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DOCTORAL THESIS

BIOPSYCHOSOCIAL MELANOMA RESEARCH – STRESS REACTIVITY IN PATIENTS WITH MALIGNANT MELANOMA

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Abstract

Background: The rising, almost epidemic incidence of cutaneous malignant melanoma (MM) worldwide is a point of careful investigation. In the past years MM incidence has shown an increase that exceeds all other solid tumours, especially in high developed countries with white population. There exist some studies that suggest a link between cancer and psychological distress, but only little is known about possible mechanisms although there is evidence in literature that psycho-social stress plays a role in the development of MM. The aim of this investigation was to get more detailed information about the individual stress reactivity of patients suffering from MM.

Methods: 68 in-patients (25 suffering from MM, 22 with non-melanoma skin cancer [non_MM] and 21 patients of a control group with benign processes), mean age 51.6 years participated in a defined test procedure. According to the present state of science reactivity of psycho-vegetative parameters (in particular blood pressure [BP] and blood pressure variability [BPV]) to a standardised stress stimulus were measured with the Task Force® Monitor.

Results: Patients suffering from MM showed a higher reactivity of psycho-vegetative parameters due to a mental stressor compared to non_MM group and control group. Furthermore MM patients showed lower values concerning positive stress coping strategies in comparison to patients of the control group.

Conclusion: From a biopsychosocial point of view MM patients seem to show higher levels of vegetative strain than controls and non_MM patients respectively. Together with a reduced resilience, strain might play a more important role in MM development than supposed.

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List of abbreviations

ALM	Acrolentiginous Melanoma
ANS	Autonomic Nervous System
BP	Blood Pressure
BPV	Blood Pressure Variability
BP_SD	Standard Deviation of Blood Pressure (Blood Pressure Variability)
ContBP	Continous Blood Pressure
dBP	Diastolic Blood Pressure
ECG	Electrocardiography
HRV	Heart Rate Variability
ICG	Impedance Cardiography
LENT.MAL	Lentigo Maligna
LENT.MAL.MEL	Lentigo Maligna Melanoma
mBP	Mean Blood Pressure
MM	Malignant Melanoma
Non_MM	Non Melanoma Skin Cancer
OscBP	Oscillometric Blood Pressure
PKM	Primär Knotiges Melanom (Primary Nodular Melanoma)
sBP	Systolic Blood Pressure
SSM	Superficial Spreading Melanoma
SVF	Stressverarbeitungsfragebogen (Stress Coping Questionnaire)
TICS	Trierer Inventory of Chronic Stress
TPR	Total Peripheral Resistance

1 Background

Melanoma incidence has shown an increase in the past years that exceeds all other solid tumours (Yurkovetsky *et al.*, 2007). As a potentially lethal disease it causes >79% of skin cancer-related deaths. The stage at the time of diagnosing is crucial - when discovered at early stages, melanoma is surgically curable; detected after regional and systemic dissemination the prognosis is far threatening (Yurkovetsky *et al.*, 2007).

The incidence rate of malignant melanoma (MM) varies within Europe with the highest numbers of patients reported in Scandinavia, the lowest in southern countries. Incidences in Styria are higher than expected by the north-south decline. The reasons for that remained unclear, but a study conducted by Richtig et al. is based upon an investigation of 1082 patients (511 males, 571 females, mean age 58.2 years) with primary melanoma in Styria. The results demonstrate that districts with higher number of sun hours and higher altitude show lower melanoma incidences (Richtig *et al.*, 2007).

"The biopsychosocial model of illness (organic unity theory or body – mind unity theory) is now regarded as the most significant theory to describe the relationship between body and mind, thus somewhat satisfactorily resolving the centuries old logical and empirical scientific problem of "psychosomatics" on a systems theoretical (and semiotic) basis […] Illness sets in when the organism cannot sufficiently provide the auto-regulative competency on various different levels of the human system in order to cope with disorders arising and relevant control cycles for the functional efficiency of human beings are overtaxed or fail. Due to the parallel interconnection of system levels it is not as significant on which level or area a disorder is generated or currently taking place, but which damage can be caused to the relevant system level or subordinate or superordinate systems. Illness and health are not defined as a condition in the biopsychosocial model, but as dynamic occurrence" (Egger, 2005, 2008a).

Empiric studies demonstrated the impact of emotions (limbic system) on different physiological parameters. It is a fact that central nervous system (CNS), autonomic nervous system (ANS), endocrine system (ES) and immune system (IS) are interlinked (Egger, 2005).

Egger defines health as the sufficient competence of our organism to cope with any disturbances on any system level auto-regulatively. Neither the absence of pathogen factors nor the absence of disease/abnormality in psycho-social fields represents health but the competence of controlling these pathogen factors sufficiently (Egger, 2005, 2008a, b).

Resilience factors like social integration, social support and the availability of a person of trust are protective factors that decrease the individual vulnerability (Egger, 1998).

Within the biopsychosocial model illness and health are not seen as states but as dynamic processes. Therefore health must be “created” in every second of our life (Egger, 2008a).

Although the term *“stress”* is in general use, it is so imprecise that different working group examined separately variables that are commonly regarded as components of stress

These include:
- depression, anxiety, panic disorder
- social isolation and lack of quality of social support
- acute and chronic life events
- psychosocial work characteristics

(Bunker *et al.*, 2003)

The stress process is a psycho-physiological competency of our organism to react on threatening stimuli with reflexes of defence and/or flight (Trapp *et al.*, 2009a).

The individual response to a stressor (strain) depends on intensity, duration, frequency of exposition and subjectively experienced importance of stressors. Concerning the aetiopathogenesis of diseases both daily hassles and life events can be seen as important factors (Egger, 1998).

Emotions like loss of control or helplessness can provoke very intense stress reactions like bradycardia (Miggitsch *et al.*, 2008; Wurst *et al.*, 2008).

Subjects, who react with a high degree of social isolation (measured with Trierer Inventory of Chronic Stress - TICS) after stress exposition, show a higher blood pressure variability (BPV) post stress (vigilance test – test d2). Increased BPV is associated with higher incidence of cardiovascular events. There exists a positive correlation between coping behaviour and BPV post stress as a predictor of cardiovascular risk (Miggitsch *et al.*, 2009b).

There is strong evidence that chronic stress exposure can cause an increased reactivity of cardiologic parameters after stress exposition. Schwaberger demonstrated that the amount of vegetative reaction after a mental stress depends on the aerobic fitness of healthy individuals (Schwaberger, 1987).

The results of Schwaberger could be confirmed by utilising HRV-parameters. It could be shown that aerobic fitness influences physiological reactivity after a mental stress (reduced strain) (Trapp *et al.*, 2009c).

Söllner et al. investigated patterns of social support and coping behaviour in 385 early stage melanoma patients utilizing standardized instruments (questionnaires) that assess social support, coping behaviour and tumour-related distress. Findings show that high social support and active coping are associated with good adjustment, whereas low perceived support and depressive coping behaviour show significantly

poorer adjustment in MM patients (Söllner *et al.*, 1999).
There are some studies that suggest a link between cancer and psychological distress (Salander *et al.*, 1996; Manne, 1999; Tschuschke *et al.*, 2001; Gold *et al.*, 2003). Although evidence of a link between cancer and distress has been consistent, the magnitude of reported associations has been quite weak and only little is known about possible mechanisms (Honda *et al.*, 2005).

More is known about the correlation between cancer, depression and quality of life (Yen *et al.*, 2006). Giese-Davis et al. tried to prove the correlations between depression and the physiological reactivity on a stress stimulus (modified version of the Trier Social Stress Test [TSST]) within patients that suffered from metastatic breast cancer (MBC). The study investigated how depression affects stress reactivity *(Giese-Davis et al., 2006).* It was demonstrated that patients that suffered from MBC showed alterations in autonomic regulation (reductions in respiratory sinus arrhythmia, RSA) both at baseline and during stress test (Giese-Davis *et al.*, 2006).

Wilson et al. confirm that depression and anxiety disorders are common among patients receiving palliative care. These disorders lead - according to the authors - to a diminished quality of life among people who are finally dying of cancer (Wilson *et al.*, 2007).

In the past years, some studies examined the interactions between psychological distress and coping strategies in patients with malignancies. Tschuschke describes that adult leukemia patients who respond to the diagnosis with a fighting spirit have longer survival than those who react with hopelessness (Tschuschke *et al.*, 2001).

Similar results could be shown by Fawzy et al. (1993). He demonstrated that psychiatric interventions that aim to improve coping strategies and that reduce the distress of patients with MM have positive effects on survival (Fawzy *et al.*, 1993).

The relationships between acute social stress, immunological alterations and the development of pulmonary melanoma metastases were analyzed by Vegas et al. (2006) in mice. It was shown that subjects engaging in (negative) coping strategies that are characterized by an absence of attack, low non-social exploration levels and high levels of defense, subordination and avoidance, developed most pulmonary metastases (Vegas *et al.*, 2006).

There is evidence in literature that psycho-social stress plays a role in the onset of MM. Havlik et al. described the impact of stress on the clinical presentation of MM. It could be shown that MM patients had significantly more major life crises (divorce, bankruptcy, unemployment, etc.) in the 5 years prior to clinical presentation (Havlik *et al.*, 1992).

In order to understand the influence of chronic stress and UV radiation on the increase to susceptibility to skin cancer, Saul et al. (2005) investigated mediators of a stress-induced increase in emergence and progression of UV-induced squamous cell carcinoma. It could be shown that stressed mice had a shorter median time to first tumour. In addition they had lower IFN-γ, CCL27/CTACK and CD3ε gene expression, lower numbers of infiltrating CD4+ cells, more regulatory/suppressor CD25+ cells infiltrating tumours and more CD4+ and CD25+ cells in circulation. The findings substantiated that chronic stress increased susceptibility to squamous cell carcinoma (Saul *et al.*, 2005).

Hamama-Raz et al. (2007) examined the relative contributions of objective illness-related factors and subjective factors (appraisal) to the psychological adjustment of 300 melanoma survivors. The results of this study show that lower threat appraisal and higher appraisal of subjective ability to cope reduced the distress of subjects. So it was concluded by the authors that subjective factors are more important than objective medical factors in predicting patients' adjustment (Hamama-Raz *et al.*, 2007).

Yen et al. (2006) compared psychological factors like quality of life, depression and stress between patients with malignant breast cancer and those with benign breast tumours. Results showed that subjects with malignant breast cancer had poorer physical and psychological quality of life and higher life stress (Yen *et al.*, 2006).

Preclinical and clinical studies in vivo and in vitro have established the immunomodulatory influence of the autonomic nervous system, which may contribute to immunological abnormalities in diseases associated with chronic higher sympathetic activity. The immunological consequences of chronic elevations in sympathetic tone in humans are not examined to the same extend as they are in animals. It is hypothesized that a chronic elevation of the sympathetic tone is contributed to immunologic abnormalities in diseases (Friedman & Irwing, 1997).

Stress itself has effects on melanoma-relevant immunological parameters such as CD3+, CD4+ T-cells and CD19+ B-cells. All decreased after being exposed to defined stressors (e.g. a mental arithmetic task), whereas lymphocytes, granulocytes, natural killer cells and natural killer cell activity increased (Isowa *et al.*, 2004, 2006).

Associations between natural killer cells (NK), proinflammatory cytokine stress responsivity and cardiac autonomic responses (indexed by heart rate and heart rate variability) were explored in 211 middle-aged men and women by Owen et al. (2003). Blood was drawn at baseline and immediately after a defined stress task (color–word interference and mirror tracing tasks) in order to assess natural killer cell numbers (NK). Furthermore blood was taken 45 minutes post stress to investigate plasma interleukin 6 (IL-6) and tumour necrosis factor α (TNFα) responses. They found increases in NK cell counts following stress and a positive association with heart rate responses independently of age, sex, socioeconomic status, smoking, and change in hematocrit. Furthermore a positive association of heart rate, TNFα and plasma IL-6 45 minutes post stress was found, independently of covariates (Owen & Steptoe, 2003).

At the same level with sun exposure, induced immune suppression due to overexercise is considered to be an additional risk factor for non Melanoma skin cancer in athletes doing endurance training (Möhrle, 2008).

To identify potential melanoma markers, 150 marathon runners were investigated, by taking part voluntarily in a skin cancer screening campaign. After completing a questionnaire about melanoma risk factors, types of sportswear and training programs, the participants received a total skin examination. Number of lentigines and nevi on the left shoulder and the left buttock were counted, using templates in standardized positions. Furthermore Richtig and colleagues evaluated the association of training sportswear and training parameters with the number of lentigines and nevi on the left shoulder. It could be shown, that runners with higher heart rates while training, higher training velocities and higher physical strain indices showed more nevi on the shoulder than the other runners ($p = 0.029, 0.046, 0.038$, respectively). Thus it was concluded that sun exposure and high physical strain cause an increase in melanoma markers such as lentigines and nevi in marathon runners. This study substantiates the fact that marathon runners have several risk factors to develop MM, particularly sun exposure, frequent sunburns, the development of new nevi and lentigines in sun exposed areas and the presence of atypical and changing nevi. In addition, immunosuppression due to over-exercise could be of importance in the genesis of MM. As a result it was shown that high-intensity training especially increases the number of nevi and therefore the risk of developing a MM (Richtig *et al.*, 2008).

