Chapter 12

Continuous assessment of finger blood pressure and other haemodynamic and behavioral variables in everyday life

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Dedicated to Thure von Uexküll who
more than 20 years ago
inspired a dream now realized
through this research

Introduction

"Every affection of the mind that is attended with either pain or pleasure, hope or fear, is a cause of an agitation whose influence extends to the heart". With these words William Harvey, the great 17th century English anatomist, summarized his observations of the effect of emotions on the heart and its functions in his famous treatise EXERCITATIO ANATOMICA DE MOTU CORDIS ET SANGUINIS IN ANIMALI, in which he gives the first accurate description of the blood circulation – a milestone in the history of medicine (Harvey, 1628). Today, more than three and a half centuries later, his statement can still be seen to be an important theme in recent medical, neurophysiological and psychophysiological research aiming at evaluating his hypothesis in greater detail and with much more sophisticated tools and methods not available in his time. Various medical schools and traditions are still debating about the clinical importance or unimportance of the fact, which has in the meantime been widely recognized, that emotions affect the cardiovascular system.

A number of significant risk factors has been identified which predict morbidity and mortality of circulatory and cardiovascular diseases, rare conditions when Harvey was alive, but today the major causes of death in about half the population in most of the world´s industrialized countries. Although many traditional cardiovascular risk factors, and among them blood pressure, predict the future risk in a dose-response relationship, together they explain only about half the variance of the incidence of the single most frequent cause of death, coronary heart disease. The recognition of this fact has initiated the search for additional potential cardiovascular risk and protective factors. This research, which has been partly successful, has among other things identified a number of psychosocial and emotional conditions as possible predictors of future cardiovascular events. These include anger, hostility, social status or lack of social support (Dembroski, MacDougall, Costa & Grandits, 1989; Miller, Smith, Turner, Guijarro & Hallet, 1996). There are many anecdotal reports and several uncontrolled case se-

ries pointing to emotionally stressful events preceding and appearing to trigger the onset of acute myocardial infarction (Schmidt, Adler, Langosch & Rassek, 1995). Recently it has been shown that an episode of anger may at least double the relative risk of myocardial infarction in the next two hours (Mittleman, Maclure, Sherwood, Mulry, Tofler et al., 1995). In accordance with Harvey´s initially cited statement, a major hypothesis in this research area is that the social environment and emotional behavior evoke cardiovascular risk or stress reactions, day-in, day-out, via neural and neuroendocrine mechanisms. Blood pressure rises thus induced may vary in frequency, degree and duration, and the risk associated with these psychosocial, emotional and behavioral factors may partly be transmitted by such blood pressure fluctuations.

This hypothesis has created a huge body of mainly laboratory based studies in which the influence of psychological and behavioral factors on cardiovascular reactions is investigated in many situations. The underlying reasonable but unproven hypothesis this research is based on is that, for instance, the blood pressure rises exhibited by an anger-prone subject in an experimentally induced, mildly anger provoking situation in the laboratory also occur in everyday life situations more often and/or to a higher degree, when compared to the blood pressure responses of a non-anger-prone person. Blood pressure is usually measured in such experiments at intervals of one minute at the shortest, using automatic blood pressure devices based on the Korotkoff or Marey´s oscillometric method. This means for instance, that during the Korotkoff measurement the pressure values are only determined at that one heart beat when the cuff pressure equals the systolic pressure, and some heart actions later the diastolic pressure. When blood pressure is measured in everyday life using such portable automatic devices, it is usually only done at 15 or 20 minute intervals. Elaborate and excellent psychophysiological studies have been carried out with such devices (Fahrenberg, Heger, Foerster & Müller, 1991; Käppler, 1994), but it has become very clear that such measurements do not allow the evaluation of the full dynamics of blood pressure responses in daily life. These tools are very limited in answering the question about whether and to what extent cardiovascular reactivity differences seen in the laboratory generally take place in everyday life.

Knowing today more about the individual variation of blood pressure in daily life, it is astonishing that blood pressure was discovered to be such an important predictor of future cardiovascular risk in epidemiological studies, when it was only measured a few times and usually at rest. These studies have revealed that it is the height of blood pressure which increases the risk, and kills! No lower or upper limit of blood pressure has been identified at which there is a sudden rise in risk. There is rather a continuous rise in cardiovascular risk from low to high blood pressure levels, i.e., the higher the pressure the higher the risk, and the pressure of every single heart beat may contribute to this risk. How much better should we then be able to predict the risk associated with blood pressure, if we knew in detail the individual´s blood pressure in everyday life, recorded continuously on a beat-to-beat basis!

Research programs aimed at investigating this were, however, greatly restricted and were bound to fail because of the limitations of the available instrumentation which enabled continuous blood pressure recordings to be carried out only using invasive intraarterial measurements.

Development of the continuous noninvasive recording of finger arterial blood pressure

For more than a century there has existed the desire to record noninvasively the arterial pressure waveform, calibrated in mmHg, and there have been many attempts to achieve this goal (Wesseling, 1995). But it is only the recent rapid development of electronics, control theory, informatics and microcomputers which has enabled success through the creation of the branch of mechatronics, the advantageous combination of mechanics and electronics. This success is based on the pioneering ideas and creative investigations of the Czech physiologist, Jan Peňáz, and his innovative devices, the first prototypes using the photo-plethysmographic volume-clamping of finger arteries in which a servo system clamps the finger arteries under a dynamically unloading cuff to a set point (Peňáz, 1969; Peňáz, 1973). The cuff pressure is made to equal intra-arterial pressure at each instant, the arterial wall no longer being distended, but instead it is volume clamped at its unstretched diameter at zero transmural pressure. By recording cuff pressure, intra-arterial pressure is measured indirectly, since transmural pressure is zero at all times, and therefore cuff pressure continuously equals finger arterial blood pressure.

It was the Dutch medical physicist, Karel Wesseling, who introduced the Physiocal criteria which establish the set point level and provide for a computerized periodic, automatic setpoint adjustment (Wesseling, de Wit, van der Hoeven, van Goudoever & Settels, 1995). Wesseling together with his research team laid with ability and inventive skills the bases for the development of the first commercially available devices for measuring noninvasively the continuous finger arterial waveform – a long awaited, important step forward in cardiovascular physiological research. With these devices, Finapres and its portable version, Portapres model 1, as well as the recently developed smaller and lighter version, Portapres model 2, it is now possible to record continuously the pressure signal of the finger arteries over long periods of time in stationary as well as ambulatory subjects, even over 24 hours. Continuous finger blood pressure measured this way with all its changes closely resembles the invasive "gold standard", measured more proximally in the radial or the brachial artery, or in the aorta (Imholz et al., 1993; Parati, Casadei, Gropelli, Di Rienzo & Mancia, 1989), although these pressures are never identical, as the transmission of pressure and flow pulsations in the arterial system causes distortion of the pulse waves. This distortion mainly affects the systolic pressure, which is usually a few mmHg higher in the finger than in the more proximal arteries. In addition it was almost invariably found that noninvasively measured finger blood pressure underestimates brachial diastolic and mean arterial pressures (Imholz, Wieling, Langewouters & Van Montfrans, 1991); this is greater with an increasing flow, due to a pressure gradient in the small arteries (Wesseling, Settels, Van der Hoeven, Nijboer, Butijn & Dorlas, 1985).

These new instruments, Finapres and Portapres, have now become simple to apply, although a critical and attentive mind is still needed to avoid artifacts and measurement errors, or to recognize malfunction of the devices. They have initiated a burst of research activities in many laboratories around the world to find the answer to questions about the normal and pathologic circulation of humans for which no adequate noninvasive tools were previously available (Bibliography Finger Arterial Pressure [Finapres], 1995).

Portapres Model 1 and Model 2

We had the opportunity of using one of the very first Portapres model 1 instruments available, and later on also the new model 2. We show here some of the data collected using these two devices. Both models consist of a main unit, a patient frontend box with two finger cuffs, and a height correction system. In the case of model 1 the main unit weighs 3000 g and contains the necessary electronics, a seven channel TEAC cassette FM instrumentation recorder (storing the analog finger blood pressure waveform as well as beat-to-beat systolic, diastolic and mean arterial pressure, heart rate and the height correction signal), a Lithium battery pack, and a pump to generate the air supply. It can be worn on the stomach by means of two belts, or hung from the shoulder, or carried in a rucksack. The main unit of model 2 (320 g), containing a proprietary processor board equipped with a 4 Mbyte flash memory card which stores the full pressure waveform together with the hydrostatic height signal and other relevant information, is carried together with the pump (345 g) and battery pack (415 g) in a waist belt, and is operated by a control unit which is used to select the mode of measurement and to start and monitor the measurement of finger blood pressure. The control unit (408 g including batteries) is usually not carried around by the subject, as Portapres becomes fully automatic when the measurement has been started, and will continue without operator intervention unless some irrecoverable error occurs.

