all day long, or there are no discomforts at all
8. Cervical spine syndrome with tension and/or pain in the neck region
9. Meteorosensitiveness, in particular in changing weather conditions and when air pressure is low
10. Sleep disorders, in particular night-time waking with tachycardias

These exams were done on patients of the naturopathic NaturMed Health Resort Davutlar (Western Turkey) who stayed there between October 2006 and October 2007. Included in the exams done according to this variation were 356 patients out of 864 patients who had a BET done, and whose resting systolic blood pressure was <110mmHg. These were 41.1% of BET tested patients, comprising 129 men (36.2% and 227 women (63.7%). The age range of this population was 20 to 89 years. The mean age was 53.6 ± 13.4 years. The age distribution was a normal (Gaussian) distribution. Because all patients at the NaturMed Health Resort pay out of their own pockets for their treatment, they all were very motivated and for the most part exercised strict self-discipline in following their Asclepian treatment.

## Variation 2

In variation 2 we found 56 patients (40.5%) with a resting systolic blood pressure of <110mmHg among 138 patients who had had the BET administered in the spring of 2009. With these patients we used the German variation of the Hospital Anxiety and Depression Scale (D-HADS). The Hospital Anxiety and Depression Scale (HADS; Zigmond und Snaith 1983) is a well-established tool for the self-assessment of mild and moderate forms of anxiety and depression which has been designed for use in somatic patients. The German version (D-HADS) was validated by Herrmann et al. (1995) and is available as a testing manual (Herrmann et al. 1995). In the German calibration sample (n=6200) a Cronbach’s alpha of 0.80 was determined for the anxiety subscale, and of 0.81 for the depression subscale. The retest reliabilities after

two weeks were r=0.84 (anxiety) and r=0.85 (depression), respectively. The HADS records seven measures of the depression subscale. Assessment follows this scheme (Herrmann et al. 1995):

HADS Depression values: negative (0-7) ambiguous (8-10) positive (≥11).

Other than this the same treatment conditions applied to the patients of variation 2 as to all other patients.

### Variation 3

In a small sample of 13 patients, all of them participants in an Asclepian treatment in the fall of 2009, who showed significant problems in the mornings ("morning low" syndrome) and were symptom-free in the afternoons, we measured their blood oxygen saturation ($SpO_2$) in their left ring fingers at two different times during the day, using an „Onyx II“ oximeter.

### 4. Variation 4

In order to determine whether the concomitant clinical symptoms of low blood pressure could also be observed in patients with higher blood pressure, we included 449 patients in the study (all of them participants in Asclepian treatments between October 2006 and October 2007) who had been given a relaxation blood pressure test on a daily basis and had been found to have a resting systolic blood pressure of 71-130 mmHg. Other than that patients experienced the same conditions as those of variation 1.

## Statistics

Significance tests were done using the Wilcoxon test for correlated samples. All calculations were done using the statistics software package SPSS 12.0.1.

Differences with p-values of $p<0.05$ (*), $p<0.01$ (**), or $p<0.001$ (***) were considered significant. Differences with a p-value of $p>0.05$ were deemed not significant (n.s.).

# Results

## Test Variation 1

Mean blood pressure values

The mean values from 356 patients (129 men, 227 women) of the baseline value are listed in Table 1, and of the resting blood pressure in Table 2.

Table 1. Mean baseline BET values

| | Overall | Men | Women |
|---|---|---|---|
| Systolic baseline blood pressure (mmHg) | 115 ± 11 | 118 ± 10 | 113 ± 12 |
| Diastolic baseline blood pressure (mmHg) | 68 ± 7 | 69 ± 7 | 68 ± 8 |
| Baseline blood pressure amplitude (mmHg) | 47 ± 10 | 49 ± 9 | 45 ± 10 |
| Baseline heart rate ($min^{-1}$) | 73 ± 12 | 71 ± 12 | 74 ± 111 |

Table 2. Mean resting BET values

| | Overall | Men | Women |
|---|---|---|---|
| Resting systolic blood pressure (mmHg) | 98 ± 8 | 100 ± 6 | 97 ± 8 |
| Resting diastolic blood pressure (mmHg) | 63 ± 8 | 63 ± 8 | 63 ± 8 |
| Resting blood pressure amplitude (mmHg) | 35 ± 8 | 37 ± 7 | 34 ± 8 |
| Resting heart rate ($min^{-1}$) | 71 ± 11 | 69 ± 11 | 72 ± 10 |

As the tables show, there was a mean difference of about 17mmHg between the baseline and the resting blood pressure for the entire group (Wilcoxon test $p<0.0001$, men: 18mmHg, women: 16mmHg). The mean baseline systolic values are in the normotension range, and the mean resting systolic relaxation values are in the hypotension range. The diastolic blood pressure values are very low at baseline already and thus are lowered by only 5mmHg during the BET.

## Concomitant clinical symptoms in low blood pressure

### Occurrence of symptoms

As seen in Table 3, 20.2% of low blood pressure patients had none of the typical symptoms. In 34.3%, symptoms were only seen in the mornings, and 45.5% experienced symptoms all day long.