Regarding results of Motivala and colleagues (2008), levels of ACTH, cortisol, and cardiovascular activity increased as well as monocyte production of TNFα among patients with rheumatoid arthritis after a defined stress task (Trier Social Stress Test). The TSST is a standardised laboratory task in which subjects are evaluated on their performance of public speaking and serial subtraction math tasks. This task is used to induce psychological and physiological stress increasing self reported stress, cardiovascular responses, and immunological parameters (Motivala *et al.*, 2008).

Buske-Kirschbaum (2002) investigated 36 patients with atopic dermatitis and a non atopic control group (n = 37). They were exposed to a laboratory stressor (Trier Social Stress Test - TSST). Blood samples were collected 10 minutes before and 1, 10 and 60 minutes after the stress test as well as 24 hours after the experiment. Several blood parameters were analysed: 10 minutes post TSST lymphocytes, monocytes, neutrophil and basophil granulocytes increased significantly with no significant differences between the two groups. Furthermore the TSST caused an elevation of IFN-γ with no significant differences in both groups 20 minutes post stress. IL-4 significantly dropped for the total group following the TSST and similarly to IFN-γ no differences were observed in both groups with regard to IL-4 levels (Buske-Kirschbaum *et al.*, 2002).

Furthermore Buske-Kirschbaum et al. (2007) investigated 23 patients with psoriasis vulgaris and 25 healthy controls. They described a significant increase of numbers of leukocyte subpopulations (lymphocytes, granulocytes, CD3+, CD8+, CD16+/CD56+ and CD3+/HLA-DR+) after the TSST within patients who suffered from psoriasis vulgaris (PSO). Number of CD4+ cells were found to be significantly higher in PSO patients (Buske-Kirschbaum *et al.*, 2007).

Proinflammatory cytokines are sensitive to emotional stress. Steptoe et al. found out that there is no relationship between socioeconomic status and stress-induced cytokine responses; yet they could observe sex differences in increase of TNFα (higher in men), IL-6 and IL-1Ra (higher in women) (Steptoe *et al.*, 2002).

Acute stress responses are strongly influenced by activity of the sympathetic nervous system. In a study Kimura et al. determined the association of sympathetic activity with immune responses to acute stress. Therefore 15 female undergraduates engaged in a continuous mental arithmetic task for 14 minutes. Blood samples were collected after the first period of rest (10 minutes), while performing the mental task (2, 5, 8 and 11 minutes after beginning) and immediately after the second period of rest (15 minutes) in order to assess immune indices like CD3+, CD4+ and NK-cells. Moreover, saliva samples were taken at three points (at baseline, immediately after

stress task and after a second period of rest) in order to get information about serum-IgA and cortisol. ECG and blood pressure were measured continuously during the experimental session. Kimura could find out that typical immune responses to acute stress can appear, particularly concerning NK cells, which increase significantly after 2 minutes, whereas CD3+ and CD4+ T-cells decrease significantly at 5 respectively 8 minutes after initiation of the task. Because of that fact he assumed that the immune system reacts at a very early stage of acute stress situations (Kimura *et al.*, 2005).

Circulating inflammatory markers are influenced by acute psychological stress (Stroop color-word interference task, public speaking, mental arithmetic task, anger recall, and the Trier Social Stress Test). Therefore psychosocial factors on cardiovascular risk, psoriasis and rheumatoid arthritis may be altered by these effects. Inflammatory responses can be observed under controlled experimental conditions. Results showed increased levels of circulating IL-6 ($r = 0.19$, $p = 0.001$) and IL-1b ($r = 0.58$, $p < 0.001$) following acute stress (Steptoe *et al.*, 2007).

In the past decades, Heart Rate Variability (HRV) has become an important tool in the field of psychophysiology (van Ravenswaaij-Arts *et al.*, 1993; Lombardi *et al.*, 1996; Task Force of the ESC and NASPE, 1996; Berntson *et al.*, 1997; Dishman *et al.*, 2000; Iwanaga *et al.*, 2005). We could demonstrate that HRV represents a more sensitive diagnostic tool than heart rate itself in order to prove psycho-vegetative reactivity (Trapp *et al.*, 2006). Beside HRV, there are further psycho-vegetative parameters, particularly Blood Pressure Variability, that describe vegetative arousal (Hot *et al.*, 2005; Miggitsch, 2005; Trapp, 2005; Harrison *et al.*, 2006; Miggitsch, 2006; Trapp, 2006; Wijnen *et al.*, 2006).

There exist some results that confirm that psycho-social stress influences pathogenesis and tumour progression but yet there is quite little known about associations between chronic stress and psychological coping depending on psycho-vegetative parameters in patients with MM.

The aim of this study was to get more detailed information about the individual stress reactivity of patients suffering from MM, by measuring psycho-vegetative parameters (blood pressure and blood pressure variability) and psychological parameters (stress-coping strategies, subjectively experienced chronic stress and the experience of emotions).

1.1 Specific aims

The aim of this study was to investigate the arousal of the autonomic nervous system in patients with MM compared to patients with non-melanoma skin cancer and a control group with benign skin diseases. To date there are very little data regarding the reactivity of psycho-vegetative parameters in persons suffering from MM. A few studies focused on the influence of distress on tumour progression. It is not known whether patients with MM show a divergent psycho-vegetative reactivity to mental stressors than patients that do not suffer from a malignancy.

According to the present state of the science, physiological reactivity in particular blood pressure and blood pressure variability on a standardised stress stimulus (vigilance test d2) has been investigated.

Following questions should be answered:

1. Do patients with MM show a higher vegetative reactivity (measured by BP and BPV) to a mental stress stimulus compared to patients with non-melanoma skin cancer and patients of the control group?
2. Is there a correlation between tumour thickness and BP and BPV respectively during defined conditions (baseline, mental stress, post stress)?
3. Do patients with MM use different coping strategies, do they experience more stress three month before surgery and how do they handle their emotions compared to the control group?

1.1.1 Hypothesis 1

Rozanski et al. describe that neuroendocrine changes caused by psychological stressors can induce a state of heightened physiologic response to acute stress (Rozanski & Kubzanzky, 2005).

- *Apart from the question if patients with MM suffered more stress before the onset of their disease or if they experience the receipt of the diagnosis as health threat, it was hypothesised that patients with MM show a higher reactivity of cardiovascular (BP, BPV) parameters due to a mental stressor compared to patients with non-melanoma skin cancer (non_MM group) and patients with benign processes (control group).*

1.1.2 Hypothesis 2

There exists an interconnection of coping styles and neuroimmunological processes. Temoshok points out that psychosocial factors play an important role in the development and/or progression of malignancies (Temoshok, 1985).

In addition it is described that Type C-behaviour (passive, appeasing, helpless) - more than Type A-behaviour (active, impatient, in control) - correlates positively with tumour thickness and level of invasion (Temoshok, 1985). Zozulya et al. showed that passive coping style is associated with a decrease in the number of monocytes, an elevation of eosinophile counts and low IFN. “People with passive coping style (Type "C") might be at higher risk of infectious diseases and cancer, while people with active coping style (Type "A") might be predisposed to coronary, allergic, and autoimmune diseases” (Zozulya *et al.*, 2008).

We could demonstrate that subjects, who react with a high degree of “social isolation” (passive coping) show higher vegetative strain (BPV) after a stress exposition (Miggitsch *et al.*, 2009a).

- *It was assumed that MM patients with higher tumour thickness (that are described as more passive, appeasing, helpless) have lower vegetative arousal (BPV) post stress and lower values concerning their positive stress coping strategies.*

1.1.3 Hypothesis 3

Fawzy et al. described that coping strategies that reduce distress of patients with MM have positive effects on survival (Fawzy *et al.*, 1993). Tschuschke revealed the correlation between fighting spirit and longer survival (Tschuschke *et al.*, 2001).

Vegas et al. could demonstrate that subjects engaging in passive coping strategies developed more pulmonary metastases (Vegas *et al.*, 2006). Animal models revealed that social isolation and social stress are associated with an increase in development of tumour metastases (Strange *et al.*, 2000; Wu *et al.*, 2000; Azpiroz *et al.*, 2008). In animal models Azpiroz et al. found out that after social stress exposition subjects that are characterized by passive-reactive coping strategies (submission, flee, avoidance behaviours) had a higher number of tumour foci, a higher level of corticosterone and a lower NKG2D receptor expression than subjects with active-proactive coping behaviour (Azpiroz *et al.*, 2008).

- *In order to investigate if patients with MM are stress-prone it was hypothesised that patients with MM have less positive and more negative coping strategies, a higher chronic stress exposure and a worse experience of emotions compared to patient of the control group.*

2 Methods

2.1 Test design

Each patient fulfilling inclusion criteria was asked to participate in the investigation. All participants of this study received a detailed explanation of the potential risks and benefits of the study and provided signed informed consent before participating in the study.

The participants were pointed out to the fact that they take part in a physiological, non-invasive investigation and got the information that their data are treated absolutely confidential. The participation in the study occurred voluntarily and gratuitously. The participants had the possibility to stop the investigation anytime without explaining any reasons.

To guarantee the anonymity, each participant received an ID number which was used for identification. The investigation was carried out on the day before surgery (e.g. tumour excision).

2.1.1 Inclusion criteria

Patients who met following inclusion criteria were invited to participate in the study:

- Age: 18 - 68 years
- Written informed consent
- Sufficient compliance
- Good command of the German language

2.1.2 Exclusion criteria

As psycho-vegetative parameters are influenced by external and internal factors, following exclusion criteria were formulated to guarantee the validity of data:

- Neuropathy
- Arrhythmias
- Pregnant or lactating women
- Insufficient compliance
- Individuals with psychiatric disorders
- Consumption of caffeine, nicotine as well as alcohol 3 hours before beginning of the test procedure

All institutional rules governing clinical investigation of human beings were strictly followed and the Helsinki declaration with respect to human subjects in bio-medical research has been conformed.

Ethical approval was obtained by the local Ethic Committee.

2.1.3 Test procedure

- Collection of socio-demographic data (name, weight, size, education, profession, medication)
- Explanation of the test d2 (vigilance test)
- Positioning of electrodes and sensors for measuring psycho-vegetative parameters
- Period of rest in seated position with closed eyes (duration: 6 minutes)
- Performance of vigilance test (duration: 4 minutes 40 seconds)
- Period of rest in seated position with closed eyes (duration: 6 minutes)
- Accompanying questionnaires

2.1.4 Sequence of test procedure

Table 2.1.4.1. Sequence of test procedure and legend

rest 1 (6 minutes)	vigilance test	rest 2 (6 minutes)	AQ

	periods of rest
	vigilance test (Test d2 – stress task)
	accompanying questionnaires

2.1.5 Sample

68 inpatients (27 women and 41 men), mean age 51.7 years (range: 23 to 68 years) took part in this investigation. Depending on the diagnosis the study cohort was subdivided into three groups (see table 2.1.5.1).

Patients with non-melanoma skin cancer (non_MM, n = 22), patients with malignant melanoma (MM, n = 25) and patients with benign skin diseases (controls, n = 21) attending surgery the next day were included.

- **Group 1 (non_MM):**

Patients with non–melanoma skin cancer like squamous cell carcinoma, basal cell carcinoma, dermatofibrosarcoma protuberans

- **Group 2 (MM):**

Patients with malignant melanoma (MM)

- **Group 3 (controls):**

Patients with benign diseases like varicoses, epidermal cysts, leg ulcus, chondrodermatitis nodularis helicis, hidradenitis suppurativa, nevi to be excised, acne inverse, sarcoidosis and cheilitis

Table 2.1.5.1

Groups

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	non_MM	22	32,4	32,4	32,4
	MM	25	36,8	36,8	69,1
	controls	21	30,9	30,9	100,0
	Total	68	100,0	100,0	

2.1.6 Descriptive statistics

The following table shows overall descriptive statistics regarding age.

Table 2.1.6.1

Age

	N	Minimum	Maximum	Mean	Std. Deviation
Age	68	23	68	51,67	11,982
Valid N (listwise)	68				

Following table shows the mean age and standard deviation within the three groups.

Table 2.1.6.2

			Mean	Standard Deviation
Groups	non_MM	Age	57	9
	MM	Age	51	12
	controls	Age	46	12

The table below lists the count of men and women within the three groups.

Table 2.1.6.3

				Count
Groups	non_MM	Sex	men	10
			women	12
	MM	Sex	men	9
			women	16
	controls	Sex	men	8
			women	13

Regarding MM-types, the study cohort (MM group) showed following distribution:

Table 2.1.6.4

MM_type

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Lent mal mel	2	8,0	8,0	8,0
	Lent.mal	2	8,0	8,0	16,0
	SSM	17	68,0	68,0	84,0
	PKM	3	12,0	12,0	96,0
	ALM	1	4,0	4,0	100,0
	Total	25	100,0	100,0	

2.2 Physiological methods

Following psycho-physiological data were measured with Task Force® Monitor (CNSystems, Graz, Austria).

- Blood pressure (BP)
- Blood pressure variability (BPV)
- Impedance cardiography (ICG)

Within this paper following parameters were statistically analysed:

- Blood pressure (BP)
- Blood pressure variability (BPV)
- Impedance cardiography (ICG) / total peripheral resistance (TPR)

The proper use of device of Task Force® Monitor is defined for non-invasive measurements of patients' hemodynamic parameters applying impedance cardiography (ICG), electrocardiography (ECG), oscillometric (oscBP) and continuous blood pressure (contBP) measurement. All signals are derived non-invasively.

