Chapter 10
Ambulatory assessment of parasympathetic/sympathetic balance by impedance cardiography

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Theoretical background

Ambulatory monitoring and the reactivity hypothesis

Research into the connection between stress and cardiovascular disease is based on the assumption that hyperreactivity of the cardiovascular system is implicated in elevated risk for the future development of hypertension and coronary heart disease (Matthews, Weiss, Detre, Dembroski, Falkner, Manuck & Williams, 1986). At the present time this assertion has the status of a plausible hypothesis. Individual differences in stress reactivity have mainly been determined by exposing subjects in the laboratory to standardized laboratory stressors. This approach has yielded useful information with respect to the origins of the individual differences in reactivity observed. For example, reactivity is stronger in subjects with a family history of hypertension (de Visser, van Hooft, van Doornen, Hofman, Orlebeke & Grobbee, 1995), sex differences have been suggested (Stoney, Matthews, McDonald & Johnson, 1988) and coronary prone persons may be more reactive under certain circumstances (Houston, 1992). In addition to this, well-controlled use of elegant measurement techniques available in the laboratory like impedance cardiography (Sherwood, Allen, Fahrenberg, Kelsey, Lovallo & van Doornen, 1990), beat-to-beat blood pressure measurement (Mulder, 1988), and occlusive plethysmography (Anderson, 1987), have furnished a detailed insight in the nature of the cardiovascular stress response, yeilding parameters like the systolic time intervals, baroreflex sensitivity, and forearm blood flow.

Although our laboratory research has been necessary and fruitful, we should realize that the possible adverse health effects of excessive reactivity will derive from repeated exposures to stress in daily life. The question arises to what extent individual differences in reactivity in the laboratory have predictive value for reactions to real-life situations. Ecological validity of laboratory reactivity has been seriously challenged in a thorough review of the available literature (van Doornen & Turner, 1992). Indices of real-life reactivity as assessed by ambulatory monitoring, like work-home differences, and reactions to well defined real-life stressors like exams or public speaking, do not correspond well with the reactivity of the same subjects to laboratory stressors. Several reasons have been put forward to explain the disappointing correspondence between laboratory and real-life reactiv-

ity. The first reason is a methodological one. The predictive validity of laboratory reactivity may be limited by its low test-retest reliability. Also, although this is often neglected, there may be low test-retest reliability of real-life stress reactivity itself. However, reliability of laboratory nor real-life reactivity seems to be a crucial factor. The test-retest correlations for HR and systolic blood pressure responses are in the acceptable range of .50 - .60 (Steptoe & Vögele, 1991). When the reliability of both laboratory and real-life reactivity is further optimized by repeating both the laboratory and the real-life stressor their correspondence remains low (van Doornen, Willemsen, Knol & de Geus, 1994). A second reason put forward to explain the low correspondence is of a psychological nature. There is a clear lack of correspondence between the psychological meaning of the laboratory and the real-life situation. Laboratory to real-life comparison might be improved if laboratory tasks were chosen that better mimic daily situations (Ewart & Kolodner, 1993). Though fruitful in principle, a limitation of this approach is that it is hardly feasible to simulate in the laboratory the entire variety of stressful situations encountered in real-life.

We think that, in fact, the crucial reason for the lack of correspondence is a physiological one. The physiological mechanisms involved in the response to short-lasting laboratory stressors are different from the mechanisms involved in the more long standing physiological changes during real-life stress. Reactivity in the laboratory generally means an increase over a pre-stressor baseline for several minutes. Recovery is expressed as the number of minutes it takes to return to this baseline after the stressor. In 24-hour data, reactivity often means average daily increases in HR and blood pressure in comparison to the average level of 6 to 8 hours of sleep. This difference in time scale has profound impact on the interpretation of cardiovascular mechanisms underlying the reactivity measures studied. Even within a relatively short-lasting laboratory stressor, a shift in cardiovascular regulatory mechanisms can be demonstrated. In the initial stage cardiac beta-adrenergic activation prevails whereas with time the influence of vascular processes increases (Carroll & Roy, 1989; Miller & Ditto, 1988). This may be related to a gradual down-regulation of beta-receptors during longer term elevation of adrenaline levels (Tohmeh & Cryer, 1980; Larsson, Martinsson, Olsson, & Hjemdahl, 1989). It is noteworthy that down-regulation was only found after longer term adrenaline infusion or a 2-hours lasting examination stressor, but not after a 15-minute stressful reaction time task (Larsson et al., 1989; Stock, Zimmerman, & Teuchert-Noodt, 1993). Since beta-receptor density and sensitivity are important determinants of the HR elevation during stress (Mills, Dimsdale, Ziegler, Berry, & Bain, 1990), differences in laboratory and real-life effects on these receptors may account for low laboratory to real-life correlations. This is further complicated by the fact that the HR increases during stress not only reflect the influence of the sympathetic but also of the parasympathetic branch of the autonomic nervous system (Allen & Crowell, 1989; Grossman & Svebak, 1987). It is unknown whether the relative contribution of vagal and sympathetic cardiac effects differs for laboratory stressors and real-life stress, and whether this balance changes over time during prolonged exposure to stress. Vagal cardiac control is partly dependent on baroreflex control over blood pressure. The short-term increases in blood pressure during stress are generally matched by a decrease in baroreceptor sensitivity, which may explain part of the lowered vagal tone found. Longer term increases in blood pressure, however, will trigger different blood pressure control mechanisms, including a resetting of baroreceptors and changes in renal control over blood volume. It is unknown how this will affect vagal contribution to the HR elevation.

Admittedly, at present very little is known about longer-term adrenoceptor and baroreceptor regulation systems during stress. There is, however, no a priori reason to assume that the effects of stressors differing in time scale by an hour or more will be at all comparable. It may not be surprising that laboratory to real-life

comparison yields meager results since entirely different physiological mechanisms are measured. Because we believe that an association between stress and cardiovascular disease must be based on repeated and protracted exposure to real-life stressors, we tend to favor investigation by 24-hour ambulatory monitoring. As an additional advantage, ambulatory monitoring allows the assessment of psychologically more ecological valid situations than laboratory stressors. A case in point is the assessment of work stress where it is frankly difficult to envisage a laboratory test battery that simulates the complex set of factors found in real-life settings, like workload, time pressure, climate, and social support or harrassment by clients, peers and superiors. Yet, it will be chronic exposure to such complex social situations that ultimately gives rise to disease. In short, the physiological processes assessed with 24-hour monitoring are 1) different from those in laboratory tasks, 2) more relevant to cardiovascular pathology, and 3) more ecologically valid from a psychosocial perspective.