Table 3: Occurrence of symptoms (mean ± standard deviation)

| Number of patients | no symptoms<br>N = 72 | Symptoms only in the morning<br>N = 122 | Symptoms all day<br>N = 162 |
|---|---|---|---|
| (Percentage) | **22,2 %** | **34,3 %** | **45,5 %** |
| Resting systolic pressure | 100 ± 8 | 99 ± 7 | 96 ± 8 |
| Resting diastolic pressure | 63 ± 8 | 64 ± 8 | 62 ± 8 |
| Resting pressure amplitude | 37 ± 8 | 35 ± 7 | 34 ± 8 |
| Resting heart rate ($min^{-1}$) | 69 ± 9 | 71 ± 11 | 73 ± 1 |

The mean blood pressure values of the three groups differ only slightly. That said, the values of symptom-free patients differ from those experiencing symptoms all day long for the systolic blood pressure, amplitude and heart rate (Mann-Whitney U test $p<0.02$). Mean values for systolic blood pressure in all cases were in the hypotension range. The same is true of the diastolic values.

### Details of symptoms in patients with a systolic blood pressure of <110mgHg

An overview of these results and the corresponding resting blood pressure values are given in Table 4. All symptoms are accompanied by hypotension of nearly the same level.

Table 4: Percentage of clinical symptoms of the entire group (n=356) and the associated mean values and standard deviations for systolic and diastolic blood pressure values

| Symptom | Frequency of concomitant clinical symptoms (%) | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| "Morning low" syndrome | 78.6 | 97.4 | 7.47 | 62.7 | 7.76 |
| Chronic fatigue, lack of drive | 78.6 | 97.4 | 7.47 | 62.7 | 7.76 |
| Depressive symptoms | 75.6 | 97.4 | 7.47 | 62.7 | 7.76 |
| Vertigo | 77.5 | 97.4 | 7.49 | 62.8 | 7.67 |
| Headache, empty feeling in the head | 77.5 | 97.5 | 7.46 | 62.8 | 7.67 |
| Cervical spine symptoms | 84.5 | 97.6 | 7.48 | 62.7 | 7.67 |
| Meteorosensitiveness | 80.9 | 97.5 | 7.51 | 62.7 | 7.82 |
| Sleeping disorders | 47.5 | 96.8 | 7.71 | 62.2 | 7.67 |
| Tinnitus | 28.3 | 96.9 | 8.03 | 62.0 | 7.83 |
| Migraines | 24.1 | 95.1 | 8.44 | 61.6 | 7.26 |

As can be seen from this table, during the structural history taking, depressive symptoms were found in 75.6% and cervical spine symptoms were found in 84.5% of the 356 low blood pressure patients (resting systolic pressure <110mmHg). Sleeping disorders, mainly night-time waking with tachycardia, was reported by 47.5% of those studied. "Morning low" syndrome, lack of drive, and chronic fatigue were named by 78.5%. Vertigo (77.5%), head aches (77.5%) and meteorosensitiveness (80.9%) were also predominant in low blood pressure patients.

Of the 269 low blood pressure patients who experienced depressive symptoms, 101 (37.5%) had been treated before their treatment at NaturMed Health Resort with antidepressants for a duration of 0.5 to 12 years, with frequently switched drugs and very limited success.

All these drugs were discontinued starting on their first day at the Health Resort, without any signs of withdrawal. In 31 of these patients treated with antidepressants

restless legs syndrome was observed, which we interpreted to be a side effect of the antidepressant therapy because this symptom disappeared after discontinuation of the antidepressants.

In the brief routine interviews conducted at the end of the Asclepian treatment (after 2 to 4 weeks of treatment) 265 patients reported that their depressive symptoms had partially or completely disappeared. Our observation of the patients' behavior during their treatment and conversations with them confirmed these assessments. Only four male Turkish patients (aged 45, 49, 51 and 54 years) did not show any improvement. In spite of stimulating conversations they did not participate in the treatment program. They spent a lot of time lying in bed or, in the daytime, in the trees' shadows or drank tea in the men's circle. At most they would accept massages. Their wives complained about the laziness of their husbands.

Two case reports are given here as examples of the positive effect of the Asclepian treatment in depressive patients.

1. One female 23 year old patient had attempted suicide (sleeping pills) 6 weeks earlier in an acute depressed state following a failed university exam and the associated psychological blackmail by her dominant father. Since that time, according to her mother, she had been severely depressed. She received different antidepressants. Because of her pronounced lack of motivation, psychotherapy had not been possible. The patient arrived at the Health Resort in a severely depressed state. Her resting systolic blood pressure was <90mmHg. Her sleeping profile recorded by an automatic electrophysiological sleep analyzer showed more than 30% of waking time, massively reduced REM sleep and reduced deep sleep. Her entire sleep profile was pathologically arrhythmic. Her electrodermal activity was indicative of utter exhaustion. All her pills (antihypertensives and benzodiazepine) were taken from the patient. She received a combination of silicon minerals (zeolithe) and glycine as well as magnesium and vitamin C. She accepted two other female patients of the same age to introduce her to the treatment program as we had asked them to do. Every day, private conversations were conducted with her, which she enjoyed. In conjunction with the relaxation blood pressure test she learned to breathe meditatively. In addition, she was included in optimistic group dynamics. Every day she received a 50 minute massage of the shoulder