2.2.1 Hemodynamic parameters

(From CNSystems Medizintechnik AG: Task Force® Monitor 3040i Operator's Manual V 2.2)

The software used offers various possibilities of analyses:

- Non-invasive beat-to-beat blood pressure measurement with automatic correction to oscillometric blood pressure (absolute values)
- Non-invasive evaluation of stroke volume and cardiac output for every heartbeat
- Evaluation of total peripheral resistance
- Evaluation of positive inotropy of the heart

- Real-time analysis of sympathetic tone and vagal tone derived from heart rate and blood pressure variability and evaluation of baroreflex sensitivity

RR-Interval (RRI)

The RR-interval [ms] describes the time interval between two R-peaks in the ECG (QRS-complex).

$$RRI = t_{QRSi+1} - t_{QRSi}$$

Heart Rate (HR)

The heart rate is the number of heart beats within a period of 1 minute. The HR is derived from the ECG signal using the following formula.

$$HR = \frac{60 \times 1000}{RRI}$$

Blood Pressure (systolic, diastolic and mean), Pulse Pressure (PP)

These values [mmHg] are derived from the pressure curve of the continuous blood pressure device.

As mentioned before the absolute values are corrected to the values assessed by the oscillometric device.

$$SBP = \max(p(t))$$

$$DBP = \min(p(t))$$

$$MABP = \frac{1}{t_{SBPi+1} - t_{SBPi}} \int_{t_{SBPi}}^{t_{SBPi+1}} (p(t)dt$$

$$PP = SBP - DBP$$

Total Peripheral Resistance (TPR) and TPR Index (TPRI)

TPR is the resistance [dyn*sec/cm5] of the small and large vessels against which the left ventricle is pumping the blood. The default setting of the central venous pressure (CVP) is 3 mmHg. TPRI [dyn*sec*m2/cm5] is indexed to the BSA of the patient:

$$TPR = \frac{MABP - CVP}{CO} \times 80$$

$$TPRI = \frac{MABP - CVP}{CI} \times 80$$

2.3 Psychometric methods

The accompanying questionnaires were presented to the patients subsequent to the test procedure.

All of the questionnaires used in this study showed high internal consistency and validity.

2.3.1 German stress-coping-questionnaire (SVF 120)

The German stress-coping-questionnaire “Stressverarbeitungsfragebogen 120 (SVF 120)” evaluates the individual coping strategies that are used during/after stressful situations. The questionnaire measures both positive (e.g. evaluation of the stressful condition and application of personal resources [control of the situation], minimization, positive self-instruction) and negative coping strategies (e.g. stress avoidance) (Janke *et al.*, 1985; Janke & Erdmann, 1997).

Each of the 120 items begins with the statement:

„Wenn ich durch irgendetwas oder irgendjemanden beeinträchtigt, innerlich erregt oder aus dem Gleichgewicht gebracht worden bin…“

Every item completes the statement and offers the possibility to select the adequate answer within a five-level rating scale.

The SVF 120 consists of 120 items that are divided into 20 subtests. Every subtest consists of 6 items.

Coping strategies can be divided in positive and negative strategies. Positive strategies effect efficient stress reduction and can be described as adequate coping strategies. Negative strategies are associated with a stress-enhancing behaviour.

Internal consistency coefficients (Cronbachs Alpha) for the subtests vary between 0.66 und 0.92. The test is widely utilised and quality criteria are fulfilled (Hogrefe, 2009).

The SVF 120 takes 10 - 15 minutes to fill in. SVF 120 was presented as a paper pencil version.

2.3.2 Trier inventory of chronic stress (TICS)

Subjectively experienced chronic stress was assessed with the German version of the Trier Inventory for Chronic Stress (TICS) (Schulz *et al.*, 2004).

This questionnaire consists of 57 items that are subdivided into 9 stress-scales:

1. Work overload
2. Social overload
3. Pressure to succeed
4. Work discontent
5. Occupational excessive demand
6. Lack of social recognition
7. Social stress
8. Social isolation
9. Chronic worries

Subjects are asked to remember how often they experienced a certain situation in the last three months.

There exist numerous results concerning the construct validity of the test.
Internal consistency coefficients (Cronbachs Alpha) for the scales are between 0.84 und 0.91 (M = 0.87). The Rasch reliabilities vary between 0.78 und 0.89 (M = 0.83) (Testzentrale, 2009).

The questionnaire takes 10 - 15 minutes to fill in. The TICS was presented as a paper pencil version.

2.3.3 Experience of Emotions-Scale (SEE)

This questionnaire assesses the emotional experience and emotional regulation and consists of 42 items that are subdivided into 7 independent scales (Behr & Becker, 2004):

1. Acceptance of emotions
2. Experiencing overflow of emotions
3. Experiencing lack of emotions
4. Body focused symbolisation of emotions
5. Imaginative symbolisation of emotions
6. Experiencing emotional regulation
7. Experiencing self control

These scales measure how persons experience, appraise and cope with emotions.

Internal consistency coefficients (Cronbachs Alpha) for the scales are between 0.70 and 0.86.

The questionnaire takes 10 - 15 minutes to fill in. The SEE was presented as a paper pencil version.

2.3.4 Test d2

The vigilance test d2 was implemented in the test procedure as a standardised stressor. The Test d2 is a vigilance test that assesses concentration and selective attention. “The technical manual contains instructions for administration, scoring and interpretation as well as documenting statistical research to date and the extent to which the d2 test fulfils standard test criteria. Reliability (internal & test-retest) is high. Criterion, construct and predictive validity have been demonstrated in numerous research studies. […] On the reverse side is the standardised test form in a landscape layout of 14 test lines with 47 characters in each line. Each character consists of a letter ’d’ or 'p' marked with one, two, three or four small dashes. The respondent is required to scan the lines and cross out all occurrences of the letter 'd' with two dashes while ignoring all other characters. […] Internal consistency coefficients […] are above .90 regardless of the statistics used or the sample. Test-retest coefficients were all above 0.7 for these three scales“ (Hogrefe_Ltd., 2008).

2.3.5 Histological classifications

For all primary melanoma, melanoma type, Clark level, tumour thickness in mm, special histological features including regression, ulceration, microsatellites and vascular invasion were evaluated according to the AJCC (American Joint Committee on Cancer, 2001).

2.4 Statistical methods

Kruskal-Wallis Test was applied for determining whether values of BP/BPV differ between the three groups. Mann-Whitney U-test was used for pair wise comparisons within the groups. The Spearman's rho that measures the rank-order association between two scale variables was applied to describe the relationship between two variables. Statistics were calculated using the commercially available software program SPSS, version 16.0.1 (SPSS Inc., Chicago, Illinois, USA). Probability values of $p < 0.05$ were considered as statistically significant.

3 Results

3.1 Reactivity of blood pressure and blood pressure variability

BP and BPV were measured continuously during the test procedure. In order to assess the amount of blood pressure reactivity due to a mental stress task, differences of diastolic, mean and systolic blood pressure were calculated. Following tables and graphs demonstrate differences of BP- and BPV-reactivity between the groups (differences of BP/BPV: vigilance_test_minus_rest1, rest2_minus_rest1 and rest2_minus_vigilance test).

3.1.1 Differences of blood pressure reactivity between the groups: vigilance_test_minus_rest1

Differences of blood pressure reactivity (vigilance_test_minus_rest1) between the groups were analysed using Kruskal-Wallis test: There are significant differences of diastolic, mean and systolic blood pressure reactivity values between the three groups as can be seen in table 3.1.1.2.

✧ $p < 0.05$

✧✧ $p < 0.01$

Group 1: non_MM

Group 2: MM

Group 3: Controls

Table 3.1.1.1

Ranks

	Groups	N	Mean Rank
dBP_mean_vigil_minus_rest1	non_MM	22	30,64
	MM	25	43,16
	controls	20	26,25
	Total	67	
mBP_mean_vigil_minus_rest1	non_MM	22	29,68
	MM	25	42,92
	controls	20	27,60
	Total	67	
sBP_mean_vigil_minus_rest1	non_MM	22	29,09
	MM	25	42,60
	controls	20	28,65
	Total	67	

Table 3.1.1.2

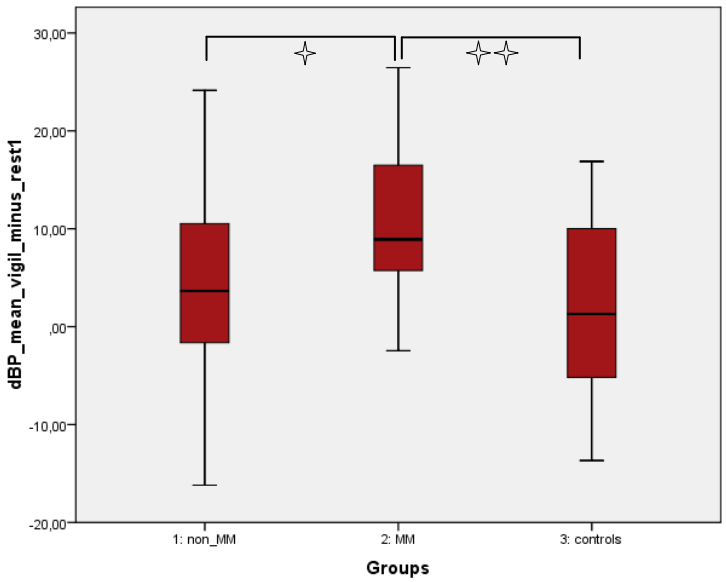
Test Statistics[a,b]

	dBP_mean_vigil_minus_rest1	mBP_mean_vigil_minus_rest1	sBP_mean_vigil_minus_rest1
Chi-Square	9,345	8,477	7,774
df	2	2	2
Asymp. Sig.	,009	,014	,021

a. Kruskal Wallis Test

b. Grouping Variable: Groups

Differences between the groups regarding diastolic blood pressure reactivity are illustrated in graph 3.1.1.1.



Graph 3.1.1.1

Further analysis revealed group differences in detail (using Mann-Whitney-U test):

Following tables (3.1.1.3 – 3.1.1.5) demonstrate which groups differ regarding diastolic blood pressure reactivity.

Table 3.1.1.3

Test Statistics[a]

	dBP_mean_vigil_minus_rest1
Mann-Whitney U	*174,000*
Wilcoxon W	*427,000*
Z	*-2,153*
Asymp. Sig. (2-tailed)	*,031*

a. Grouping Variable: Groups 1 vs. 2

Table 3.1.1.4

Test Statistics[a]

	dBP_mean_vigil_minus_rest1
Mann-Whitney U	*122,000*
Wilcoxon W	*332,000*
Z	*-2,924*
Asymp. Sig. (2-tailed)	*,003*

a. Grouping Variable: Groups 2 vs. 3

Table 3.1.1.5

Test Statistics[a]

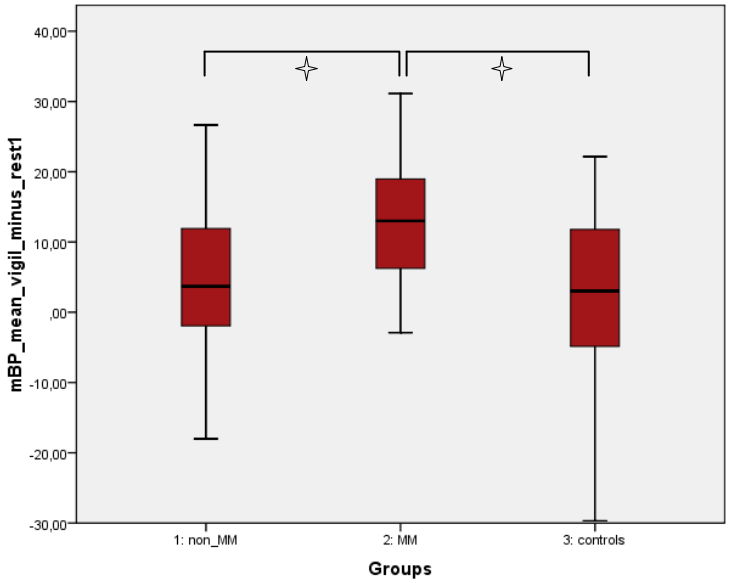
	dBP_mean_vigil_minus_rest1
Mann-Whitney U	*193,000*
Wilcoxon W	*403,000*
Z	*-,680*
Asymp. Sig. (2-tailed)	*,497*

a. Grouping Variable: Groups 1 vs. 3

Differences in diastolic blood pressure reactivity (vigilance_minus_rest1) between the groups non_MM vs. MM and between MM vs. controls were significant (p = 0.031, p = 0.003, respectively). There is no difference in diastolic blood pressure reactivity between the non_MM group and controls.

Differences of mean blood pressure reactivity are demonstrated in tables 3.1.1.6 – 3.1.1.8.

Differences between the three groups are illustrated in graph 3.1.1.2.



