Faculty
Health Sciences

School for Physiology, Nutrition and Consumer Sciences

Cardiovascular Function, Coping and Cortisol in Urbanised Africans: The SAPBA Study

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B.Sc. Hons

2008

Dissertation submitted in the fulfilment of the requirements for the degree Magister Scientiae in Physiology at the North-West University (Potchefstroom Campus). Supervisor: Prof L. Malan; Co- supervisors: Prof J.M. van Rooyen, Dr J.C. Potgieter.

YUNIBESITI YA BOKONE-BOPHIRIMA
NORTH-WEST UNIVERSITY
NOORDWES-UNIVERSITEIT

Potchefstroomkampus

Acknowledgements

I would like to thank all the following people:

Prof L. Malan, for her excellent guidance throughout this study and her never ending enthusiasm and love for the subject.

Prof J.M. van Rooyen, for his support and guidance throughout this study.

Dr J.C. Potgieter for his excellent advice and invaluable input.

My mother, Freda Meyburgh for always believing in my ability to succeed in anything I do and her support throughout the year.

Stephan Konrad Gintner, for never allowing me to give up.

Prof. L. A. Greyvenstein for the language editing.

Opsomming

Motivering:

Omgewingstressors het psigologiese en biologiese effekte en die onvermoë om die stressors effektief te hanteer beïnvloed die gemoed en kan moontlik tot kardiovaskulêre siektes lei. Kroniese stres lei tot versteuring van die hipotalamiese pituïtêre adrenale aksis (HPAA) wat lei tot 'n verhoogte konsentrasie streshormone in die sirkulasie nl. adenokortikotropiese hormoon en kortisol. Onvoldoende terugvoer na die HPPA en onvoldoende glukokortikoïed reseptorbinding in die hippokampus vind ook plaas. Stres en geassosieerde gesondheidskwale is 'n groot probleem in die hedendaagse lewe en daarom is navorsing oor die psigobiologiese verwandskap tussen stres en siekte van die uiterse belang.

Doel:

Die doel van die studie is om die verwantskap tussen kardiovaskulêre funksie, kortisol en stress-hanteringstrategieë asook hul bydrae tot eindorgaanskade te ondersoek.

Metodologie:

Die SABPA (***S**ympathetic **A**ctivity and **A**mbulatory **B**lood **P**ressure in **A**fricans)* studie was 'n teiken populasiestudie met 'n steekproef van vastende, verstedelikte swart Afrikane, van 21-62 jarige ouderdom, van een van die vier Dr Kenneth Kaunda onderwysdistrikte. 'n Totaal van 200 vastende deelnemers (N=101 mans, N=99 vrouens) het vrywillig deelgeneem. Bloeddruk (BD) metings volgens die Rocci/Korotkoff metode was geneem, gevolg deur Finometer BD data, rustende BD en speekselmonsters voor stressorblootstelling. Stressors het die koue-pressor-toets (KPT) en die kleur-woord-konflik toets (KWK) ingesluit. Analisering van die speekselmonsters is deur ensiem gekoppelde immuunsorbante bepalings gedoen. Rustende speeksel kortisol waardes was 45 minute na ontwaking versamel, om die kortisolontwakingsrespons te vermy, en voltooi voor 10vm volgens gestandaardiseerde prosedures. Kortisolversamelingtye nl. 1. was tussen 06h30-07h00 en tyd 2 tussen 08h30-09h00. Speeksel kortisol was 30 minute na stressorblootstelling geneem. 'n Tweevlekinfusiestel was gebruik, deur 'n geregistreerde verpleegster om vastende bloedmonsters te neem van brangiale vena vertakkings, vir serum estrogeen en natrium fluoried glukose. Die Coping Strategie iIndikator (CSI), wat suksesvol in die Suid Afrikaanse konteks gebruik word is gebruik om streshanteringsstrategieë van die deelnemers te identifiseer. Die CSI is 'n faktor analitiese meeting waar drie strategieë na vore kom: probleemoplossing, vermyding en 'n soeke na sosiale ondersteuning. Die etiesekomitee van die Noord-Wes Universiteit, Potchefstroom kampus, het die studie goedgekeur.

Resultate:

Meer mans as vrouens is hipertensief (63%; 34%) onderskeidelik. HT mans en vrouens toon verhoogde vaskulêre response tydens rus en tydens stressor blootstelling. Beide die NT en HT mans en vrouens se bloedglukose en kortisolwaardes is hoognormaal. Kortisolreaktiwiteit is negatief geassosieer met die ontwikkeling van eindorgaanskade in HT mans ($p=0.06$). Rustende kortisol waardes in beide mans en vrouens is betekenisvol laer gedurende kortisolinsamelings tyd 2, ($p \geq 0.001$).

Parsiële korrelasies, gekorrigeer vir ouderdom, BMI en kortisolinsamelingstyd, toon dat hoë probleemoplossing en hoë vermyding met sentrale BD response korreleer tydens blootstelling aan die KPT in die HT mans. Nekomtrek en hoë probleemoplossing korreleer met sentrale BD response gedurende die KWK toets in HT vrouens. Geeneen van die hanteringsstrategieë is geassosieer met die ontwikkeling van eindorgaanskade in beide mans of vrouens nie.

HT vrouens is meer sentraal obees as hulle NT eweknieë, sowel as die HT mans. Tenspyte hiervan is obesiteit nie geassosieer met die ontwikkeling van eindorgaanskade in HT vrouens nie. Sentrale obesiteit en glukose is wel positief geassosieer met die ontwikkeling van eindorgaanskade in HT mans

Gevolgtrekking:

Glukose en sentrale obesiteit is positief geassosieer met die ontwikkeling van eindorgaanskade in HT mans. Verlaagde kortisolreaktiwiteit is geassosieer met die ontwikkeling van eindorgaanskade in HT mans. Dit stel 'n moontlike HPPA hipoaktiwiteit weens kroniese stres voor, maar meer navorsing is nodig om die spekulasie te bevestig. Geen strategieë vir die hantering van stres blyk geassosieer te wees met die ontwikkeling van eindorgaanskade nie.

Summary

Motivation:

Environmental stressors have psychological and biological effects and the inability to cope with the stressor affects the mood and could lead to cardiovascular disease (CVD). Chronic stress leads to deregulation of hypothalamic pituitary adrenal axis (HPAA) which leads to increased circulating adenocorticotropic hormone (ACTH), cortisol, impaired feedback regulation of the axis and impaired glucocorticoid receptor binding in the hippocampus. Stress and related health impairments are major problems in human life, therefore, the investigation into the psychobiological pathways that link stress and disease are of great importance.

Aim:

The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage.

Methodology:

The SABPA (***S****ympathetic* ***A****ctivity and* ***A****mbulatory* ***B****lood* ***P****ressure in* ***A****fricans)* study was a target population study which included a sample of fasting urban black Africans, aged 21-62 years, from one of four education districts in the Dr Kenneth Kaunda Education districts, North-West Province. There was a total of 200 fasting participants (N=101 men, N=99 women). Blood pressure (BP) measures according to the Rocci/Korotkoff method were taken, followed by Finometer BP data, resting blood and saliva sampling before stressor application. Stressors included: the cold pressor test (CPT) and colour word conflict test (CWC). Cortisol saliva sample analysis was done with an enzyme-linked immunosorbant assay. Resting salivary cortisol levels were taken 45 minutes after awakening, avoiding the Cortisol Awakening Response (CAR), and completed before 10am according to standardized procedures. Cortisol sampling time 1 was between 06h30-07h00 and time 2 between 08h30-09h00. Saliva cortisol sampling was done 30 minutes after exposure to each stressor (Salivette Sarstedt®). A winged infusion set was used, by a registered nurse, to sample blood from brachial vein branches; for serum estrogen as well as sodium fluoride glucose. The Coping strategy indicator (CSI), which has been has been successfully used in South Africa, was used. The CSI is a factor analytical derived measure of coping where three fundamental coping strategies are revealed: Problem solving, seeking social support and avoidance. The Ethics Committee of North-West University, Potchefstroom Campus, approved the study.

Results:

More men than women (63%; 34%) respectively are hypertensive. Hypertensive (HT) men show increased vascular responses when subjected to the cold pressor test (CPT) and HT women show similar vascular reactions, but only to the colour word conflict test (CWC) test. Irrespective of blood pressure (BP) status, men and women have high-normal blood glucose levels and high-normal cortisol values. Decreased cortisol reactivity is associated with the progression of target end organ damage in the HT men ($p=0.06$). Resting cortisol values in both men and women are significantly lower during sampling time 2, ($p \geq 0.001$).

Partial correlations, adjusted for age, BMI and cortisol sampling time, indicate that high problem solving as well as high avoidance correlates with central BP response changes during the CPT in HT men. Neck circumference (NC) and high problem solving correlate with central increases in BP in HT women during the CWC test. None of the coping strategies are associated with the progression of target end organ damage in either the men or the women.

HT women are more centrally obese than their NT counterparts, and even than the HT men. Despite this, obesity is not associated with the progression of target end organ damage in the HT African women. Interestingly glucose and central obesity is positively associated with the progression of target end organ damage in the men.

Conclusion:

Glucose and central obesity is positively associated with the progression of target end organ damage and atherosclerosis in HT men. Decreased cortisol reactivity is associated with the progression of target end organ damage in the men, indicating possible HPPA hypoactivity due to chronic stress. However more research is needed to confirm this speculation. Coping strategies did not seem to be associated with progression of target end organ damage.

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List of Abbreviations

ACTH	Adeno-corticotrophin hormone
BMI	Body mass index
DBP	Diastolic blood pressure
CAR	Cortisol awakening response
CBG	Corticosteroid binding globulin
CIMT	Carotid intima media thickness
CO	Cardiac output
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CSI	Coping strategy indicator
CVD	Cardiovascular disease
Cw	Windkessel Compliance
HPAA	Hypothalamic pituitary adrenal axis
HT	Hypertensive
NC	Neck circumference
NT	Normotensive
SBP	Systolic blood pressure
SV	Stroke volume
TPR	Total peripheral resistance
WC	Waist circumference
11ß-HSD	11ß-hydroxysteroid dehydrogenase

CHAPTER ONE

PREFACE AND OUTLINE OF THE STUDY

Cardiovascular function, coping and cortisol in urbanised Africans: The SAPBA study.

1.1 PREFACE

Chapter 1 gives the preface and outline of the study. Chapter 2 gives a literature overview of all the applicable variables under discussion in this study. Cardiovascular function, coping styles and cortisol, including confounding factors, are discussed in detail in Chapter 2. Interactions between the above mentioned variables are also discussed. This dissertation consists of one manuscript in Chapter 3, which *will* be submitted for publication in a peer-reviewed journal*. Once the article is submitted to the relevant journal for publication, the references will be in accordance to the prescribed style of the journal itself. Relevant references are given at the end of Chapter 2 and Chapter 4 as instructed by the mandatory style enforced by the North-West University, Potchefstroom Campus, South Africa.

* Manuscript (Chapter 3): Journal for submission – International Journal of Psychophysiology.

1.2 OUTLINE OF STUDY

The outline of the study is as follows:

Chapter 1: Preface and outline of study.

Chapter 2: Introduction, literature overview, questions arising from literature, motivation and aim

Chapter 3: Manuscript – Cardiovascular and cortisol responses, and coping in urbanised Africans: The SAPBA study

Chapter 4: Summary, discussion and findings, confounding and bias, power of study, conclusion and recommendations.

1.3 AUTHORS' CONTRIBUTION

The contribution of each of the researchers involved in this study is given in the following table:

Table 1.1 Authors contribution list

Ms Danelle Meyburgh (B.Sc. Hons) (Physiologist)	Responsible for literature searches, statistical analysis, design and planning of the manuscript, interpretation of results and writing of the manuscript
Prof L. Malan (Ph.D) (Physiologist)	Supervisor. Supervised the writing of the manuscript, project leader, collection of data, initial planning and design of manuscript
Dr J.C. Potgieter (Ph.D) (Psychologist)	Co-supervisor. Supervised the writing of the manuscript and collection of data
Prof J.M. van Rooyen (D.Sc) (Physiologist)	Co-supervisor. Supervised the writing of the manuscript and collection of data

The following is a statement from the co-authors confirming their individual roles in this study and giving their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above mentioned manuscript, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the M.Sc. dissertation of Danelle Meyburgh.

Prof L. Malan

Dr J.C. Potgieter

Prof J.M. van Rooyen

CHAPTER TWO

INTRODUCTION AND LITERATURE STUDY

1. Introduction

The intimate connection between the brain and the heart was presented by Claude Bernard more than 150 years ago (Thayer & *Lane.,* 2009). Psychological status influences cardiovascular function and due to feedback from the cardiovascular system to the brain, the condition of the cardiovascular system can directly or indirectly influence the mood. This bi-directional association is described in humans, but the precise neurobiological processes and mediators are not fully known or understood (Freedland *et al.*, 2003; Grippo, 2009).