and neck area. After only five days her motivation had improves so much that she participated in the full Asclepian program, exhibiting self discipline. After only two weeks of this treatment the depressive symptoms had been significantly reduced. Her sleep profile showed normal contours, however, it exhibited a REM excess of 36% of the total sleep time. Her resting systolic blood pressure varied between 95mmHg and 100mmHg from day to day. At the end of the four week treatment her depressive symptoms had fully disappeared. Her sleep profile showed almost normal contours. Her low resting systolic blood pressure of 100mmHg remained. Unfortunately we did not receive any feedback about the sustainability of her resolved depressive symptoms.

2. A 63 year old Turkish patient (teacher) was admitted to the Health Resort in an utterly exhausted stated and with “suicidal” thoughts. He had received four different antihypertensives and two antidepressants daily for about five years, as well as an occasional sleeping aid (benzodiazepine). He was hardly able to walk 200 meters. At the time of admission his resting systolic blood pressure was between 80mmHg and 85mmHg. His sleeping profile showed about 40% of waking time of his entire time in bed, as well as no REM sleep and a reduced deep sleep. On the second day of his treatment all medications were discontinued. He received daily a combination of silicon minerals (zeolithe) and glycine as well as magnesium (300 mg) and vitamin C. In addition, he received daily alternating treatments of classic massages and Pneumatic Pulsating Therapy (PPT) in the neck and shoulder area. Starting on the third day of treatment, the patient began to participate in the program. On day 7 of treatment he already hiked 5km, on day 14 he hiked 10km. At the same time his sleep profile had normalized except for a strong REM excess (39% of his entire sleeping time). His systolic blood pressure was measured at between 100mmHg and 105mmHg. His depressive symptoms, including the concomitant symptom of low blood pressure, had almost completely disappeared. After three weeks of Asclepian treatment this patient left the resort. He still showed hypotension, but otherwise his findings were normal, his depressive symptoms had been fully resolved. At his return to the Health Resort 12 months later, the patient continued to be free of depressive

symptoms. His sleep profile was normal. He had hiked up to 10km daily in the past year. His resting systolic pressure was in the range of 100mmHg. The patient reported not to have taken any antihypertensives or antidepressants.

This case report shows that the patient, who actually had low blood pressure, had been treated with four antihypertensives for five years, based on an erroneous measurement by his physician and without any follow-up on his blood-pressure. This, in conjunction with his low blood pressure and his cervical spine syndrome led to severe depression.

## Test Variation 2

Test variation 2 was used to verify results from variation 1 with a different method for determining the depressive symptoms, i.e., using the D-HADS instrument. To this end, in April and May of 2009, 56 patients (36 women and 20 men) who had a systolic blood pressure of <110mmHg out of a group of 138 patients who had received a daily relaxation blood pressure test were tested. These patients participated in the Asclepian treatment in the same way as the patients in variation 1. Additionally, they received massages and PPT and were given micronutrient supplements. The results are summarized in Table 5.

Mean resting systolic blood pressure (n=56): 93,3±8,3 mm Hg

Mean resting diastolic blood pressure (n=56): 62,9±7,8 mmHg

Table 5: D-HADS values of 56 patients with low blood pressure and some concomitant symptoms of low blood pressure

| Symptom | Number | Percentage |
|---|---|---|
| HADS-value >11, positively depressed | 48 | 85.7% |
| HADS-value 8-10, not clearly depressed | 2 | 3.6% |
| HADS-value 0-7, not depressed | 6 | 10.7% |
| “Morning low” syndrome | 44 | 78.5% |
| Chronic fatigue, lack of motiviation | 46 | 82.1% |
| Head aches and head related discomforts | 46 | 82.1% |
| Sleeping disorders | 32 | 57.2% |

Note that in this group 27 patients (56.7%) of the 48 depressed patients had been treated without significant success for 2 to 12 years with various antidepressants. In some of these patients side effects occurred, mainly manifesting as restless legs syndrome (in 10 of the 27 patients treated with antidepressants).

For 7 of these patients we repeated the D-HADS assessment between day 10 and day 13 of their treatment at the Resort. The results of this assessment are summarized in Table 6.