Graph 3.1.1.2

Table 3.1.1.6

Test Statistics[a]

	mBP_mean_vigil_minus_rest1
Mann-Whitney U	*163,000*
Wilcoxon W	*416,000*
Z	*-2,388*
Asymp. Sig. (2-tailed)	*,017*

a. Grouping Variable: Groups 1 vs 2

Table 3.1.1.7

Test Statistics[a]

	mBP_mean_vigil_minus_rest1
Mann-Whitney U	*139,000*
Wilcoxon W	*349,000*
Z	*-2,535*
Asymp. Sig. (2-tailed)	*,011*

a. Grouping Variable: Groups 2 vs. 3

Table 3.1.1.8

Test Statistics[a]

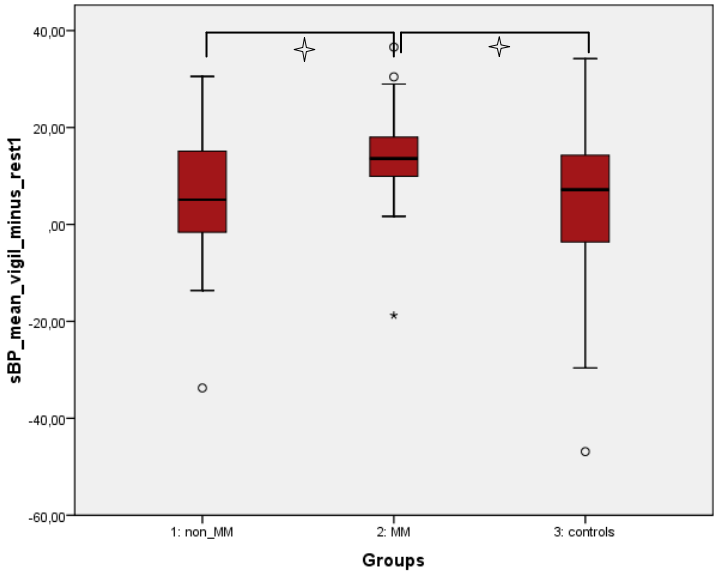
	mBP_mean_vigil_minus_rest1
Mann-Whitney U	*203,000*
Wilcoxon W	*413,000*
Z	*-,428*
Asymp. Sig. (2-tailed)	*,669*

a. Grouping Variable: Groups 1 vs. 3

Differences of mean blood pressure reactivity (vigilance_test_minus_rest1) between the groups non_MM vs. MM and between MM vs. controls were significant ($p = 0.017$, $p = 0.011$, respectively). There was no difference in mean blood pressure reactivity between the non_MM group and controls.

Differences of systolic blood pressure reactivity are demonstrated in tables 3.1.1.9 – 3.1.1.11.

Differences between the groups are illustrated in graph 3.1.1.3.



Graph 3.1.1.3

Table 3.1.1.9

Test Statistics[a]

	sBP_mean_vigil_minus_rest1
Mann-Whitney U	*160,000*
Wilcoxon W	*413,000*
Z	*-2,452*
Asymp. Sig. (2-tailed)	*,014*

a. Grouping Variable: Groups 1 vs. 2

Table 3.1.1.10

Test Statistics[a]

	sBP_mean_vigil_minus_rest1
Mann-Whitney U	*150,000*
Wilcoxon W	*360,000*
Z	*-2,284*
Asymp. Sig. (2-tailed)	*,022*

a. Grouping Variable: Groups 2 vs. 3

Table 3.1.1.11

Test Statistics[a]

	sBP_mean_vigil_minus_rest1
Mann-Whitney U	*213,000*
Wilcoxon W	*423,000*
Z	*-,176*
Asymp. Sig. (2-tailed)	*,860*

a. Grouping Variable: Groups 1 vs. 3

Statistical analysis showed differences of systolic blood pressure reactivity (vigilance_minus_rest1) between the groups non_MM vs. MM and between MM vs. controls ($p = 0.014$, $p = 0.022$, respectively). There is no significant difference in systolic blood pressure reactivity between the non_MM group and controls.

Summary:

It could be demonstrated that patients with MM react with a higher rise in diastolic, mean and systolic blood pressure to a mental stressor compared to non_MM and controls. Non_MM patients and controls react with the same extend of blood pressure alteration to stress exposition.

3.1.2 Differences of blood pressure variability reactivity between the groups: vigilance_test_minus_rest1

In order to analyse the reactivity of blood pressure variability (BPV) to a mental stressor (vigilance test) differences of standard deviation (SD) of diastolic, mean and systolic blood pressure were calculated (vigilance test_minus_rest1).

Table 3.1.2.1

Ranks

	Groups	N	Mean Rank
dBP_SD_vigil_minus_rest1	non_MM	22	35,00
	MM	25	31,32
	controls	20	36,25
	Total	67	
mBP_SD_vigil_minus_rest1	non_MM	22	35,11
	MM	25	32,14
	controls	20	35,10
	Total	67	
sBP_SD_vigil_minus_rest1	non_MM	22	35,32
	MM	25	32,48
	controls	20	34,45
	Total	67	

Table 3.1.2.2

Test Statistics[a,b]

	dBP_SD_vigil_minus_rest1	mBP_SD_vigil_minus_rest1	sBP_SD_vigil_minus_rest1
Chi-Square	,798	,363	,263
df	2	2	2
Asymp. Sig.	,671	,834	,877

a. Kruskal Wallis Test

b. Grouping Variable: Groups

Overall statistics (Kruskal Wallis Test) did not show any significant differences regarding blood pressure variability (SD of BP) reactivity between the groups.

3.1.3 Differences of regeneration of blood pressure- and blood pressure variability between the groups: rest2_minus_rest1

In order to quantify the amount of regeneration of BP and BPV after a mental stress task, difference of BP and BPV post stress minus baseline (rest2_minus_rest1) was calculated.

Overall statistics (Kruskal-Wallis Test) did not show any significant differences of BP- and BPV-regeneration between the groups (see tables below).

Table 3.1.3.1

Ranks

	Groups	N	Mean Rank
dBP_mean_rest2_ minus_rest1	non_MM	22	33,39
	MM	25	39,68
	controls	20	27,58
	Total	67	
mBP_mean_rest2_ minus_rest1	non_MM	22	31,32
	MM	25	39,68
	controls	20	29,85
	Total	67	
sBP_mean_rest2_ minus_rest1	non_MM	22	30,95
	MM	25	38,60
	controls	20	31,60
	Total	67	

Table 3.1.3.2

Test Statistics[a,b]

	dBP_mean_rest2_minus_rest1	mBP_mean_rest2_minus_rest1	sBP_mean_rest2_minus_rest1
Chi-Square	*4,321*	*3,448*	*2,234*
df	*2*	*2*	*2*
Asymp. Sig.	*,115*	*,178*	*,327*

a. Kruskal Wallis Test

b. Grouping Variable: Groups

Table 3.1.3.3

Ranks

	Groups	N	Mean Rank
dBP_SD_rest2_minus_rest1	non_MM	*22*	*30,64*
	MM	*25*	*35,84*
	controls	*20*	*35,40*
	Total	*67*	
mBP_SD_rest2_minus_rest1	non_MM	*22*	*29,86*
	MM	*25*	*37,48*
	controls	*20*	*34,20*
	Total	*67*	
sBP_SD_rest2_minus_rest1	non_MM	*22*	*29,84*
	MM	*25*	*38,62*
	controls	*20*	*32,80*
	Total	*67*	

Table 3.1.3.4

Test Statistics[a,b]

	dBP_SD_rest2_minus_rest1	mBP_SD_rest2_minus_rest1	sBP_SD_rest2_minus_rest1
Chi-Square	*,982*	*1,791*	*2,484*
df	*2*	*2*	*2*
Asymp. Sig.	*,612*	*,408*	*,289*

a. Kruskal Wallis Test

b. Grouping Variable: Groups

3.1.4 Differences of regeneration of blood pressure- and blood pressure variability between the groups: rest2_minus_vigilance_test

In order to quantify the amount of regeneration of BP and BPV after a mental stress task, difference of BP and BPV post stress minus vigilance test (rest2_minus_rest1) was calculated.

Table 3.1.4.1

Ranks

	Groups	N	Mean Rank
dBP_mean_rest2_ minus_vigilance_test	non_MM	22	38,00
	MM	25	26,64
	controls	20	38,80
	Total	67	
mBP_mean_rest2_ minus_vigilance_test	non_MM	22	37,45
	MM	25	27,48
	controls	20	38,35
	Total	67	
sBP_mean_rest2_ minus_vigilance_test	non_MM	22	36,50
	MM	25	28,94
	controls	20	37,58
	Total	67	

Table 3.1.4.2

Test Statistics[a,b]

	dBP_mean_ rest2_minus_ vigilance_test	mBP_mean_ rest2_minus_ vigilance_test	sBP_mean_ rest2_minus_ vigilance_test
Chi-Square	5,708	4,488	2,721
df	2	2	2
Asymp. Sig.	,058	,106	,256

a. Kruskal Wallis Test

b. Grouping Variable: Groups

Table 3.1.4.3

Ranks

	Groups	N	Mean Rank
dBP_SD_rest2_minus_ vigilance_test	non_MM	22	32,05
	MM	25	37,02
	controls	20	32,38
	Total	67	
mBP_SD_rest2_minus_ vigilance_test	non_MM	22	30,45
	MM	25	37,78
	controls	20	33,18
	Total	67	
sBP_SD_rest2_minus_ vigilance_test	non_MM	22	28,73
	MM	25	40,14
	controls	20	32,12
	Total	67	

Table 3.1.4.4

Test Statistics[a,b]

	dBP_SD_ rest2_minus_ vigilance_test	mBP_SD_ rest2_minus_ vigilance_test	sBP_SD_ rest2_minus_ vigilance_test
Chi-Square	,961	1,705	4,279
df	2	2	2
Asymp. Sig.	,618	,426	,118

a. Kruskal Wallis Test

b. Grouping Variable: Groups

Overall statistics (Kruskal-Wallis Test) did not show any significant differences regarding BP and BPV reactivity (rest2_minus_vigilance_test) between the groups (see tables 3.1.4.1- 3.1.4.4).

3.2 Correlations of tumour thickness (MM) with total peripheral resistance, blood pressure and blood pressure variability

Correlations of tumour thickness (in mm) with total peripheral resistance (TPR), BP and BPV revealed significant results.

3.2.1 Tumour thickness vs. total peripheral resistance and blood pressure: rest1 (baseline)

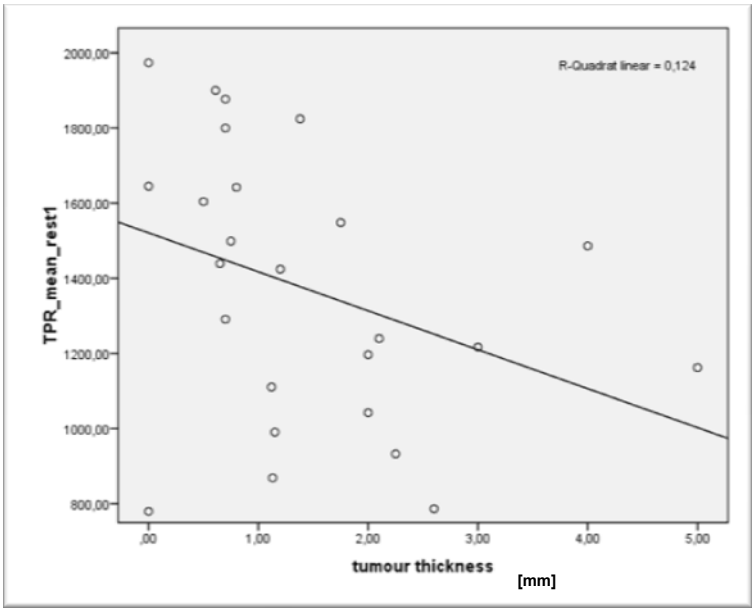
Correlations of tumour thickness with total peripheral resistance (TPR), dBP and mBP at rest1 (baseline) were significant (see following tables and graphs):

Table 3.2.1.1

Correlations

			TPR_mean_rest1
Spearman's rho	tumour.thickness	Correlation Coefficient	-,459 *
		Sig. (2-tailed)	,021
		N	25

*. Correlation is significant at the 0.05 level (2-tailed).