Environmental stressors have psychological and biological effects; for example psychological appraisal or coping with the stressor affects the mood and could lead to cardiovascular deregulations e.g. hypertension, endothelial dysfunction and changes in vascular resistance (Bairey Merz *et al.,* 2002; Schwartz *et al.,* 2003). It was postulated by O'Donnell *et al.* (2008) that neuroendocrine pathways partly mediate the relationship between coping and health. According to Malan *et al.* (2006a), no cultural specific coping strategies for Africans are known, but urban living in Africans is associated with cardio metabolic diseases such as hypertension and higher than normal blood glucose levels (Malan *et al.*, 2008). Increased cardiovascular stress responses to stress/challenges are associated with increased risk for cardiovascular disease (CVD) (Wright *et al.,* 2007). It is still not fully clear how acute/chronic stress differentially affects the Hypothalamic-Pituitary-Adrenal Axis (HPAA) (Helhammer *et al.*, 2009) and Kudielka *et al.* (2009) suggested that salivary cortisol responses to acute challenges show large intra and inter-individual variability. Since stress and related health impairments have become major problems in human life, investigation in the biological pathways that link stress, coping and disease are of major importance (Kudielka *et al.,* 2009). Research regarding the prevalence of hypertension and cardiovascular diseases in African populations is in great demand (Opie & Seedat, 2005). There is also an urgent need for studies to be done in Africa to determine the risk factors associated with hypertension in specific living circumstances (World Health Organisation, 1999). Opie and Seedat (2005) reported that further studies are needed on black Africans, who may (or may not) be genetically and environmentally different from African Americans and each other, due to the vastness of the African continent.

Due an interaction that is seen between stress, coping and CVD, further research is needed to evaluate this interaction (Johnsen *et al.,* 2002; Kudielka *et al.,* 2009; Thayer & Fischer, 2005) especially in Africans (Opie & Seedat, 2005; World Health Organisation, 1999). These functions are now discussed.

2. Stress and coping

According to Steptoe (2007), the effects of stress manifest in four domains; physiology, behaviour, subjective experience and cognitive function. Factors that contribute to the variations in these effects are 1) the nature of the stressor, 2) coping responses, 3) time course of experience, 4) genetic factors, 5) temperament of the person, 6) previous experience and 7) social support available (Steptoe, 2007). Coping responses are deliberate and effortful attempts to manage stress; this includes constantly changing cognitive and behavioural attempts to control internal and external demands of the situation, which exceeds the resources of a person (Amirkan & Auyeung, 2007; Lazarus & Folkman, 1984).

Environmental stressors have psychological and biological effects, where psychological appraisal of the stressor could affect the mood leading to cardiovascular deregulations e.g. hypertension, endothelial dysfunction, changes in vascular resistance (Bairey Merz *et al.,* 2002; Schwartz *et al.,* 2003). Exposure to chronic stress is a good predictor of cardiovascular disease (Schubert *et al.,* 2009). Chronic stress leads to deregulation of HPAA which leads to increased circulating adenocorticotropic hormone (ACTH), cortisol, corticosterone, impaired feedback regulation of the axis and impaired glucocorticoid receptor binding in the hippocampus, cortex and dorsal raphe nucleus (Grippo, 2009). Hans Selye proposed a syndrome to understand glucocorticoid secretion during stress. The syndrome is better known as the 'General Adaptation Syndrome' (Vinson, 2009). Stage 1: The Alarm reaction; this describes all the non-specific systemic reactions elicited by sudden exposure to adverse stimuli. Stage 2: Resistance and re-establishment of homeostasis; during which pathological changes in the heart, vasculature and adrenal cortex can be expected. Stage 3: Exhaustion; the non-specific responses are no longer able to maintain homeostasis (Vinson, 2008). This profile applies to both chronic and severe stress (Vinson, 2008).

2.1. Stress and coping in urban Africans

African centred coping is viewed as an effort to maintain a sense of harmony and balance within the physical, metaphysical, and collective and the spiritual/psychological realms of existence (Utsey *et al.,* 2000). When this balance is disturbed, stress and subsequent disease is the result (Utsey *et al.,* 2000).

According to Malan *et al.* (2006b), specific cultural coping strategies for Africans need further investigation. It is also not well described how a particular coping style is associated with factors that maintain and aggravate psychosomatic diseases in Africans (Malan *et al.,* 2006a). According to Malan *et al.* (2006b, 2008), stress due to urbanised living in Africans is associated with cardio metabolic diseases such as hypertension and higher than normal blood glucose levels. High levels of stress due

to urban living have been associated with increases in blood pressure (BP) (Seedat, 2000; Malan *et al.*, 2008). Africans exhibit exaggerated cardiovascular reactivity and peripheral resistance responses at rest and when exposed to stressful situations (Malan *et al.,* 2006a). Psychological factors such as urban living conditions and confrontation with an individualistic value system, which is different from their traditional collectivistic value system in which interdependence is important, could lead to these enhanced cardiovascular responses in urban Africans (Wissing &Van Eeden, 2002).

Persistent psychological stress resulting from urban living in South Africans could lead to increased allostatic load and decreased ability to cope (McEwen, 2003; Malan *et al.,* 2006b). According to Malan *et al.* (2008), urbanised Africans are more vulnerable to CVD and metabolic syndrome than their rural counterparts. The possibility of emergence of the metabolic syndrome in urbanised active coping males is 17.2 % and in passive coping males 11.8 % (Malan *et al.,* 2008).

Active coping/problem solving evokes a β-adrenergic response which increases the BP via a central mechanism: systolic blood pressure (SBP) is increased with an increase in cardiac output (CO) and stroke volume (SV) (Henry *et al.,* 1986; Suzuki *et al.,* 2003). A β-adrenergic response is evoked when a person sees a stressor as a challenge and actively copes with the stressor (Malan *et al.,* 2006a). Passive coping evokes a α-adrenergic response when a person experiences little or no control during stressor and is indicative of surrendering and feelings of helplessness (Malan *et al.,* 2006a).

Malan *et al.* (2008) found that urban African men who have an active coping style had higher cardiovascular risk than African men from rural areas. These findings are contradictory to O'Donnell *et al.* (2008) who found that individuals who coped actively by problem engagement and seeking support had lower cortisol levels. Malan *et al.* (2008) proposed a mechanism for the above mentioned phenomena: a shift in BP response from a central (β- adrenergic) to a more vascular (α-adrenergic) response in urbanised individuals occurs. Suzuki *et al.* (2003) stated that a α-adrenergic pattern is usually associated with an emotion-focused/passive coping pattern. Then how is it possible that active copers react physiologically like passive copers? Malan *et al.* (2008) proposed an answer: behaviourally an active coping strategy is followed, but physiologically a passive/emotional coping strategy dominates. During exposure to chronic psychosocial stress in urban living the traditionally African collectivistic culture decreases with resultant lower social support and stressful situations could feel uncontrollable (Malan *et al.,* 2006b). It is proposed that enhanced vascular reactivity and increased norepinephrine secretion during α-adrenergic stimulation would occur with, a synergistic effect on cortisol which may further impact on depression or distress via the HPPA (Björntrop, 2001).

2.2. Coping in other ethnical groups

In a study done on 110 African American women, perceived racism was positively associated with changes in SBP (Clark, 2006). Seeking social support as a coping mechanism moderated this relationship between perceived racism and SBP (Clark, 2006). According to Utsey *et al.* (2006), cognitive ability and social support moderated the relationship between stress and quality of life in African Americans. Seeking social support appeared to be a very beneficial strategy for handling work pressures and avoidance related to poor mental health in a study conducted by Jackson and Saunders (2006).

Over 300 African American women participated in a study describing psychological distress and gendered racism, using the Africultural Coping Styles Inventory (Thomas *et al.,* 2008). Cognitive-emotional coping styles mediated gendered racism and distress (Thomas *et al.,* 2008). There were no mediating effects with spiritual-centred, collective and ritual-centred coping (Thomas *et al.,* 2008).

A study conducted by Patterson (2003) found that problem-focused coping in Caucasian police officers had a reverse buffering effect on wellbeing, thus resulting in higher distress. Seeking social support buffered the relationship between work events and distress (Patterson, 2003). Patterson (2003) stated that social support protects workers from the negative effects of stress in two ways; 1) social support has a direct effect on psychological well being regardless of level of stress, 2) when social support outside the work related environment is high, the negative effects of work related stress is reduced significantly. Social support inside work-related environment was associated with greater distress and increased negative effects on well being (Patterson, 2003). No evidence was found of social support acting as a mediator between perceived work demand and burnout (Devereux *et al.,* 2009). The people who had the lowest level of support had the highest personal accomplishment scores when perceived work demands were high (Devereux *et al.,* 2009). In a study done on 31 Caucasian fathers of children with cancer, distancing and avoidance was associated with higher levels of psychological distress (Koraman & Defne, 2006). Painful problem solving, confrontational coping and seeking social support in these fathers was not related to levels of psychological distress experienced (Koraman & Defne, 2006).

A study done on teachers in the George region by Oliver and Venter (2003) found that some teachers lack coping mechanisms to combat excess stress effectively and this could lead to serious physical conditions such as hypertension and heart disease. Knowledge about stressors that teachers encounter could be valuable in order to avoid and/or manage these stress-inducing factors (Oliver & Venter, 2003). Teacher stress in South Africa is extremely high and little appears to be done within the education sector to combat these high levels of stress (Milner & Khoza, 2008).

2.3. Coping Strategy Indicator

According to Amirkhan (1990), The Coping Strategy Indicator (CSI), a factor analytical derived measure of coping, three fundamental coping strategies are revealed: problem solving, seeking social support and avoidance. The CSI is a brief self-report inventory of 33 items (Amirkhan & Auyeung, 2007; Desmond *et al.,* 2006). It was empirically and inductively derived and taps the strategies most often revealed in coping studies (Amirkan & Auyeung, 2007). CSI has demonstrated acceptable psychometric strength within adult populations in terms of a) internal consistency, b) external reliability, c) significant correlations to established measures of coping, personality and pathology, d) discriminate validity, with no associations to indices of social desirability; and e) criterion validity, with prediction of actual coping responses made both in laboratory and real world settings (Amirkhan, 1990).

Intercorrelations exist between subscales approximate to zero, except for a minor overlap between problem-solving and social support seeking (Amirkhan, 1990; Bijttebier & Vertommen, 1997). This is a unique feature of the CSI in comparison with other coping instruments e.g. COPE (Amirkhan, 1990; Bijttebier & Vertommen, 1997). High scores on more than one coping style reflect flexibility in coping, and not the use of a single strategy defined by the variance shared among scales (Amirkhan, 1990; Bijttebier & Vertommen, 1997).

Problem-solving coping can be defined as a person-environment relationship which is changed by instrumental action. It is a direct assault strategy (Amirkhan, 1990; Lazarus & Folkman, 1984). Seeking social support is defined as actively turning to others for support, help and advice. Avoidance is defined as a flight tendency involving physical and/or psychological withdrawal from the stressor (Amirkhan, 1990; Lazarus & Folkman, 1984).

Whether stress measures relate to health equally across ethnic groups remains unclear, therefore, psychological characteristics of health must be considered within cultural and ethnic contexts to be fully understood (Consedine *et al.*, 2006). Despite extensive study of the interaction between coping and other aspects of human functioning and the subsequent development of coping models, little has been done to identify the differences in coping between different cultural groups (Utsey *et al.,* 2000).

3. Salivary cortisol as a measure of stress

3.1. Cortisol induced hypertension

McEwen and Seeman (1999) summarize cortisol main actions as follows:

- Mobilization of energy
- Increases cerebral perfusion rates and glucose utilisation
- Increases cardiovascular output and respiratory rates
- Redistribution of blood flow
- Increase energy delivery to brain and muscle
- Modulating immune function.

Studies conducted by Scheuer and Bechtold (2002) showed that administration of corticosterone in normotensive rats over a period of days leads to modulation in the baroreflex function without affecting basal cardiovascular parameters. Although after extended treatment, increases in basal BP were seen (Sheuer & Mifflin, 2001). This indicates that glucocorticoids have a significant role to play in the central control of the cardiovascular system during stress (McDougall *et al.,* 2005).

Since most patients with Cushing's syndrome do not have symptoms that are consistent with hypermineralocorticoidism such as hypokalemia and hyporeninemia, glucocorticoids appear to cause hypertension by a mineralocorticoid-independent mechanism (Greenspan & Gardner, 2004).