Table 6: D-HADS scores at the beginning of the Asclepian treatment and after 10 to 13 days of treatment, individual examples

| | Patient code | Age | Sex | BP (mmHg) before treatment | **D-HADS score before treatment** | Treat-ment days | BP (mm Hg) | **D-HADS score after 10-13 days of treatment** | Anti-depressant use before treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1 | NS | 47 | f | 95/63 | **18** | 13 | 89/66 | **3** | 4 years |
| 2 | SV | 48 | f | 97/69 | **17** | 13 | 102/63 | **5** | 9 years |
| 3 | O.S | 59 | m | 98/62 | **20** | 10 | 103/62 | **7** | 8 years |
| 4 | K-U. | 37 | f | 96/70 | **15** | 10 | 81/58 | **3** | alcoholism |
| 5 | AK | 54 | f | 101/71 | **17** | 10 | 93/72 | **8** | 5 years |
| 6 | BE | 46 | f | 84/52 | **17** | 10 | 88/50 | **4** | none |
| 7 | UM. | 68 | f | 90/60 | **19** | 10 | 92/52 | **6** | none |

As this table shows, within 10 to 13 days of the Asclepian treatment D-HADS scores were reduced for the 7 patients shown, with a tendency towards normal scores. The resting systolic blood pressure values did not change significantly during this time. In all 7 patients the cervical spine symptoms had disappeared.

## Test Variation 3

In order to verify the suspected cerebral hypoxia (cerebral microhypoxia) as a consequence of the concomitant occurrence of low blood pressure and cervical spine syndrome, we studied blood oxygen saturation in a small sample of 13 low blood pressure patients who suffered significantly from concomitant clinical symptoms in the morning and performed well in the afternoons. Measurements were done:

in the mornings between 6:00 a.m. and 6:30 a.m. (immediately after waking)

in the afternoons between 3:30 p.m. and 4:00 p.m.

Measurements were done on the ring finger of the left hand using an Onyx II oximeter. Reference values are given as ≥95%.

The results are summarized in Table 7.

**An Ignored Factor in Depression Pathogenesis: Chronic Co-Morbidity of Low Blood Pressure and Cervical Spine Symptoms**

**Karl Hecht, Hans-Peter Scherf, Klaus Heinz Kehl, Peter Meffert**

Table 7: Oxygensaturation ($SpO_2$) in patients with low blood pressure, measured in the morning and afternoon

| | | | | Morning | | | | Afternoon | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No.** | **Patient code** | **Sex** | **Age** | **RPD syst mmHg** | **RPD diast. mmHg** | **$SpO_2$** | **Findings** | **RPD syst. mmHg** | **RPD diast. mmHg** | **$SpO_2$** | **Findings** |
| 1 | M. S. | female | 68 | 90 | 62 | **91%** | exhausted, tired, depressed, unmotivated | 95 | 65 | **98%** | well |
| 2 | D. F. | female | 26 | 85 | 51 | **92%** | exhausted, tired, depressed, unmotivated | 88 | 53 | **97%** | relatively well |
| 3 | A. Ö. | female | 47 | 89 | 60 | **93%** | exhausted, tired, depressed, unmotivated | 94 | 64 | **99%** | very well |
| 4 | N. Ü. | female | 63 | 95 | 65 | **91%** | exhausted, tired, depressed, unmotivated | 100 | 68 | **97%** | well |
| 5 | G. G. | female | 34 | 85 | 60 | **94%** | exhausted, tired, depressed, unmotivated | 88 | 60 | **99%** | very well |
| 6 | H. E. | male | 52 | 91 | 61 | **92%** | exhausted, tired, depressed, unmotivated | 96 | 60 | **98%** | well |
| 7 | Y. A. | male | 67 | 101 | 68 | **88%** | exhausted, tired, depressed, unmotivated | 105 | 70 | **95%** | relatively well |
| 8 | M. S. | female | 70 | 92 | 56 | **91%** | exhausted, tired, depressed, unmotivated | 94 | 57 | **97%** | well |
| 9 | I. M. | female | 52 | 87 | 53 | **92%** | exhausted, tired, depressed, unmotivated | 88 | 52 | **99%** | very well |
| 10 | Z. S. | female | 43 | 96 | 65 | **93%** | exhausted, tired, depressed, unmotivated | 96 | 66 | **98%** | very well |
| 11 | A. A. | female | 45 | 84 | 58 | **94%** | exhausted, tired, depressed, unmotivated | 89 | 56 | **100%** | very well |
| 12 | H. T. | male | 49 | 100 | 67 | **91%** | exhausted, tired, depressed, unmotivated | 105 | 65 | **94%** | relatively well |
| 13 | C. G. | male | 44 | 84 | 44 | **93%** | exhausted, tired, depressed, unmotivated | 86 | 45 | **98%** | well |

In computing the median of these data it was found that the morning resting blood pressure was 91/60mmHG and the evening resting blood pressure was 94/60mmHg. Oxygen saturation showed a median of 92% in the morning and of 98% in the afternoon. After waking, all patients felt exhausted, tired, depressed, and unmotivated, but in the afternoon they all were relatively well to very well and able to perform.

## Test Variation 4

The question arose whether the concomitant symptoms of low blood pressure (resting systolic blood pressure of <110mmHg) are also observed when the blood pressure >110mgHg.

To answer this, we included 449 patients (participants in the Asclepian treatment) in the study who had daily relaxation blood pressure tests and showed resting systolic blood pressures between 71mmHg and 130mmHg.

They were stratified according to their resting systolic blood pressure as follows:

71–80mmHg (n=10)

81–90mmHg (n=45)

91–100mmHg (n=145)

101–110mmHg (n=154)

111–120mmHg (n=52)

121–130mmHg (n=43)

Results are shown in Figures 2 and 3 below.