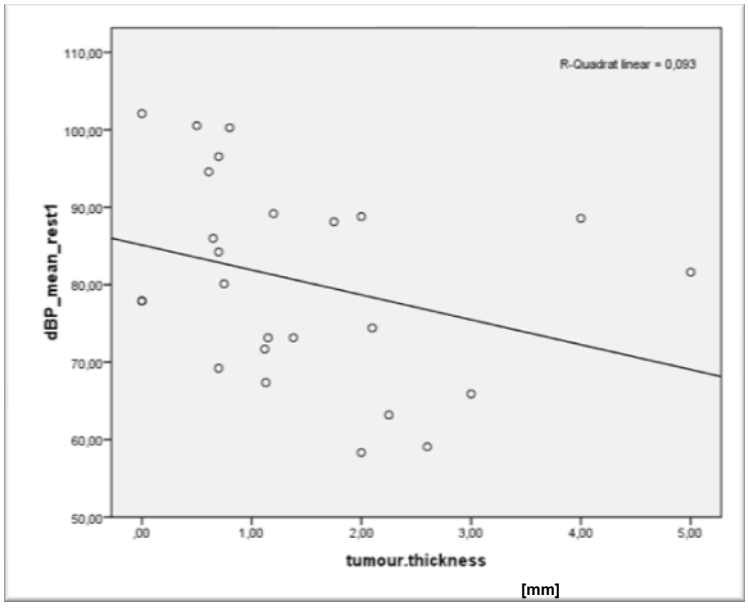
Graph 3.2.1.1

Table 3.2.1.2

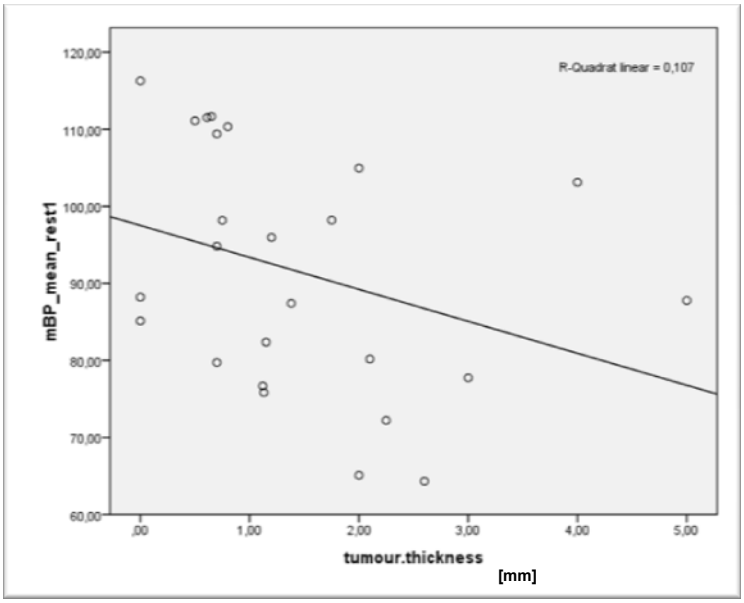
Correlations

			dBP_mean_rest1	mBP_mean_rest1	sBP_mean_rest1
Spearman's rho	tumour.thickness	Correlation Coefficient	*-,432* *	*-,487* *	*-,371*
		Sig. (2-tailed)	*,031*	*,014*	*,068*
		N	*25*	*25*	*25*

*. Correlation is significant at the 0.05 level (2-tailed).



Graph 3.2.1.2



Graph 3.2.1.3

3.2.2 Tumour thickness vs. blood pressure: vigilance_test

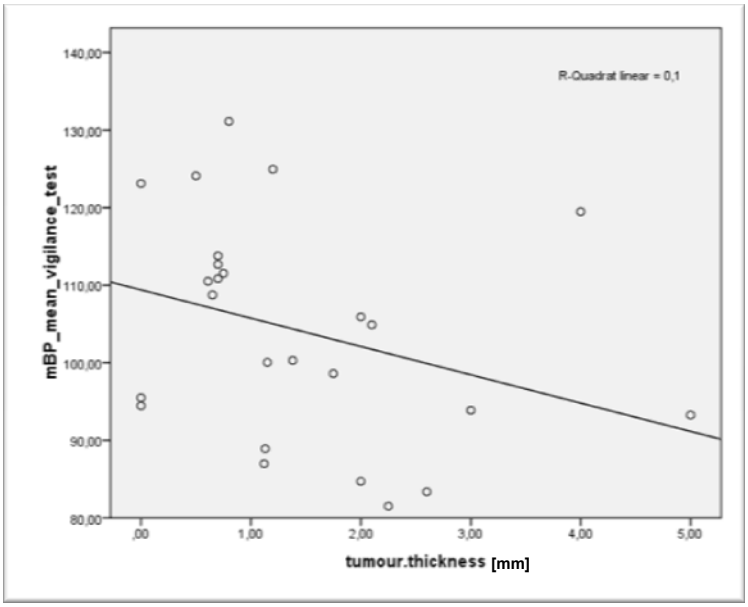
Correlations of tumour thickness with mBP during vigilance test (stress task) revealed significant results (see table 3.2.2.1 and graph 3.2.2.1).

Table 3.2.2.1

Correlations

			dBP_mean_ vigilance_test	mBP_mean_ vigilance_test	sBP_mean_ vigilance_test
Spearman's rho	tumour.thickness	Correlation Coefficient	-,381	-,415 *	-,281
		Sig. (2-tailed)	,060	,039	,173
		N	25	25	25

*. Correlation is significant at the 0.05 level (2-tailed).



Graph 3.2.2.1

3.2.3 Tumour thickness vs. blood pressure: rest2 (post stress)

Correlations of tumour thickness with BP during rest2 (post stress) did not show any significant results (see table 3.2.3.1).

Table 3.2.3.1

Correlations

			dBP_mean_rest2	mBP_mean_rest2	sBP_mean_rest2
Spearman's rho	tumour.thickness	Correlation Coefficient	*-,390*	*-,325*	*-,178*
		Sig. (2-tailed)	*,054*	*,113*	*,394*
		N	*25*	*25*	*25*

Summary:

Results demonstrate that tumour thickness correlates significantly negatively with total peripheral resistance (TPR), dBP and mBP at rest1 (baseline). A tendency of correlation can be seen between tumour thickness and sBP at rest1(r = -0.371;

p = 0.068). In addition tumour thickness correlates significantly with mBP and dBP by trend during the mental task. Post stress there was no correlation between tumour thickness and dBP, mBP, sBP respectively. Only dBP post stress showed a correlation with tumour thickness by trend (r = -0.390; p = 0.054).

3.2.4 Tumour thickness vs. blood pressure variability

Results of correlations between tumour thickness and BPV at rest1 are given in table 3.2.4.1.

Table
3.2.4.1

Correlations

			dBP_SD_ rest1	mBP_SD_ rest1	sBP_SD_ rest1
Spearman's rho	tumour.thickness	Correlation Coefficient	-,256	-,179	-,232
		Sig. (2-tailed)	,217	,392	,264
		N	25	25	25

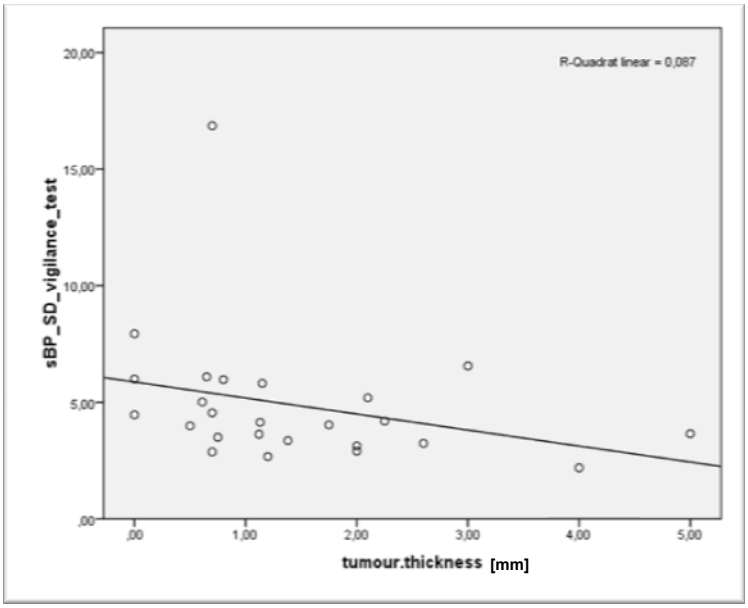
Systolic blood pressure variability (sBP_SD) during vigilance test correlated significantly with tumour thickness (see table 3.2.4.2 and graph 3.2.4.1).

Table 3.2.4.2

Correlations

			dBP_SD_ vigilance_test	mBP_SD_ vigilance_test	sBP_SD_ vigilance_test
Spearman's rho	tumour.thickness	Correlation Coefficient	-,113	-,254	-,422 *
		Sig. (2-tailed)	,592	,221	,036
		N	25	25	25

*. Correlation is significant at the 0.05 level (2-tailed).



Graph 3.2.4.1

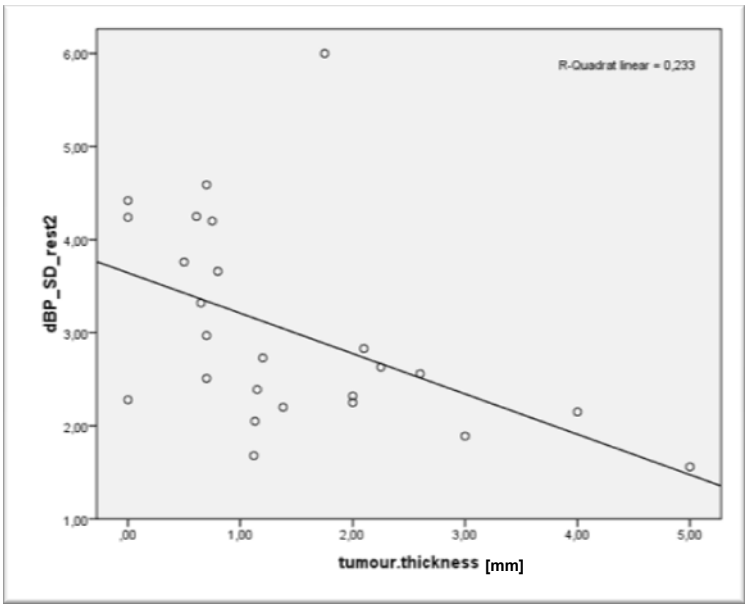
Following tables and graphs show correlations between tumour thickness and BPV post stress (rest2):

Table 3.2.4.3

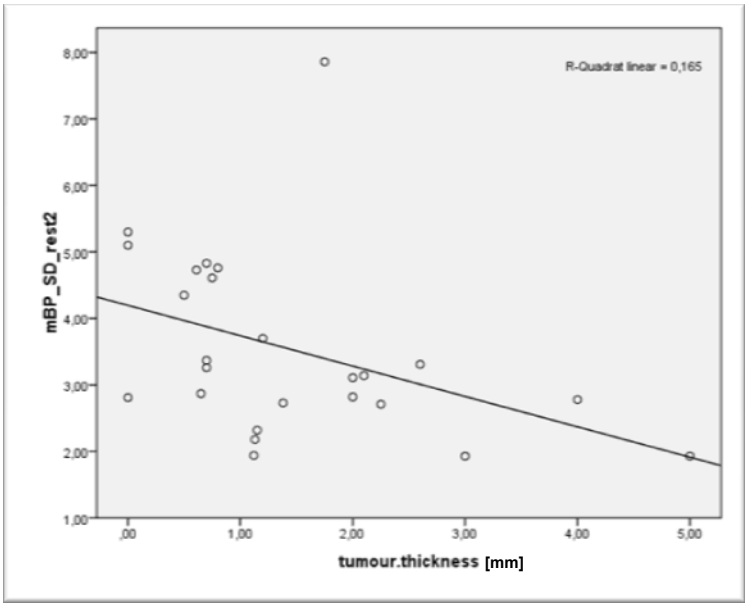
Correlations

			dBP_SD_rest2	mBP_SD_rest2	sBP_SD_rest2
Spearman's rho	tumour.thickness	Correlation Coefficient	-,565 **	-,540 **	-,643 **
		Sig. (2-tailed)	,003	,005	,001
		N	25	25	25

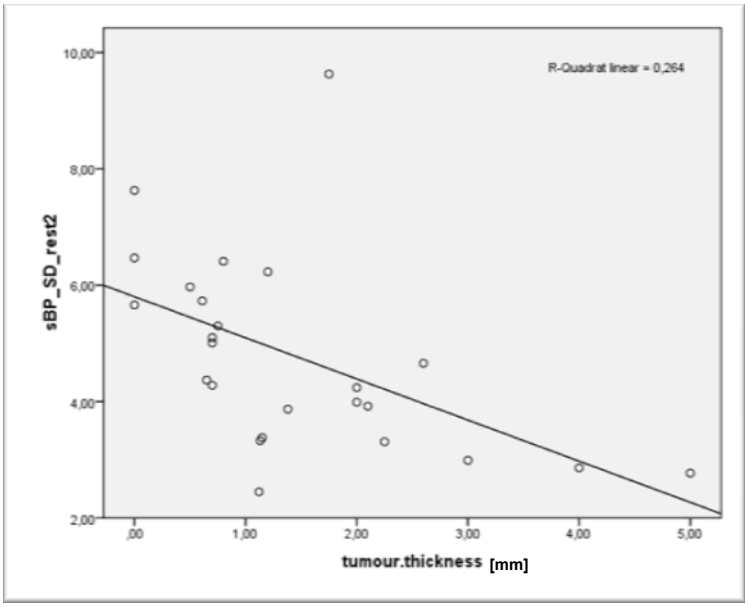
**. Correlation is significant at the 0.01 level (2-tailed).



Graph 3.2.4.2



Graph 3.2.4.3



Graph 3.2.4.4

Summary:

Results demonstrate that there was a significant negative correlation between tumour thickness and SD of sBP during vigilance test and SD of dBP, mBP and sBP during period of rest2. Post stress BPV showed high significant inverse correlation with tumour thickness (see tables 3.2.4.2 and 3.2.4.3).

3.2.5 Tumour thickness, blood pressure variability post stress and stress-coping

Within the MM group tumour thickness was subdivided into three equal groups (2 cut points with 33.33%). In order to evaluate whether the two “extreme-groups” (group1: low tumour thickness, < 0.7mm; group3: high tumour thickness, > 1.76mm) come from the same distribution, Mann-Whitney U-test was applied.