In the proposed mechanism as summarized by Greenspan and Gardner (2004) increased cortisol has the following effects:

- Decreased reactivity to vasodilator systems such as kinins and prostaglandins. This leads to increase in total peripheral resistance (TPR)
- Degradation of catecholamines is inhibited and this causes vasoconstriction
- Increases vascular reactivity to vasoconstrictors
- Increases renin substrate formation (Angiotensinogen); therefore an increase in plasma renin concentration and plasma renin activity follows
- The increased angiotensin II causes further vasoconstriction
- Increased epinephrine production by the adrenal medulla
- Increased fluid shift from the intra to the extracellular fluid compartments; thus an increase in plasma volume is seen
- Cortisol may occupy mineralocorticoid receptors. Mineralocorticoid receptors are unable to distinguish between aldosterone and cortisol leading to sodium and water retention (Mantero & Boscaro, 1992; Dotsch *et al.,* 2001).

Increased plasma volume leads to increased cardiac output whilst increased TPR and cardiac output (CO) causes hypertension (Greenspan & Gardner *et al.,* 2004).

Congenital deficiency or inhibition of 11ß-hydroxysteroid dehydrogenase (11ß-HSD) activity resulting in the inability to convert cortisol to the inactive cortisone is associated with hypertension and mineralocorticoid excess symptoms (Sandeep & Walker, 2001). When this protective mechanism is lost, cortisol concentrations become much higher than aldosterone concentrations, which results in flooding of mineralocorticoid receptors (Sandeep & Walker, 2001). Excessive mineralocorticoid (e.g. hypokalemia, decreased plasma renin activity) effects are seen in patients with hypercortisolism, this is caused by an elevated cortisol: cortisone ratio (Dotsch *et al.,* 2001). There is insufficient conversion of cortisol to cortisone via 11ß-HSD 2 and increased binding of the cortisol to mineralocorticoid receptors (Dotsch *et al.,* 2001) This could be a possible explanation for the cause of hypertension and this effect seems to be independent of the role of ACTH in the mechanism of hypercortisolism (Dotsch *et al.,* 2001).

11ß-HSD 2 is mainly found in mineralocorticoid target tissue such as the kidney, sweat glands, salivary glands and colonic mucosa, but also in other non-target tissues such as the blood vessel walls (Sandeep & Walker, 2001). The inactivation of cortisol in resistance vessels could modulate the blood vessels response to glucocorticoids and catecholamine and the inhibition of 11ß-HSD 2 action could be a possible mechanism for the development of hypertension (Sandeep & Walker, 2001).

Patients with essential hypertension do not necessarily show signs of mineralocorticoid excess, but BP levels correlate positively with plasma sodium and negatively with plasma potassium. This suggests that corticosteroids and thus inhibition of 11ß-HSD 2 may play a role in its pathogenesis (Hammer & Stewart, 2006).

There is still uncertainty about the relationship between cortisol reactivity and the cardiovascular stress response, but Roy *et al.* (2001) concluded that basal cortisol rather than cortisol stress reactivity plays a permissive role in increasing sympathetically driven cardiovascular stress responses. As indicated by Roy *et al.* (2001) in their study, systolic pressure stress responses were clearly associated with resting cortisol levels.

A rise in salivary cortisol concentration is delayed with minutes in comparison to cardiovascular responses after exposure to psychological stressors, therefore, cardiovascular responses are unlikely to be functionally dependent upon cortisol reactions (Roy *et al.*, 2001).

3.2. Diurnal response of cortisol

Glucocorticoids are secreted according to a circadian rhythm and during acute or mild stress (Vinson, 2009). Under normal circumstances the highest cortisol production is in the second half of the night with a peak in the early morning hours. The highest peak is reached 20-30 minutes after awakening, this is known as the cortisol awakening response (CAR) (O'Donnell *et al.,* 2008; Tsigos & Chrousos, 2002; Williams *et al.,* 2005). Light induces the expression of clock genes in the adrenal glands, which increases cortisol production, independent of ACTH release (Helhammer *et al.*, 2009). A steady decrease is seen as the day progresses with the lowest levels seen in the first part of the night (Tsigos & Chrousos, 2002).

Time of awakening and stress influences the magnitude of CAR (Stalder *et al.,* 2009; Williams *et al.,* 2005). The CAR is usually assessed with saliva samples and is of considerable psychoneuroendocrinological significance (Williams *et al.,* 2005). According to a study conducted by Williams *et al.* (2005), the CAR was greater in subjects working early shifts than later shifts, indicating that time of waking does influence the magnitude of CAR. After adjusting for stress levels the magnitude of CAR between the two groups were no longer significant. The influences of time of waking and psychosocial factors are therefore difficult to disentangle (Williams *et al.,* 2005). Further observations indicated CAR as being stress dependent, especially stress experienced during the first hour after waking (Williams *et al.,* 2005).

Another factor that needs to be considered is the quality of sleep. Quality of sleep was found to be inversely associated with subjective stress experienced in the morning (Williams *et al.,* 2005). It remains difficult to disentangle the effects of sleep quality and subjective stress on CAR (Williams *et al.,* 2005). In contradiction to Williams, Stalder *et al.* (2009) found CAR to be unaffected by sleep quality. Health status and age also appear to have an impact on the magnitude of CAR (Kudielka & Kirschbaum, 2003). Individuals who have health problems have elevated cortisol concentrations after awakening (Kudielka & Kirschbaum, 2003). There are no significant relationships between coping style and CAR or cortisol slope during the day. However, despite the considerable research interest and a growing number of studies, no common consensus has emerged to the role of CAR (Stalder *et al.,* 2009).

Due to the circadian rhythm that cortisol follows, the time of day which blood is sampled has a large effect on cortisol concentration which is detected. Adjustment for the time of sampling is, therefore, of the utmost importance (Smith *et al.,* 2005).

3.3. The effect of smoking and alcohol consumption on cortisol secretion

Results of cortisol levels between smokers and non-smokers have been very inconsistent (Steptoe & Ussher, 2006). Sidhartha *et al.* (2009) describes smoking as affecting the HPAA in various ways leading to changes in the physiological stress response. Steptoe and Ussher (2006) found a general elevation in cortisol levels of smokers when compared to non-smokers; CAR was also greater in smokers. Women who smoke demonstrate a blunted cortisol response when compared to women who do not smoke (Back *et al.,* 2008). According to Back *et al.* (2008), smoking status did not affect cortisol response in men, suggesting that women are more sensitive to the impact of smoking. Confirming the above observations, chronically induced nicotine could elevate ACTH/cortisol levels and cause a blunted HPAA response during acute stress (Phillips *et al.,* 2009; Kudielka *et al.,* 2009). Heavy drinkers, as compared to light social drinkers, also show an attenuated HPAA response to alcohol challenge (Bau *et al.,* 2007).

3.4. Salivary cortisol as a marker in stress research

Salivary cortisol is frequently used as a biomarker in stress research to determine the effect of a stress stimulus on the HPAA indirectly (Helhammer *et al.*, 2009). The HPAA is complex in nature and its responses are modulated by numerous psychological and biological events. It is generally assumed that a high covariance should exist between HPAA activity and psychological stressors (Bujs & Van Eden, 2000), but studies proved this to be contradictory (Cohen *et al.,* 2000; Osward *et al.,* 2004).

The cortisol levels in the saliva are partly dissociated from other HPAA endocrine signals e.g. C-reactive protein (CRP), ACTH, vasopressin, cortisol urine and blood levels (Helhammer *et al.*, 2009). Reasons for this discrepancy are as follows: 1) the degree to which the HPAA is activated depends on the psychological appraisal of the stressor e.g. unpredictability, uncontrollability, anticipation, perceived stress and habituation (Kudielka *et al.,* 2007), 2) a large time lag exists between psychological and endocrine responses to stressors (Smyth *et al.,* 1998; Scholtz *et al.,* 2008), 3) gender is known to impact self reported stress levels (Helhammer *et al.,* 2009), 4) corticosteroid binding globulin (CBG)-binding and saturation.

Free cortisol represents the fraction of the hormone which is biologically active and, therefore, salivary cortisol has been considered to be a better measure of adrenocortical function than serum cortisol (Vining 1982). However this was challenged by Levine *et al.* (2007) who suggested that CBG-bound cortisol may have physiological effects on target tissue.

Proportion of salivary cortisol to total cortisol ranges from 1-2% in lower and 8-9% in higher ranges (Helhammer *et al.,* 2009). Therefore, salivary cortisol levels have to be treated with caution, since the linearity between the two is compromised in response to a challenge or under conditions that affect CBG-bound cortisol levels e.g. oral contraceptives, menstrual cycle and pregnancy (Helhammer *et al.,* 2009). CBG-saturation differs in men, women and in women taking oral contraceptives (Helhammer *et al.,* 2009). Higher serum cortisol levels before total CBG saturation are found in women taking oral contraceptives compared to other women and overall in women than in men (Helhammer *et al.*, 2009). According to Levine *et al.* (2007), 14% of cortisol in saliva is bound and 30% is enzymatically converted to cortisone in saliva and this leads to relatively low salivary cortisol compared to serum cortisol. Adrenal sensitivity, capacity and cortisol binding affect the total and free cortisol levels in the blood and this determines the salivary cortisol level.

Despite the above, salivary cortisol levels can be expected to correlate reasonably well with total cortisol levels in the upper and lower ranges. Thus salivary measures are the method of choice in stress research, at least in measuring free cortisol levels (Helhammer *et al.*, 2009).

3.5. Measuring the stress response

In a psychophysiological laboratory, the autonomic response can be provoked by physical, mental and psychosocial stressors but the HPAA response seems to be specific to psychosocial challenges that involve the ego (Kajantie & Philips, 2006). To assess stress responsiveness a reproducible stressor is needed, that would reveal differences between individuals (Kajantie & Philips, 2006). The limitations of laboratory tasks are as follows; participant habituation to task, uncertain degree of challenge, and the inability to measure the concurrent activation of several biological paths (Loft *et al.,* 2007).

Mental tasks such as the "Stroop test" produce sympathoadrenal stimulation (mixed α and β reactivity) and HPAA response to this test alone has been rarely studied (Kajantie & Philips, 2006). Physiological stimuli such as the cold pressor test (CPT), which is the most commonly used laboratory stressor, can be used to assess individual differences in the stress response, as it is thought to increase vasopressin secretion via the hypothalamus which potentiates corticotropin-releasing hormone (CRH) action and induces α-adrenergic reaction which increases TPR, decreased SV and CO remains unchanged (Kajantie & Philips, 2006; Schwabe *et al.,* 2008). CPT evokes strong sympathetic nervous system activation, but low to moderate HPAA response (Schwabe *et al.,* 2008). One of the major criticisms of early studies was that the stressors used were only sufficient enough to study the autonomic nervous system response and not the HPAA response (Kajantie and Philips, 2006).

3.6. Gender and cortisol

The influence of sex steroids on HPAA activity is complex and not completely understood and has predominantly only been studied in rodents (Helhammer *et al.*, 2009). Women in the follicular phase of the menstrual cycle show smaller ACTH and salivary cortisol responses to stressors than men, while women during any time of the cycle phase show higher salivary cortisol 45–60 min after awakening (Wüst *et al.,* 2000). Between puberty and menopause, women show lower HPAA and autonomic responses than men in the same age group, but HPAA responses are higher in the luteal phase (Kajantie & Philips, 2006). Free cortisol levels in the luteal phase almost reach levels of that found in men (Kajantie & Philips, 2006). Equal ACTH levels in follicular and luteal phase indicate enhanced adrenal sensitivity in the luteal phase (Kirschbaum *et al.,* 1999). Postmenopausal women show an increase in sympathoadrenal responsiveness (Kajantie & Philips, 2006).

Sex differences in autonomic function are a result of estrogens, which attenuates sympathoadrenal responsiveness (Kajantie & Philips, 2006; Serova *et al.,* 2005). Estrogens also increase the synthesis of CBG and thus the concentration of free cortisol levels decrease. Estrogens modulate responses to stress affecting HPAA, catecholamine biosynthesis in central and peripheral noradrenergic systems, thus influencing the cardiovascular system and BP (Serova *et al.,* 2005). Additionally, estrogens modulate adaption of the cardiovascular system to stress, decreasing sympathetic stimulation (Serova *et al.,* 2005; Kajantie & Philips, 2006). There is considerable evidence from clinical studies suggesting that estrogens has a regulating effect on autonomic stress responsiveness, decreasing sympathetic activity and increasing parasympathetic activity (Kajantie and Philips, 2006). Estrogens modulate the adaption of the cardiovascular system to stress and modulate BP through a direct effect on the vascular system by catecholamine and nitro oxide synthetases release (Serova *et al.,* 2005).