The clinical symptoms of low blood pressure that we used in our study as criteria for the characterization of said low blood pressure were shown to be predominant and strong for four of the above ranges of resting systolic blood pressure (71-110mmHg). In the range of 111–130mmHg they were rarely seen. The differences between these two ranges were statistically highly significant.

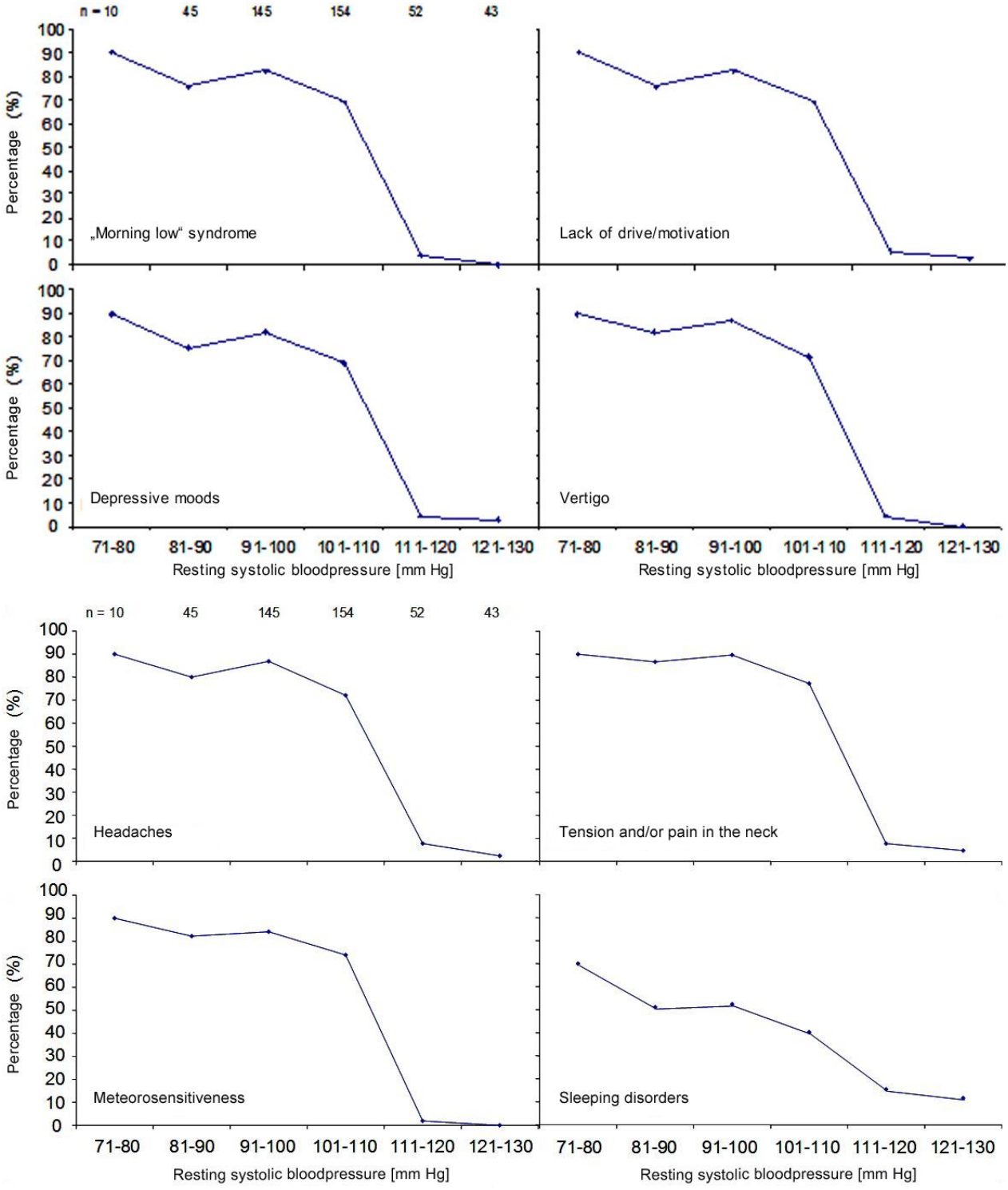


Fig. 2: Percentage of occurrence of typical concomitant symptoms of arterial hypotension as related to resting systolic blood pressure. Diastolic blood pressure results were analogous.

We also used these results to very the boundary between hypotension and normotension. Figure 3 shows data for the “morning low” syndrome as an example. All of the studied concomitant symptoms of low blood pressure showed the same curve.