The frontend unit (350 g) contains an air pressure control valve, a pressure transducer, an infrared cuff LED controller, a photodiode amplifier and a two-finger switching device, and is carried on the back of the hand or at the wrist. In model 1 the measurement automatically switches every 30 minutes between the two finger cuffs which are usually wrapped around the middle finger and the ring finger of the non-dominant hand. The switching intervals can be chosen in model 2 at 15, 30 or 60 minutes and additionally at one minute just for checking purposes in the laboratory.

The height correction system consists of a liquid filled tube connected at one end to a pressure transducer which is placed at the measured finger, and closed at the other end with a compliant plastic bag contained in a small cylindrical housing which is taped at heart level (for instance at the left anterior axillar line just below the processus xyphoideus of the sternum). This system continuously senses height changes of the measured finger. The height signal is lowpass filtered and subtracted from the finger pressure. Slow changes in blood pressure due to hydrostatic effects are therefore compensated. Dynamic pressure effects due to quick hand movements are not compensated and may introduce motion artifacts.

In model 1 a 7-channel TEAC replay unit is necessary for later analyses of taped data, as well as computer equipment (analog-digital converter etc.) and adequate software (BEAT-FAST). The data of model 2 can be directly transferred from the flash card via a serial port to a PC, onto which the beat-to-beat analyses can be run using the available software (PORTA).

Haemodynamic assessment with Modelflow analysis

According to Ohm´s law, mean arterial pressure equals the product of cardiac output (which is the product of stroke volume and heart rate) and peripheral resistance. Pressure changes can therefore be due to different haemodynamic patterns: to changes in cardiac output, changes in peripheral resistance, or to various combinations of changes in both. The question still remains unanswered, as to whether the risk related to blood pressure is just due to the height of the pressure, independent of its haemodynamics, or whether pressure elevations are associated with a higher risk for different disease or mortality endpoints, when these are caused either by a rise in cardiac output or in peripheral resistance. The accurate determination of stroke volume and cardiac output, which also enables the calculation of total peripheral resistance, has up to now been based on invasive methods such as thermodilution or dye dilution which, however, are not beat-to-beat measures. Such invasive haemodynamic measurements are restricted to the clinical cardiovascular laboratory, the operating room or the intensive care unit. Repeated invasive haemodynamic measurements have only very rarely been performed in a psychophysiological context (Brod, Fencl, Hejl & Jirka, 1959; Groen et al., 1982; Schmidt, 1983).

Based on the continuous recording of the arterial pressure waveform, measured either invasively in the aorta, or in the brachial or radial artery, or noninvasively at the finger, Wesseling recently developed the Modelflow analysis which allows on a beat-to-beat basis the accurate determination of relative changes of stroke volume, cardiac output and peripheral resistance (Wesseling, Jansen, Settels & Schreuder, 1993). This analysis uses a model of the afterload of the heart including three major parameters: (a) aortic characteristic impedance, (b) arterial Windkessel compliance, and (c) total peripheral resistance. One pressure signal is additionally needed to define the pressure in the Windkessel at the start of ejection, which is the enddiastolic pressure. Together these four parameters form a nearly complete description of the left ventricular afterload. The Windkessel function of the aorta is characterized by its pressure-volume diagram. The shape of this diagram is mainly determined by age and gender, and to a lesser degree by height and body weight. The arterial pressure wave is applied to the model, which then calculates an aortic flow wave. The integrated aortic flow over one heart beat equals the stroke volume. As pressure is usually not measured in the aorta but in more peripheral arteries, further adjustments have to be performed. The Modelflow analysis can be calibrated with invasive methods in individual subjects or patients. Such a calibration would then enable the continuous measurement of absolute levels of the haemodynamic parameters. A series of software programs, the FAST-mf/-cZ system, developed by Wesseling (1993) enables the off-line Modelflow analysis of Portapres data.

With these new tools, Portapres and the Modelflow analysis, it is now possible to record noninvasively blood pressure changes as well as its underlying haemodynamics on a beat-to-beat basis not only in the cardiovascular laboratory but also in ambulatory subjects in everyday life. For a cardiovascular researcher this recent development would appear to offer many new research opportunities.

Assessment of haemodynamic and behavioral variables in everyday life

We started the first 24 hour measurements using Portapres in various groups of young healthy male volunteers. From previous studies, in which we continuously recorded heart rate in everyday life, we were aware of the enormous impact of physical activity on cardiovascular functions (Johnston et al., 1994). The study of reactivity differences or of the effect of emotional factors on the cardiovascular system in everyday life must therefore control for the effects of physical activity.

In the first Portapres study, as well as blood pressure and the other haemodynamic variables, we recorded integrated thigh-EMG with the Bioport system (ZAK, 1982) as a continuous measure of physical activity together with using a diary in which the subjects regularly reported on their major activities and events as well as on their moods during the previous half hour (Schmidt et al., 1991; Schmidt, Wittenhaus, Steinmetz, Piccolo & Lüpsen, 1992; Schmidt, Steinmetz, Wittenhaus, Piccolo & Lüpsen, 1992). In the first studies a paper-pencil diary was used, and later on an electronic diary was introduced (PSION 3, see Jain, Martens, Mutz, Weiss & Stephan, this volume). The subjects

were asked to live as normally as possible a life during the monitored day, despite the somewhat heavy equipment.

Figure 1 gives an example of such a 24 hour Portapres model 1 recording of a 25 year old healthy male medical student. Based on one minute mean values, it shows systolic (SBP) and diastolic blood pressure (DBP), as well as heart rate (HR) and the Modelflow analyses of stroke volume (SV), cardiac output (CO), and peripheral resistance (PRU), together with integrated thigh-EMG. Above and below the cardiovascular parameters and the thigh-EMG recording, the diary notes of mood changes and other major activities are reported. With the diary notes and an interview after completion of the measurements, the day and the activities of the student can be described in some detail.

During the first half of the 24 hour recording quite dynamic changes of blood pressure, heart rate and the other haemodynamic variables can be seen in this subject, whereas after returning home at around 19.30 the course of these parameters is much calmer during the rest of the day, while he is mainly watching TV, as well as at low levels during sleep at night, with the exception of peripheral resistance which rises during sleep *(for details see legend Figure 1).*

When thigh-EMG, our measure of physical activity, is used in this subject to predict the changes in the cardiovascular parameters within 24 hours, this is positively correlated in regression analysis with all the haemodynamic variables except peripheral resistance which correlates negatively. Thus a higher level of physical activity is related to a higher blood pressure, heart rate, stroke volume and cardiac output as well as to a lower peripheral resistance, and vice versa. Based on one minute mean values, a substantial amount of the variance in the various haemodynamic parameters is explained by just this one measure of physical activity: 37% in SBP, 22% in DBP, 38% in HR, 20% in SV, 58% in CO, and 27% in PRU. This analysis does not include the time delayed effects of physical activity which may explain an additional amount of the variance (Schmidt et al., 1991). A simple way to experience such delayed effects of physical activity on cardiovascular functions oneself is to rest after some physical effort which elevates heart rate. The faster heart rate, for instance after climbing stairs, is retained for a while until it slows down again to the usual resting levels. The time course of these heart rate changes may depend on various factors and their interaction such as the amount of activity and the degree of excertion as well as physical fitness and body weight.

Moreover, it should be possible to explain an even larger proportion of the variance of blood pressure and its haemodynamic components, if additional measures of physical activity are included, such as arm movements and posture. In his diary the subject also recorded whether he was sitting, standing or lying down during each half hour interval when he was awake. However, these diary recordings of posture are not precise enough to allow postural changes to be exactly related to the cardiovascular functions. For this purpose we had to develop a continuous measure of posture which then allowed blood pressure and its haemodynamic components to be accurately related to posture and its changes in daily life. Therefore we combined measurements of Portapres and Vitaport 1, a device for the ambulatory recording of multiple physiological signals, which enabled simultaneous recordings of the various cardiovascular variables together with the continuous assessment of posture by measuring the hydrostatic pressure difference between heart level and left ankle, as well as movements of the dominant arm with an accelerometer at the wrist, and integrated thigh-EMG (Jain, Schmidt & Johnston, 1995). This combination of the continuous assessment of haemodynamic variables and activity measures now allows a more detailed and exact analysis of the impact of physical activity on blood pressure, heart rate and other haemodynamic variables.