Bouma et al. (2009) studied the effect of gender, menstrual cycle phase and oral contraceptive use on cortisol responses in a large sample of adolescents. They found that the gender differences in cortisol responses to social stress in adolescents are comparable to those found in adults: being stronger in men compared to women (Bouma *et al.,* 2009). No significant effects of gender and menstrual phase were found on cortisol response to awakening, but girls using oral contraceptives displayed a blunted cortisol response (Bouma *et al.,* 2009; Kajantie & Philips, 2006). Cortisol response to stress between boys and free cycling girls had a p-value of $p < 0.001$, between oral contraceptive users and girls not using oral contraceptive $p < 0.001$ (Bouma *et al.,* 2009). No effect of menstrual cycle phase on cortisol response to stress was found (Bouma *et al.,* 2009).

According to Uhart *et al.* (2006), males have a greater HPAA response to psychological stressors than females, but females have greater hormonal reactivity to pharmacological stimulation. Therefore,

gender differences are of great importance when considering health risks (Uhart *et al.,* 2006). In contrast to the above, Paris *et al.* (2009) found that women are more vulnerable to aberrant HPAA responses to stress than men and healthy men had higher basal cortisol levels than women, but after a stressor, cortisol levels were higher in the women.

According to the above, it is important to take menstrual phase, oral contraceptive users and gender into account in a study design (Kajantie & Philips, 2006). Differences in the results found between studies can be due to type of stressor exposure and/or pathological status of individuals and hormones at work (Paris *et al.,* 2009).

3.7. Acute and chronic stress and cortisol

The question whether HPPA hyper or hyporesponsivity to acute stress in individuals who are chronically stressed or not able to cope with environmental demands, is still open to debate (Kudielka *et al.,* 2009). HPAA hypoactivity seems to be likely in humans experiencing chronic stress (Helhammer *et al.*, 2009). According to Bellingrath and Kudielka (2008), a dampening in HPAA reactivity was seen in people experiencing chronic work stress. It is interesting to note that the appraisal or the perception of experiencing chronic stress was associated with elevated salivary cortisol on awakening (Watts *et al.,* 2005; Wust *et al.,* 2000) It is still not fully clear how acute/chronic stress differentially affects vasopressin, CRP and which role each plays in ACTH release under stress (Helhammer *et al.,* 2009). Adrenal release of cortisol is under control of both ACTH and preganglionic sympathetic neurons (Bornstein *et al.*, 2008). The adrenals sensitivity to ACTH is modulated by several factors, such as chronic stress, long term physical activity and gonodal steroids. HPAA is highly stress responsive and, therefore, chronic stress can induce changes in the activity (Fries *et al.,* 2005; McEwen *et al.,* 2001). Chronic or repeated stressors causes the HPAA to habituate or decrease sensitivity to stimuli, therefore, hypoactivity can result (Jaferi & Bhatnagar, 2007). Diurnal cortisol variation can be significantly reduced in exhausted individuals (Lindeberg *et al.,* 2008) and the possible association between HPAA and exhaustion is increasingly focused on (Fries *et al.,* 2005).

It remains unclear how chronic stress influences physiological and neuroendocrine responses during acute stress (Loft *et al.,* 2007). According to Mizoguchi *et al.* (2001), when rats were exposed to acute stress a basal plasma elevation in corticosterone occurred which lasted for 5 hours after termination of the stressor. Chronically stressed rats had the same elevation, but it decreased rapidly after 2 hours. The conclusion that Mizoguchi *et al.* (2001) made was the following: chronic stress induces a hyper suppressive state for corticosterone secretion in response to acute stress. This is caused by partial habituation, coping and adaptation to the stressor. Chronic stress induces a hypo suppressive state for

basal cortisol secretion which is caused by glucocorticoid receptor down-regulation in the hippocampus (Mizoguchi *et al.,* 2001).

According to Matthews *et al.* (2001) people who have higher levels of chronic stress show lower SBP in response to tasks and lower levels of cortisol during recovery. According to Loft *et al, (*2007), chronic stress caused slower SBP recovery and lower salivary cortisol levels.

Two opposing theories exist about glucocorticoids' role in the development of disease during chronic stress:

1. Raison and Miller (2003) state that decreased cortisol signalling at cellular receptor level might be an important pathway for development of disease, and an excess production of glucocorticoids may be a beneficial adaptive mechanism to diminish stress-related physiological processes.
2. Contradicting, Fries *et al.* (2005) proposed that HPPA axis hyporesponsiveness and associated exhaustion may constitute a protective response to damaging effects of excess glucocorticoids during chronic stress.

3.8. Race and cortisol

HPAA may play a role in the development of raised BP in Afro-Caribbean people (Boyne *et al.*, 2008). People of African ancestry may have different circadian patterns than Caucasians and this raises the possibility that Africans may be more sensitive to the tissue actions of glucocorticoids, producing a greater pressure effect to given cortisol concentration (Boyne *et al.*, 2008). According to Chong *et al.* (2008), differences in HPAA response to stress may cause differences in susceptibility to a variety of diseases. In a study conducted by Chong *et al,* (2008) Caucasians had 36% greater mean cortisol response than blacks to the Trier Social stress test even after adjustment for social and psychological confounders. Caucasians also had significantly higher mean ACTH values compared to blacks at 25 minutes after the Trier Social stress test (Chong *et al.,* 2008).

3.9. Visceral obesity and cortisol

HPAA function is disturbed in obesity and insulin resistance and it has been proposed that this dysfunction is driven by stress activation (Björntorp, 2001). According to Reynolds *et al.* (2003), the HPAA regulation is altered in obesity causing decreased plasma cortisol concentration. Bjorntrop and Rosmond (2000) reported that the decreased plasma cortisol concentration could be due to elevated

peripheral disappearance of cortisol, because cortisol secretion is elevated during obesity. Obesity has clinical features of hypercortisolism, seen in Cushing's syndrome, such as central fat distribution, excess body-fat mass, a 'Buffalo hump', increased BP, insulin resistance, impaired glucose tolerance and dislipedemia (Bjorntrop & Rosmond, 2000).

4. Cardiovascular function

4.1. Neural control of the circulation

The amygdala is the major efferent source of modulation of cardiovascular, endocrine and autonomic function (Thayer & Lane, 2009). There is prefrontal cortical control of cardiac activity which tonically inhibits the amygdala (Thayer & Lane, 2009). In a healthy system both the sympathetic and parasympathetic branches to the heart, are tonically active. Very important is that the heart rate is continuously under inhibitory control via the vagus (Levy, 1990). With activation or disinhibition of the amygdala the heart rate will increase and a decrease in heart rate variability will be seen (Thayer & Lane, 2009).

Emotional arousal such as sadness and disgust is associated with decreased heart rate variability, due to decreased inhibitory control on the amygdala by the prefrontal cortex (Thayer & Lane, 2009). The amygdala becomes active and the prefrontal cortex becomes hypoactive during threat and uncertainty (Thayer & Lane, 2009). The activation of the amygdale in itself is necessary to act in situations of threat and uncertainty, however, when this state of activation is chronically prolonged, it produces unnecessary wear and tear on the body (McEwen & Seeman , 1999; Thayer & Sternberg, 2006). This wear and tear is referred to as allostatic load by McEwen (1998). Psychopathological states such as anxiety, post traumatic stress disorder and depression are characterised by prefrontal hypoactivity and lack of inhibitory neural processes as reflected in poor habituation, failure to recognise safety signals, attentive bias to threat information, increased negativity bias (Shook *et al.*, 2007).

The autonomic nervous system controls both central and peripheral cardiovascular functions. The first branch is the sympathetic/adrenergic nervous system that causes secretion of nor-epinephrine and adrenaline from neurons and adrenaline and cortisol from the adrenal gland. Norepinephrine and adrenaline act on cardiac α- and β- adrenergic receptors (Opie, 2006). Adrenaline acts on β1 receptors; the effect is increased CO, SBP and DBP. The decreased DBP is due to adrenaline's effect on β2 receptors in the arterioles which causes vasodilatation and thus decreases the total peripheral resistance (TPR). Norepinephrine causes an increased SBP by acting on cardiac-β1receptors and increased DBP by acting on vascular-α2 receptors that cause vasoconstriction (Opie, 2006).

Environmental stressors have psychological and biological effects (Bairey Merz *et al.,* 2002; Schwartz *et al.,* 2003). Failure to resolve negative emotional states such as anxiety, depression and anger can cause an imbalance between the sympathetic and parasympathetic nervous system (Schubert *et al.,* 2009). An increase in the sympathetic: parasympathetic ratio is now being linked to increased cardiovascular morbidity and mortality. The key regulator of cardiovascular reactivity is the balance between sympathetic and parasympathetic tone (Kajantie & Philips, 2006). Hypertensives have been found to have a more reactive cardiovascular system and enhanced HPAA responses than normotensives (Nyklíček *et al.,* 2005). Hypertensive's show a greater mean DBP reactivity and enhanced salivary cortisol when stressed. A central stress mechanism proved to be responsible for the greater stress response in hypertensive's, compared to normotensives (Nyklíček *et al.,* 2005).

Cardiovascular risk factors, such as hypertension, diabetes, abnormal cholesterol and age are associated with decreased vagal function as shown by decreased heart rate variability (Thayer & Fischer, 2005). People with lower resting heart rate variability show larger cortisol responses to mild cognitive challenges that persist into the recovery period, compared to those with high resting heart rate variability (Johnsen *et al.,* 2002). There is thus a connection between cardiovascular dysfunction, decreased vagal inhibition and increased cortisol (Johnsen *et al.,* 2002; Thayer & Fischer, 2005). Risk factors for cardiovascular disease includes; dyslipedaemia, hypertension, smoking, stress, diabetes, abdominal obesity, physical inactivity, poor nutrition and excessive alcohol intake (Schenck-Gustafsson, 2009). Confounding risk factors of cardiovascular function will be discussed.

4.2. Confounding factors of cardiovascular function

4.2.1. Aging

The association between BP and major cardiovascular events are well documented in both normotensive and hypertensive individuals, and its association is greatly influenced by age (Nichols, 2005). Due to increase in age, functional and structural changes are seen in the arterial wall media e.g. hypertrophy, extra cellular matrix accumulation and calcium deposits (Mitchell *et al.,* 2004). There are also changes in the vascular endothelium that include a decreased release of vasodilators and an increased synthesis in vasoconstrictors, these changes ultimately result in decreased elasticity and an increase in arterial wall stiffness (Mitchell *et al.,* 2004). According to Van Bortel and Spek (1998), pulse pressure increases with age and is a major risk factor for cardiovascular disease (CVD).

4.2.2. Obesity

The prevalence of obesity and hypertension has risen since urbanization started in South Africa (Akinboboye *et al.,* 2003; Steyn *et al.,* 2005). Mathew *et al.* (2007) reported that hypertension is the most important complication that arises due to obesity, but the pathophysiology still needs further research. Urban African women have significantly higher BP levels and arterial stiffness than Caucasian women, but their obesity is weakly related to traditional cardiovascular risk factors when compared to Caucasian women (Schutte *et al.,* 2005). Important to note is that urbanised African women do show a positive relationship between obesity and insulin resistance, indicating that an increase in westernization could increase the relationship between obesity and cardiovascular risk (Schutte et *al.,* 2005).

In contrast to gluteo-femoral fat, the accumulation of fat around the viscera is strongly related to coronary artery disease and atherosclerosis independently of age and subcutaneous fat (Hamdy *et al.,* 2006; Kawamoto *et al.,* 2007). Similarly Silva *et al.* (2008) found an association between hypertension, central obesity and left ventricular hypertrophy in women. The causation was linked to increased sympathetic activity and insulin resistance (Silva *et al.,* 2008). African Americans are less likely to have visceral than subcutaneous fat, when compared to Caucasians (Considine *et al.,* 2008). According to Srdić *et al.* (2005), men have more visceral fat than pre-menopausal women, but post-menopausal women have 49% more intra-abdominal fat compared to premenopausal women. According to Ben-Noun *et al.* (2001), neck circumference (NC) measurements are a simple and time saving screening measure that can be used to identify overweight and obese people. Men with NC ≥ 37 cm and women with a NC ≥ 34 cm are considered to be overweight (Ben-Noun *et al.,* 2001). Changes in BP also correlate with NC and other components of the metabolic syndrome like glucose levels (Ben-Noun & Loar, 2004, 2003).

4.2.3. Smoking and alcohol consumption

Smokers were found to have lower SBP, DBP reactions and lower heart rate reactivity to stress than non-smokers, even though smoking causes increased hemodynamic activity. This confirms the idea that smoking causes a blunted reactivity to mental stress (Phillips *et al.,* 2009). Smoking is commonly known to contribute to the development of CVD, this risk is not a function of increased reactivity, but rather attributed to blunted sympathetic nervous activity (Phillips *et al.,* 2009). Alcohol has protective and harmful effects on cardiovascular health, illustrated by a J-shaped curve (Bau *et al.,* 2007). Alcohol induced endothelial damage or protection may be related to the following markers: nitric oxide, cortisol, endothelin-1, adhesion molecules, tumour necrosis factor alpha, interleukin-6 and C-reactive protein

(Bau *et al.,* 2007). Heavy alcohol consumption is an established risk factor for hypertension (Bau *et al.,* 2007).