PEP and RSA

For some time now it has been possible to monitor HR in field settings. This has substantially increased our knowledge about cardiovascular responses to real-life stress as is amply demonstrated in the other chapters of this book. Unfortunately, the underlying mechanisms behind changes in HR in a real-life setting have remained largely uncharted. HR is controlled by the combined effect of parasympathetic and sympathetic cardiac innervation. It would be highly valuable to be able to index both branches separately. So far, indexing of the vagal-sympathetic balance in the field has been attempted solely through the use of spectral analyses. Frequency decomposition of ambulatory heart rate variability (HRV) allows the identification of several frequency bands, including a high frequency band and a low frequency band, which are postulated to index parasympathetic-sympathetic interactions in cardiac functioning (Pagani, Lombardi, Guzzetti, Rimoldi, Furlan, Pizzinelli et al., 1986). However, with regard to sympathetic tone from spectral powers, the low frequency band proved to be an unreliable index of the sympathetic influence on the heart (Saul, Rea, Eckberg, Berger & Cohen, 1990; Kamath, Fallen & McKelvie, 1991). A major improvement in this regard would be the ambulatory monitoring of thoracic impedance to calculate the Pre-Ejection Period (PEP). PEP is an index of cardiac contractility (Newlin & Levenson, 1979) that has proven to be a reliable indicator of the sympathetic influence on the heart in pharmacological blockade studies and studies manipulating beta-adrenergic tone by exercise or emotional stress (Harris, Schoenfeld & Weissler, 1967; Newlin & Levenson, 1979; Sheps, Petrovick, Kizakevich, Wolfe & Craige, 1982; Sherwood, Allen, Obrist & Langer, 1986). Although valid interpretation of PEP needs to take into account changes in pre- and afterload (Heslegrave & Furedy, 1980), an elegant dual blockade study clearly confirmed that between-subject differences in PEP reflect differences in cardiac sympathetic tone fairly well (Cacioppo, Berntson, Binkley, Quigley, Uchino & Fieldstone, 1994; Berntson, Cacioppo, Binkley, Uchino, Quigley & Fieldstone, 1994).

The use of variability in the HR to index vagal tone derives from the direct cardiorespiratory interaction that is reflected in a phenomenon known as respiratory sinus arrhythmia (RSA). RSA can be derived by peak-to-through estimation (Grossman, 1992) that uses the time series of inter beat intervals (IBIs) in combination with the respiration signal, or by various quantification techniques that use only the IBI time series, like spectral analysis (Akselrod, Gordon, Ubel, Shannon, Barger & Cohen, 1981) and time domain filtering (Porges & Bohrer, 1990). Although some disagreement has risen over which method "best" indexes RSA (Grossman, 1992; Byrne & Porges, 1993) these measures have in fact shown excellent correspondence in various resting and task conditions

(Grossman, van Beek & Wientjes, 1990; Fahrenberg & Foerster, 1991; Hayano, Skakibara, Yamada, Yamada, Mukai, Fujinama, Yokoyama, Watanabe & Takata, 1991; Litvack, Oberlander, Carney & Saul, 1995).

Since cell physiological evidence points to a dominant role of cholinergic influences on RSA (Berntson, Cacioppo & Quigley, 1993), and all RSA measures are sensitive to cholinergic rather than beta-adrenergic blockade (Akselrod, Gordon, Madwed, Snidman, Shannon, & Cohen, 1985; Hayano et al., 1991; Grossman & Kollai, 1993; Cacioppo et al., 1994) such measures have been increasingly used as indices of cardiac vagal tone in exercise physiology as well as psychophysiological research (Porges, 1986; Grossman & Svebak, 1987, Langewitz & Rüddel, 1989; Billman & Dujardin, 1990; de Geus, van Doornen, de Visser & Orlebeke, 1990; Grossman, Brinkman, de Vries, 1992; Sloan, Shapiro, Bagiella, Boni, Paik, Bigger, Steinman & Gorman, 1994, Berntson et al., 1994). Recently, however, various studies have cautioned against the use of RSA as an index of cardiac vagal tone, both within subjects (Saul, Berger, Chen & Cohen, 1989; Allen & Crowell, 1990; Grossman, Karemaker & Wieling, 1991; Hayano, Mukai, Hori, Yamada & Fujinama, 1993; Grossman & Kollai, 1993) when no simultaneous assessment of respiratory behavior is made. Only when respiratory variables are held constant, or are statistically controlled for, there is evidence of a reasonable correspondence between variations in RSA amplitude and pharmacological indices of vagal tone. Clearly, no experimental control over respiration is possible during the spontaneous breathing encountered in real-life situations. When assessing vagal tone from RSA in the field, therefore, it becomes necessary to measure respiration rate to be able to control for it statistically.

Ambulatory assessment of PEP and RSA

The VU-AMD

Recently an ambulatory monitoring device (VU-AMD) to measure cardiac autonomic balance has been developed at the Department of Instrumentation of the Faculty of Psychology of the Vrije Universiteit Amsterdam. Simultaneous measurement of the ECG and ICG signals allows us to assess HR, PEP, RSA and RR in field settings on a time scale of 24 to 48 hours, with minimal intrusion on daily life. The VU-AMD is kept small (dimensions 32x65x120 mm) and weighs only 225g. It can be worn underneath clothing and it allows subjects to follow their normal routines without having their movement constrained in any way.

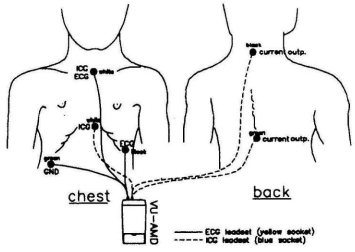


Figure 1: Placement of the six spot electrodes for combined measurement of ECG and thoracic impedance with the VU-AMD.

The ECG and thoracic impedance signals are obtained from 6 disposable pregelled Ag/AgCl electrodes (AMI type 1650-005 Medtronic) according to the configuration in Figure 1.

Electrode resistance (DC) is kept below 10 KOhm by cleaning with alcohol and rubbing. One electrode is a combined ECG/ICG electrode and is placed 4 cm above above the jugular notch of the sternum. The other measuring ECG electrode is placed at the apex of the heart over the ninth rib and a ground electrode is placed above the right iliac crest. The second ICG measuring electrode is placed directly over

the tip of the xiphoid process of the sternum. Input impedance of the measuring system is 10 KOhm. The two ICG current electrodes are placed at the back, at the base of the neck (C3/C4) and over vertebrae T8/T9.

The bipolar ECG signal is relayed into a differential amplifier with 1 MOhm impedance and through a band pass filter of 17 Hz (Q=33). The R-wave peak is recognized with a level detector with automatic level adjustment (Thakor, Webster & Thompkins, 1983) and at each R-wave peak a millisecond counter is read and reset to obtain the IBIs, which are stored continuously. To obtain thoracic impedance (Z0) a tetrapolar spot electrode configuration is used, derived from Zhang, Qu, Webster, Thompkins, Ward & Bassett (1986). Through the electrodes at the back, the AMD yields a 350 mA constant current source with 50 kHz oscillator frequency across the thorax. The resulting impedance signal (Z0), measured by the electrodes over the sternum, is amplified, relayed to a precision rectifier, and filtered at 750 Hz. DZ is obtained from Z0 by continuously subtracting the integrated Z0 over the last 10 sec. This procedure keeps dZ within amplifier range without producing discontinuities and is equivalent to the balancing circuit described by Hurwitz, Lu, Reddy, Scheiderman & Nagel (1993). The dZ is differentiated at 33.3 Hz to derive a dZ/dt that is subsequently passed through a 30 Hz high cut-off filter (12 dB/octave roll off). The resulting Z0, dZ and dZ/dt are transmitted to the AD converter of the microprocessor. Z0 is sampled directly after the occurrence of each R-wave. Dz is sampled with a frequency of 10 Hz and dZ/dt is sampled at 250 Hz. DZ/dt values are sampled only during a short period (512 msec) around each R-wave and ensemble averaged over a fixed period (default length: 60 sec) according to Muzi, Ebert, Tristani, Jenter, Barney & Smith (1985). All ensemble averages of the dZ/dt signal are stored in the VU-AMD, including the average Z0 from all beats in that minute period.