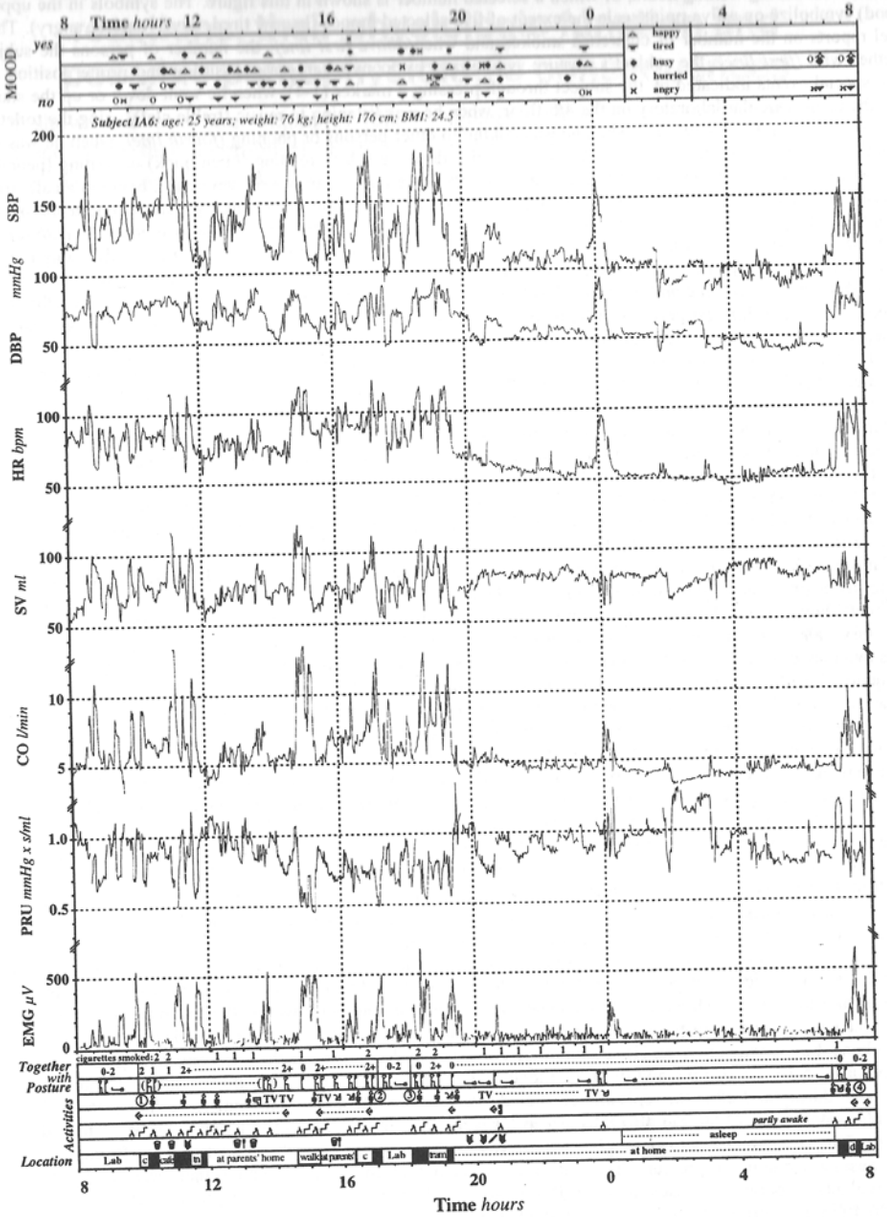

Figure 1: Blood pressure, haemodynamic responses and physical activity in a healthy male medical student aged 25 years (IA6) as recorded with Portapres model 1 and Bioport. Based on one minute mean values, systolic (SBP) and diastolic (DBP) blood pressures are displayed over the course of 24 hours of everyday life as well as heart rate (HR), stroke volume (SV), cardiac output (CO), peripheral resistance (PRU) and physical activity as measured by integrated

thigh-EMG. Other activities, events and moods are recorded by the subject in a paper-pencil self-report diary at 30 minute intervals during waking hours, of which a selected number is shown in this figure. The symbols in the upper panel (mood) symbolize on a five point scale the extent of five selected moods (happy, tired, busy, hurried, angry). The lower panel reports on the number of cigarettes smoked and when*(above first line)*; the number of persons the subject was together with *(first line)*; the subject´s posture symbolized by icons of an upright, sitting and prone position *(second line)*; special events indicated by the subject through pressing a marker (1-4), when he went down or up the stairs from or to the cardiovascular laboratory on the 4th floor; when he was listening to music (treble clef), using the toilet, micturating or watching TV *(third line)*; when he was talking to other persons or phoning *(fourth line)*; when he was walking or climbing stairs *(fifth line);* when he was eating (fork), drinking (glas), reading (open book) or writing (pencil) *(sixth line)*; where he was and when (locations) [being in the lab, traveling by car as a passenger (c), being in a cafe, travelling by train (tn), being in his parent´s home, going for a walk in the vicinity, traveling by tram, being at his own home, driving a car (d)], the black fields indicating that the subject is on his way from one place to another *(seventh line)*.
From 8.00 to 9.50 as well as from 17.00 to 18.00 measurements are carried out in the cardiovascular laboratory during standardized laboratory tasks. During these investigations the 10 minute rest periods in a prone position can easily be identified by the low systolic and diastolic blood pressure levels, and the five minute multiple choice reaction time task immediately before this rest period can be recognized by the highest blood pressure peak during the laboratory measurements. During everyday life it can be seen that the blood pressure and most haemodynamic changes are somewhat related to the physical activity measure, the thigh-EMG, which is supported by the amount of variance explained by the integrated thigh-EMG, and which ranges between 20% in stroke volume and 58% in cardiac output.
The student´s day can be described in some detail, as follows:
At 09.50 he leaves the laboratory and goes down the stairs from the 4th floor of the medical school (this activity is marked by 1 in a circle) to meet a friend waiting nearby in his car (c); they drive together in the car for about 10 minutes while the subject smokes two cigarettes. Then his friend parks the car near a cafe. From the car they walk for about 10 minutes to the cafe where the subject drinks two cups of coffee and smokes two cigarettes. Here he feels relaxed and quite happy. At 10.50 he leaves the cafe and walks somewhat hurriedly with some additional baggage to the station where he arrives 10 minutes later. At the station he stands for about 5 minutes in the vestibule before going upstairs to the platform where he waits for another 5 minutes. At 11.20 he enters the train and sits down. During the journey (tn) he talks to his neighbor and listens to music on his walkman. At 11.35 he gets off the train, walks downstairs and home to his parents´ house, where he arrives at around 11.50; he will be staying there until 16.15. At home he is quite happy and fairly busy, talking to his family and smoking two cigarettes. At around 13.00 he has lunch together with his family, drinks two glasses of cola as well as a cup of coffee and smokes a cigarette. After the meal at 13.20 he goes to the toilet. At around 13.30 he reports that he is fairly busy (perhaps helping to clear the table). Between 13.45 and 14.30 he watches a film on TV together with members of his family, and talks to them. At 14.30 he sets off for a walk in the vicinity during which he smokes a cigarette. He returns a little after 15.00. Then he talks to his family and watches TV, and later on, after 15.30, he drinks three cups of coffee, eats some more food, smokes a cigarette, and goes to the toilet. Before leaving his parents´ home at around 16.20 together with his sister who drives him back (c) to the medical school, he goes to the toilet again. During the journey he smokes two cigarettes. About five minutes before arriving at the medical school at around 16.50 he becomes very angry arguing with his sister, which results in a blood pressure rise from resting levels of around 100/60 mmHg up to 180/80 mmHg. This blood pressure rise occurs before he climbs the stairs to the laboratory on the forth floor (marker 2). According to the diary self-reports he takes about 3 hours to calm down again from being very angry to the zero level. Just after 18.00 he leaves the laboratory, goes downstairs (marker 3) and walks to the tram station. While he is waiting for the tram he smokes two cigarettes and listens to loud music on his walkman. At 18.30 he takes a tram, changes the connections and arrives at his destination at around 19.00. He takes about 15 minutes to walk home. During the tram journey he smokes two cigarettes and is listening to very loud music on his walkman, and notices that people are staring at him because of this. During this time his blood pressure rises and reaches peak values of 200/90 mmHg. At home he goes to the toilet and lies down on the couch at 19.30 where he reads, writes, watches TV, and smokes seven cigarettes until midnight. At about 20.30 the phone rings and he gets up to pick up the phone, but nobody answers. He is somewhat annoyed and then angry, as this has happened quite often during the past few days. A rise in systolic and diastolic blood pressure as well as in peripheral resistance for about half an hour can be seen during and after this episode. He lies down again on the couch and watches a James Bond film on TV (Gideon´s sword) until 23.50, but also falls asleep for some time in-between. Then he prepares to go to bed at around midnight. This is combined with some physical activity, as he has to arrange the AC adapter for Portapres at bedtime which causes a rise in blood pressure, heart rate and cardiac output. In his diary he notes that these arrangements induce some involuntary abdominal muscle training. Before going to bed at 0.15 he goes to the toilet. Between 04.00 and arising at 06.40 in the morning he reports on disturbed sleep, when noisy fellow-lodgers return home. During this time peripheral resistance is lowered again in contrast to when he was fast asleep, when it was up and rising. After getting up he smokes a cigarette and at 07.30 he takes his car to drive (d) to the laboratory in the medical school, where he arrives after a 15 minute drive. At 07.15 he climbs upstairs to the fourth floor (marker 4). In the laboratory the measurements are finished at 08.00.