Table 3.2.5.1

Test Statistics[b]

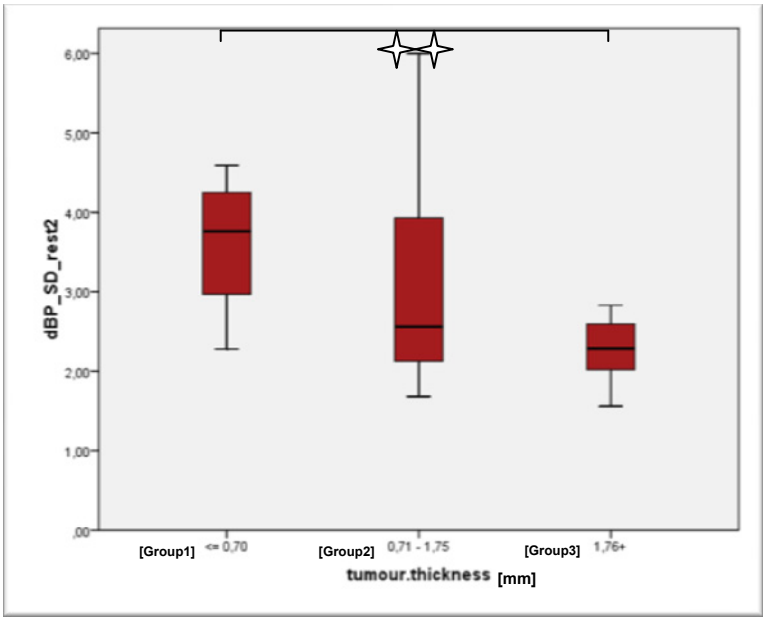
	dBP_SD_ rest2	mBP_SD_ rest2	sBP_SD_ rest2	SVF.positive. strategies	SVF.negative. strategies
Mann-Whitney U	7,000	8,000	2,000	15,000	35,000
Wilcoxon W	43,000	44,000	38,000	51,000	80,000
Z	-2,791	-2,696	-3,272	-2,021	-,096
Asymp. Sig. (2-tailed)	,005	,007	,001	,043	,923
Exact Sig. [2*(1-tailed …	,004 [a]	,006 [a]	,000 [a]	,046 [a]	,963 [a]

a. Not corrected for ties.

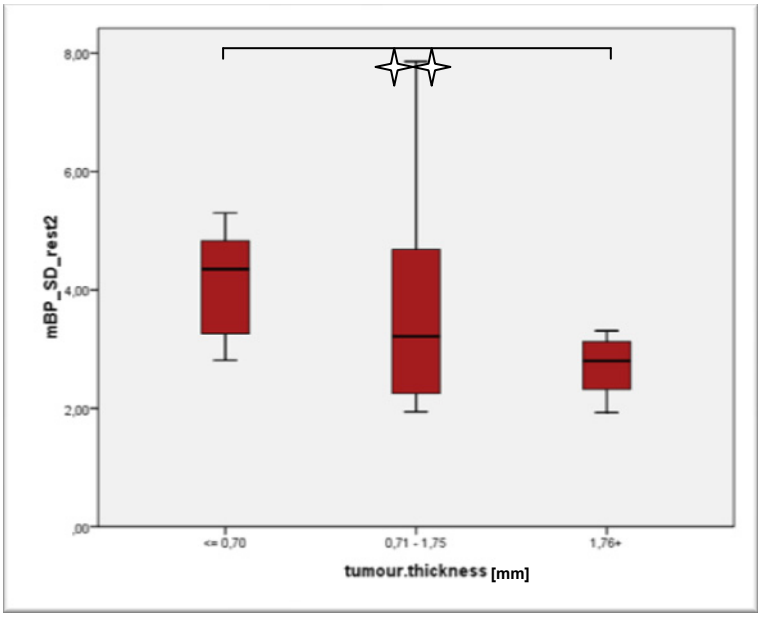
b. Grouping Variable: tumour.thickness(Klassiert)

Table 3.2.5.1 lists the significances of differences between group 1 (low tumour thickness) and 3 (high tumour thickness).

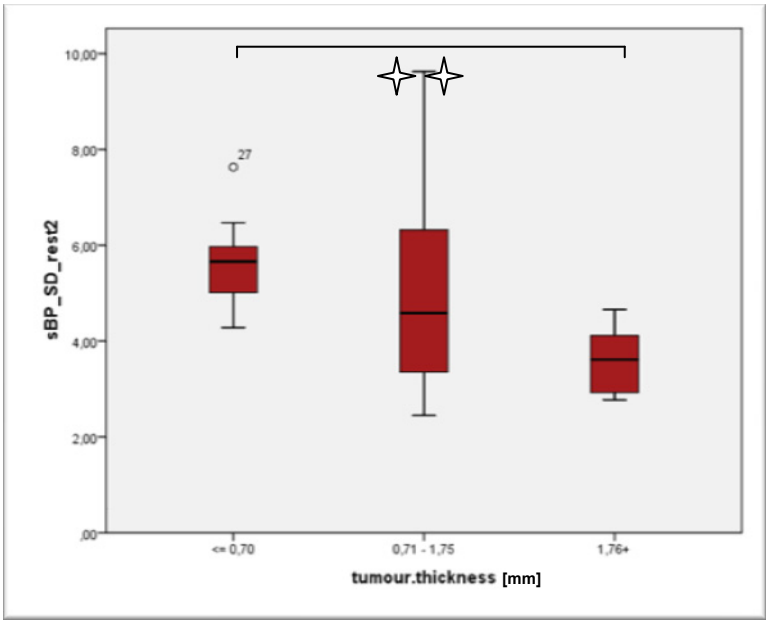
Statistical analysis revealed that group 1 (low tumour thickness) and 3 (high tumour thickness) showed significant differences concerning parameters sBP_SD_rest2 (p = 0.001), mBP_SD_rest2 (p = 0.007), dBP_SD_rest2 (p = 0.005) and SVF.positive.strategies (p = 0.043). With SVF negative.strategies no significant difference could be found.



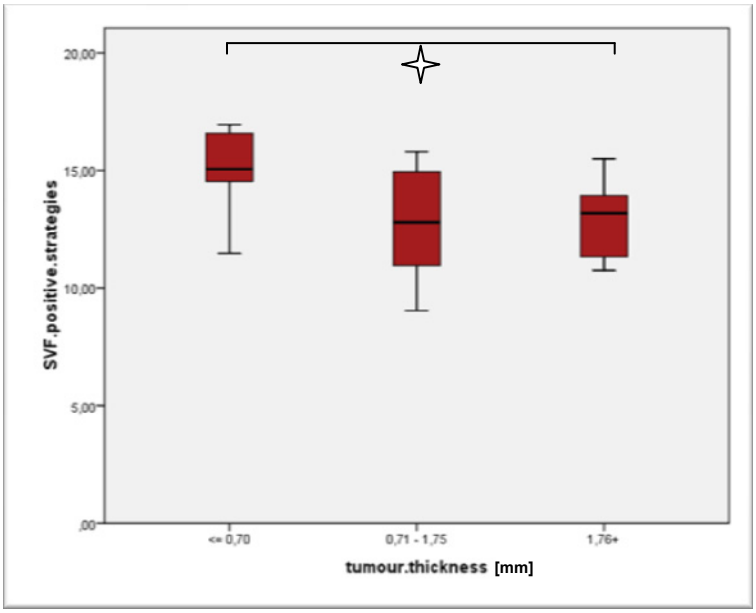
Graph 3.2.5.1



Graph 3.2.5.2



Graph 3.2.5.3



Graph 3.2.5.4

<u>Summary:</u>

Graphs 3.2.5.1 – 3.2.5.4 illustrate that patients with lower tumour thickness have higher values of BPV-parameters and use more positive strategies coping with stressors compared to those patients with higher tumour thickness.

3.2.6 Correlation between blood pressure and blood pressure variability

Values of BP and BPV measured during rest1, vigilance_test and rest2 correlated significantly as can be seen in tables below. Because of the positive correlation of particular parameters between the varying conditions it can be seen that participants with lower BP/BPV values at rest1 (in intra group comparisons) have lower values during vigilance_test and rest2.

Table 3.2.6.1 Correlations of BP and BPV between rest1 and vigilance_test

Correlations

			dBP_mean_ vigilance_test	dBP_SD_ vigilance_test	mBP_mean_ vigilance_test	mBP_SD_ vigilance_test	sBP_mean_ vigilance_test	sBP_SD_ vigilance_test
Spearman's rho	dBP_mean_rest1	Correlation Coefficient	,731**					
		Sig. (2-tailed)	,000					
		N	67					
	dBP_SD_rest1	Correlation Coefficient		,359**				
		Sig. (2-tailed)		,003				
		N		67				
	mBP_mean_rest1	Correlation Coefficient			,684**			
		Sig. (2-tailed)			,000			
		N			67			
	mBP_SD_rest1	Correlation Coefficient				,326**		
		Sig. (2-tailed)				,007		
		N				67		
	sBP_mean_rest1	Correlation Coefficient					,714**	
		Sig. (2-tailed)					,000	
		N					67	
	sBP_SD_rest1	Correlation Coefficient						,307*
		Sig. (2-tailed)						,011
		N						67

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 3.2.6.2 Correlations of BP and BPV between rest1 and rest2

Correlations

			dBP_mean_rest2	dBP_SD_rest2	mBP_mean_rest2	mBP_SD_rest2	sBP_mean_rest2	sBP_SD_rest2
Spearman's rho	dBP_mean_rest1	Correlation Coefficient	,831**					
		Sig. (2-tailed)	,000					
		N	67					
	dBP_SD_rest1	Correlation Coefficient		,513**				
		Sig. (2-tailed)		,000				
		N		67				
	mBP_mean_rest1	Correlation Coefficient			,780**			
		Sig. (2-tailed)			,000			
		N			67			
	mBP_SD_rest1	Correlation Coefficient				,481**		
		Sig. (2-tailed)				,000		
		N				67		
	sBP_mean_rest1	Correlation Coefficient					,778**	
		Sig. (2-tailed)					,000	
		N					67	
	sBP_SD_rest1	Correlation Coefficient						,427**
		Sig. (2-tailed)						,000
		N						67

**. Correlation is significant at the 0.01 level (2-tailed).

Further data analysis revealed that BP and BPV (SD of BP) correlatesd significantly during rest1. No significant correlations between BP and BPV could be found during vigilance_test and rest2 (post stress). Following tables show correlations between the mentioned parameters:

Table 3.2.6.3 Correlations of BP and BPV during rest1 (baseline)

Correlations

			dBP_SD_rest1	mBP_SD_rest1	sBP_SD_rest1
Spearman's rho	dBP_mean_rest1	Correlation Coefficient	,268*		
		Sig. (2-tailed)	,029		
		N	67		
	mBP_mean_rest1	Correlation Coefficient		,356**	
		Sig. (2-tailed)		,003	
		N		67	
	sBP_mean_rest1	Correlation Coefficient			,243*
		Sig. (2-tailed)			,047
		N			67

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 3.2.6.4 Correlations of BP and BPV during vigilance_test (stress task)

Correlations

			dBP_SD_ vigilance_test	mBP_SD_ vigilance_test	sBP_SD_ vigilance_test
Spearman's rho	dBP_mean_vigilance_ test	Correlation Coefficient	,122		
		Sig. (2-tailed)	,326		
		N	67		
	mBP_mean_vigilance_ test	Correlation Coefficient		,057	
		Sig. (2-tailed)		,644	
		N		67	
	sBP_mean_vigilance_ test	Correlation Coefficient			-,072
		Sig. (2-tailed)			,560
		N			67

Table 3.2.6.5 Correlations of BP and BPV during rest2 (post stress)

Correlations

			dBP_SD_ rest2	mBP_SD_ rest2	sBP_SD_ rest2
Spearman's rho	dBP_mean_rest2	Correlation Coefficient	,072		
		Sig. (2-tailed)	,561		
		N	67		
	mBP_mean_rest2	Correlation Coefficient		,136	
		Sig. (2-tailed)		,273	
		N		67	
	sBP_mean_rest2	Correlation Coefficient			,064
		Sig. (2-tailed)			,605
		N			67

3.3 Stress, stress coping and emotional differences between the groups

In order to analyse if there exist differences regarding stress coping behaviour, subjectively experienced stress and the individual experienced emotions, MM group and control group were compared regarding psychological parameters.

3.3.1 Stress coping behaviour (SVF 120): MM vs. control group

Table 3.3.1.1 revealed that there were significant differences in the subtests situational control, resignation and self pity between the MM and control group.