Extracting PEP and RSA

Around the VU-AMD we have build the Ambulatory Monitoring System (VU-AMS), a package of dedicated software that, among others, extracts HR, systolic time intervals, RSA and RR from the ECG, dZ/dt and dZ signals. In general, these programs automatically score the raw signals and then present the user with the opportunity for interactive inspection of the resulting data. For the extraction of PEP and LVET the following algoritms are used:

PEP

The ensemble averaged complexes of the dZ/dt are used to detect three significant points: the B-point, dZ/dt-max point and the X-point (see Figure 2). The dZ/dt-max point is simply defined as the highest point in the entire dZ/dt fragment. There is virtually no ambiguity in the automatic detection of this point.To detect the B-points all zero-crossings in either first and second derivative of dZ/dt are first identified and defined as possible "candidates". Valid B-point candidates, furthermore, have to lie within the interval between the R-wave and the dZ/dt-max "Bonus" points are assigned to these candidates based on preset criteria. The B-point candidates receives 3 points if they represent a zero crossing in 1st rather than second derivative, 2 points if they are the first candidate after the R-wave, 3 points if the candidate's amplitude is near the electrical dZ/dt=0 line, 5 points if the candidate is followed by the positive slope in the dZ/dt with the greatest amplitude, 2 points if the candidate is within 20 msec of the location of the previous B-point and 2 points if the candidate yields a PEP that fits the equation PEP = 132-0.4*HR (\(+- 15 msec). During interactive visual scoring, the candidate with the most points is suggested by the program as the prime candidate for the B-point. However, the user can choose to select one of the other candidates.

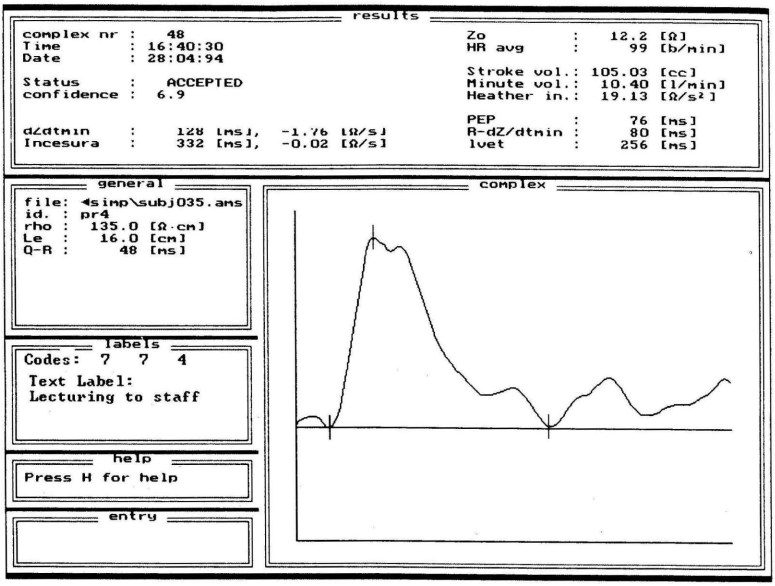


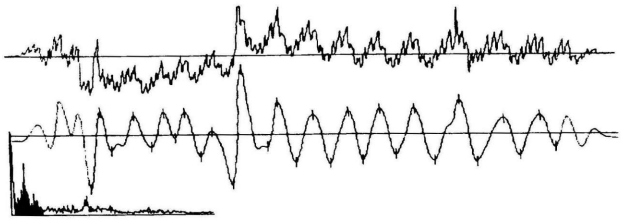
Figure 2: A one-minute ensemble average of dZ/dt waveforms collected on 99 beats. The B-point, dZ/dt-min and X-points are indicated with cursors. The top of the registration displays the values of the variables that can be derived from this ensemble averaged dZ/dt. In the "labels" window to the left, the current activity of the subject is indicated ("lecturing to academic peers"). The three numerical codes denote posture (7=standing), mood state (7=angry), and social situation (4=with peers).

A similar procedure is followed for the X-point. Again only zero-crossings in either first and second derivative of dZ/dt are considered candidates. Valid X-point candidates have to lie in an interval of 50 msec after the dZ/dt-max to 500 msec after the R-wave. Candidates receive 10 bonus points if they are the minimum value in this window, 5 points if they fall within 50 msec of the X-point in the previous complex, 4 points if they are more than 20% of dZ/dt-min amplitude below the dZ/dt=0 line, and 3 bonus points if they are the second zero-crossing in the first derivative. Again interactive visual scoring can be used to select the final candidate. After detection of these crucial points the R-wave to B-point interval (RBI) is computed. Adding a fixed Q-R interval of 48 msec yields the PEP. The left ventricular ejection time (LVET) is defined as the time between the B- and X-points.

RSA

For the extraction of RSA and RR the IBI time series is used in combination with the 10 Hz sampled dZ signal. The dZ signal contains three major components: high frequent impedance changes due to the ejection of blood into the aorta during systole, low frequent impedance changes due to arm and upper body movement, and, in between these frequencies, the thoracic impedance changes due to respiration. To get rid of the high and low frequencies, 100 sec fragments of the dZ signal are bandpass filtered

Registration date:	19-05-94	Start of display:	0:21.10
Start of block 23:	00:21.30	Duration:	100 s
Low frequency cut off:	0.05 Hz	High frequency cut off:	0.40 Hz



ALL CYCLES:					
RR:	10.7 [c/min]	RSA:	132 [msec]	HR:	61 [bpm]
ACTIVE CYCLE no 21					
Start time:		00:22:01.6 19-05-94			
Inspiration, min ibi:		1800 789	expiration, max ibi:	3400	938 RSA OK
TC:	5200 [msec]	mean-IBI:	1100 [msec]	RSA:	149 [msec]
Codes 3	1 1	Text Label :	Sleeping		

Figure 3: 100 secs of the thoracic impedance signal before and after filtering with a digital band pass filter. In this example high and low cut-off was set to 0.05 and 0.40 Hz respectively. Filtering generally leads to a clearly recognizable respiration signal which strongly resembls the strain-gauge signal from the laboratory and presents little or no problems to the software that automatically detected start and end of respiratory intervals and RSA. The lower window displays information on the currently active cycle. The text label indicates that this fragment was recorded during sleep. Numerical codes denote posture (3=lying), mood state (1=relaxed), and social situation (1=alone).

with variable cut-offs after tapering with $(\sin(x))^2$. An interactive program is used to choose upper and lower cut-off points for each fragment until an optimal respiration signal is obtained in the visual display. Different band-pass filters can be tried per subject and per fragment to better fit the individuals range of breathing frequencies. In the filtered signal three points are automatically identified in each single breath using the first derivative of the filtered dZ (see Figure 3). The point on the uphill slope where the first derivative begins to exceed a minimal trend is the start of inspiration. Inspiration ends and expiration starts at the heighest point in the complex. When the downhill slope falls below the minimal trend, expiratory pause commences lasting till the start of inspiration in the next cycle. The minimal trend is computed as 80% of the square root of the maximal value in the 1st derivative reached in the uphill or downhill slope respectively.

Several precautions are taken to exclude the introduction of movement artefacts or small respiratory irregularities as extra breathing-cycles. First of all, the algorithm specifies a minimum depth of the breath. Secondly, there is an amplitude modulator built into the algorithm that detects an amplitude difference of more than 30% between two adjacent cycles. A cycle less than 30% amplitude of the previous one is interpreted to constitute part of the preceding or following cycle rather than a separate breath. Finally, all automatic scoring is verified by visual inspection. Breathing cycles that are not considered valid are marked by mouse-clicking and removed from further processing. The

starting points of inspiration and expiration are used to compute total inspiration time, total expiration time and the total cycle Time (TC) on a breath to breath basis. For ease of reading, TC (in msec.) is recoded to the average RR in cycles per min.