The haemodynamic patterns of cardiovascular stress reactions, their physiologic function and possible pathophysiologic consequences

Figure 2 shows two one hour examples (diagrams A and B) of such a combined recording in a 74 year old overweight subject taken from a 24 hour measurement with Portapres model 2 and Vitaport 1 (Jain, Martens, Mutz, Weiss & Stephan, 1996, this volume). All variables are displayed at two second intervals based on four second moving averages. Normotensive at rest, this subject exhibits two most pronounced cardiovascular stress reactions, one in the morning during mild physical activity *(left diagrams:* A*)* and the other in the early evening while sitting and watching TV at apparent physical inactivity *(right diagrams:* B*)*. Both blood pressure elevations are due to quite different haemodynamic patterns.

In the morning example, shown on the left side of Figure 2 (A), blood pressure is raised by an elevation of cardiac output due to both a rise in heart rate as well as in stroke volume, while peripheral resistance is somewhat lowered. This haemodynamic pattern is typical in physical activity such as walking, although a systolic pressure rise with peak values of up to 280 mmHg while just walking slowly outside on the level and going up a few steps inside the clinic is extraordinary. The onset and end of this physical activity can be followed exactly in the continuous recordings of the arm movements, thigh-EMG activity and posture. During this walking activity the diastolic pressure is typically somewhat lowered, i.e., in such a sequence diastolic blood pressure correlates negatively and systolic blood pressure positively with physical activity. These systolic and diastolic pressure changes result, however, in an elevation in mean arterial finger blood pressure of up to around 150 mmHg. The enormous systolic blood pressure rise is probably at least partly due to the subject´s obesity. Like a weight lifter who can never put down his weight, he has to carry an extra 25 kg continually around with himself. Another reason may be that this aged subject exhibits even at rest an elevated peripheral resistance, which is more than twice as high as that of the young subject shown in Figure 1. Although a comparison between different subjects of absolute PRU values determined with Modelflow analysis must be regarded with caution, a peripheral resistance elevated to such an extent points to an altered wall/lumen ratio of the resistance vessels in the older man, which may lead to stronger pressure rises due to, for instance, neural or humoral adrenergic stimulation. The haemodynamic pattern of this cardiovascular response to physical activity closely resembles the changes which can be observed when adrenaline is infused (Figure 3).

In the evening example, displayed on the right side diagrams (B) of Figure 2, the blood pressure elevation while watching TV is due to the emotional content of the program and to a rise in peripheral resistance, which doubles without cardiac output changes. During about 30 minutes there is a continuous rise in both systolic and diastolic blood pressures from normotensive levels to peak values of above 240/140 mmHg. This results in a mean arterial finger blood pressure elevation of up to 179 mmHg.

A similar simultaneous rise in systolic and diastolic blood pressure can also be seen during the infusion of noradrenaline (Figure 3). When compared to the cardiovascular response pattern evoked by environmental stimuli via the central nervous system, which is coordinated in the hypothalamus, the changes in the other haemodynamic parameters during such a "passive" infusion of noradrenaline are, however, different: Blood pressure is raised by an elevation in stroke volume and cardiac output, and this creates a decrease in heart rate via the baroreceptor reflex. During centrally initiated situational blood pressure rises the baroreceptor reflex is usually suppressed.

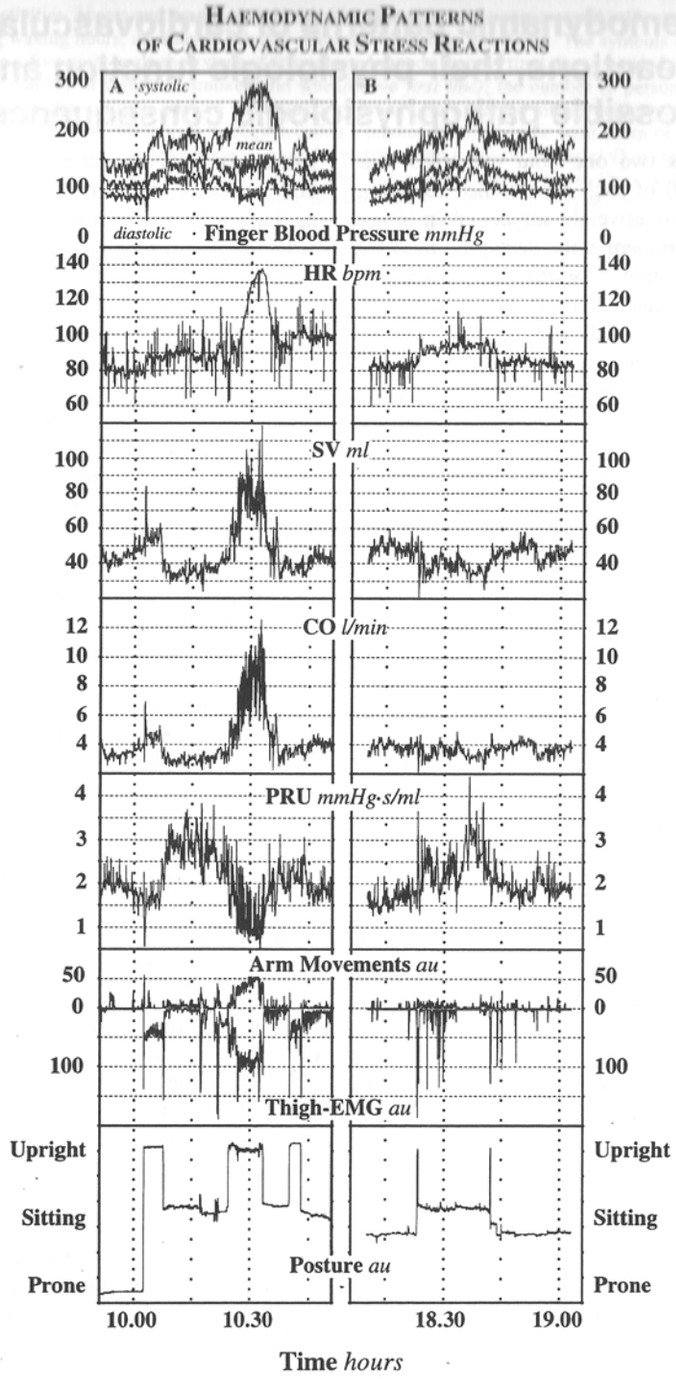

Figure 2: Examples of two different haemodynamic patterns of cardiovascular stress reactions in a 74 year old overweight man (height = 1,67 m; body weight = 81 kg; BMI = 29) during two one hour periods (A: morning and B: evening) taken from a 24 hour ambulatory monitoring with Portapres model 2 and Vitaport 1. The following cardiovascular and physical activity parameters are displayed at two second intervals based on four second moving averages: Systolic, mean and diastolic finger blood pressure, and heart rate (HR), as well as stroke volume (SV), cardiac output (CO), and peripheral resistance (PRU) according the Modelflow analysis, and also movements of the dominant arm, integrated thigh-EMG, and posture.

The diagrams on the left hand side (A) show normotensive blood pressure values while the subject is resting in a prone position for 10 minutes in the laboratory, and a pressure rise to somewhat hypertensive levels while he is standing upright for 5 minutes at rest. While sitting at 10.09 he has to prepare a talk mentally (about an anger inducing person and situation) for 3 minutes, and then delivers his speech for slightly more than one minute. After 10.18 he puts one of his feet into 4 ^{0}C of cold water for another two minutes (cold pressor test). At 10.26 he starts off for a walk outside the clinic accompanied by a young female medical student monitoring that he is walking at a slow pace, and goes up a few steps before resting again in a sitting position after 10.33. Then he stands up for a few minutes and sits down again. The walking activity triggers a most pronounced systolic blood pressure rise which is caused by a rise in heart rate and stroke volume and thus cardiac output, while peripheral resistance is lowered.

The diagrams on the right hand side (B) show a continuous blood pressure rise from normotensive levels by more than 120 mmHg systolic and 60 mmHg diastolic over the course of about 30 minutes in the early evening. This pressure rise is due to a doubling in peripheral resistance, while cardiac output remains more or less unchanged. During this time the subject is sitting and watching TV. The posture recording reveals that the subject changes his sitting position to a more upright sitting position for about 20 minutes, after which he returns to his original somewhat more prone sitting position. Changing posture he shortly stands up twice. These changes in his sitting position are also reflected in haemodynamic alterations: The more upright sitting position is related to a heart rate which is higher by about 10 bpm as well as to a stroke volume which is lower by about 10 ml, resulting in an unchanged cardiac output.

In an interview after completion of the 24 hour measurements, when he was asked about the content of the TV program triggering this cardiovascular stress reaction, he reported that he is a fan of the German soccer team Werder Bremen, and later that Sunday night there was an important game being played against its major rival, Borussia Dortmund. The continuous pressure rise took place when he discovered that the famous coach of his favorite team, Otto Rehagel, had announced that he would be leaving his team after many successful years to become the coach of the much richer team Bayern München. This news, together with an interview with the coach and associated discussions excited him so much that his blood pressure rose to such a considerable extent at apparent physical rest in a sitting position. This kind of haemodynamic response can only be seen during a cardiovascular stress reaction at physical rest.