4.2.4. Gender

Due to estrogens vasoprotective effect, cardiovascular disease is rare in premenopausal women when compared to men of similar age (White *et al.,* 1997). Estrogens have cardioprotective mechanisms and acts as an immunomodulator during the inflammatory process of atherosclerosis (Baker *et al.,* 2003). After menopause the gender differences in CVD prevalence diminish (White *et al.,* 1997) and, therefore, women develop CVD 10-15 years later in life than men (Baker *et al.,* 2003). CVD was traditionally viewed as the males' illness, but according to the World Health Federation, CVD is the most neglected health problem regarding women of the developed and developing world (Schenck-Gustafsson, 2009). CVD account for nearly 50% of female deaths (Baker *et al.,* 2003).

4.2.5. Race

There is an increased prevalence of cardiovascular diseases in urbanised Africans (Opie & Seedat, 2005; Schutte *et al.,* 2006). According to Steyn *et al,* (2005) and Seedat (2009), reliable data regarding the prevalence of CVD and the contributing factors are limited in black African populations. Evidence that black Africans suffer from a higher prevalence of hypertension than Caucasians is often documented (Schutte *et al.,* 2006).

The last decade of South Africa's history is characterised by increased urbanization of the black population. Therefore, the total demographical picture according to Sliwa *et al.* (2008) is highly urbanised groups compared to remote and traditional rural groups. Epidemiological studies show that hypertension is the leading form of CVD in Africa (Cappuccio *et al.*, 2004). Hypertension in Sub-Saharan Africa is a problem due to the rising prevalence of hypertension in the black population, especially in the urban areas. A contributing factor to the severity of the problem is the frequent under diagnosis of hypertension (Opie & Seedat, 2005). There is a need for further research regarding the above (Opie & Seedat, 2005).

4.2.6. Glucose

CVD is a major cause of death and disease associated with diabetes (Marks & Raskin, 2000). A French study showed that those who have diabetes are twice as likely to develop peripheral arterial disease as those who have normal fasting blood glucose values (Tapp *et al.,* 2007). All definitions for impaired fasting blood glucose were associated with increased risk for coronary heart disease, but women seem to have elevated risk for coronary heart disease at lower glucose levels than men (Levitzky *et al.,* 2008). Increased risk for CVD is related to duration of diabetes, hyperglycemia, hypertension, dyslipaemia, insulin resistance and gender (Marks & Raskin, 2000).

4.2.6. Intima media thickness as indicator of end-organ damage

Ludwig *et al.* (2003) reported that an early sign of atherosclerosis is hypertrophy of the arterial wall. Intima media thickness is an indicator that predicts future CVD (Ludwig *et al.,* 2003). According to El-Saed *et al.* (2008), there is a positive correlation between coronary artery calcification and carotid intima media thickness (CIMT). Coronary artery calcification is also more predictive of CIMT in African than White middle aged men. According to Kablak-Ziembicka *et al.* (2007) and Ross (1999), atherosclerosis is a systemic disease that involves several vascular beds that include supra-aortic, coronary, renal and lower limb arteries. CIMT is specific and sensitive and has the ability to indicate the number of vascular territories involved (Kablak-Ziembicka *et al.,* 2007). With increase in CIMT the probability of having more territories with advanced atherosclerosis also increases (Kablak-Ziembicka *et al.,* 2007). Hypertension frequently occurs with metabolic disturbances, such as dyslipidaemia, and could work synergistically at the arterial wall to enhance atherosclerosis (Chapman & Sposito, 2008).

According to Trijp *et al.* (2006), CIMT is related to an increase in low density lipoprotein cholesterol. Arterial stiffening can be caused by calcifications and attachment molecules (Ross *et al.,* 1999). They contribute by changing collagen cross-links, proteoglycans, integrins and fibronectin in the endothelium. High pulse pressure may occur and inflict serious vascular damage as normally seen in elderly individuals with high SBP (Ross *et al.,* 1999).

5. Aim

The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage.

6. Hypotheses

Our hypotheses are as follows, 1) a predominantly vascular (α-adrenergic) response would be seen in hypertensives during exposure to stressors, 2) increased cortisol levels would be related to the progression of target end organ damage and 3) high problem solving will contribute to the progression of target end organ damage in African men and women.

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CHAPTER THREE
MANUSCRIPT

INSTRUCTION FOR AUTHORS: INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY

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CHAPTER 3

CARDIOVASCULAR AND CORTISOL RESPONSES, AND COPING IN URBANISED AFRICANS: THE SAPBA STUDY

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CARDIOVASCULAR AND CORTISOL RESPONSES, AND COPING IN URBANISED AFRICANS: THE SAPBA STUDY

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Abstract

The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage in a group of 200 urbanised fasting black Africans, aged 21-62 years from the SAPBA (***S**ympathetic **A**ctivity and **A**mbulatory **B**lood **P**ressure in **A**fricans)* study. Groups were stratified into normotensive (NT) and hypertensive (HT) men and women. Non-invasive continuous arterial blood pressure (BP) recordings were obtained with the Finometer device during rest and after application of the cold pressor (CPT) and colour word conflict tests (CWC). Saliva cortisol analyses were done with an enzyme-linked immunosorbant assay. The Coping strategy indicator (CSI) was used to obtain information about participants preferred coping strategies. High resolution ultrasound carotid intima media (CIMT) scan determined target end organ damage. One way ANCOVA's, adjusted for body mass index (BMI) and age, revealed increased total peripheral resistance (TPR), decreased Windkessel compliance (Cw) during rest as well as increased vascular responsiveness during stressor application in HT men and women. Salivary cortisol values differed significantly between sampling times in men and women ($p \geq 0.001$). Stepwise multiple regressions showed that progression of target end organ damage (CIMT) as dependent variable, was associated with fasting glucose, waist circumference (WC) and cortisol reactivity in men and not women, despite the women's greater central obesity.

Keywords: Cardiovascular responses; Cortisol responses, Coping strategies; Africans

1. Introduction

Exposure to chronic stress is a good predictor of future cardiovascular disease (CVD) (Schubert *et al.,* 2009) and the risk for CVD is increased by an exaggerated blood pressure (BP) response to stress (Lovallo, 2005). Hypertensives have more reactive cardiovascular systems, indicated by greater vascular reactivity, enhanced hypothalamic-pituitary-adrenal axis (HPAA) activity and enhanced salivary cortisol when stressed (Nyklíček *et al.,* 2005).

Psychological appraisal of stress affects the mood and could contribute to cardiovascular deregulation through hypertension, endothelial dysfunction and changes in vascular function (Bairey Merz *et al.,* 2002; Schwartz *et al.,* 2003). Persistent psychological stress resulting from urban living in Africans could lead to increased allostatic load and decreased ability to cope (McEwen, 2003; Malan *et al.,* 2006a). The negative effect that such stress could have on a person's health and wellbeing could, however, be either minimized or exacerbated by his/her choice of coping responses (Folkman & Moskowitsz, 2000). Coping can be defined as deliberate and effortful attempts to manage situations that we appraised as potentially harmful or stressful (Lazarus & Folkman, 1984).

This includes constantly changing cognitive and behavioural attempts to control internal and external demands of the situation, which exceeds the resources of a person (Amirkhan & Auyeung, 2007).

Malan *et al.* (2008) revealed that urban African men utilizing an active coping/ problem solving style, which represents a direct assault strategy (Lazarus and Folkman, 1984; Amirkhan, 1990), showed higher cardiovascular risk than African men from rural areas. These findings are contradictory to O'Donnell *et al.* (2008), who found that Caucasian individuals who coped by problem engagement and seeking support had lower cortisol levels and possible lower CVD risk. According to Utsey *et al.* (2000) cognitive ability and *social* support moderated the relationship between stress and quality of life in African Americans. Seeking social support appeared to be a very beneficial strategy for handling work pressures in a study conducted by Jackson and Saunders (2006), and avoidance related to poor mental health.

Chronic stress leads to deregulation of the HPAA with resultant increased circulating adrenocorticotropic hormone (ACTH), cortisol, corticosterone, impaired feedback regulation of the axis and impaired glucocorticoid receptor binding in the hippocampus (Grippo, 2009). This could indicate the role of glucocorticoids in central control of the cardiovascular system during stress (McDougal *et al.,* 2005). Roy *et al.* (2001), concluded that resting, rather than cortisol stress reactivity, plays a permissive role in sympathetically driven cardiovascular stress responses.

Since stress and related health impairments have become major problems in human life, investigation in the psychobiological pathways that link stress and disease are of major importance (Kudielka *et al.,* 2009). Therefore, the aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage.

2. Methods

2.1. Study design and subjects

The SABPA study was a target population study which included a sample of fasting urban black Africans, aged 21-62 years, from one of four education districts in the Dr Kenneth Kaunda Education districts, North-West Province. Hereafter, the black Africans will be referred to as Africans. There was a total of 200 participants (N=101 men, N=99 women).

Exclusion criteria for the study were: pregnancy, lactation, temperature above 37°C and users of alpha- and beta blockers. Participants were included who had not donated blood or been vaccinated in the previous 3 months.

Permission to participate was granted by the North-West Education Department and support ensured from the South African Democratic Teachers Union. The Ethics Committee of the North-West University approved the study (00036-07-S6) and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki, 2004.

A standard subject information sheet was given to the subjects at their screening visit, and an informed consent form was signed prior to the start of the study.

2.2. Measuring instruments and apparatus

2.2.1. Anthropometrics

The measurements involved height, weight, waist circumference and neck circumference. Calculation of body mass index and waist-to-hip ratio were made using the 'Invicta Stadiometer, IP 1465,U.K.; Precision Health scale, A & D Company, Japan, Holtain unstrechable flexible 7 mm wide metal tape.

2.2.2. Blood pressure

Participants were in semi-Fowlers position for BP measurements. After a 5 minute rest period two Riva-Rocci/Korotkoff BP measurements, with a 3 minute rest period between measurements, were obtained. A *suitable* cuff size was applied to the nondominant arm. The second measurement classified participants as hypertensive according to the cut-off points of the European society of Hypertension Guidelines (Korotkoff sound I: resting SBP $\geq$ 140mm Hg and/or Korotkoff sound V: resting DBP $\geq$ 90mmHg) (ESH, 2007). Non-invasive continuous arterial blood pressure recordings were obtained with the Finometer device (Wesseling *et al.,* 1993). Results were analyzed with the Fast Modelflo computer programme to provide: systolic (SBP) and diastolic blood pressure (DBP), cardiac output (CO), total peripheral resistance (TPR) and arterial compliance (Cw) values.

2.2.3. Salivary cortisol

Resting salivary cortisol levels were obtained 45 minutes after awakening, avoiding the Cortisol Awakening Respose (CAR), and completed before 10am according to standardized procedures (O'Donnel *et al.,* 2008). Cortisol sampling time 1 was between 06h30-07h00 and time 2 between 08h30-09h00. Saliva cortisol sampling was done 30 minutes after exposure to each stressor (Salivette Sarstedt®).

2.2.4. Stressors

Participants were subjected to stressors for 1 minute in a counterbalanced design. This included the Stroop Color-Word Interference Task Color Chart (CWC) and the Cold Pressor test (CPT), which involved the immersion of the left foot up to the ankle in ice water (4 degrees Celcius) (MacArthur & MacArthur, 2003).

2.2.5. Carotid Intima media thickness (CIMT)

High resolution ultrasound carotid intima media scan (Liang *et al.,* 1998) determined target end organ damage. CIMT images, from at least two optinum angles of the left and the right common carotid artery, carotid bulb and internal carotid arterial (ICA) segments were acquired from the participants using a Sonosite Micromaxx ultrasound system (SonoSite Inc., Bothell, WA, USA) and 6-13 MHz linear array transducer, using the Rudy Meijer protocol (Liang *et al.,* 1998). The images were digitized and imported into the AIMS automated software for dedicated analysis of CIMT. A maximal 10 mm segment with good image quality was chosen for analysis. The program automatically identifies the borders of the CIMT of the near and far wall.