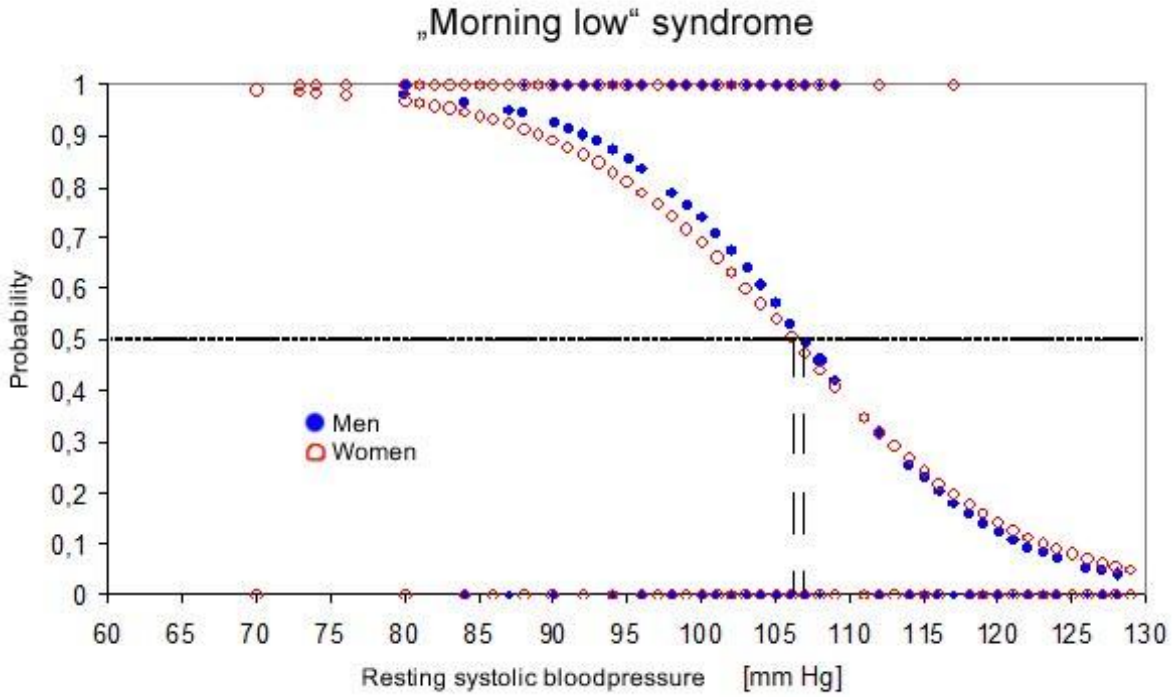


Fig. 3: Illustration of the determination of the boundary between arterial hypotension and arterial normotension based on the resting systolic blood pressure for male and female patients. The boundary for the example “morning low” syndrome is 107 mmHg. The 50% value was derived by logistic regression and splits patients in 2 groups: Above this value, less than 50% experience the syndrome, below this value more than 50% experience it.

There were no significant differences between male and female patients.

Similar observations for the resting diastolic blood pressure resulted in a boundary value of 72mmHg.

## Discussion

The results presented here reveal the dynamic interactions of several functional systems in pathophysiological processes. Based on practical experience that has been confirmed by these results, low blood pressure has been considered the cause of specific concomitant clinical symptoms (Gaethgens 1994, Huep 1973, Hahn 1990, Leibold (2002), Maier (2003), Reiner and Hecht 2001, Sinz and Witzleb 1993, Hecht et al. 1991, 2001, Koch 1992).

However, it had remained unclear why not all patients with low blood pressure exhibited these concomitant clinical symptoms. We also were not able to find quantitative data on the prevalence of these concomitant symptoms in the relevant literature. For the first time, we were able to present figures, namely: Only 21.5% of patients were without concomitant symptoms. In the morning, 34.0% of the low blood pressure patients we studied showed these symptoms, and 45.5% of them suffered from them all day.

While these figures may not be representative, they still give us an idea of the prevalence of the concomitant symptoms of low blood pressure, which always included depressive symptoms. What is certain is the following:

Patients who were affected in the morning or all day long (a total of 79.5% of all those studied with low blood pressure) complained about a high level of suffering. They felt temporarily or permanently stressed, very exhausted and experienced an associated depressed state and reduced quality of life. As we were able to show as well, the concomitant clinical symptoms were actually associated with a resting systolic blood pressure of <110mmHg. They were only rarely observed at a higher resting systolic blood pressure. Of the concomitant symptoms in our study, those symptoms were predominant that are associated with depression, such as chronic fatigue, lack of motivation, "morning low” syndrome, and sleeping disorders. The physicians who treated these patients before their Asclepian treatments also interpreted these symptoms as signs of depression and prescribed antidepressants (in 37.5% of the cases in our study variation 1, in 56.2% of the cases in study variation 2). We confirmed the co-morbidity of low resting systolic blood pressure (<110mmHg) and depressive symptoms both with structural history taking and, in one group, with a specific test, the D-HADS. What was most conspicuous, however, was that during the 2 to 4 weeks of treatment the depressive symptoms as well as

the concomitant clinical symptoms of low blood pressure were reduced in most cases and fully disappeared in some. Blood pressures, on the other hand, remained low. Consequently, there had to be other factors involved that we were able to influence with our Asclepian treatment.