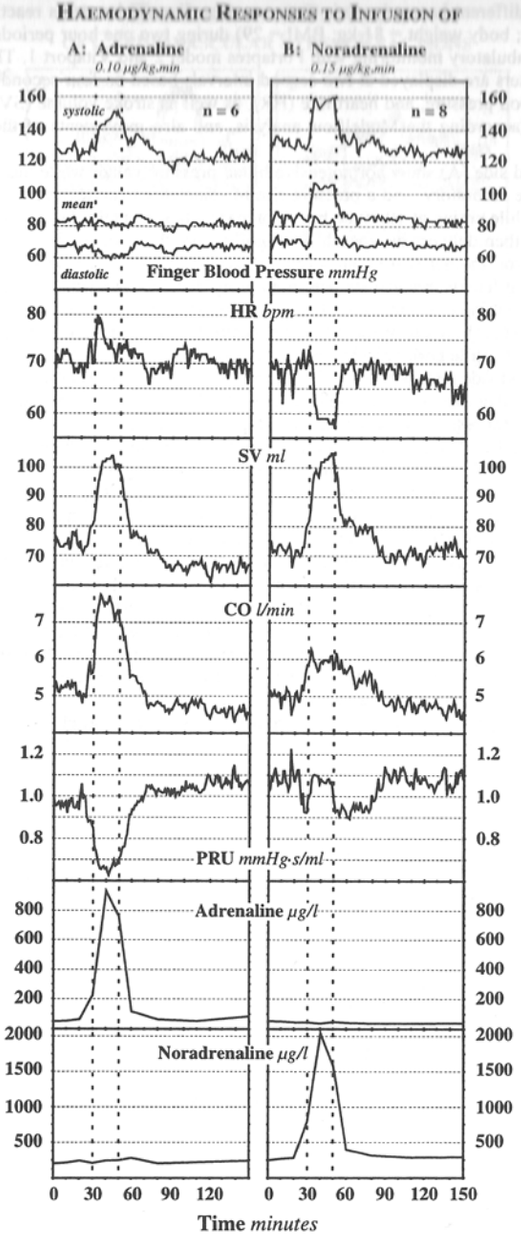

Figure 3: Haemodynamic responses to infusion of adrenaline (0.10µg/kg.min) (A) and of noradrenaline (0.15µg/kg.min) in six and eight healthy male volunteers aged 20 to 26 years respectively. Based on one minute mean values over the course of 150 minutes, systolic, mean and diastolic finger blood pressure and heart rate (HR) as measured with Portapres model 1 are displayed, together with the Modelflow analysis of stroke volume (SV), cardiac output (CO), and peripheral resistance (PRU), as well as serum levels of adrenaline and noradrenaline taken at various time intervals. The vertical dotted lines indicate start and end of the adrenaline and noradrenaline infusions.

Both adrenergic humoral responses, consisting of an increase in adrenaline and noradrenaline blood levels, are part of the emotional, behavioral and cardiovascular adaptation to the environment, and the amount released of each of these hormones may depend on the situational demand. A "pure" adrenaline or noradrenaline response, such as shown in Figure 3 A and B, may, however, rarely occur in daily life.

Based on the observation that the same environmental stimuli may initiate a blood pressure rise in one situation and case, but not in another, von Uexküll & Wick (1962) coined the conception of situational hypertension ("Situationshypertonie") pointing to the fact that the cardiovascular responses depend on the specific meaning of the stimulus for each individual, and especially on its perceived emotional content, which is strongly influenced by the individual learning history. Acute as well as chronic emotional arousal, both being caused by various types of social interaction, depends on neuroendocrine stimulation and together with genetic factors appears to play an important role in the development of hypertension in animals and man (Henry et al., 1993; Henry, Stephens & Ely, 1986). Recent research shows that specific perceptions of control result in different patterns of neuroendocrine activation. A challenge perceived as being easy to handle will elicit an active coping response and a release of noradrenaline. Testosterone will rise as the subject savours success. With increasing anxiety this active coping shifts to a more passive mode and the behavior becomes less assured as control is lost. The noradrenaline/adrenaline ratio decreases as adrenaline, prolactin, renin and fatty acids rise. As the outcome becomes still less certain and distress grows, adrenocorticotropic hormone and cortisol levels arise (Henry, 1992). Anger and hostility may trigger fighting behavior, which is associated with the release of noradrenaline and an elevated blood pressure, whereas uncertainty and anxiety may lead to flight, the release of adrenaline and the corresponding cardiovascular adaptations.

What is the reason behind such cardiovascular stress reactions with differing haemodynamics, or what is their physiologic function?

The circulatory function certainly serves to adapt the organism to the tissue´s changing requirements; this has to be regarded as a regulatory system for supplying the tissue with nutrients and oxygen. The basis for this is a blood volume adapted to the demand, as well as a sufficient pressure gradient between the arteries and veins. The tissue´s changing requirements demand a complex regulatory system which can change the total blood flow in the cardiovascular system as well as the relative blood flows to the various vascular areas, according to their needs. The height of arterial blood pressure, which is determined by cardiac output and peripheral vascular resistance, are, together with blood pressure changes, mainly responsible for the height of the pressure gradient and its variation. Situational blood pressure rises increase the pressure gradient for the time of their duration, i.e., with an unchanged resistance they simultaneously enable a higher blood flow, or the same blood volume can be transported against a higher resistance.

Situational blood pressure rises enable rapid shifts of blood volume from one area of the body to another. As the investigations of Jan Brod have shown, whether a situational blood pressure rise is produced by a rise in peripheral resistance or in cardiac output, or in both, there is always an increase in skeletal muscle blood flow (Brod, Fencl, Hejl & Jorka, 1959). The integration of this reaction pattern takes place in the hypothalamus. This "hypothalamic defense reaction" is a major influence on blood pressure control (Abrahams, Hilton & Zbrozyna, 1960; Eliasson, Folkow, Lindgren, Uvnaes, 1951). As Folkow (1985; 1987) has pointed out, the term "defence reaction" may give the inappropiate

impression that it is only involved in very threatening situations. This reaction pattern is in fact activated whenever the organism is even slightly alerted; it is part of the normal life responses. It is a highly differentiated response that overrides the brainstem´s homeostatic mechanisms and adjusts the cardiovascular system in an "anticipatory" fashion, so that the body is prepared for vigorous physical activity to meet environmental challenges. It is a state highly suited for either attack or flight in the event of a challenge such as a confrontation with a rival. There is excitation of adrenergic fibres to all parts of the vascular bed and heart, and the release of catecholamines is greatly enhanced. The arterial blood pressure rises, the skeletal muscle blood flow increases while flow through the kidney is redistributed and reduced. Salt and water absorption by the gut increases and its excretion by the kidney decreases. Vasoconstriction centralizes blood volume and salt appetite increases to further protect fluid-salt resources. Sympathetic activation of the kidneys increases renin release and, by stimulating β_2-receptors, adrenaline increases lead to noradrenaline release (Henry, Stephens & Ely, 1986).

Many stimuli can elicit this preprogrammed reaction pattern and with it the situational blood pressure rises. As muscular activation is associated with vasodilatation of the appropiate vessel areas, this physiologic reaction pattern guarantees a better blood supply to the working musculature and hinders a sudden pressure fall, which might otherwise result because of the necessary vasodilatation during motor action. Here we can see why numerous environmental stimuli are able to elicit the defense reaction as a cardiovascular preparation and an adjustment to imminent motor action. The environment, so to speak, has to be under continuous observation for the possibility or probability of an acute danger or situation, in which case the organism must be able to react immediately with a powerful motoric action. It is obviously quite possible, then, for situational pressure peaks to occur most of the time in the absence of real need, that is, when no motoric action is necessary. An example of this is displayed in the right hand side diagrams of figure 2 (B). Elicited by symbolic stimuli in the TV program and their emotional content, the pressure gradient between arteries and veins is here greatly enlarged by a consistently rising total peripheral resistance, which prepares the organism – like a drawn bow which might soon release the arrow – to transport an enormous amount of blood volume rapidly to the muscles as soon as they have to act.

On the other hand, a powerful motoric response without a preceding cardiovascular adjustment would lead to the rapid fatigue of working muscles, which could have fatal consequences in acute danger. Viewed in this way, the utility of the defense reaction becomes directly evident, and so we can understand why the organism is programmed to react with even more situational pressure rises than are actually necessary. In other words, although often triggered by symbolic stimuli, the reaction is quite often not needed in modern life, as a major motoric response is inappropiate; fortunately, however, this reaction pattern is there in times of real need.