2.2.6. Questionares

The Coping strategy indicator (CSI) of Amirkhan (1990), which has been successfully used in the South African context, was administered in order to identify participants' preferred coping strategies. The CSI is a factor analytical derived measure of coping where the following three fundamental coping strategies are revealed: problem solving, seeking social support and avoidance. Smoking and alcohol consumption were determined as categorical predictors. Physical activity index (PAI) was determined, where a score of 3 indicated vigorous and 1, indicated low activity. The Global Physical Activity Questionnaire (GPAQ), according to the World Health organisation (2003), measured physical activity in METS (Physical Activity Energy Expenditure (kcal), taking Resting Metabolic Rate (RMR) into account)

2.2.7. Biochemical analysis

Cortisol saliva sample analyses were done with high sensitivity enzyme-linked immunosorbant assay (ELISA). The intra-assay and inter-assay coefficients

of variation for cortisol were respectively 7.7% and 9.8% and did not differ between men and women. A winged infusion set was used, by a registered nurse, to sample fasting blood from brachial vein branches for serum estrogens as well as sodium fluoride glucose. Analyses were done with the Sequential Multiple Analyzer Computer, KonelabTM 20i, Finland. An antibody test was done to determine HIV/AIDS status of each participant.

2.3. Experimental procedure

During the working week days a physical activity meter was fitted to each participant between 07h30 and 08h00. The educators then resumed their normal daily activities and stayed overnight at the Metabolic Unit Research Facility of the North-West University. Each participant was subjected to the following procedures: Between 17h00 and 18h00 the group of 4 participants each received his/her own private bedroom and were familiarized with the experimental setup, to lessen anticipation stress (Obrist, 1981).

Pre-counselling for AIDS was given by a registered nurse. The Psychology battery questionnaire was done under supervision of registered psychologists. A standardized dinner (according to fat, carbohydrates and protein content) was provided. Participants refrained from consuming food, alcohol, caffeine, smoking, exercising and tooth brushing 8 hours prior to saliva and blood sampling.

At 05h45 the following morning, the participants were awakened and anthropometric measurements were obtained in triplicate by registered anthropometrists according to standardized measures. BP measurements according to the Rocci/Korotkoff method were taken, followed by Finometer BP data, resting blood and saliva sampling before stressor application. 30 minutes after stressor application saliva sampling was done followed by the same procedure for next stressor (excluding the resting sampling). Ultrasound scanning followed for carotid intima media thickness (CIMT). Immediate feedback was given on available data, postcounseLling regarding HIV status and referrals were made. Thereafter, they received incentives, breakfast and went back to school.

2.4. Statistical analysis

A 2 x 2 analysis of covariance (ANCOVA), adjusted for age, BMI and resting BP and cortisol values was conducted to determine interaction between the main effects, i.e. gender and BP status and each of the different variables. Gender groups were stratified according to the ESH guidelines (RivaRocci Korotkoff 2nd measurements) into BP=120-139/80-89 mmHg and BP$\geq$140/90 mmHg, hereafter referred to as normotensive and hypertensive African men and women. Coping strategies using median splits determined clear high and low responders. Subsequent one way ANCOVA's followed, adjusted for BMI and age. Adjustment for cortisol sampling times [1; (06h30-07h00), time 2; (08h30-09h00)] and resting values was done during cardiovascular and cortisol reactivity analyses (Fig 2).

Partial correlations, adjusting for age, BMI, cortisol sampling times and resting values followed (table is not shown). Stepwise multiple regression analyses followed with CIMT as dependant variable for the CPT and CWC test and were done independent of age, BMI, WC, NC, glucose, BP and cortisol resting and reactivity values, cortisol sampling times, estrogen, high problem and high avoidance coping strategies.

Sensitivity analysis for estrogen on cortisol was performed and no differences were found. All values with $p \leq 0.05$, $r \geq 0.35$ and adjusted $R^2 \geq 0.25$ were regarded as significant.

3. Results

Significant interactions on the main effects showed for low problem solving ($F(1,41)$ 4.01, $p=0.05$) and

TPR reactivity during the CWC test (F(1,181) 4.31, p=0.004).

Men: From Table 1 and Fig 2, it is clear that HT men are older and showed increased vascular BP during rest and the CPT (DBP and TPR as well as decreased Cw reactivity) when compared to their NT counterparts

Fig 1a, the resting cortisol values are significantly higher (p=0.001) during cortisol sampling time 1: 06h00-07h00 than sampling time 2: 08h30-09h00. Resting cortisol and cortisol reactivity values correlates positively with central BP increases in HT men.

Partial correlations, adjusted for age, BMI and cortisol sampling times (table not shown), indicates that high problem solving (r=0.73; p=0.03) as well as high avoidance (r=0.76; p=0.01) correlates with central BP response changes during the CPT. None of the coping strategies were associated with the progression of target end organ damage.

In Table 2, the stepwise regression analyses indicated that fasting plasma glucose and central obesity, during α and ß mental stressors, are positively associated with the progression of target end organ damage during the CPT and CWC test, in HT men. Cortisol reactivity is negatively associated with the progression of target end organ damage during the CWC test, in HT men.

Women: In Table 1 and Fig 2, similar trends as found in HT men are found in HT women, namely they are older with increased vascular BP during rest and CWC test (DBP, TPR and lower Cw) than their normotensive counterparts. In addition HT women showed more central obesity (WC; p=0.01) as well as wider neck circumferences (NC) than their normotensive counterparts.

Fig. 1a, Cortisol rest values are significantly higher (p=0.001) during cortisol sampling time 1: 06h00-07h00 than sampling time 2: 08h00-09h00.

Partial correlations, NC (r=0.61; p=0.002) and high problem solving (TPR, r=-0.99, p=0.01) correlate with central BP increases in HT women. None of the coping strategies were associated with the progression of target end organ damage.

Table 2, Stepwise regression analyses indicated that age is the only factor associated with the progression of target end organ damage in HT women.

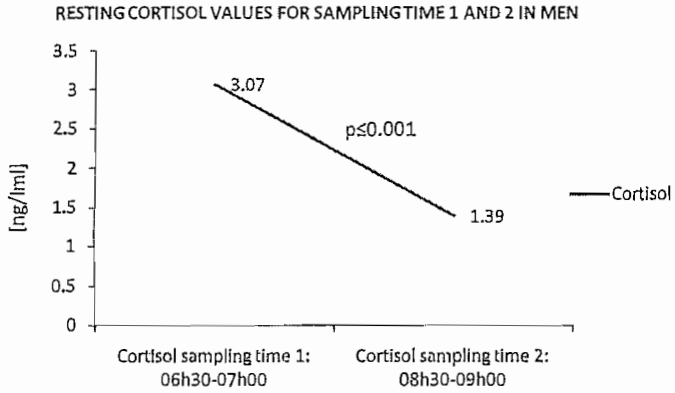
Sensitivity analysis

Firstly adjustments for cortisol sampling time 1: 06h30-07h00 and time 2: 08h30-09h00 was done on all data, following the one way ANCOVA's, to eliminate the effect of the time of sampling. Secondly, adjustment for estrogen levels was done, but no significant changes in the differences, regarding cortisol or BP values, between BP groups or relationships between BP and cortisol were found in either men or women.

Table 1: Descriptive statistics and analysis of covariances, adjusted for age and BMI, between normotensive and hypertensive African men and women.

	Men		Women	
	NT BP (120-139/80 -89 mmHg)	HT BP (≥ 140/90 mmHg)	NT BP (120-139/80 -89 mmHg)	HT BP (≥ 140/90 mmHg)
N	37	64	65	34
*Age (yrs)	40.9 ± 7.65[a]	44.5 ± 8.04[a]	43.7 ± 6.65[b]	48.6 ± 9.01[b]
*BMI (Kg/m²)	26.1 ± 5.12	28.4 ± 6.01	31.1 ± 5.88[c]	35.9 ± 8.47[c]
Anthropometrics :				
WC (cm)	93.5 (91.7,95.3)	93.6 (92.3,95.1)	91.9 (89.9,93.9)[d]	96.8 (93.9,99.6)[d]
NC (cm)	37.8 (37.1,38.5)	37.6 (37.1,38.1)	33.1 (30.6,35.6)[e]	37.5 (33.9,41.2)[e]
WHR (cm)	0.93 (0.83,1.03)	0.97 (0.89,1.05)	0.81 (0.79,0.84)	0.85 (0.81,0.88)
CV parameters:				
SBP rest (mmHg)	137 (131;143)[f]	152 (147;156)[f]	131 (128;134)[g]	146 (142;151)[g]
DBP rest (mmHg)	81.1 (77.7;84.5)[h]	88.6 (86.1;91.2)[h]	74.6 (72.8;76.4)[i]	82.1 (79.5;84.6)[i]
CO rest (L/min)	6.79 (6.20;7.38)	6.67 (6.22;7.12)	7.08 (6.67;7.49)	6.90 (6.32;7.49)
TPR Rest (mm Hg/ ml/s)	0.97 (0.87;1.07)[j]	1.13 (1.05;1.20)[j]	0.89 (0.79;0.99)[k]	1.09 (0.95;1.24)[k]
Cwk Rest (ml/mm Hg)	2.03 (1.93;2.14)[l]	1.79 (1.70;1.87)[l]	1.94 (1.87;2.00)[m]	1.70 (1.61;1.81)[m]
Other parameters:				
IMTn Mean (mm)	0.71 (0.66,0.76)	0.68 (0.65,0.72)	0.67 (0.64,0.69)	0.66 (0.62,0.69)
IMTf Mean (mm)	0.72 (0.68,0.77)	0.69 (0.66,0.73)	0.67 (0.64,0.71)	0.68 (0.64,0.72)
Cortisol basis (ng/mL)	2.27 (1.58,2.96)	2.39 (1.87,2.91)	1.81 (1.38,2.22)	1.86 (1.26,2.46)
Glucose (mmol/L)	5.79 (5.21;6.39)	5.50 (5.07;5.93)	5.61 (5.00;6.23)	5.77 (4.89;6.64)
Smoking n (%)	10 (27.0)	21 (32.8)	0 (0.00)[n]	3 (8.82)[n]
Alcohol usage n (%)	13 (35.1)	28 (43.8)	6 (9.23)	5 (14.7)
HT med. (%)	5 (13.5)	10 (15.6)	10 (15.4)[o]	11 (32.4)[o]
Diabetic med. (%)	2 (5.41)	1 (1.56)	2 (3.08)	1 (2.94)
HIV n (%)	*2 (5.41)[p]*	*11 (17.2)[p]*	3 (4.62)	2 (5.88)
PAI low n (%)	30 (81.1)	48 (75.0)	45 (69.2)	24 (70.6)
Coping strategies:				
High Problem solving	31.2 (30.2,32.3)	31.1 (30.3,32.1)	31.2 (30.3,32.1)	31.1 (29.7,32.2)
Low Problem solving	23.1 (21.5,24.8)[q]	25.0 (23.6,26.5)	23.9 (21.7,26.1)	22.2 (19.6,24.8)
High Avoidance	24.8 (23.1,26.5)	23.4 (21.9,24.9)	23.2 (21.5,24.9)	24.3 (22.3,26.3)
Low Avoidance	16.5 (15.2,17.8)	17.3 (16.3,18.4)	17.8 (16.5,19.1)	18.4 (16.8,20.1)
High Social support	28.9 (28.0,29.8)	29.5 (28.7,30.2)	29.0 (28.1,30.1)	28.1 (26.5,29.5)
Low Social support	20.4 (18.3,22.6)	21.5 (20.0,22.9)	20.6 (18.9,22.3)	20.3 (18.4,22.3)

Values are given with 95% confidence interval. * Values are given according to mean ± standard deviation.
NT, normotensive; HT, hypertensive; BP, blood pressure; N, number per group; BMI, body mass index; WC, waist circumference; NC, neck circumference; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; TPR, total peripheral resistance; Cw, Windkessel compliance; IMTn; intima media thickness of the near wall; IMTf, intima media thickness of far wall; HT med, hypertension medication; HIV, human immune deficiency virus; PAI, physical activity index. Means with the same superscript letter differ significantly when $p \leq 0.05$, when in italic $p \leq 0.09$.



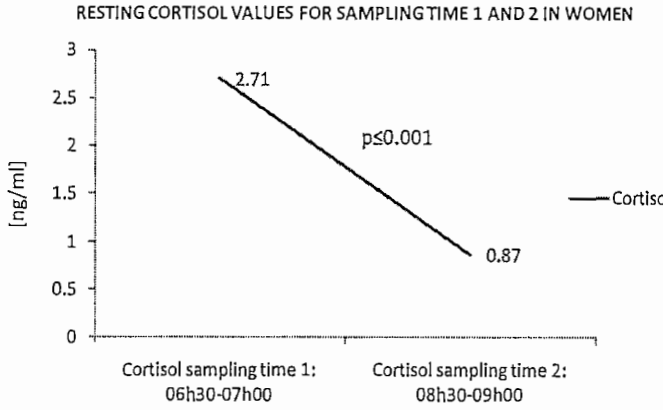


Fig1. Resting cortisol values for men and women during cortisol sampling time 1 and 2 adjusted for age, BMI and estrogen.