Using the respiratory intervals, RSA is computed for each breath using the peak-to-through method (for details see Grossman, van Beek & Wientjes, 1990). In the inter-beat-intervals time series, the difference between the shortest inter beat interval during HR acceleration in the inspiratory phase and the longest inter beat interval during deceleration in the expiratory phase is used as an index of RSA. When no respiratory phase-related acceleration or deceleration is found, the breath is assigned a RSA score of zero.

HRV

In addition to PEP and RSA, HRV in various separate frequency ranges can be easily computed from the time series of interbeat intervals (IBI) obtained from the R-waves. Since many excellent commercial packets exist for detailed screening of the stationarity and integrity of IBI time series, we have made no effort to implement our own. Instead the VU-AMS provides output on the IBIs in the format of the CARSPAN program (Mulder, 1988). CARSPAN performs extensive cheking of the IBI time series for ectopic beats or missing IBIs. It then performs frequency domain analysis of the interbeat intervals based on sparse Discrete Fourier Transformation which yields a power-frequency spectrum from 0.01 to 0.50 Hz. With regard to vagal-sympathetic balance three frequency bands are deemed of interest: the frequency band around the intrinsic blood pressure oscillations (0.07-0.14: HRV-medium) that reflects both vagal and sympathetic influences, the high frequency band that reflects vagal influence only (0.15-0.40: HRV-high) and a frequency band around the central respiratory frequency (HRV-resp) that reflects the vagal cardiorespiratory connection most closely (Mulder, 1988; Langewitz & Rüddel, 1989). When only an ambulatory ECG signal is present, spectral analysis cannot be performed with a precise definition of the individuals respiratory frequency band. The VU-AMD obtains the respiration signal in addition to the IBI time series. This advantage is used by the VU-AMS software to define a respiratory band for spectral analysis, e.g., by taking the average respiratory frequency in the condition plus/minus 1 standard deviation in Hertz.

Event sampling strategy

Although technically sophisticated, the implementation of ambulatory thoracic impedance measurement is not more than a straightforward application of techniques that had been in use in laboratory research for years. However, the interpretation of ambulatory PEP and RSA, in terms of the effects of daily events on autonomic state, is a completely uncharted area. In contrast to data from the laboratory, ambulatory data are not sampled under standardized conditions and the number of factors influencing the autonomic balance on a 24-hour time scale are sheer overwhelming. It is of crucial importance, therefore, that a detailed report is obtained of the activities that the subject is engaged in during the measurement period. Although field observation or videotaping are the most reliable ways of charting a subjects activities, most field settings will not allow this. A self-kept diary is often the only practical solution. However, diaries become unreliable when too much time elapses between the activity itself and the actual writing up by the subject. Yet, it is undesirable to have the subject fill out a detailed diary every few minutes, since this would interfere with normal daily behavior. For this reason, we developed a scheme where the subject fills out the diary only after being prompted by a beep of the VU-AMD. Beeping can be set to occur after fixed or random periods. Duration of periods

can be chosen freely, but 15 to 60 minutes would be normal values. In the diary subjects provide only a general indication of activities performed since the last entry. However, a more detailed description of activity, bodily posture (lying, sitting, standing, walking), mood state and social situation is given of the last 5 minutes preceding the prompt. Prompting is disabled during nightly hours.

This procedure yields detailed and reliable reports of activity, posture, mood and social situation on the 5-minute periods before each diary prompt. Consequently, we are mainly interested in the physiological data collected during these 5-minute periods. Instead of collecting beat-to-beat data throughout, the VU-AMD collects beat-to-beat HR data and the dZ and dZ/dt signals only during the 5-minute periods. In the interval between two prompts, 30 sec averages of HR are recorded and a global indication of HRV, the mean square of succesive differences in IBIs in this 30 sec period. With this method large parts of the day are only crudely monitored. Within the 5-minute beat-to-beat recording periods, however, there is a close link between physiological and behavioral data. As a corollary, the amount of ambulatory data becomes more manageable. Beat-to-beat recording of a 24-48 hour period normally yields a huge data set that is hard to analyse in all of its detail in the scope of most ordinary research projects. This is particularly true in repeated measurement designs (workday-weekend) in large subject groups. Our use of the event sampling method of daily activities as a means of data reduction seems to deal with this problem efficiently. Clearly, some caution is in order with this strategy in research designs were emphasis is on specific events like a panic attack, conflict situations, examination or public speaking. To enable us to monitor such special events during the day we have provided an event-button on the outside of the VU-AMD. The subject can be instructed to push this event button at adequate moments. The event button will record the time of the event and initiate a detailed beat-to-beat recording immediately.

The data reduction/event sampling strategy above has been implemented in the VU-AMS software. Before starting the recording in a field situation the VU-AMD is connected to a (portable) IBM compatible p.c. by an infrared interface suitable for the RS232 serial port. To ensure optimal quality, the incoming ECG and ICG signals are monitored on-line while the subjects are asked to breath deeply and to move about a bit. If signal quality is poor the electrodes can be refastened and/or new cables used. Identification, time and date of recording are then set and the sample rates for the recorded variables. In addition, the duration of the beat-to-beat recording periods is set as well as the duration of the interval between two BBR periods. Also, the user chooses to keep this interval fixed or random. The latter may have the advantage of not alerting the subject to the next diary prompt. We ourselves have used a 5 minute beat-to-beat recording with a fixed 25 minute interval in most of our studies. However, the duration of beat-to-beat recordings and the interval in-between can be chosen freely by the user. In fact, continuous recording on a beat-to-beat basis is possible also, for instance during monitoring of known real-life stressors like public speaking or exams. RAM memory of the current version, however, limits continuous beat-to-beat recording time to 9 hours.

Posture and activity

As with HR and blood pressure, PEP and RSA are highly sensitive to posture (Sloan, Shapiro, Bagiella, Fishkin, Gorman, Myers, 1995; Hayano, Skakibara, Yamada, Kamiya, Fujinami, Yokonama, Watanabe & Takata,1990) and physical activity (Billman & Dujardin, 1990). This is unfortunate because, being psychophysiologists, our main interest is in behavioral influences. To be able to disentangle these from 'mere' physical ones, we make each diary entry contain an obligatory checklist for subjective report on posture/physical activity (lying/quiet sitting/active sitting/standing/walking/bycicling) and a 5-point scale on degree of physical exertion. Secondly, a motion detector is built into the VU-AMD. Bodily movement of the subject, called "motility" is measured as the vertical acceleration of the subject, which is an indicator of its physical load (Montoye, Washburn, Servais, Erit, Webster & Nagle, 1983). The accelerometer consists of an active acceleration sensor and its output is amplified, rectified, sampled and reset each 5 seconds. The motility values are determined by averaging these samples over periods of 30 seconds and they have a range of 0 to 4 gsec with a resolution of 0.008 gsec. To secure the VU-AMD in a fixed position on the body it is placed in a belt around the waist.