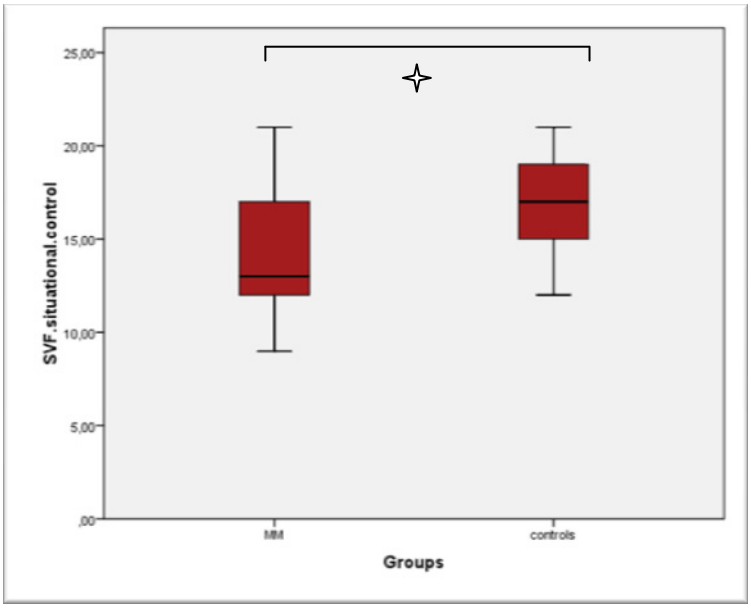
Table 3.3.1.1

Test Statistics[a]

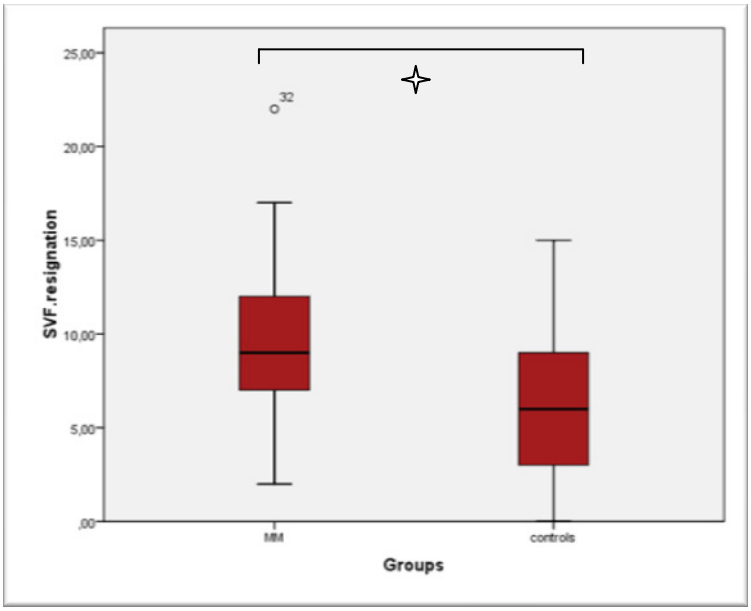
	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
SVF.trivialisation	192,500	423,500	-1,361	,173
SVF.disparagement	202,500	502,500	-1,129	,259
SVF.defence.from.guilt	248,500	479,500	-,310	,757
SVF.diversion.from.situation	208,500	439,500	-,995	,320
SVF.substitute.gratification	215,000	446,000	-,845	,398
SVF.self.affirmation	249,500	480,500	-,057	,954
SVF.relaxation	201,500	501,500	-1,151	,250
SVF.situational.control	165,000	490,000	-2,161	,031
SVF.reactional.control	206,000	437,000	-,841	,400
SVF.positive.self.instruction	227,500	527,500	-,560	,575
SVF.need.social.support	250,500	481,500	-,034	,973
SVF.avoidance	222,500	453,500	-,673	,501
SVF.escape	156,000	366,000	-1,809	,070
SVF.social.withdraw	224,500	455,500	-,841	,400
SVF.intrusive.thoughts	240,500	471,500	-,262	,793
SVF.resignation	158,000	389,000	-2,147	,032
SVF.self.pity	161,500	392,500	-2,069	,039
SVF.self.blame	206,000	437,000	-1,051	,293
SVF.aggression	224,500	455,500	-,630	,529
SVF.drug.use	242,500	542,500	-,228	,820
SVF.positive.strategies01	255,500	580,500	-,155	,877
SVF.positive.strategies02	259,000	490,000	-,077	,938
SVF.positive.strategies03	218,500	543,500	-,971	,331
SVF.positive.strategies	237,000	562,000	-,562	,574
SVF.negative.strategies	223,000	454,000	-,871	,384

a. Grouping Variable: Groups 2 vs. 3

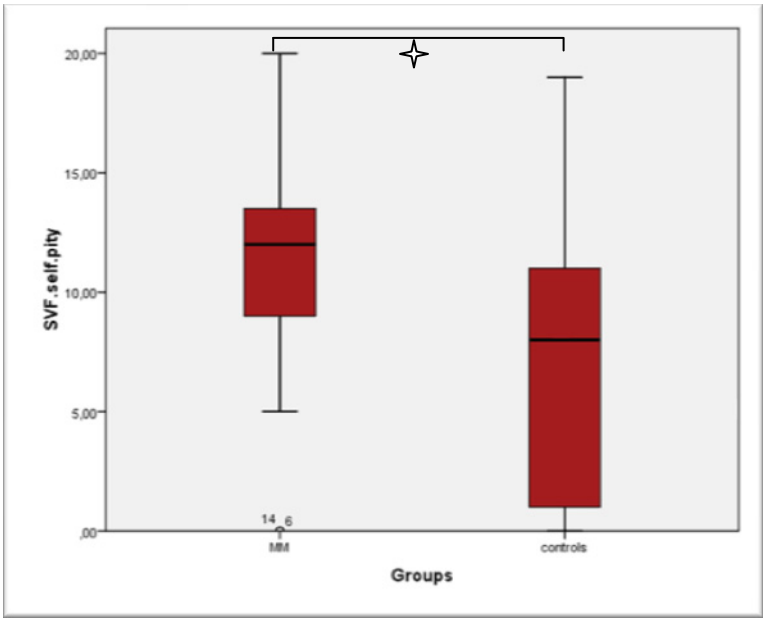
The Graphs 3.3.1.1., 3.3.1.2 and 3.3.1.3 specify the differences. Results demonstrate that patients with MM had significant lower values concerning situational control and significant higher values concerning resignation and self pity.



Graph 3.3.1.1 Groups (MM / control group) vs. coping strategy situational control



Graph 3.3.1.2 Groups (MM / control group) vs. coping strategy resignation



Graph 3.3.1.3 Groups (MM / control group) vs. coping strategy self pity

It was demonstrated that patients with MM have a significant divergent coping behaviour compared to patients of the control group (less situational control, more resignation and self pity, respectively).

3.3.2 Subjectively experienced chronic stress (TICS): MM vs. control group

A comparison between MM patients and the control group did not show any significant differences concerning the experienced stress parameters referring to three month before surgery. The particular parameters are listed in table 3.3.2.1.

Table 3.3.2.1

Test Statistics[a]

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
TICS.work.overload	*221,500*	*452,500*	*-,696*	*,487*
TICS.social.overload	*209,500*	*419,500*	*-,721*	*,471*
TICS.pressure.to.succeed	*232,500*	*557,500*	*-,400*	*,689*
TICS.work.discontent	*259,000*	*584,000*	*-,077*	*,938*
TICS.occupational.excessive.demand	*240,500*	*471,500*	*-,488*	*,625*
TICS.lack.of.social.recognition	*225,000*	*435,000*	*-,355*	*,722*
TICS.social.stress	*233,000*	*558,000*	*-,390*	*,696*
TICS.social.Isolation	*246,000*	*477,000*	*-,137*	*,891*
TICS.chronic.worries	*219,000*	*429,000*	*-,713*	*,476*
TICS.screening.scale.chronic.stress	*224,500*	*434,500*	*-,583*	*,560*

a. Grouping Variable: Groups 2 vs. 3

3.3.3 Experience of Emotions-Scale (SEE): MM vs. controls

In this psychometric test no statistically significant differences between MM patients and controls were found (see table 3.3.2.1).

Table 3.3.2.1

Test Statistics[a]

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
SEE.acceptance.of.emotions	*239,500*	*564,500*	*-,510*	*,610*
SEE.experiencing.overflow.of.emotions	*250,500*	*481,500*	*-,266*	*,790*
SEE.experiencing.lack.of.emotions	*197,500*	*428,500*	*-1,442*	*,149*
SEE.body.focused.symbolisation.of.emotions	*245,000*	*570,000*	*-,387*	*,699*
SEE.immaginative.symbolisation.of.emotions	*261,000*	*492,000*	*-,033*	*,974*
SEE.experiencing.emotional.regulation	*252,000*	*577,000*	*-,233*	*,816*
SEE.experiencing.self.control	*222,000*	*453,000*	*-,896*	*,370*

a. Grouping Variable: Groups 2 vs. 3

4 Discussion

4.1 Hypothesis 1

Apart from the question if patients with MM suffered more stress before the onset of the malign process, or if they experience the receipt of diagnosis as health threat it was hypothesised that patients with MM show a higher reactivity of cardiovascular parameters (BP, BPV respectively) due to a mental stressor.

Rozanski et al. describe that neuroendocrine and neuroplastic changes emanating from psychological stressors can “induce a state of heightened physiologic responsivity to acute stress which may interact with chronic stressors to cause more adverse effects” (Rozanski & Kubzanzky, 2005).

In chapter 3.1 it was demonstrated that patients who suffer from MM have a significant higher BP reactivity to a mental stressor than patients with non melanoma skin cancer (non_MM group) and patients with benign processes (controls). Although it cannot be concluded that the higher reactivity is due to an intense chronic stress exposure that is associated with an immunosuppression and that led to disease´s onset, the significant altered reactivity of blood pressure can be interpreted as aberrance in reactivity.

The association between chronic stress, a heightened physiologic reactivity and a higher cardiovascular risk was described by Rozansky et al. “… data suggest that enhanced physiologic reactivity to acute stress is clinically important, linked to subclinical atherosclerosis and interacting with known psychosocial risk factors to produce greater degrees of subclinical atherosclerosis. Clinical observations suggest that chronic stress, per se, may be an important cause for such enhanced physiologic reactivity. For instance, depressed, hostile, and low-SES (socioeconomic status) subjects all manifest exaggerated physiologic responses to acute stressors. These observations are complemented by experimental animal studies that indicate that repeated exposure to a chronic stressor results in increased adrenal and pressor responses to acute novel stressors. Other animal research indicates that the

mimicking of chronic stress by experimentally elevating glucocorticoids within the brain produces enhanced adrenocorticotropic hormone responses and increases in both baseline arterial blood pressure and heart rate responses to an acute novel stressor" (Rozanski *et al.*, 2005).

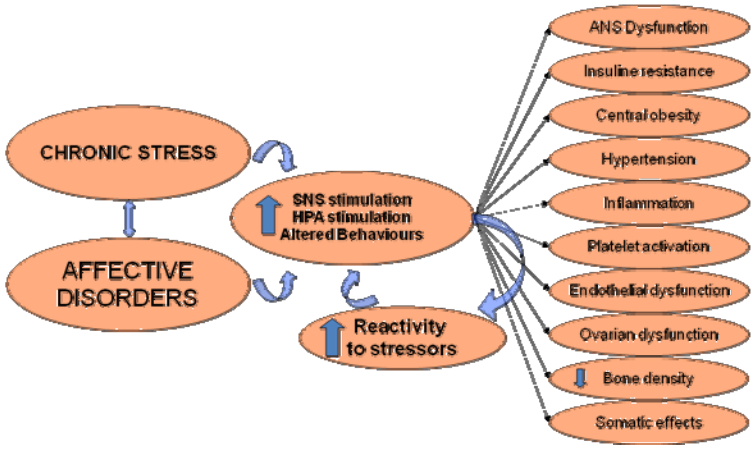


Figure 4.1.1 (Rozanski *et al.*, 2005)

Figure 4.1.1. illustrates the associations between chronic stress exposure, autonomic and endocrinologic variances, a heightened psycho-physiological reactivity and pathologic peripheral effects (Rozanski *et al.*, 2005).

In addition it must be emphasised that a lot of social and psychological factors are associated with states of potential hyperarousal. Figure 4.1.2 lists some factors that cause chronic stress and an increase in cardiovascular reactivity:

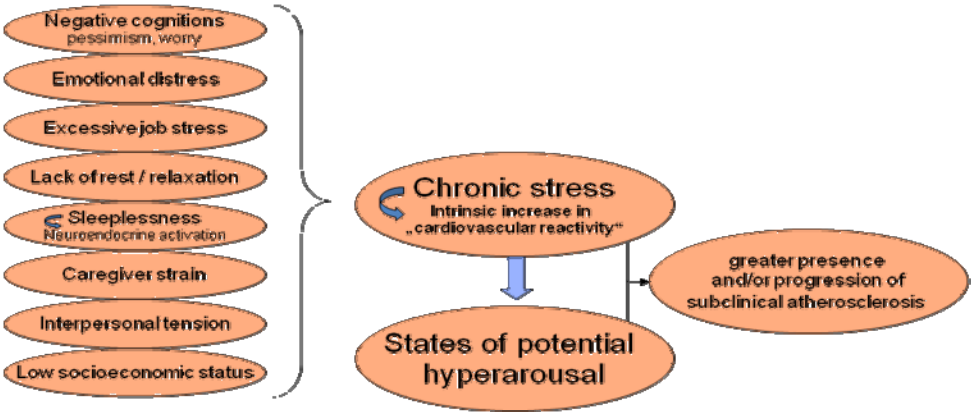


Figure 4.1.2. Factors causing states of potential hyperarousal (Rozanski & Kubzanzky, 2005)

The hyperreactivity can be seen as a process that is associated with reduced resilience. Within the enhanced biopsychosocial model health is defined as the sufficient competence of our organism to cope with any disturbances on any system level auto-regulatively. As a consequence not the absence of pathogen factors or the absence of disease/abnormality in psycho-social fields represents health but the competence of controlling these pathogen factors sufficiently (Egger, 2005, 2008a). It can be concluded that within the enhanced biopsychosocial model illness and health are not seen as states but as dynamic processes. Therefore health must be “created” in every second of our life (Egger, 2005, 2008a, b).