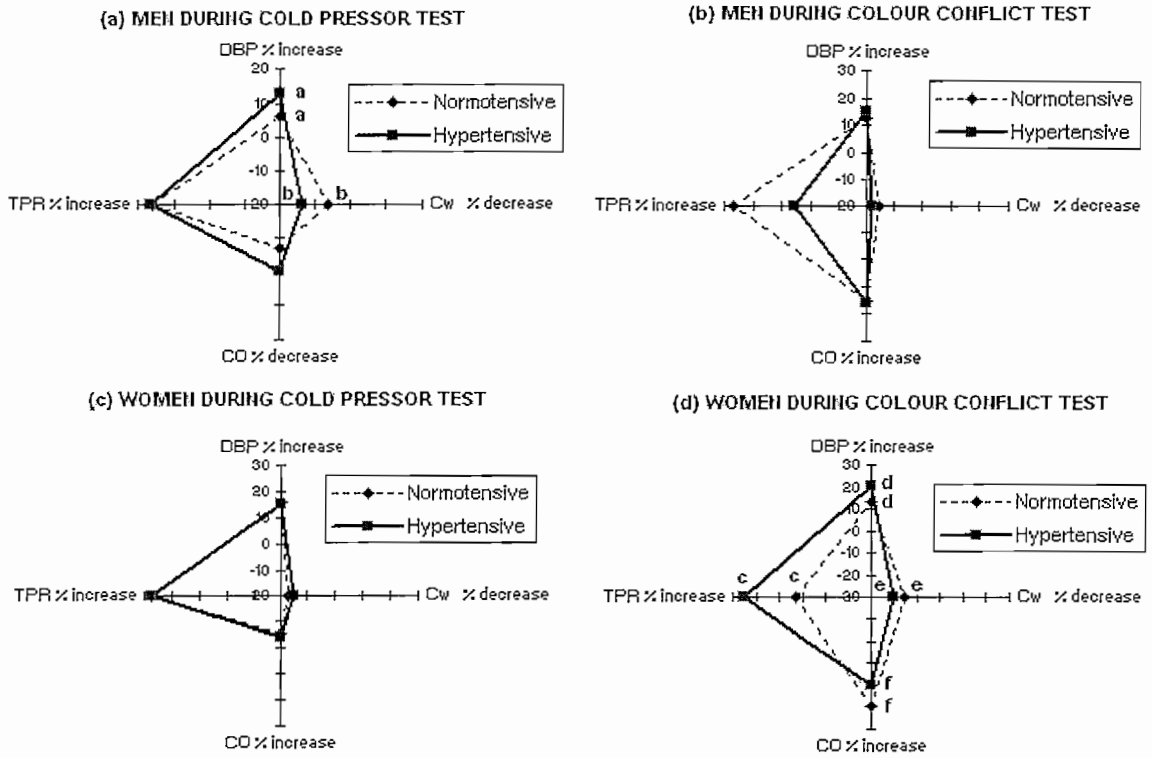


Fig. 2a-d. Values are given according to 95% confidence interval. A representation of the cardiovascular reactivity for hypertensive and normotensive men (a,b) and women (c,d). Fig 2. a,c. Cold pressor test and b,d Colour word conflict test. Adjustments for age, BMI, resting BP values and cortisol sampling time were made. DBP, diastolic blood pressure; Cw, Windkessel compliance; CO, cardiac output; TPR, total peripheral resistance. Values with the same superscript letter differ significantly, a, p=0.09; b, p=0.06; c, p=0.04; d, p=0.004; e, p=0.06; f, p=0.08.

Table 2: Stepwise regression with target end organ damage as dependent variable in HT African men and women

	HT African men (N=24)		HT African women (N=21)	
	CIMT during CPT	CIMT during CWC	CIMT during CPT	CIMT during CWC
Adjusted R^2	0.75	0.7	0.31	0.31
	ß coefficient (SE)	ß coefficient (SE)	ß coefficient (SE)	ß coefficient (SE)
BMI	-	-	-	-
WC	**0.68 (0.11)***	**0.67 (0.13)***	-	-
NC	-	-	-	-
Age	**0.33 (0.11)***	0.24 (0.13)	**0.56 (0.20)***	**0.71 (0.22)***
Glucose	**0.33 (0.10)***	**0.29 (0.12)∞**	-	-
SBP rest	-	-	-	-
DBP rest	-0.23 (0.11)**	**-0.29 (0.13)∞**	-	-
TPR rest	-	-	-	-
CO rest	-	-	-	-
Cw rest	-	-	-	-
SBP reactivity	-	-	-	-
DBP reactivity	-	-	-	-
TPR reactivity	-	-	-	-
CO reactivity	-	-0.18 (0.14)	-	-
Cw reactivity	-	-	-	-
Cortisol rest	-	-	-	-
Cortisol reactivity	-0.21(0.11)**	-	-	-
Cortisol sampling time	-	-	-	-
Low problem solving	-	-	-	-
High problem	-	-	-	-
High avoidance	-	-	-	-

Values are given as standard error. CIMT, carotid intima media thickness; BMI, body mass index; WC, waist circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TPR, total peripheral resistance; CO, cardiac output; Cw, Windkessel compliance. Values in bold are significant: *, p≤0.01; ∞, p≤0.05; **, p≤0.06.

4. Discussion

The aim of the study was to assess the relationship between cardiovascular and cortisol responses, and coping in urbanised Africans.

CIMT did not exceed 1.3mm, which is the cutoff point according to Signorelli *et al.* (2005), in the present study and the CIMT did not differ in the NT and HT groups, therefore, end organ damage was not present in any of the subjects.

As seen in Table 1, more men than women were hypertensive (63%; 34%) respectively. HT status in men and women were associated with older age, vascular BP responses at rest and during stressor exposure, higher HIV prevalence in men and smoking and obesity in the women

In Fig 2, HT men showed increased vascular reactions, only when subjected to the CPT. HT women showed similar vascular reactions, but only on exposure to the CWC test. The CWC predominantly evokes a β-adrenergic stress response, but in the present study a classic α-adrenergic reaction was evoked. Malan *et al.* (2008) found that a shift in BP response from central to more vascular response could be due to the stress of urban life in Africans. This could indicate that African women feel overwhelmed with the present day problems which they face. These findings strengthen the idea of more peripheral cardiovascular reactions to stress in hypertensive Africans (Seedat, 2009; Malan *et al.,* 2008).

In support Nyklíček *et al.* (2005) stated that hypertensives have been found to have a more reactive cardiovascular system than normotensives, and that they show a greater mean DBP reactivity when stressed. Therefore, this study strengthens these findings and those of Malan *et al.* (2006b) which states that Africans exhibit peripheral resistance responses at *rest* and when exposed to *stressful situations*.

Both HT men and women seemed to experience high levels of stress as indicated by higher resting cortisol, glucose values and increased vascular responsiveness.

Table 1, shows that men and women, independent of BP status, have high-normal blood glucose levels, which are above 4.9mmol/l according to Port *et al.* (2005) and could, therefore, imply increased cardiovascular risk. In developing countries such as South Africa where cultural disruptions lead to increased stress experienced in urban areas, stress could accentuate this problem of CVD risk (Malan *et al.,* 2008; Seedat, 2009).

Salivary cortisol levels in both the NT and HT men and women were high-normal, 0.76ng/ml-2.94ng/ml (The Merck Manual, 1999). HPAA hypoactivity seems to be likely in humans experiencing chronic stress, but there is increasing resting cortisol due to receptor down regulation in the hippocampus (Hellhammer *et al.,* 2009; Mizoguchi *et al.,* 2001). The high resting cortisol values in both NT and HT men and women could be due to impaired negative feedback to the hippocampus, due to down regulation of receptors and, therefore, they are possibly experiencing chronic stress or exhaustion. Urine samples collected over 8-24hours have, however, not been done and is a limitation of the study.

Resting cortisol values in both men and women were significantly lower during sampling time 2, ($p \geq 0.001$) indicating that the time of cortisol sampling is an important confounder to be considered. Due to the circadian rhythm that cortisol follows, the time of day which blood is sampled has a large effect on cortisol concentration which is detected and adjustment for the time of sampling is, therefore, of the utmost importance (Smith *et al.,* 2005).

After adjustments for cortisol sampling time and other confounders were made (table not shown), resting cortisol correlated with an increase in SBP reactivity during the CWC test (r=0.32 p=0.03) in men. As indicated by Roy *et al.* (2001), systolic pressure stress responses were clearly associated with resting cortisol levels. Cortisol reactivity correlated with an increase in CO reactivity during the CWC test. This indicates that resting and cortisol reactivity may increase BP via central (β-adrenergic) mechanisms.

With enhanced vascular reactivity and increased norepinephrine secretion during α-adrenergic stimulation, a synergistic effect is seen on cortisol and this may further impact on depression or distress via the HPPA (Björntorp, 2001). There is an interaction between the HPPA, cortisol and the leptin system which may explain why centralization of body fat is associated with perturbations of the HPPA (Björntrop & Rosmond, 2000). During regression analyses (Table 2), cortisol reactivity was negatively associated with target end organ damage in the men (p=0.06). This indicates that stress and possible HPAA hypoactivity could be important factors in African men's cardiovascular health and that the HPPA perturbations seen in the men could have an impact on the central obesity. No correlations between cortisol and cardiovascular reactivity were found in women.

Regarding coping styles, high problem solving correlated with central BP/β-adrenergic responses in both men and women. When considering the typical α-adrenergic pattern seen in genders during stressor application, a more emotion-focused/passive coping pattern is suggested. Suzuki *et al.* (2003) postulated that an α-adrenergic/peripheral physiological reaction is usually associated with an emotion-focused/ passive coping pattern. An α-adrenergic response is evoked when a person experiences little or no control during a stressor and is indicative of surrendering and feelings of helplessness (Malan *et al.,* 2006a). These findings could indicate that Africans feel overwhelmed and, therefore, unable to find appropriate solutions for the problems they face. This idea is strengthened in the women where high avoidance correlated positively with peripheral BP responses (TPR, r=0.84, p=0.07). However, more research is needed, since high avoidance also correlated positively with central BP responses (SBP, r=0.76; p=0.01) in the men, which contradicts Suzuki *et al.* (2003) and the above conclusions drawn. None of the coping styles contributed to the progression of end organ damage in either the men or women.

This central obesity is also an important predictor of CVD (Mathew *et al.,* 2007). Despite the central obesity of the HT women, obesity was not associated with the progression of end organ damage.

In conclusion: Glucose and WC is positively associated with the progression of target end organ damage in HT men. Decreased cortisol reactivity is negatively associated with the progression of target end organ damage in the men, indicating possible HPPA hypoactivity due to chronic stress, but more research is needed to confirm these speculations. Coping strategies did not seem to be associated with progression of target end organ damage.

The mechanism thought to be active in the HT men is as follows: stress leads to increased cortisol which has a permissive effect on catecholamines, the catecholamines inhibit insulin production and, therefore, increases blood glucose (Widmaier, 2004). The high normal blood glucose increases α-adrenergic responses and the risk for CVD (Marks & Raskin, 2000; Tapp *et al.,* 2007).

Limitations and weaknesses of this study include groups that were too small when different coping strategies were considered within the existing BP stratification. Small groups could have caused the psychological aspect of this study to lose its strength. An additional stress-related hormone such as nor-

epinephrine could have clarified the mechanistic approach. Urine samples collected over 8-24hours have, however, not been done, to indicate chronic stress.

Strengths of this study include the novel confounding factor, cortisol sampling time. It is, to the knowledge of the authors, the first time in South Africa that this confounding factor is considered. The analysis of saliva cortisol and vascular reactivity simultaneously in black South Africans are also novel.

It is recommended that future studies with an interest of coping styles, use active (problem solving) and passive (avoidance) coping as risk indicators. This approach will ensure large enough groups to illustrate the real impact that psychology has on cardiovascular physiology and health.

Acknowledgements

The author acknowledges the assistance of Chrissie Lessing (RN) and Szabolcs Peter (MD) and all the collaborators involved. This study was financially supported by the National Research Foundation (NRF), South Africa, North-West University (NWU) Potchefstroom campus, South Africa and the Metabolic Syndrome Institute, France.

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CHAPTER FOUR

GENERAL FINDINGS AND CONCLUSIONS

4.1. Introduction

A summary of the main findings from the article reported in this dissertation is given. The results will be discussed, interpreted, elucidated and compared to relevant literature reviewed in Chapter 2. Conclusions are subsequently drawn and recommendations are made to researchers investigating cardiovascular and cortisol responses and coping in urbanised African men and women. The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage

4.2. Summary of the main findings

The significant findings of the article in this dissertation were:

4.2.1. Cardiovascular and cortisol responses and coping in urbanised Africans.

The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards progression of target organ damage.