In Chapter 8 of this book, Johnston demonstrated how EMG/motility signals can be used to continuosly correct the HR for body movement In principle, a similar strategy could be used with the motility signal of the AMS. We have, however, opted so far for an entirely different strategy. Rather than comparing across different physical activity levels, our efforts mainly go into selecting representative samples of the subjects ambulatory physiology during activities where posture and physical activity are relatively fixed. This means that only a part of the 24-hour data is used for detailed analyses, namely that part where subjects have retained a stable posture and did not change the type of activity they were engaged in throughout the 5 minute beat-to-beat recording. For instance, if we compare work to sleep, we would first select fragments of the workday where subject are engaged in clearly described activities (administrative work while sitting, talking to colleagues/students while walking, sitting at a meeting, lecturing standing). We would then reject for further analyses all fragments that do not fall into two or more of these categories, e.g when a subject is doing administrative work but is either interrupted for a phone call, or stand up to get coffee. In addition to this, we tend to favor a priori selection of fragments where physical activity is low or moderate at best. In fact, we specifically ask the subjects not to perform any heavy physical activity (sports, gardening, lifting heavy objects etc) on the measurement day. Clearly, this compromises ecological validity even further. However, both RSA and PEP scoring become increasingly more difficult with increasing levels of physical activity. The identification of the B-point and X-points in average dZ/dt waveform complexes, a pervasive problem in the analysis of impedance waveforms even in the laboratory (Sherwood et al., 1990) increases rapidly when movement and breathing artefacts are increased. Also statistical correction of RSA for RR will yield undesirable results if high active and low active periods are pooled in one analysis (Grossman et al., 1991). With our strategy not all data are analysed, and a bias is introduced in the sampling of "real-life". However, the data that remain suffer very little from confounding of posture and activity and interpretation in terms of effects of behavioral influences is optimized.

Our data selection strategy is reflected in the organization of the VU-AMS software for data processing. At the end of recording, raw data are read out and graphically displayed with a time scale on the x-axis. Scrolling through the entire 24-hour period the user can classify all activities recorded in the diaries with a text describing the type of activity plus a code for posture and movement, and additional information like social situation and mood. To obtain the fragments with well-controlled posture and

physical activity, self-report diary data are both verified and supplemented by the motility recording. Such recording clearly shows transitions in posture and activity like standing up, sitting down, walking, etc. Since the graphical program displays physiological data simultaneously with motility on the same time scale on the x-axis, it is possible to specify the start and end times of the activities more precisely. For instance, if a subject indicated to have walked to the canteen and sat down for a cup of coffee in the interval 11.00 to 11.15, the graphical inspection of the motility and HR signals can be used to set the beginning and end of the walking (e.g., 11.02 to 11.06) and the begin and end of the seated period (e.g., 11.06 to 11.18). Once such "pure" fragments have been defined, it becomes easy to select those with relatively stable posture and activity.

In summary, our efforts mainly go into selecting representative samples of the subjects' ambulatory physiology during activities where posture and physical activity are relatively fixed. Once these are appropriately selected and labeled with codes describing mood state, social situation, activity, posture, etc., all further analyses will automatically add these codes to any variable derived from the physiological recordings. In figures 2 and 3, for instance, the graphic screens of the VU-AMS programs that score PEP and RSA are shown. The text and values reported in these screens will be copied to the output files of these programs. Note the 3 codes and a text label describing the condition in which the PEP of the current ensemble average was measured. Similarly, several codes and a text label are provided for the RSA of the active breath, i.e., the breath currently scored by the program. Thus all VU-AMS scoring directly yields HR, PEP, RSA, and RR values that have been labeled with the codes describing in detail the activity during which this value for the variable was attained. The task remaining for further statistical packages is to aggregate the various instances of similar activities to an average value for each individual.

Reliability, Feasibility, and Validity

Cross-instrument reliability

To determine the reliability of the VU-AMD, the ECG and ICG were simultaneously recorded with the VU-AMD and a standard laboratory impedance device in 25 volunteer subjects, 12 man and 13 women. Details of the experimental set-up can be found in Willemsen, de Geus, van Doornen & Carroll (1996) and de Geus, Klaver, Willemsen & van Doornen (1996). Cross-instrument correlation was computed both across subjects and within subjects. To create within-subject variance, the participants were subjected to various conditions including mental stress testing, reading aloud, standing quietly, walking, paced breathing at 6 or 12 cycles per minute and bicycling at 50 Watts. All these conditions lasted between 2 to 4 minutes and were interspersed with quiet sitting at rest. The effects of these manipulations on PEP and RSA as measured by the VU-AMD are shown in Figure 4.

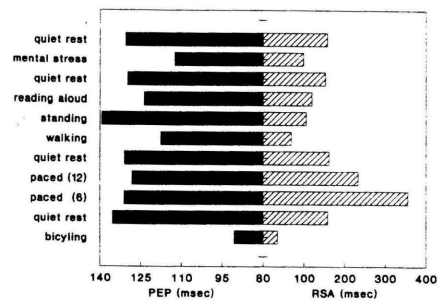


Figure 4: Average responses of the PEP and RSA to 11 short-lasting laboratory conditions.

Table 1: Between-subject correlation of laboratory and ambulatory devices in each of the 11 experimental conditions

Condition	HR	PEP	LVET	RSA	RR
quiet rest	1.00	0.92	0.99	0.98	0.52
stress	1.00	0.92	0.92	0.96	0.92
quiet rest2	0.99	0.90	0.99	0.84	0.97
reading aloud	1.00	0.95	0.99	0.96	0.83
standing	0.98	0.90	0.99	0.89	0.92
walking	1.00	0.92	0.97	0.93	0.74
quiet rest3	1.00	0.85	0.99	0.65	0.93
paced 12 cpm	1.00	0.92	0.99	0.86	n.s.
paced 6 cpm	1.00	0.87	0.99	0.69	n.s.
quiet rest4	0.98	0.85	0.98	0.94	0.62
bicycling	0.98	0.91	0.93	0.61	0.87

All correlations significant at $p<0.01$.

Table 2: Within-subject correlation of laboratory and ambulatory devices over 11 different conditions.

Subject	HR	PEP	LVET	RSA	RR
1	.98	.98	.81	.83	.76
2	.92	.85	.91	.70	.96
3	.99	.93	.72	.62	.89
4	.97	.68	.99	.73	.98
5	1.00	.68	.91	.69	.90
6	.99	.79	.91	.93	.99
7	.98	.97	.93	.76	.87
8	.90	.79	.79	.68	.90
9	.99	.72	.83	.73	.92
10	1.00	.91	.73	.96	.96
11	.99	.82	.55	.73	.95
12	.98	.93	.90	.99	.94
13	1.00	.62	.88	.92	.96
14	1.00	.88	.81	.76	.94
15	0.98	.74	.95	.82	.96
16	1.00	.78	.95	.82	.88
17	.96	.83	.89	N.S	.98
18	1.00	.91	.95	.99	.96
19	1.00	.82	.86	.98	.93
20	.98	.72	.81	.69	.92
21	.99	.92	.89	.72	.89
22	.99	.81	.87	.84	.94
23	1.00	.77	.82	N.S	.97
24	.75	N.S.	N.S.	.93	.96
25	.93	.64	.70	.99	.94

All correlations significant at $p<0.01$.

In each of these conditions, the between subject correlation for HR, PEP, RR and RSA derived from the laboratory devices and VU-AMD was good to excellent as shown in Table 1. The only exception was a low cross-instrument correlation for RR during paced breathing. This does not point to low reliability but merely reflects that between-subject variance in respiratory time intervals is virtually zeroed in these conditions.

Results from within-individual comparison across all 11 conditions further substantiated the reliability of the VU-AMD (see Table 2).