The organism´s ability to link this reaction pattern together with new environmental stimuli through learning processes is of great importance. It can thus probably be evoked as a conditioned response, enabling a better preparation and adaptation of the circulation to a great variety of environmental conditions in which it would be necessary for the organism to have a motoric response. In other words, an easier release of the hypothalamic defense reaction could have been an advantage during evolution under certain environmental conditions. But what may have been an important and necessary advantage for survival in the short run can be a risk in the long run. The inappropiate release of the defense reaction places more stress and strain on the heart and vessels, which may heighten the risk for the development of atherosclerosis, coronary heart disease, myocardial infarction, and sudden cardiac death. According to the "response-to-injury" hypothesis (Ross, 1986) blood pressure rises may vulnerate the endothelium of the arteries and together with other cardiovascular risk factors speed up the development of atherosclerosis. In rats it has been shown that stress induced blood pressure rises cause a 500% elevation of the endothelial cell replication rate. Such an injury may promote atherogenesis (Hirsch, Maksem & Gagen, 1984). Another mechanism may be of importance in triggering the onset of acute myocardial infarction in the middle-aged and older population with pronounced atherosclerotic lesions in the coronary arteries. A sudden blood pressure rise, induced for instance by an episode of anger, may rupture such a vulnerable atherosclerotic plaque and initiate the events leading to the thrombotic occlusion of the coronary artery and thus to myocardial infarction or sudden death (Tofler & Muller, 1992, Mittleman, Maclure, Sherwood, Mulry, Tofler et al., 1995).

Physical activity as predictor of blood pressure and heart rate variation

The simultaneous continuous recording of blood pressure, heart rate (Portapres model 1) and measures of physical activity such as posture, arm movements and integrated thigh-EMG (Vitaport 1) in a group of 15 healthy male volunteers aged 22 to 29 years made possible for the first time a more detailed and accurate analysis of the effects of physical activity on the variation of blood pressure and heart rate in everyday life. Figure 4 shows the results of stepwise multiple regression analyses as box plots, which describe the relative proportions of variance explained by the various measures of physical activity. Since the one minute mean values on which these regression analyses are based show serial dependency, the results should only be understood as a description; they are not to be used for statistical significance tests.

In Figure 4 the variation of systolic and diastolic blood pressure and heart rate during 24 hours as well as only during waking hours is predicted by the various measures of physical activity. Each of the three activity measures is either shown as a single predictor, or additional time lags of up to 30 minutes are also introduced as possible predictors. This allows the comparison of the relative importance of each activity measure. It is obvious from figure 4 that more variance of blood pressure and heart rate is explained when the full 24 hour period is analysed. This, of course, is due to the fact that during sleep at night in contrast to the active daytime period these cardiovascular as well as activity measures are on very low levels and do not change very much. However, the active daytime period is of special interest, when we can analyse how much of the blood pressure and heart rate variance during that usually most dynamic phase within the 24 hour period is explained just by physical activity, and how much of the variance is left over for other possible predictors.

When thigh-EMG, arm movement and posture are taken as single predictors on a minute-to-minute basis during waking hours *(first three white columns in every diagram)* all three activity measures explain a similar small proportion of the systolic blood pressure variance of just below or up to 10% on average (median). In diastolic blood pressure there seems to be a gradient between these predictors in the proportion of the variance they explain, with thigh-EMG contributing almost nothing and posture explaining just above 10%. These predictors explain a considerably higher amount of the variance in heart rate, which is 38% in thigh-EMG, 35% in arm movement, and 25% in posture. When all three activity measures are taken together *(fourth white columns)* the explained variance improves to about 20% on average in systolic and diastolic blood pressure, but shows a wide range of between 4% and 60% in individual subjects.

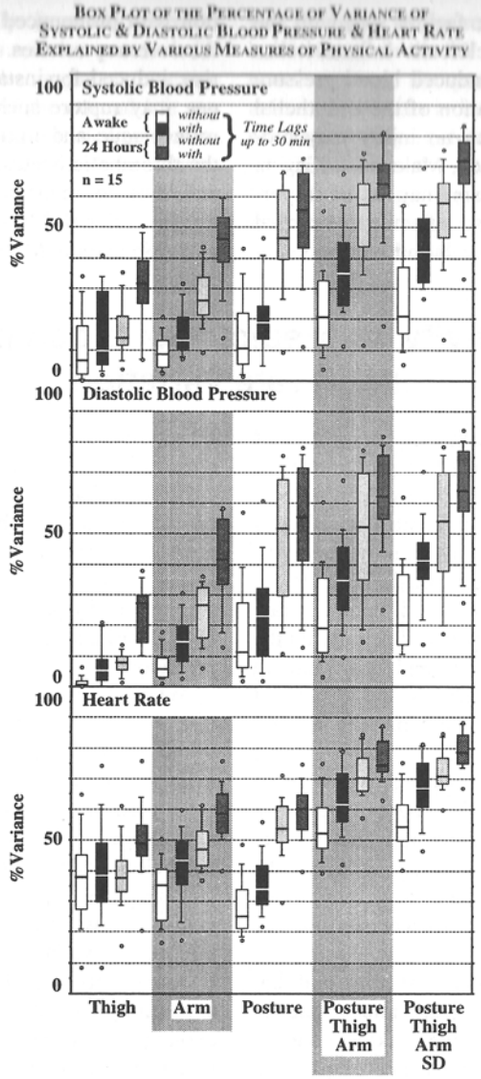

Figure 4: Box plot of the percentage of variance of systolic blood pressure *(upper diagram)*, diastolic blood pressure *(middle diagram)* and heart rate *(lower diagram)* in everyday life during waking hours *(white and black columns)* and over 24 hours *(light and dark shaded columns)*, explained by various measures of physical activity (integrated thigh-EMG, movements of the dominant arm, posture) when used as single or multiple predictors in univariate or stepwise multiple regression analysis without *(white and light shaded columns)* and with time lags of up to 30 minutes of these activity measures *(black and dark shaded columns)*. These analyses are based on 15 young healthy male subjects and on one minute mean values. SD indicates the standard deviations of the activity measures during one minute which are additionally introduced as possible predictors in multiple regression analyses. The horizontal line in the middle of each column (box) represents the median, the T-bars its lower and upper end the 25th and 75th percentile, the lines below and above the columns the 10th and 90th percentile, and the circles below and above these lines the single individuals below the 10th and above the 90th percentile.

Only in heart rate do all three single predictors taken together explain above 50% of its variation during active waking hours, with single subjects ranging between 40% and 75%. Including the one minute standard deviations of the activity measures does not on average add to the explanation of variance in this analysis *(fifth white column)*.

Introducing time lags of up to 30 minutes of the single activity measures as possible predictors *(first three black columns)* into stepwise multiple regression analyses improves the predicted variance by an additional ~5% to above 10%, with the exception of heart rate and thigh-EMG where this does not change very much; when taken together prediction is improved by these three activity measures including time lags by an additional ~15% in systolic and diastolic blood pressure and just below 10% in heart rate, which amounts on average to an explained variance of 35% in systolic and diastolic blood pressure and 61% in heart rate *(fourth black columns)*.

One of the most interesting questions is here, how much of the blood pressure and heart rate variance during the active daytime remains, or is unexplained by physical activity. The best analysis for answering this question is in our case when all three activity measures are taken as possible predictors together with their standard deviations and time lags. This might give the most realistic picture concerning the effect of physical activity on the variation of blood pressure and heart rate during waking hours. In this case the standard deviations of the activity measures improve the prediction by an additional 5% to 8% *(fifth black columns)*. The figures show that on average (median) about 43% of the variance of systolic blood pressure during the active daytime is explained by posture, thigh-EMG, movements of the dominant arm and the one minute standard deviations of these activity measures, including time lags of up to 30 minutes, as possible predictors. In single individuals the explained variance extends from 27% to 69%, depending on their activity pattern during that day. For diastolic blood pressure the figures are similar: On average 41% of the variance is explained, ranging from 14% to 71% in single individuals. It is only in heart rate that the explained variance is with an average of 66% somewhat larger, extending from 46% to 81%. This demonstrates the importance of individual differences, and also that a substantial amount of blood pressure and heart rate variation during the active daytime remains unexplained by these major parameters of physical activity. Part of the unexplained variance could be due, of course, to other physical activities not measured by these three variables, but it could also be due to emotional factors and other psychosocial influences.

Analysing the full 24 hour period reveals a great difference between the three activity measures in the proportion of variance they can explain. The smallest amount is explained by thigh-EMG without *(first light shaded columns)* and with inclusion of time lags *(first dark shaded columns)* which is on average 14% and 32% in systolic, 8% and 28% in diastolic blood pressure, as well as 37% and 49% in heart rate. The corresponding values for arm movements *(second light and dark shaded columns)* are 26% and 46% in systolic, 27% and 41% in diastolic blood pressure as well as 47% and 58% in heart rate. The greatest amount of the variance in systolic and diastolic blood pressure, as well as in heart rate is explained by posture without *(third light shaded columns)* and somewhat more with inclusion of time lags *(third dark shaded columns)*, which is on average 47% and 56% in systolic, 52% and 55% in diastolic blood pressure, as well as 54% and 60% in heart rate. The fact that posture alone is such an important predictor is due to the fact that it is confounded with the other activity measures and especially with thigh-EMG, because it is usually only in the upright position that major activities of the legs take place and there is usually only little or no physical activity in the prone position, for instance during sleep at night.

Compared to posture alone, the three activity measures taken together only explain less than an additional 10% of the systolic and diastolic blood pressure variation within 24 hours, and in heart rate about an additional 15%.