The main results were as follows: more men than women (63%; 34%) respectively were hypertensive. Hypertensive (HT) men showed increased vascular responses when subjected to the cold pressor test (CPT) and HT women showed similar vascular reactions, but only to the colour word conflict test (CWC) test. Irrespective of blood pressure (BP) status, men and women had high-normal blood glucose levels and high-normal cortisol values, according to The Merck Manual (1999). The high-normal blood glucose indicated increased cardiovascular disease (CVD) risk and stress due to urbanised living could accentuate this risk. Decreased cortisol reactivity was negatively associated with the progression of target end organ damage in the men ($p=0.06$). Resting cortisol values in both men and women were significantly lower during sampling time 2, ($p \geq 0.001$) indicating that the time of cortisol sampling is an important confounder to be considered.

Partial correlations, adjusted for age, BMI and cortisol sampling time (table not shown), indicated that high problem solving ($r=0.73$; $p=0.03$) as well as high avoidance ($r=0.76$; $p=0.01$) correlated with central BP response changes during the CPT in HT men. NC ($r=0.61$; $p=0.002$) and high problem solving (TPR, $r=-0.99$, $p=0.01$) correlated with central increases in BP in HT women during the CWC test. None of the coping strategies were associated with the progression of target end organ damage.

HT women were more centrally obese than their NT counterparts, and even than the HT men. Despite this, obesity was not associated with the progression of target end organ damage in the HT

African women. Interestingly, glucose and central obesity was associated with the progression of target end organ damage in the men.

4.3. Comparison to relevant literature

Nyklíček *et al.* (2005) postulated that hypertensives show greater mean DBP reactivity when stressed, indicating a typical vascular reaction. Malan *et al.* (2006a) additionally revealed that Africans have increased vascular changes during rest as well as during exposure to stressors. The present study supported this finding in HT African men and women

Both NT and HT men and women had high-normal salivary cortisol values. High levels are associated with α-adrenergic stimulation, enhanced vascular reactivity and increased norepinephrine secretion. A synergistic effect is seen on cortisol and this may further impact on depression or distress via the hypothalamic pituitary adrenal axis (HPAA) (Björntrop, 2001). Glucocorticoid receptor downregulation in the hippocampus (Hellhammer *et al.*, 2009; Mizoguchi *et al.*, 2001) and thus HPAA hypoactivity could also lead to increased cortisol levels. This could imply that stress was experienced, irrespective of BP status, but only the HT subjects reacted with increased vascular reactivity, indicating a possible defeated or helpless reaction towards stress by these participants.

HPAA hypoactivity seems to be likely in humans experiencing chronic stress (Hellhammer *et al.*, 2009). According to Bellingrath and Kudielka (2008), a dampening in HPAA reactivity was seen in people experiencing chronic work stress. The possible association between HPAA and exhaustion is increasingly in focus (Fries *et al.*, 2005). Chronic or repeated stressors causes the HPAA to habituate or decrease sensitivity to stimuli, therefore, hypoactivity could result (Jaferi & Bhatnagar, 2007). Decreased cortisol reactivity was associated with target end organ damage in the HT men ($p=0.06$). This seems to indicate that an inability to handle stress and possible HPAA hypoactivity to be important factors in African men's cardiovascular health.

High-normal blood glucose, ≥4,9 mmol/L, increases the risk for CVD (Port *et al.*, 2005). Increased risk for CVD is related to duration of diabetes, hyperglycemia, hypertension, dyslipaemia, insulin resistance and gender (Marks & Raskin, 2000). All definitions for impaired fasting blood glucose have been associated with increased risk for coronary heart disease, but women seem to have elevated risk for coronary heart disease at lower glucose levels than men (Levitzky *et al.*, 2008). This seemed not to be true in the present study, as glucose and central obesity was only associated with the progression of target end organ damage in the men and not women.

Suzuki *et al.* (2003) stated that an α-adrenergic/vascular pattern is usually associated with an emotion-focused/passive coping pattern. During exposure to chronic psychosocial stress in urban

living, cohesiveness in the traditional African collectivistic culture decreases and this could cause stressful situations to feel uncontrollable (Utsey *et al.*, 2000). Therefore, it seems that HT African men and women may experience their situation as stressful and uncontrollable, causing them to react physiologically with a typical α-adrenergic/ vascular pattern. This idea is strengthened in the women where high avoidance correlated positively with peripheral BP responses, but more research is needed, since high avoidance also correlated positively with central BP responses (SBP, r=0.76; p=0.01) in the men, which contradicts Suzuki *et al.* (2003) and the above conclusions drawn. None of the coping styles contributed to the progression of target en organ damage in either the men or women.

Central obesity is also an important predictor of CVD (Mathew *et al.,* 2007). Even though HT women were more centrally obese than their NT counterparts, and the HT men, obesity did not contribute to the progression of target end organ damage in the HT African women but only in the men.

4.4. Discussion and findings

4.4.1 Chance, bias and confounding

Chance: It is important to reflect on some of the important factors that might have affected the results. There are some methodological issues, such as the use of the Coping Strategy Indicator (CSI) which has been successfully used in South African context, but still is not validated for all African cultures, that could have caused weaknesses in the study and, therefore, might have influenced outcomes.

Bias: Views, such as interpreting the coping strategies out of a Caucasian viewpoint and not considering the unique African culture and how it affects the interpretation of the same coping strategies, could have caused bias in the study

Confounders: Age, BMI, cortisol sampling time and estrogens could have influenced the results by causing over or under estimation of associations between cardiovascular function, coping and cortisol. By adjusting statistically for these confounders, the possible incorrect estimations were avoided.

4.4.2. Weaknesses of the study

The number of subjects included in this study could be questioned, especially the number of HT women (N=34) which in itself would be sufficient, but due to the dependent variable being BP, various

coping styles needed to be allocated to each of the subjects. This additional division caused some groups to become as small as N=9. The strength of the psychological aspect of the study was severely diminished by the small groups.

The addition of other stress hormones, such as catecholamine's, could have added depth and impact. This would definitely be considered in future studies. Urine samples collected over 8-24hours have, however, not been done to indicate chronic stress.

4.4.3. Discussions of main findings

The aim of the study was to assess the relationship between cardiovascular, cortisol and coping responses in urbanised Africans as well as its contribution towards the progression of target organ damage. Investigation into the psychobiological pathways that link stress and disease are of major importance (Kudielka *et al.,* 2009).

More men than women (63%; 34%) respectively were hypertensive. HT men and women showed increased vascular responses, when subjected to stressors.

Both HT and NT men and women had high-normal blood glucose levels and high-normal cortisol values. Cortisol reactivity was negatively associated with target end organ damage in the men ($p=0.06$). Resting cortisol values in both men and women were significantly lower during sampling time 2, ($p \geq 0.001$) indicating that the time of cortisol sampling is an important confounder to be considered. Women were more centrally obese than their NT counterparts and the HT men. Despite this, obesity was not associated with the progression of end organ damage in the HT African women. Interestingly, glucose and central obesity were associated with the progression target end organ damage in the men.

Regarding coping styles, high problem solving correlated with central BP/β-adrenergic responses in both men and women. When considering the typical α-adrenergic pattern seen in both gender groups during stressor exposure, a more emotion-focused/passive coping pattern is suggested. Suzuki *et al.,* (2003) postulated that a α-adrenergic/ peripheral physiological reaction is usually associated with an emotion-focused/passive coping pattern. A α-adrenergic response is evoked when a person experiences little or no control during a stressor and is indicative of surrendering and feelings of helplessness (Malan *et al.,* 2006b). These findings could indicate that Africans feel overwhelmed and, therefore, unable to find appropriate solutions for the problems they face. This idea is strengthened in the women where high avoidance correlated positively with peripheral BP responses (TPR, $r=0.84$, $p=0.07$). However, more research is needed, since high avoidance also correlated positively with central BP responses (SBP, $r=0.76$; $p=0.01$) in the men, which contradicts

Suzuki *et al.* (2003) and the above conclusions drawn. None of the coping styles contributed to the progression of target en organ damage in either the men or women.

4.5. Conclusion

Glucose and WC is positively associated with the progression of target end organ damage in HT men. Decreased cortisol reactivity is negatively associated with the progression of target end organ damage in the men, indicating possible HPPA hypoactivity due to chronic stress, but more research is needed to confirm these speculations. The mechanism suggested to be active in the HT men is shown in Fig 3. Coping strategies did not seem to be associated with progression of target end organ damage.

4.6. Recommendations

The following recommendations are proposed for future studies: Where coping styles are of interest, the use of active (problem solving) and passive (avoidance) coping as main risk factors are recommended. This approach will ensure large enough groups to illustrate the real impact that coping styles has on health and to see whether it has any mediating effects on CVD risk.

Further in-depth investigation into the effect of cortisol sampling time is needed, and was not completely covered in this study due to the complexities surrounding this concept. Inclusion of this aspect would have complicated the study. For example: comparing associations and interactions between variables when groups are stratified into cortisol sampling time 1 and 2.

The addition of other stress hormones, such as catecholamines, would add depth and impact. It is, therefore, strongly recommended for future studies which focus on psychophysiology.

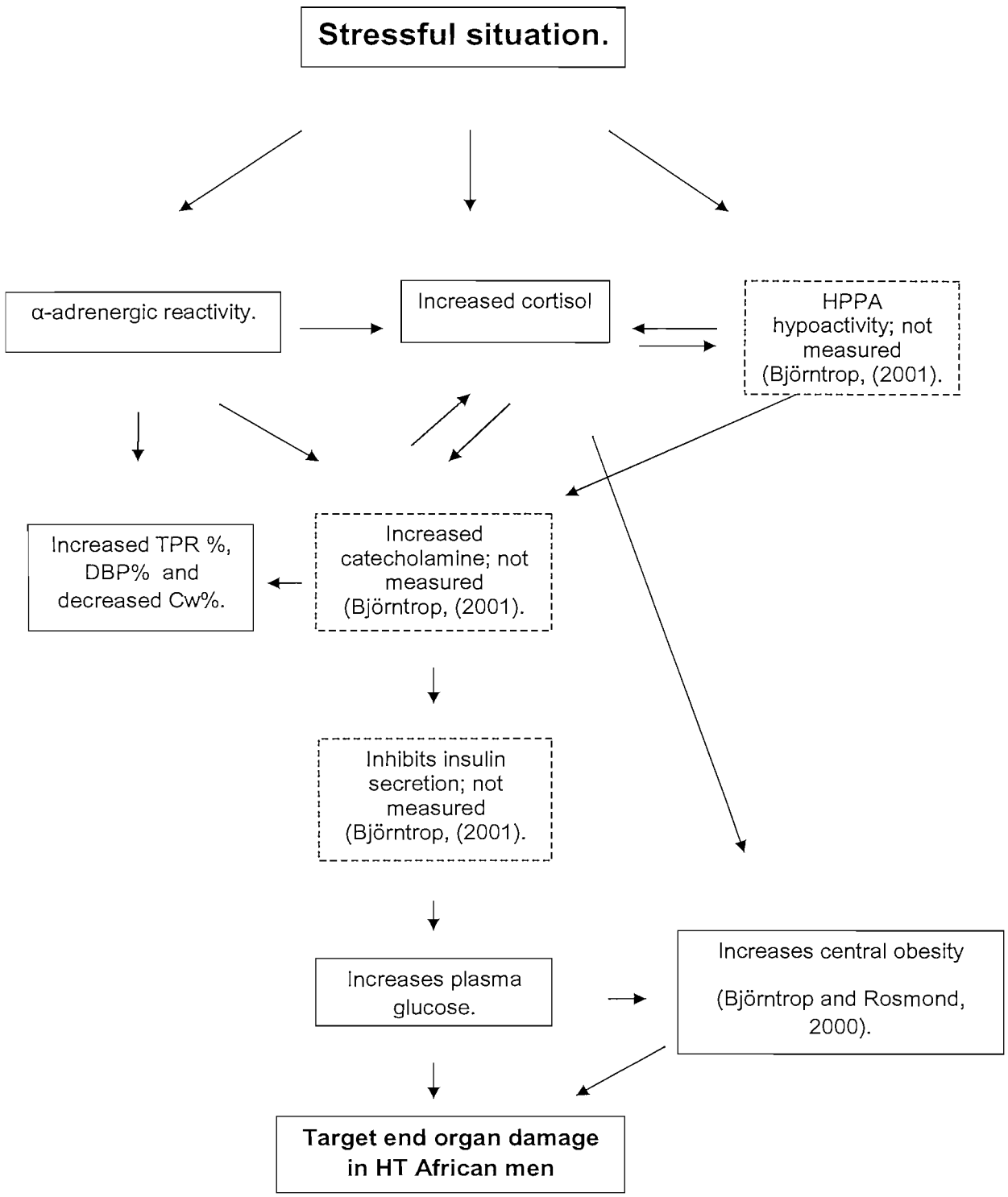

Fig 3. Diagrammatical representation of main findings. Dashed boxes adapted from Björntrop (2001) and Björntrop and Rosmond (2000).

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