For IBI, all intra-individual correlations were excellent with only one subject lower than .90. For PEP all correlations were generally good (>.75), in the moderate range in 7 subjects (.62 - .74) and non-significant in one subject. For RSA, within-subject correlations varied from moderate to excellent (.62 - .99). In two subjects

no significant correlation was found. This was due to incorrect detection of the separate inspiration and expiration periods in a part of the breaths. In spite of these problems, RR assessed from the filtered thoracic impedance signal showed excellent correlation with the RR from the laboratory strain gauge signal, even in these two subjects.

Feasibility of 24-hour monitoring

In a second phase, 24-hour recordings with the VU-AMD were performed in two subject groups to determine the feasibility of monitoring with the device in true ambulatory settings. In a first study we made 24-hour recordings of 10 academic staff members (age = 32.2, 7 male, 3 female) and 30 students (age = 21.2, 11 male, 19 female) on a normal workday. Around nine o'clock in the morning, subjects visited the laboratory where the VU-AMD was attached. Sample rates were set such that within each interval of 30 minutes, a 5 minute beat-to-beat recording was initiated followed by a beep prompting the subjects to fill out their diary. At the outset of the study our major concern regarding feasibility was data loss by loose electrodes. To prevent such data loss, the device was set to constantly check both the IBIs and Z0 signal throughout the entire ambulatory recording period. If no new R-wave arrived within 5 sec after the previous R-wave or if the Z0 left the 5-20 Ohm range, data storage was suspended whereupon the VU-AMD emitted a loud audible signal. When the subject refastened the electrodes and regularity of the incoming ECG was reestablished, the alarm signal was silenced and data storage continued. The clock times of the suspension and continuation of the data storage were always stored.

In 31 out of 40 subjects data recording was virtually complete over the entire measurement period. In many subjects one or more electrodes had come loose a couple of times, but the alarm had rapidly made the subjects reattach them, resulting in minimal data loss. In total, 1470 fragments of 5 minute beat-to-beat recording were obtained on these subjects. In 9 of the 40 subjects, however, substantial loss of data occurred due to equipment malfunction. No more than 211 beat-to-beat periods were salvaged, i.e., no more than 45% of all beat-to-beat periods of the entire 24-hour cycle. In 6 cases this was clearly due to loose electrodes during the day-time that went undetected in spite of our efforts. In 3 cases the cause of the malfunction of the VU- AMD was unknown, but loose electrodes were suspected here too.

In addition to the data loss during recording, a significant part of the data had to be discarded during visual signal inspection. Out of the 8402 1-minute ensemble averages of the dZ/dt signal, 11% had to be rejected during interactive scoring. Signal distortion due to movement artefacts was the main reason for rejection. Reliable respiration signals could be obtained from the band pass filtered thoracic impedance for the major part of the recorded signals. An average of 6.8 % of all breaths was considered unreliable during visual scoring, even after trying different band-pass filters per subject per 5-minute period. The main cause for rejection of breaths were movements of the thorax in the respiratory frequency range. Although the rejection of these breaths increases the reliability of ambulatory monitoring of respiration it may at the same introduce a bias since the occurrence of unreliable breaths may not occur random in the field. Out of 17.032 breaths 1160 were finally considered unusable. There was a large overlap between rejection of breaths and rejection of simultaneously recorded PEPs! This suggests that similar factors affect reliability of scoring of PEP and RSA. When all hardware and signal detection problems are summed, a remaining 82% of the total beat-to-beat recording time was considered to yield reliable HR, PEP, RSA and RR. Importantly, none of the subjects reported discomfort from the device, not even during the night.

Validity of ambulatory measurements

The study also yielded some insight in the validity of ambulatory recording of PEP and RSA with the VU-AMD. Subjects were provided with a written diary were they could score global activity on 25 minutes intervals and details on posture/activity, work load and social situation (alone, significant other, collegue, boss, friends, mixed) during the 5 minutes beat-to-beat periods preceding the diary prompt. Since not all subjects undertook the same activities, various diary entries were grouped together in 7 main activity categories to facilitate comparison across subjects. These categories were: sleeping, watching television, social interaction at home (talking to spouse/partner; also includes evening meal), social interaction at work (with collegues, clients or patients, telephone conversations), solitary intellectual work (reading, PC work, administrative, writing), pauses with coffee/smoking, and public transportation or car driving. For each of these activities all available 5-minute periods were averaged, provided the subjects were sedentary throughout the entire period. In total, 12 subjects had to be left out for not having valid data in one or more of these activities.

Although one would generally not include such categories in studies on the effects of psychological stress, in this exploratory phase we also decided to include the categories of walking, bicycling, household activities (cooking, dish washing, ironing), personal hygiene (dressing, toothbrush, toilet, washing), and moderate physical activity (cleaning, carrying, repair, gardening). Only those 5-minute periods were used where the subject's posture and activity level where stable, e.g., 5 minutes of cooking or toothbrushing would have to be done entirely standing with no walking about. An additional 7 subjects had to be left out because they had no complete data in these activity categories. The results are summarized in Table 3.

The first main finding was a clearcut difference between sleeping levels and waking levels of all variables. Intermediate levels were found while subjects watched television, mostly in leisure time in the evening hours. In all instances the effects on PEP and RSA where in the expected direction, i.e., an increase in PEP and RSA with increasing relaxation signifying the expected reduction in cardiac sympathetic

Table 3: Average levels of ambulatory HR, PEP, RSA and RR as a function of daily activities.

Activity	HR	PEP	RSA	RR
(N=28)				
sleeping	62.1	125.0	112.4	12.4
watching television	72.4	107.9	86.8	15.5
social interaction at home	73.6	100.3	62.6	20.4
social interaction at work	75.5	93.1	55.3	15.7
solitary intellectual work	78.3	95.3	61.9	17.2
pauses with coffee/smoking	81.1	94.8	56.9	18.2
public transportation or car driving	74.1	101.6	85.2	16.0
(N=21)				
walking	89.1	82.2	61.2	19.3
household activities	82.9	91.4	45.1	24.0
moderate physical activity	91.3	74.2	45.0	19.5
bicycling	87.4	69.1	39.4	22.0

drive and increase in cardiac parasympathetic drive respectively. A second main finding was the decrease in both RSA and PEP with increasing physical activity. Together these results suggest that the VU-AMD validly tracks shifts in autonomic balance. Unfortunately, the difference between psychosocially relevant activities, e.g., social interaction in free time with partner versus social interaction at work were not very striking. However, from the standard deviations it was obvious that large individual differences existed. A main goal of psychophysiological research is to relate these physiological differences to person characteristics like personality, mood or work stress. With that in mind, the results in table 3 are very encouraging.

Ambulatory PEP and RSA and the risk for cardiovascular disease

The AMD allows us to examine the physiological response to daily events as a function of individual differences in cardiovascular risk profile. By way of demonstration we will present two preliminary studies in which subjects were divided in groups differing with respect to two risk factors: the insulin resistance syndrome and a sedentary lifestyle.