Our earlier observations that changes in the cervical spine, leading to pain and tension in the neck and shoulder region and in some cases even stiffening of the entire neck muscles, may play a role in this have been confirmed by our results. The reported vertigo, head-based discomforts and feelings of emptiness in the head, in particular in an environment of high temperature led to the assumption that cervical spine symptoms and low blood pressure may lead to repeated short- or longer-term cerebral hypoxias (cerebral microhypoxias). These may result in disturbances of the cerebral circulation as well as the cerebral neurotransmitter and metabolic balance, which in turn may be reflected by depressive symptoms. Our patients felt cerebral circulation disorders most strongly when air pressure was low, in foehn conditions, and when thunderstorms were approaching. More than 80% of our patients reported meteorosensitiveness. A known phenomenon is the so called “foehn rausch” (Trenkle 1989) which supposedly results from disturbances in the cerebral transmitter system.

Patients with concomitant symptoms of low blood pressure suffer most from them right after waking up. Apparently, the reduced oxygen saturation in blood plays a role in this, as evidenced by our studies in 13 patients who presented as "two day-time personalities” (Reimer und Hecht 2001), i.e. they were depressed in the mornings and active or even hyperactive in the afternoon.

Therefore, it can be assumed that the relatively low oxygen saturation in blood triggered the feelings of exhaustion, depression, and lack of motivation in the mornings. The full day-time program of the Asclepian treatment then stimulated the patients, resulting in their oxygen saturation reaching normal levels that were reflected in their being well or even very well.

Repeated cerebral micro hypoxias as a consequence of concomitant low blood pressure and cervical spine symptoms would also explain why, in the majority of our patients, a reduction of depressive symptoms by means of our Asclepian treatment

could be shown: They hiked for 1-2 hours daily, took hot and cold baths, received massages and PPT of the neck and shoulder region, did aqua aerobics, were instructed on how to best use their pillows for sleeping and learned to relax and to breathe meditatively, in short, they were being de-stressed.

These findings agree with the results by Irwin (1996), Irwin et al. (1991), Waltman et al. (1992), Rüegg (2006), and Lötzerich et al. (1996).

A preliminary conclusion from our results is that concomitant low blood pressure and cervical spine symptoms under certain conditions may cause repeated cerebral microhypoxias. These cause a cerebral metabolic imbalance and disturbance of the cerebral neurotransmitter system, which might give rise to symptoms of depression (Rüegg 2006, Irwin 1996, Sapolsky 1996, Seligman 1979, Birbaumer and Schmidt 1996).

Suggestions of a possible connection between low blood pressure and depression were also reported by a Japanese-American group of researchers (Yamaka et al. 2005). They measured their subjects' blood pressures every 30 minutes around the clock on 7 continuous days. In addition to the usual tests, scores on the Geriatric Disease Scale (GDS), which contains a subscale for depression, were repeatedly determined in more than 140 subjects and for the first time in 172 subjects.

The authors found a weak positive (Z) association between the MESOR of systolic blood pressure and GDS scores ($r=0.171$, $p=0.025$) as well as an association between the circadian amplitude of the heart rate and GDS scores ($r=0.25$, $p=0.005$).

In our studies as well the main parameter for the relationship between symptoms of depression and low blood pressure was the resting systolic blood pressure, but less so the heart rate which we, however, did not study from a chronobiological viewpoint, as well as diastolic blood pressure.

Pathophysiologically, "primary idiopathic" essential hypotension is described as a dysregulation with insufficient central and peripheral adrenergens and symptoms of sympathetic adaptation and circulatory regulation issues(Gaethgens 1994, Sinz und Witzleb 1993).

It is said that sympathetic activity is suppressed and the vasomotor balance has been shifted towards parasympathetically stimulated responses.

Therefore, it is possible that it causes cerebral circulatory disorders, hypoxias, and metabolic disorders, in particular if accompanied by cervical spine symptoms.

Another potential Pathophysiological factor we would like to list here, referring to Kuklinski (2005, 2006, 2008a and b) is nitrosative stress. This might be responsible for the concomitant symptoms we and others (Hecht et al. 1991, Huep 1973, Leibold 2002, Maier 2003, Koch 1992) observed in low blood pressure patients. Kuklinski (2008a) observed in his clinical practice that “hypotension with systolic values of less than and around 100mmHg signals nitrosative stress.” Nitrosative stress is the term used to describe a chronic excess of NO in the human body, which often is associated with oxidative stress($O_2^-$) (Kuklinski 2005, 2006, 2008a and b, Pall 2007, Lincoln 1997 et al.).

Nitrosative and oxidative stress, i.e., the hyperoxide anion $O_2^-$ and nitric oxide NO interfere with mitochondrial activity (Pall 2007, Ghafourifar et al. 1999, Lacza et al. 2001, Bates et al. 1996, Warnke 2009, Dimmeler and Zeher 1997).

If NO is chronically increased, according to Kuklinski (2008a) it will induce a release of mitochondrial cytochrome G and thereby apoptosis (Ghafourifar et al. 1997, Dimmeler und Zeher 1997). The resultant lack of ATP activates the glutamate receptor, with a subsequent increase of intracellular $Ca^{++}$ and additional stimulation of “NO synthesis and super oxide formation”.