Together with their one minute standard deviations and time lags thigh-EMG, arm movements and posture explain on average 71% of the systolic blood pressure variation within 24 hours, ranging from 33% to 83% in individual subjects *(fifth dark shaded columns)*. In diastolic blood pressure a similar 64% of its 24 hour variation is explained, extending from 28% to 84% in individual subjects. In heart rate these predictors explain the largest proportion of the variance which is on average 78%, ranging from 68% to 89% in single individuals. These numbers reflect the great impact of physical activity on the blood pressure and heart rate variation within 24 hours. In these last analyses the varying lengths of the sleeping period at night are included. The length of the rest period at night in relation to the activity phase during the day might also have its impact on the cardiovascular risk.

These results support the view that blood pressure and heart rate changes in everyday life are mainly for adjusting the circulation to the needs of physical activity and behavioral challenges.

Does laboratory assessed cardiovascular reactivity predict blood pressure and heart rate changes in everyday life?

It is not only a theoretical question, whether cardiovascular reactivity assessed in the laboratory predicts blood pressure and heart rate variation in everyday life, but still an important practical clinical one. It is evident that cardiovascular risk accumulates in everyday life and not in the laboratory, but a short laboratory risk assessment is advantageous if it also predicts as well as the more complicated, time and manpower consuming ambulatory monitoring procedures. Continuous noninvasive ambulatory finger blood pressure monitoring appears now to be the method of choice for testing to what extent laboratory assessed interindividual cardiovascular reactivity differences predict the variation of important cardiovascular risk factors in everyday life.

Differences in laboratory assessed cardiovascular reactivity could, if at all, be expressed in everyday life in different ways. Manuck & Krantz (1984) have proposed two alternative models. One, the Prevailing State Model, hypothesizes that a higher reactivity in the laboratory may just lead in everyday life to a higher average level of the cardiovascular variable, which is lowered during rest at night to the baseline level, which then shows no difference between the high and low laboratory reactors. In the other model, the Recurrent Activation Model, reactivity differences between high and low laboratory reactors are also repeatedly elicited in daily life, but return to the same baseline levels during rest periods. A third model, the so-called Combined Model, was proposed by Light (1987) and combines the prevailing state and the recurrent activation model. Here, high reactors exhibit in daily life not only an elevated level of the cardiovascular variable but additionally also show repeatedly stronger reaction values. Different cardiovascular variables may follow different models.

It is evident from data as shown in Figure 1 and analyses as presented in Figure 4 that any such reactivity differences due to emotional stress can easily be overrun just by individual or day-to-day differences in the patterns of physical activity. Only by controlling rigorously for the effects of physical activity could there be a chance of testing adequately which of these hypotheses might be correct. And indeed, by controlling for the effects of physical activity as measured by thigh-EMG and for the effects of serial dependency (by autocorrelation) in time series analyses, we found some evidence that heart rate, if continuously recorded, may follow the recurrent activation model (Johnston, Schmidt, Albus, Vagt, MacSorley et al., 1994).

In order to test these different models further we selected 18 young healthy male volunteers out of 50 subjects aged 21 to 29 years in a pre-test, to form two extreme groups exhibiting the highest and lowest responses in rate pressure product, which is the product of systolic blood pressure and heart rate, to an active coping task, a self paced multiple choice reaction time task, in the laboratory (Jain, 1995; Jain, Schmidt & Johnston, 1994). Subjects were individually motivated to respond as fast as possible and very accurately to optical and accoustic signals, so as to achieve a high score in this five-minute test of their psychomotor performance. Rate pressure product is known to be the best noninvasive measure for myocardial oxygen consumption, an important parameter concerning the function of the heart muscle (Robinson, 1967). Compared to low reactors, high reactors exhibited a somewhat better psychomotor performance and responded faster by nearly 10% (table 2). During both the laboratory session as well as the 24 hour ambulatory monitoring period, heart rate, systolic and diastolic finger blood pressure were recorded continuously and noninvasively with Portapres model 1 and stored as one minute mean values together with integrated thigh-EMG, arm movement and posture on the ambulatory monitoring system Vitaport 1.

The reactivity differences during the laboratory reaction time task were stable over time when the test was repeated after seven weeks, immediately before the ambulatory monitoring took place. The test-retest correlation coefficients in these two extreme groups were .86 for systolic blood pressure reactions, .64 for those of diastolic blood pressure, .84 and .90 for those of heart rate and rate pressure product. High and low reactors, however, did not differ in their blood pressure, heart rate, and rate pressure product reactions to mild physical exercise.

Other activities, events and moods during the ambulatory monitoring period were assessed at 30 minute intervals by means of a paper-pencil self-report diary. Additionally, urine was collected separately during the monitored 24 hours for the waking daytime and the sleeping period at night to analyse the excretion of hormones such as adrenaline, noradrenaline and cortisol. To test the different proposed models, various reactivity measures were derived from these ambulatory data. For the two groups, defined by their laboratory reactions as high or low reactors, the reactivity measures computed from ambulatory data were then compared by appropiate t-tests (one-tailed) or ANOVAs.

For testing the Prevailing State Model, day and night levels as well as day-to-night differences were compared across groups. For diastolic blood pressure a significantly higher level during the day, but not during the night, was seen in the laboratory high reactors, thus pointing to the possibility that this variable follows the Prevailing State Model (table 1). The laboratory criteria of high and low reactors explain 12% of the interindividual variance in daytime diastolic blood pressure levels. For systolic blood pressure, heart rate and rate pressure product no such differences could be detected.

For testing the Recurrent Activation Model, various methods were used. The simple standard deviations of the cardiovascular variables did not show any differences between high and low reactors during the waking hours or during sleep at night. The standard deviation as a measure of blood pressure and heart rate variation in everyday life includes, however, all cardiovascular changes caused by physical activity and posture, main determinants of the explained blood pressure and heart rate variance as shown before. Thus this variability measure does not appear adequate, if not only simple variability differences are to be tested which could be due to different patterns of physical activity.

In order to account for the effects of physical activity and posture as well as to remove serial dependency from the data during the active daytime, regression models were formed which included time lagged effects of up to three minutes (autocorrelation) as well as current and delayed effects of physical activity (thigh-EMG, arm movements) and posture. The standard deviations of the residuals of the regression models were computed as a reactivity measure that is relatively free of influences through autocorrelation as well as current and delayed effects of posture and activity. In this measure, the high reactors showed a significantly higher daytime

Table 1: Group differences between high and low reactors for different measures of the cardiovascular variables and urinary hormone excretion.

Variable	Difference in	High Reactors		Low Reactors		df	t-value	p *one-tailed*	Effect Size w^2
		M	SD	M	SD				
DBD *mmHg*	**Level 24 Hours**	**69.8**	6.3	**64.9**	4.3	14	1.79	**.05**	**.12**
	Level Day	**76.2**	5.4	**70.9**	6.2	14	1.80	**.05**	**.12**
	Level Sleep	51.2	11.3	50.6	5.5	14	0.15	.44	
	Difference Day – Sleep	24.8	8.1	20.3	6.9	14	1.20	.12	
RPP *mmHg * bpm*	**SD of Residuals of Univariate Time Series Analysis**	**1382**	212	**1115**	225	12	2.29	**.02**	**.23**
	SD of Residuals of Multivariate Time Series Analysis	**1070**	182	**879**	146	12	2.16	**.03**	**.21**
RPP *mmHg * bpm*	**Difference High Stress**	**1772**	1075	**594**	874	14	2.40	**.02**	**.23**
HR *bpm*	**Low Stress Periods**	**8.34**	7.00	**3.55**	2.91	14	1.79	**.05**	**.12**
Adrenaline	**Day**	**1.26**	0.43	**0.90**	0.33	15	1.77	**.05**	**.11**
mg/hour	Night	0.42	0.21	0.42	0.10	15	0.10	.46	
Noradrenaline	**Day**	**3.06**	1.14	**2.10**	0.66	15	2.01	**.03**	**.15**
mg/hour	Night	1.44	0.54	1.26	0.34	15	0.80	.24	
Cortisol	**Day**	5.52	2.82	9.06	7.68	15	-1.29	.89	
mg/hour	Night	13.14	8.10	11.76	6.18	15	0.39	.35	

reactivity than the low reactors with the rate pressure product being the only variable (see Table 1), thus supporting the Recurrent Activation Model. Here the laboratory criteria explain 21% of the interindividual variance of this reactivity measure of the rate pressure product. Removing only serial dependency by autocorrelation in the regression model resulted in a slightly larger difference between high and low reactors in the residuals, explaining 23% of the variance.

Another reactivity measure was determined using the diary self-reports. Thirty minute periods of high and low self-reported emotional stress, as indicated by being angry, anxious, hurried or stressed were identified. Only those high and low stress periods were chosen in which physical activity was not higher than when slowly walking, and for each subject all high and low stress periods were averaged for the cardiovascular variables, and the differences between high and low stress periods were computed. Again, the laboratory high reactors exhibited a higher reactivity in everyday life than the low reactors in the rate pressure product, and to a lesser extent also in heart rate (Table 1). The laboratory criteria explain 23% and 12% of the interindividual variance of these emotional stress reactions of rate pressure product and heart rate in daily life. There was no difference between the two groups in the amount of reported stress, physical activity and distribution of posture, but high stress periods were characterized by a higher physical activity compared to low stress periods. Again, these results support the recurrent activation model for rate pressure product and perhaps heart rate.