PEP and the Insulin Resistance Syndrome

The main focus in stress research has been directed towards the possible role of exaggerated reactivity in the future development of hypertension and coronary heart disease. The observation in several large scale intervention studies that treating hypertension had no beneficial effect on the incidence of CHD suggests that hypertension may be not causally related to CHD risk but be merely a symptom of an underlying metabolic disorder. This idea is supported by the observation that hypertension rarely occurs in isolation but often coincides with obesity and diabetes, and with elevated levels of cholesterol and triglycerides. A central role underlying this clustering has been attributed to the resistance of the body to the effects of the metabolic hormone insulin. Therefore, this cluster of risk factors was called the insulin resistance syndrome (IRS), or as Reaven (1991) has called it: "syndrome X". The relevance with respect to stress reactivity is that there is a close connection between insulin and the sympathetic nervous system. Insulin infusion gives a rise in noradrenaline secretion, increased muscle sympathetic activity and forearm blood flow (Anderson, Hoffman, Balon, Sinkey & Mark, 1991), increased renal sodium reabsorption (DeFronzo, 1981), an increase of cardiac contractility (Rowe, Gould, Minaker, Stevens, Pallotta & Landsberg, 1981), but no effect on blood pressure (Anderson, Hoffman, Balon, Sinkey & Mark, 1992). These effects make insulin a potentially interesting hormone to study in relation to the sympathetic stress response. The only study that looked at the relation of insulin with ambulatory blood pressure was done by Narkiewicz (1991). They observed correlations of .44 with systolic blood pressure levels during the day and of .61 with systolic pressure during sleep. Stern, Morales, Haffner & Valdez (1992) categorized subjects in high and low with respect to "syndrome X" symptoms and found a hyperdynamic circulation (high HR and pulse pressure) in high "syndrome X" subjects. Considering the possible role of a hyperdynamic circulation and the associated hyperadrenergic state in the early stage of hypertension we were curious to compare the 24-hour PEP profile of subjects varying with respect to their "syndrome X" score.

Twenty-six male subjects with predominantly sedentary jobs took part in the study. Mean age was 44.8 (SD = 9.2), mean height was 183.1 cm (SD = 5.4) and mean weight was

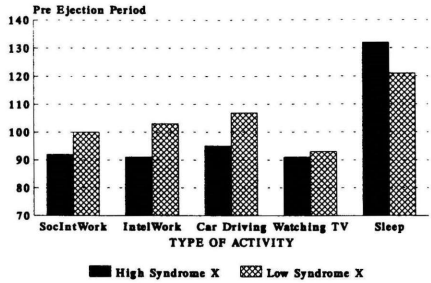


Figure 5: PEP in subjects scoring high (black bars) or low (open bars) on the syndrome X. PEPs were averaged over all recordings made during: social interaction at work (SocIntWork), solitary intellectual work (IntelWork), car driving (Car), watching TV (TV), sleep (Sleep).

79.8 kg (SD = 8.5). These subjects were part of a larger study which involved, among others, resting blood pressure measurement, anthropometric measurement, and blood sampling for the assessment of insulin, HDL cholesterol, triglycerids (Snieder, van Doornen & Boomsma, 1995). From these measurements a compound syndrome X score can be constructed as the sum of standardized scores for body mass index, waist-hip-ratio, triglycerides, systolic BP, diastolic BP minus HDL cholesterol. Based on their scores our subjects were divided into 12 high syndrome X and 12 low syndrome X subjects (on 2 subjects no complete data could be obtained; they are left out of all analyses). All subjects were measured during a normal workday and the following night. The VU-AMD was slightly modified in comparison to the validity study reported above. To reduce data loss, louder error beeping was implemented in the AMD and the subjects were encouraged to check the device each 3 hours or so by holding down the event button. This generates a 10-sec fragment of audible feedback of their heart rhythm. Subjects were asked not to perform any heavy activity throughout the measurement period.

Using only beat-to-beat periods where subjects were sitting we computed the average PEP value in the 5 activity categories separately for both groups (see Figure 5). There was a clear interaction between activity category and group. The interaction was entirely due to a larger decrease in PEP from sleep to workday in the high syndrome X group compared to the low syndrome X group. The larger increase in cardiac sympathetic drive during the day fits the observation of Stern et al. (1992) of a hyperdynamic circulation associated with the syndrome X. However, it should be noted that the group difference in PEP levels during the day were small. The greater reactivity of the syndrome X subjects was mainly caused by their longer PEP during the night. An explanation of the longer PEP during sleep might be the afterload effect of the higher DBP on PEP. Resting diastolic pressure was 6 mmHg higher in the high syndrome X group. However, an effect of afterload would show up as a lengthening of LVET (Li & Belz, 1993). The two groups did not differ in LVET, neither during sleep nor during the other activity categories (data not shown). Clearly, the paradoxically longer PEP during the night in the high syndrome X group is an intruiging finding. Preliminary analyses of night PEPs showed large individual differences in the increase in PEP in the course of the night. Most of our subjects showed rapid increase in PEP directly after sleep onset, but in 5 subjects it gradually increased throughout the night. Although the number of subjects becomes too small to relate this phenomenon to syndrome X, these results do suggest that a more detailed analyses of nightly PEP recovery is called for.

RSA in exercisers versus non-exercisers

Recent reviews of prospective cohort studies on physical activity habits support the idea that a few hours of regular vigorous exercise in leisure time (e.g., sports, jogging, fitness training) protect against myocardial infarction and sudden death (Powell, Thompson, Caspersen & Kendrick, 1987 ;Berlin & Colditz, 1990). The physiological mechanisms on which the protective effect of activity is based, remain unclear. In general, the beneficial effects of regular physical activity, in any form, are thought to be mediated by increases in cardiorespiratory ("aerobic") fitness. The latter concept reflects a broad collection of physiological characteristics that distinguish the physically active from the sedentary population, and that are known to change in response to regular exercise. These effects include improvements in the vascular structure of the muscles and the heart, improved glucose tolerance and insulin sensitivity, reduced levels of blood pressure, cholesterol and triglycerides, and increased fibrinolytic potential (Bouchard, Shepard, Stephens, Sutton & McPherson, 1988). In addition, it is hypothesized that exercise improves vagal control over the heart. This has two direct advantages: high vagal tone enhances the electrical stability of the heart and it reduces HR, with a concomittant decrease in myocardial load. Furthermore, since vagal tone plays an important role in baroreflex control of blood pressure, the increased vagal tone may also explain part of the training-induced reduction in blood pressure. Unfortunately, the contribution of vagal tone to exercise bradycardia remains enigmatic. Although some studies report higher HRV in exercisers (Kenney, 1985), others have shown no difference in HRV between exercisers and non-exercisers (Maciel, Gallo, Marin Neto, Lima Filho,Terra Filho & Manco, 1985). In a recent study even a larger HRV in the non-exercisers was reported (Sacknoff, Gleim, Stachenfeld & Coplan, 1994). So far, a decrease in the intrinsic HR, i.e., the HR obtained after complete removal of autonomic influences, appears to be the most consistent observation in the studies on training-bradycardia (Sutton, Cole, Gunning, Hickie & Seldon, 1967; Lin & Horvath, 1972; Katona, McLean, Dighton & Guz, 1982; Nylander, Sigvardsson & Kilblom, 1982).

To date, all studies have concentrated on the relationship of exercise with RSA during quiet resting conditions. However, exercisers might specifically differ from non-exercisers in vagal *reactivity* to physical or mental stress. With regard to the latter, a review of 33 studies showed that in response to mental stress, HR reactivity on average is smaller in exercisers than in non-exercisers (van Doornen & de Geus, 1993). High vagal tone might explain this reduced HR reactivity. To obtain insight in the difference in RSA of exercisers and non-exercisers in a real-life setting, we tested 32 healthy students (mean age = 23.2), who were divided in two groups with clearly different exercise habits. The exercisers group consisted of 8 male and 8 female athletes, who participated more than 4 hours per week in endurance sports. The non-exercisers consisted of 8 age-matched males and 8 age-matched females, who had not been involved in any regular exercise over the past 6 months. All subjects wore the improved VU-AMD for a period of about 24 hours on a normal weekday. Exercisers were asked not to exercise on the day before or during ambulatory monitoring. At fixed intervals of 25 minutes, a detailed 5-minute beat-to-beat recording took place. Data analysis was limited to those beat-to-beat recording periods when subjects were either lying, sitting or standing. Since both subject groups engaged in these activities a comparable part of their time, using data from three different postures did not introduce a between-group bias in terms of a difference in type of activities throughout the day. Vagal tone was computed in several ways in both time and frequency domains, but we will concentrate on RSA computed with the peak-to-through method, i.e., using both the respiration trace and the IBI time series.