According to Kuklinski (2008a), NO and $O_2^-$ form peroxynitrite ($ONOO^-$) which is neurotoxic. It “irreversibly inhibits mitochondrial enzymes and oxidizes many metabolites such as cholesterol, vitamin C, uric acid, coenzyme Q10, SH containing enzymes, polyene fatty acid”, alpha liponic acid and others.

According to Kuklinski (2008a) peroxynitrite early on harms the axons of neurons and, therefore, interferes with neurotransmitter signaling.

According to Pall (2007) this “sets into motion a vicious circle.” Warnke (2009) found that the stimulation of the hyperoxide anion and nitric oxide NO among others damage the mitochondrial genome, the nuclear genome, and the membranes.

Kuklinski (2005, 2008a and b) points to the importance of defects in the “joints of the cervical spine” which, according to his observations, lead to recurring cerebral hypoxias and may promote neurological-psychiatric disorders. Chronic recurring

cerebral hypoxias, according to studies by Kuklinski (2008a and b) cause an increase in the synthesis of nitrosative and oxidative stress.

Our results show that 84.5% of our patients had cervical spine symptoms. According to observations by Kuklinski (2008a) patients with chronic sleep disturbances and with recurring NO peaks do not feel refreshed when waking. They also, in case of cervical spine issues, exhibit a long “warming up” time in the morning. In this context the “morning low” syndrome (78.6%) and their reduced oxygen saturation in blood in our patients is to be mentioned.

Finally, Kulinski (2008a) found that chronic nitrosative and oxidative stress (spreading throughout the body) were followed by migraines, chronic fatigue syndrome, chronic exhaustion, depression, Parkinson's disease and others. We observed the same pathological symptoms in some of our patients.

According to Kuklinski (2008a), the consequences of chronic nitrosative stress will result in massive losses of vitamin B12, potassium, and magnesium. He reported that these pathological symptoms could be remedied by exercise (Nordic walking, running, jogging, etc.), switching to a low carbohydrate diet and individually differentiated administration of various micronutrients (in particular vitamins, enzymes, and minerals). Kuklinski (2008a) also found that the majority of patients experiencing the listed deficits were not responsive to medication. These and our findings would explain why antidepressant treatments frequently fail (Lohse und Müller-Oerlingshausen 2009).

Chronic oxidative and nitrosative stress leading to disturbances in the mitochondrial system and being aggressive against cells (Kuklinski 2008a und b, Pall 2007, Lincoln et al. 1997) might also explain the inhibition of the neurogenesis described by Rüegg (2006) and the loss of cerebral substance observed in depressed patients (Rüegg 2006, Sapolsky 1996, Manji et al. 2001, Sheline et al. 1996).

If pathophysiological processes such as chronic nitrosative stress are present, current antidepressants are, of course, not indicated and represent an entirely false treatment approach.

In view of our results and in those of the neurobiological understanding of depression according to which depression significantly modifies cerebral neuroplasticity, as well

as in light of Kuklinski's results (2008a and b), at the time of the diagnosis of a depressive disorder it would be absolutely necessary to supplement the psychological tools with the determination of oxidative and nitrosative stress levels, measuring the resting systolic blood pressure, sleep analysis, an examination of the cervical spine, and measuring oxygen saturation in the blood. Accordingly, a non drug treatment should be initiated, e.g. a treatment such as our rather successful Asclepian treatment. Five years of experience with this Asclepian treatment at Davutlar, in which about 3600 patients with various diseases were treated, demonstrated not only the therapeutic success described here in patients with the triad of low blood pressure, cervical spine syndrome and symptoms of depression, but also the desire of some patients to continue with the elements of the Asclepian treatment back home. Often, this was associated with an elimination of symptoms (see above, case report of a 63 year old patient). Unfortunately, we have not been able to conduct a systematic follow-up of our treatment successes. However, we have reports of individual patients who remained symptom-free after returning home and continuing the elements of their Asclepian treatment. Therefore, we are of the opinion that the Asclepian treatment or elements thereof might be effective in the treatment of patients with the triad of low blood pressure, cervical spine symptoms and symptoms of depression even in an outpatient setting.

In case of severe depression, breaking the motivational deficit with psychotherapy is indicated. Subsequently, it should be treated with the Asclepian treatment, including psychotherapy and "talking medicine" (Rüegg 2006), just the same as milder cases of depression.

In this, "talking medicine" should play a dominant role in mentally guiding the patient (Rüegg 2006), with the physician possessing the skill of empathy (Rüegg 2006). We are of the opinion that depressed patients can be treated successfully only if the holistic systemic natural functional principle of humans is taken into consideration.

We think that our studies and experience presented here have shed light on a hitherto unknown gap in the pathophysiology and therapy of depression, and that we have shown how to close that gap. We have also provided more evidence that psychosomatic, psychoneuroimmunological and neurobiological pathophysiological

processes play a role in depressive disorders that is not insignificant. More studies to confirm our results are absolutely indicated.

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