Our organism is permanently exposed to pathogenic risk factors. Both, resilience factors and risk factors of different system levels can exert influence on the dynamic process of health. Besides psychological resilience factors like confidence, internal locus of control, self-confidence/self-efficacy, feeling of self-worth, emotional stability, carefree self-evaluation, interpersonal confidence, challenge, self-awareness (Egger, 1995), also physical fitness can be seen as a resilience factor concerning chronic stress. Schwaberger (1987) revealed that the amount of vegetative reaction to a mental stress depends on the aerobic fitness of healthy individuals (Schwaberger, 1987; Trapp *et al.*, 2009b).

Figueria et al. assumed that psychoneuroimmunology research has declined in the past years because of conceptual and methodological difficulties in specific designs.

Recently there exist some new approaches in the field of biopsychosocial research. Results of the last years emphasise the importance of chronic stress associated influences of the immune system (e.g. modulation of natural killer cells activity) that correlates with tumour progression (Figueira & Ouakinin, 2008). Other authors support the importance of biopsychosocial research (Miller *et al.*, 2009).

In this context it must be considered that behavioural aspects like psychological coping are tightly interlinked with immunological functions. Kiecolt-Glaser et al. demonstrated that altered immunity is associated with coping styles like repression, denial, escape-avoidance and concealment (Kiecolt-Glaser *et al.*, 2002).

Empiric studies demonstrated the impact of emotions (limbic system) on different physiological parameters. central nervous system (CNS), autonomic nervous system (ANS), endocrine system (ES), and immune system (IS) are interlinked (Egger, 2005; Egger *et al.*, 2009).

Following figure illustrates the postulated active principle of psychoneuroimmunology:

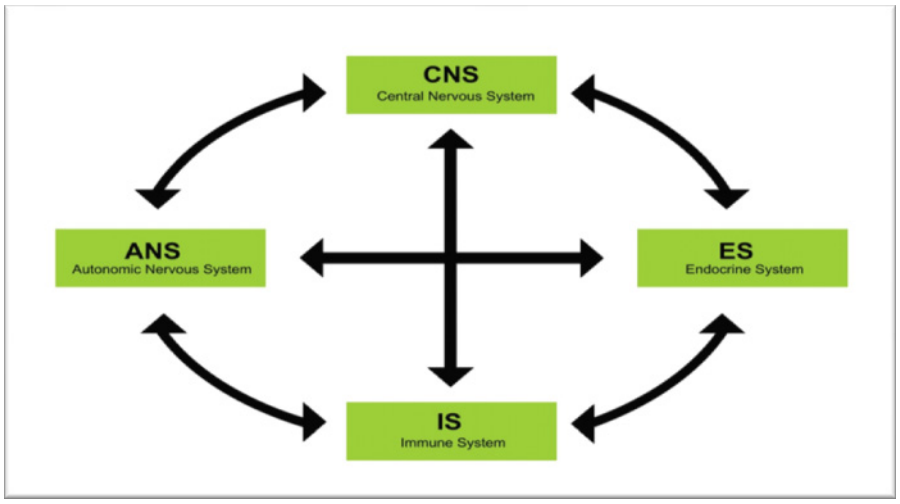


Figure 4.1.3. Parallel interrelation different system-levels of our organism (Egger, 2005)

It can be concluded that acute and/or chronic stress exposure causes an alteration in ANS that influences the central nervous system, the endocrine system and the immune system.

It can be assumed that patients with MM had a higher psychological/physiological strain due to chronic stress exposure. Consequently the development and progression of MM due to immunosuppression can be hypothesised and has to be analysed in further studies.

Furthermore it was assumed that patients with MM suffer intense anxiety and helplessness, respectively. These strong negative emotions can cause a state of psychological distress which induces the hyperreactivity of psycho-vegetative parameters.

Both approaches make a contribution to the hyperreactivity of psycho-vegetative parameters.

It can be concluded that patients with MM suffer a higher level of strain than controls. Thus we must focus on psychological and psychotherapeutic interventions for MM patients in order to guarantee the best biopsychosocial treatment. Azpiroz et al. demonstrated that social stress leads to a higher number of metastases (Azpiroz *et al.*, 2008).

Further investigations will be needed to analyse what kind of interventions cause optimal results concerning stress reduction and disease management.

4.2 Hypothesis 2

It was assumed that MM patients with higher tumour thickness (that are described as more passive, appeasing, helpless) have lower vegetative arousal (BPV) post stress and lower values concerning their positive stress coping strategies.

Results of this study confirm recent findings described in literature.

It was pointed out that Type C (passive, appeasing, helpless) correlates positively with tumour thickness and level of invasion (Temoshok, 1985) and that passive coping style is associated with a decrease in the number of monocytes, an elevation of eosinophile counts and low IFN (Zozulya *et al.*, 2008).

A study of Baumert and colleagues revealed associations between tumour thickness of MM and sociodemographic, clinical and behavioural factors. Results show that an increased tumour thickness was found in patients living alone and having low educational level (Baumert *et al.*, 2007).

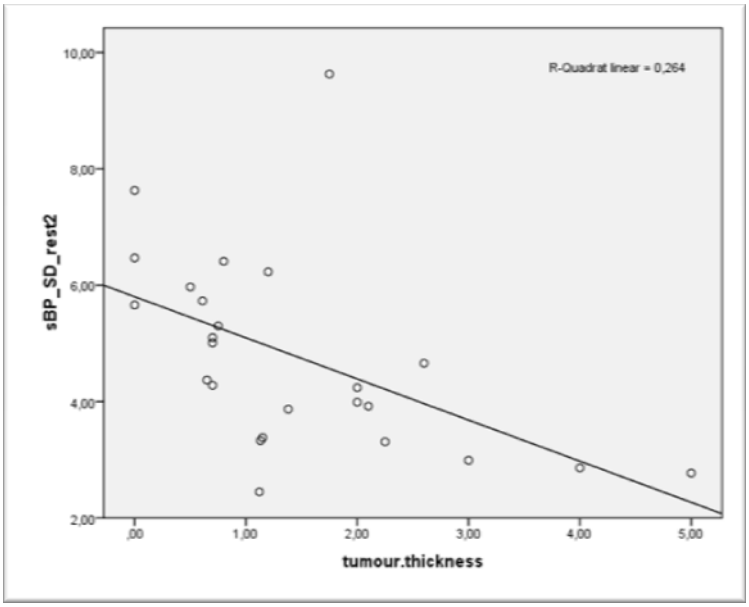
Because of the fact that “social isolation” can be seen as a passive coping strategy it was hypothesised that patients with higher tumour thickness, that are described of being more passive, appeasing and helpless, show lower BPV values post stress.

We could reveal that high BPV (SD of systolic BP) post stress correlates positively with the coping strategy “social isolation” (Miggitsch *et al.*, 2009b).

It was assumed that patients with low tumour thickness are in the know of their better prognosis. Because of the fact that a fighting spirit is an active coping strategy that is associated with a stronger activation of the ANS, it was hypothesised that tumour thickness correlates with BP/BPV negatively.

Results of this study verify hypothesis 2. Significant correlations between tumour thickness and SD of diastolic, mean and systolic BP during period_of_rest2 could be found. To put it differently, post stress BPV showed high significant (negative) correlation with tumour thickness.
In addition it could be demonstrated that patients with lower tumour thickness have more positive coping strategies.

The following graph illustrates results of this study in combination with finding of Temoshok (1985).



Less Type C
Less invasive

More Type C
More invasive

Graph 4.2.1

In chapter 3.2.1 results demonstrate that tumour thickness (in mm) correlates significantly negatively with total peripheral resistance (TPR), diastolic and mean BP at rest1 (baseline). A tendency of correlation can be seen between tumour thickness and systolic blood pressure at rest1 ($r = -0.371$; $p = 0.068$).

In addition tumour thickness correlates significantly with mBP and with dBP by trend during mental task. Post stress there was no correlation between tumour thickness

and dBP, mBP, sBP respectively. Solely dBP post stress shows a correlation with tumour thickness by trend (r = -0.390; p = 0.054). No significant correlation of baseline BPV (rest1) and tumour thickness could be found.
These results imply that at baseline (rest1) patients with lower tumour thickness that correlates with higher total peripheral resistance and higher diastolic and mean BP have a higher vegetative arousal that is associated with higher BP values.

Tschuschke et al. described that patients who respond to the diagnosis with a fighting spirit have longer survival than those who react with hopelessness (Tschuschke *et al.*, 2001).

So it can be concluded that hopelessness can be seen as a very strong stressor that seems to reduce the individual (vegetative/immunological) resilience and reduces the auto-regulative competence of our organism. Within the biopsychosocial model Egger defined health as the sufficient competence of our organism to cope with any disturbances on any system level auto-regulatively (Egger, 2008a).

The importance of coping strategies concerning resilience and tumour progression were described by Fawzy et al. (1993). It was demonstrated that psychiatric interventions that aim to improve coping strategies and that reduce the distress of patients with MM have positive effects on survival (Fawzy *et al.*, 1993).

Vegas et al. showed that subjects (male mice) engaging in (passive) coping strategies that are characterized by an absence of attack, low non-social exploration levels and high levels of defence, subordination and avoidance, developed most pulmonary melanoma metastases (Vegas *et al.*, 2006).

The results of this study go with findings of other authors that emphasise the importance of biopsychosocial aspects in the genesis and progression of cancer.

It can be concluded that patients with low tumour thickness have more positive strategies that are associated with a reduced chronic stress exposure. A reduced chronic stress exposure is associated with a higher resilience. After a stress

exposure they show higher BPV that represents a higher vegetative arousal. It can be assumed that the higher (group intern comparison) vegetative activation is a result of the active dynamic interaction with the mental challenge. Additionally we can assume that patients with lower tumour thickness have less Type C (passivity, hopelessness, etc.) personality traits and react with the mentioned fighting spirit (Tschuschke *et al.*, 2001) also in the vegetative system (higher activation).

Based on these results it can be concluded that future intervention programs must focus on biopsychosocial therapies of MM-patients in order to guarantee an optimal treatment. From these results we cannot conclude whether patients with lower tumour thickness had a higher stress exposure before the manifestation of illness. Nevertheless we can say that high degree of invasion is associated with lower BPV post stress and less positive strategies. So we must clear in a prospective longitudinal study if intervention programs that aim to strengthen positive strategies of MM-patients strengthen the individual resilience and as a matter of fact the life expectance of MM-patients.

4.3 Hypothesis 3

In order to investigate if MM patients are more stress-prone than controls, it was hypothesised that patients with MM have less positive and more negative coping strategies, higher chronic stress exposure and worse experience of emotions.

Söllner demonstrated that high social support and active coping are associated with good adjustment, whereas low perceived support and depressive coping behaviour show significantly poorer adjustment in patients with MM (Söllner *et al.*, 1999).

In chapter 3.3 it could be demonstrated that patients who suffer from MM show significant higher values regarding parameters “self pity” and “resignation” (measured by SVF 120) compared to controls. Besides, coping strategy “situational control” differs between both groups, showing lower values within MM group.

Regarding results of Fawzy (1993), Tschuschke (2001) and Azpiroz (2008) it can be summarised that coping strategies, reducing immunological resilience, contribute to poorer survival.

Fawzy et al. described that coping strategies that reduce patients’ distress have positive effects on survival (Fawzy *et al.*, 1993).

Tschuschke revealed the correlation between fighting spirit and longer survival (Tschuschke *et al.*, 2001).

Vegas et al. could demonstrate that subjects engaging in passive coping strategies developed more pulmonary metastases (Vegas *et al.*, 2006).

In animal models Azpiroz et al. found out that after social stress exposition animal subjects that are characterized by passive-reactive coping strategies (submission, flee, avoidance behaviours) had a higher number of tumour foci, a higher level of

corticosterone and a lower NKG2D receptor expression than subjects with active-proactive coping behaviors (Azpiroz *et al.*, 2008).
In this study it could be demonstrated that patients with MM have higher values concerning specific negative stress-coping strategies (self pity, resignation) and lower values in positive stress coping strategies (situational control).

Per definition persons with low values in “situational control” (SVF 120) do not analyse a specific stressful situation sufficiently and they do not plan and execute operations that aim to control the stressor and stress-reaction. High values regarding the subtest “resignation” (SVF 120) imply that persons being exposed to a stressful situation give up soon. This reaction is associated with emotions of helplessness and hopelessness. Pronounced values in “self pity” signify that persons tend to self-incrimination (Janke & Erdmann, 1997).

We could already show that emotions like helplessness induce a strong vegetative reaction followed by bradycardia (Trapp *et al.*, 2008) and contribute to a heightened vegetative load.

It can be assumed that high values of negative strategies (“self pity” and “resignation”) and low values of positive strategies (“situational control”) are associated with a high vegetative strain and consequently with immunosuppression, which is a predictor of worse course of disease.

Although there is no evidence to what extend coping strategies and chronic stress exposure contributes to the onset or progression of MM, it can be concluded that patients with MM have a reduced resilience from a biopsychosocial point of view.

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