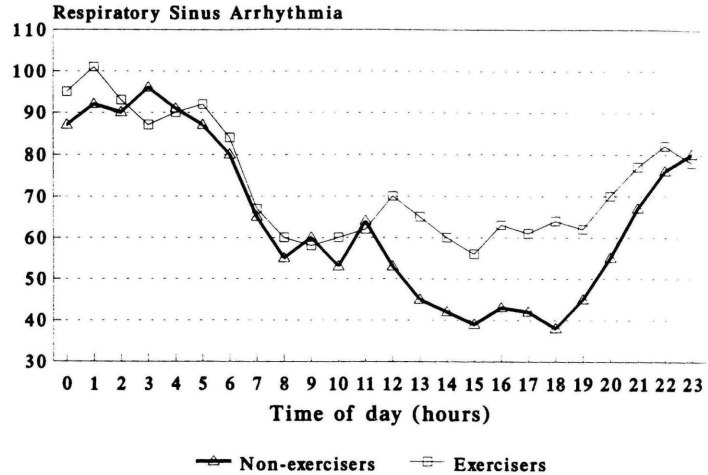


Figure 6: 24-hour profile of RSA in exercisers and non-exercisers. RSA was computed on a breath-to-breath basis on periods with little physical activity and fixed posture. The x-axis displays the average over all valid breaths found in one-hour periods.

When the day was divided in 4 segments, a significant difference was seen only in the afternoon and the evening, but not in the morning and during sleep. In the second part of the workday, exercisers maintained higher vagal tone than non-exercisers, although the difference leveled off at the close of the evening and was not found in the morning hours. The identical sleep levels of RSA are intruiging because sleep HR in the exercise group (M=54.2 bpm) was clearly lower than sleep HR in the non-exercise group (M=64.9 bpm). Possibly, this points to a methodological problem in the interpretation of RSA at very low HRs. Goldberger, Ahmed, Parker & Kadish (1994) showed that HRV as assessed by power analysis does not index vagal tone during baroreceptor stimulation, when HR is low and vagal tone is high. Likewise, in supine resting conditions, when resting HRs of athletes reached 50 bpm versus 67 in nonexercisers, the athletes where seen to have clearly lower HRV than non-exercisers (Sacknoff et al., 1994). When the heart period is close to its maximal length, further decelaration because of the increase in vagal tone in the expiratory phase may be compromised, yielding relatively low RSA values.

These results caution against the use of RSA as an index of vagal tone, without taking HR into account. At the same time they provide an excellent demonstration of the power of 24-hour measurements. In fact, if the differences in daytime RSA of our groups reflects a genuine difference in daily pattern of the vagal tone of exercisers and nonexercisers, than the ambiguity of previous laboratory research on vagal tone may have been exposed as a "laboratory-artifact".

Future research

In conclusion, the VU-AMD is a promising instrument, permitting reliable and valid assessment of HR, PEP, RSA and RR by measuring thoracic impedance and a three-lead ECG. Such measurements are entirely feasible in true field situations, including registration during sleep. The pattern of results involving PEP and RSA across different daily activities strongly suggests that valid estimation of changes in autonomic cardiac drive is possible in real-life situations. Our preliminary results have been encouraging in showing that this new device yields data that would not have been easy to extract from laboratory experiments. However, our main objective in developing this new technology was to obtain important new insights in the link between chronic stress and disease. For this, we still have a long way to go. Emphasis in the studies above has been on reliability and feasibility. As a consequence these studies have featured only a small number of subjects. More importantly we have made no effort to manipulate the levels of stress in our ambulatory monitored subjects. In fact, it may be very difficult, if not impossible, to orchestrate stress in field situations as we did in the laboratory. Fortunately, real-life provides us with plenty of opportunities to study individual differences in stress exposure. This is most dramatically shown in the field of work stress. Recent epidemiological research has shown that a high level of work stress is associated with an increased risk for cardiovascular disease (Karasek & Theorell, 1990; Siegrist, 1991). To date, the pathophysiological mechanisms underlying this epidemiologic association remain unclear.

Ambulatory monitoring allows us test to what extent work stress is associated with elevated sympathetic nervous system activity and reduced vagal activity during a work day, as well as with inadequate recovery after work and during sleep. As a first step we have started with the selection of subjects with either high or low work stress from a population with homogenous jobs (e.g., nurses and sedentary workers at a large automatisation company). With ambulatory monitoring, 24-hour recordings will be made of HR, blood pressure, PEP, RSA and RR during two representative work days and one weekend day. Since shifts in autonomic nervous system activity may be accompanied by an increase in the risk parameters of the syndrome X, blood samples will be taken at the beginning and the end of the workweek. By first examining groups with clearly different work stress levels we hope to identify those parts of ambulatory physiology that will have the most relevance for linking stress with cardiovascular disease.

Summary

This chapter reviews our current experience with a recently developed device (VU-AMD) for the ambulatory measurement of the electrocardiogram (ECG) and changes in thoracic impedance (ICG). With this device simultaneous assessment can be made of HR (HR), Heart rate variability (HRV), the Pre-Ejection Period (PEP), Left Ventricular ejection Time (LVET), Respiration Rate (RR) and Respiratory SinusArrhythmia (RSA). Our efforts to build this device were inspired by the fact that PEP and RSA are currently our best noninvasive tools to assess sympathetic and parasympathetic influences on the heart. Reliability of the VU-AMD was tested in cross-instrument comparison against the "golden standard" of our laboratory devices. Measurement of RSA and PEP by the VU-AMD was shown to be highly reliable. To determine feasibility of field measurements, a set of 40 subjects has been measured on a 24-hour basis. Error free data were obtained on 82% percent of the total recording time. Furthermore, plotting the physiological data over the various daily activities of the subjects (intellectual

work, physically active work, social interaction, relaxation, sleep) yielded plausible patterns of shifts in HR, PEP, RSA, and RR. As a final step we explored the possibilities of this new technique for research into behaviorally induced cardiovascular pathology. In two studies, 24-hour profiles of PEP and RSA were obtained with the VU-AMD in subject groups with different risk profiles for cardiovascular disease. Subjects with high scores on a compound of risk factors known as the syndrome X (body mass index, hip-waist ratio, cholesterol, blood pressure, and insulin) were compared to subjects with low scores on the syndrome X variables. The high risk group showed a significantly larger decrease in PEP from sleep to work than the low risk group, which points to greater sympathetic reactivity. In a second study, regular exercisers were compared to age and sex matched sedentary subjects. No effects were found of regular exercise on the PEP, but the 24-hour RSA profile suggested that regular exercise helps to keep vagal tone intact during the second half of the workday. Although the number of subject studied is still low, the studies above serve to convince us of the usefulness of ambulatory thoracic impedance monitoring in studying the relation between stress and cardiovascular disease. In our final paragraph we present an outline for a future research program into the effects of chronic work stress on autonomic cardiac drive.

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