Table 2: Group differences between high and low reactors in psychomotor performance and personality questionnaires.

Variable / Questionnaire	Dimension	High Reactors		Low Reactors		df	t-value	p *2-tailed*	Effect Size w^2
		M	SD	M	SD				
Performance	Total Number of Responses	362.8	24.9	335.6	30.7	15	2.01	.06	.15
Multiple Choice	Number of Correct Responses	350.2	30.5	324.6	33.0	15	1.66	.11	
Reaction Time Task	Number of Mistakes	12.6	11.0	9.1	13.0	15	0.29	.78	
STAXI	Anger In	**17.44**	3.94	**13.00**	4.53	16	2.22	**.04**	**.18**
SVF	Flight Tendency	**13.56**	4.13	**8.56**	3.71	16	2.70	**.01**	**.26**
FPI	Social Orientation	**5.33**	1.32	**6.75**	1.16	15	-2.33	**.03**	**.21**
FPI	Satisfaction with Life	**4.00**	1.58	**6.12**	1.35	15	-2.95	**.01**	**.31**
FPI	Inhibition	**6.00**	1.80	**3.37**	1.41	15	3.31	**.01**	**.37**
FPI	Extraversion	**5.11**	1.17	**7.25**	1.39	15	-3.45	**.00**	**.39**

This study demonstrates that individuals exhibiting differing responses to a laboratory stressor may also show distinct reactivity patterns in everyday life that differ between the various cardiovascular variables. But these differences can only be detected if masking effects of activity and posture can by using adequate methods be eliminated from the data. These findings indicate that this classification through testing stress responses and cardiovascular reactivity in the laboratory may have some relevance for the behavior patterns in relation to possible cardiovascular risk factors in real life. This consideration is further supported by results from personality questionnaires and catecholamine urine analyses: It was found that the high reactors released above 30% and 40% more adrenaline and noradrenaline than low reactors during the waking daytime period, but not during sleep at night (Table 1). This points to the relevance of these endocrine mechanisms in contributing to the cardiovascular reactivity differences in everyday life. On average already during the waking time the excretion of adrenaline and noradrenaline is with 16.2 µg and 39.7 µg in high reactors at the upper limit of the normal 24 hour excretion. The laboratory reactivity criteria explain 11% and 15% of the interindividual variance of the adrenaline and noradrenaline excretion during the waking daytime.

In the "State-Trait-Anger Inventory" (German adaptation by Schwenkmetzger, Hodapp & Spielberger, 1992) laboratory high reactors exhibited higher scores on the "anger-in" dimension, and in the SVF, a questionnaire investigating coping styles with stress (Janke, Erdmann & Kallus, 1985), they showed a higher tendency to try to escape from stressful situations, the laboratory reactivity criteria explaining 18% and 26% respectively of the interindividual variance. In the Freiburg Personality Inventory, a German personality questionnaire (FPI-R, Fahrenberg, Hampel & Selg, 1989), high reactors showed less social orientation,

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Reaction Time Task	Number of Mistakes	12.6	11.0	9.1	13.0	15	0.29	.78	
STAXI	Anger In	**17.44**	3.94	**13.00**	4.53	16	2.22	**.04**	**.18**
SVF	Flight Tendency	**13.56**	4.13	**8.56**	3.71	16	2.70	**.01**	**.26**
FPI	Social Orientation	**5.33**	1.32	**6.75**	1.16	15	-2.33	**.03**	**.21**
FPI	Satisfaction with Life	**4.00**	1.58	**6.12**	1.35	15	-2.95	**.01**	**.31**
FPI	Inhibition	**6.00**	1.80	**3.37**	1.41	15	3.31	**.01**	**.37**
FPI	Extraversion	**5.11**	1.17	**7.25**	1.39	15	-3.45	**.00**	**.39**

This study demonstrates that individuals exhibiting differing responses to a laboratory stressor may also show distinct reactivity patterns in everyday life that differ between the various cardiovascular variables. But these differences can only be detected if masking effects of activity and posture can by using adequate methods be eliminated from the data. These findings indicate that this classification through testing stress responses and cardiovascular reactivity in the laboratory may have some relevance for the behavior patterns in relation to possible cardiovascular risk factors in real life. This consideration is further supported by results from personality questionnaires and catecholamine urine analyses: It was found that the high reactors released above 30% and 40% more adrenaline and noradrenaline than low reactors during the waking daytime period, but not during sleep at night (Table 1). This points to the relevance of these endocrine mechanisms in contributing to the cardiovascular reactivity differences in everyday life. On average already during the waking time the excretion of adrenaline and noradrenaline is with 16.2 µg and 39.7 µg in high reactors at the upper limit of the normal 24 hour excretion. The laboratory reactivity criteria explain 11% and 15% of the interindividual variance of the adrenaline and noradrenaline excretion during the waking daytime.

In the "State-Trait-Anger Inventory" (German adaptation by Schwenkmetzger, Hodapp & Spielberger, 1992) laboratory high reactors exhibited higher scores on the "anger-in" dimension, and in the SVF, a questionnaire investigating coping styles with stress (Janke, Erdmann & Kallus, 1985), they showed a higher tendency to try to escape from stressful situations, the laboratory reactivity criteria explaining 18% and 26% respectively of the interindividual variance. In the Freiburg Personality Inventory, a German personality questionnaire (FPI-R, Fahrenberg, Hampel & Selg, 1989), high reactors showed less social orientation,

less satisfaction with life, more inhibition, and less extraversion (Table 2). The reactivity criteria explained 21%, 31%, 37%, and 39% respectively of the variance of these personality dimensions, the last three dimensions reaching the largest proportions of the variance explained in all of the investigated parameters. Obviously in this laboratory stress testing, by selecting high and low rate pressure product reactors during an active coping task, and by motivating the subjects to strive for a very good performance, it was possible to separate the subjects into two distinct groups with differing personalities. These personality differences might be responsible for the cardiovascular reactivity differences not only in the laboratory but also in everyday life – a hypothesis which has to be tested in more detail in future studies.

Future perspectives

One reason why the noninvasive measurement of the continuous finger arterial waveform which allows the beat-to-beat determination of systolic, diastolic and mean arterial blood pressure, heart rate, stroke volume, cardiac output, and peripheral resistance in everyday life is very attractive, is because it may provide new differentiated *intermediate* endpoints, for instance in intervention programs, which can be assessed much earlier than the traditional endpoints in epidemiology, morbidity and mortality. However, the reliability and validity of these new endpoints, such as measures of reactivity to emotional stress and physical activity derived from continuous noninvasive recordings in everyday life, have not yet been tested. But we may conclude from what we already know about the usefulness of blood pressure as a predictor of future cardiovascular events that these new measures shall be very valuable. This shall have to be shown in prospective studies. Such studies may clarify the role and importance of cardiovascular stress reactions in greater detail.

Geoffrey Rose, the late British epidemiologist, elaborated a fundamental axiom in preventive medicine, which might also be considered in relation to cardiovascular stress reactions in everyday life. Based on the observation of a dose-response relationship of many cardiovascular risk factors to future risk, and the more or less normal distribution of these risk factors in a population, he pointed out that a large number of people exposed to a small risk may generate many more cases than a small number exposed to a high risk (Rose, 1993). This general rule might also be applied to cardiovascular stress reactions in everyday life: The many daily mild blood pressure rises in the individuals of a population may generate more atherosclerosis and cardiovascular events over time than rare very high blood pressure peaks. So we should not underestimate even mild cardiovascular stress responses in everyday life! But do blood pressure elevations associated with physical activity really raise the risk? Regular physical activity and especially endurance training has been shown to be protective rather than risky (Hollmann, 1986; Blair, et al., 1989). How can this puzzle be solved? Are only the vulnerable atherosclerotic plaques in the elderly acutely in danger of rupturing during such activities? But does the physical training effect protect in the long run? Is the cardiovascular stress response in Figure 2B more dangerous than that in Figure 2A, as it does not involve physical activity and the mean arterial pressure peak reached is about 30 mmHg higher? Or is the response in Figure 2A related to a higher risk for a different disease endpoint because it reaches a systolic pressure peak of around 280 mmHg, which is 40 mmHg above that in Figure 2B?

There are many more open questions which the new technology of continuous noninvasive assessment of haemodynamic parameters in everyday life may enable us to answer now. This technology is still expensive and time consuming. It is rather to be considered a tool for research than for diagnostic routine or for the regular control of therapeutic results. One day we might perhaps come to the conclusion that a good and economically better way of achieving a comprehensive cardiovascular risk assessment is the combination of an up-to-date clinical investigation together with a sophisticated psychophysiological laboratory stress test, investigating typical behavioral and cardiovascular haemodynamic responses, as well as an assessment of personality dimensions by questionnaire and behavioral observation, a self-report diary for mood states and stressful life events, and the simple continuous ambulatory monitoring of physical activity.

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