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Temporal stability of ambulatory stroke volume and cardiac output measured by impedance cardiography

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Abstract

Recently, devices have become available that allow non-invasive measurement of stroke volume and cardiac output through ambulatory thorax impedance recording. If such recordings have adequate temporal stability, they offer great potential to further our understanding of how repeated or chronic cardiovascular activation in response to naturalistic events may contribute to cardiovascular disease. In this study, 24 h ambulatory impedance-derived systolic time intervals, stroke volume and cardiac output were measured in 65 healthy subjects across an average time span of 3 years and 4 months. Stability was computed separately for sleep and daytime recordings. To avoid confounding by differences in posture and physical activity across measurement days, temporal stability was computed using sitting activities only. During the day intraclass correlations were moderate for stroke volume (.29–.46) and cardiac output (.33–.46) and good for systolic time intervals (.55–.81).

When test–retest comparison was limited to two comparable days (two work days or two leisure days), correlations for both SV (.42–.46) and CO (.43–.50) improved. *Conclusion*: Moderate long-term temporal stability is found for individual differences in ambulatory stroke volume and cardiac output measured by impedance cardiography.

Keywords: Sympathetic nervous system; Temporal stability; Hemodynamic regulation; Impedance cardiography

1. Introduction

Frequent and large increases in blood pressure in reaction to psychological stress is hypothesized to be a risk factor for hypertension (Gerin et al., 2000). Blood pressure reactivity is due to a combination of changes in cardiac output (CO) and total peripheral resistance (TPR). The relative contribution of CO and TPR responses to blood pressure reactivity can vary strongly across different types of mental and emotional challenges (Kasprowicz et al., 1990; Lawler et al., 2001; Lovallo et al., 1993). In addition, within a single type of stressor the relative contribution of the TPR response seems to increase with prolonged duration of the stressors (al'Absi et al., 1997; Allen and Crowell, 1989; Carroll and Roy, 1989; Miller and Ditto, 1989, 1991; Ring et al., 2002). Most importantly, large individual differences are seen in the pattern of CO or TPR responses to psychological stress (Brod et al., 1959; Girdler et al., 1990; Kline et al., 2002; Sherwood et al., 1993). Test–retest reliability of CO and TPR reactivity to various laboratory stressors ranges from high across several weeks (Kamarck et al., 1992) to moderately high across 1 week (McGrath and O'Brien, 2001) and across 3 years (Matthews et al., 2002). This is comparable to the short term (Kamarck et al., 1993; Llabre et al., 1993; Swain and Suls, 1996) or longer term (Allen et al., 1987; Matthews et al., 2002; Sherwood et al., 1997) reliability of systolic blood pressure (SBP) and heart rate (HR) responses to laboratory stressors.

CO and TPR can be computed from the conjoint measurement of only three parameters: heart rate (HR), blood pressure (BP) and stroke volume (SV) (Sherwood et al., 1990). It is very easy to obtain HR and BP non-invasively by using ECG recordings and arm-cuff auscultatory methods, respectively. Non-invasive SV has been more elusive, but at least two techniques are now available (Harms et al., 1999; Sherwood et al., 1991) of which impedance cardiography is most often used. In impedance cardiography, two voltage electrodes, typically bands of aluminium-coated Mylar fastened with adhesive strips around the neck and waist, introduce a high-frequency alternating current to the thorax. Two inner and

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parallel bands measure the changes in the impedance of the enclosed thorax column (dZ), which is largely a function of aortic blood flow. The impedance cardiogram (ICG) is defined as the first derivative of the pulsatile changes in transthoracic impedance (dZ/dt). From the ICG, two systolic time intervals can be derived, the pre-ejection period (PEP) and left ventricular ejection (LVET). In addition, the blood volume ejection rate of the left ventricle can be estimated by the forward extrapolation of the maximum early slope of dZ or the dZ/d$t_{(min)}$ amplitude. Using the most widely used equation for the estimation of SV, the Kubicek equation (Kubicek et al., 1966), SV is computed as the product of the total duration of systolic ejection and the volume ejection rate, after taking into account the individual's resting thorax impedance and the height of the thorax column enclosed by the measuring electrodes.

Until recently, impedance cardiographic studies have been limited to the laboratory where SV and CO responses are measured in response to short lasting stressors (Light et al., 1998; Matthews et al., 2001; Neumann and Waldstein, 2001; Ring et al., 1999). This leaves uncharted how SV and CO change in response to much longer exposure to stress, such as may occur in the course of a work day. It also remains to be established how SV and CO may change from daytime periods with high sympathetic activation to nighttime periods when sympathetic activation is strongly reduced (Burgess et al., 1997; Lechin et al., 2004; Trinder et al., 2001; van Eekelen et al., 2004). The study of this more prolonged SV dynamics in naturalistic settings requires ambulatory monitoring.

Recently, various systems have become available that allow the ambulatory monitoring of SV through impedance cardiography (Cybulski, 2000; Nakonezny et al., 2001; Sherwood et al., 1998; Willemsen et al., 1996). A number of studies have demonstrated the validity of measuring systolic time intervals, SV and CO with this approach (Riese et al., 2003; Vrijkotte et al., 2004; Willemsen et al., 1996). The temporal stability of individual differences in impedance-derived ambulatory SV and CO remains to be established. In doing so, an important source of confounding will be the potential difference in (physical) activity patterns during the first and the second measurement day. Shifts in posture and physical activity strongly affect cardiac sympathetic drive as well as cardiac afterload and preload which all have an impact on SV (Cacioppo et al., 1994; Sherwood and Turner, 1993). In addition, postural changes are expected to alter the relative position of measuring and current electrodes, the exact shape of the enclosed thorax column and the resulting basal thorax impedance (Z_0) (Laszlo et al., 2001; Mohapatra, 1981; Toska and Walloe, 2002). Both the electrode distance and the basal thorax impedance are important parameters in the Kubicek equation (Kubicek et al., 1966). It is crucial, therefore, to base test–retest comparisons of SV values on carefully selected periods with unchanged posture and physical activity.

A previous study on ambulatory ICG recordings (Riese et al., 2003) showed that, in a small number of subjects, reliable detection of the B-point in the first derivative of thoracic impedance signal (dZ/d$t_{(min)}$) can be difficult. This point corresponds to the opening of the aortic valve and is used to define the PEP but also to compute the dZ/d$t_{(min)}$, a crucial parameter in SV computation. On theoretical grounds, it is more appropriate to measure dZ/d$t_{(min)}$ in relation to this B-point (SV_B) (Debski et al., 1993; Doerr et al., 1981; Mohapatra, 1981), but dZ/d$t_{(min)}$ can alternatively be measured in relation to the dZ/dt = 0 baseline (SV_0) (Sherwood et al., 1991). Since the latter can be more reliably established in all subjects, it is prudent to establish temporal stability for ambulatory SV using dZ/d$t_{(min)}$ both in relation to dZ/dt = 0 (SV_0) and to the dZ/dt B-point (SV_B).

The present study reports on ambulatory SV and CO measured by impedance cardiography in 65 subjects who were tested twice across an average time span of 3 years and 4 months. We established long-term temporal stability of individual differences in 24 h ambulatory SV_0, SV_B, CO_0 and CO_B, while accounting for differences in posture and physical activity on the two measurement occasions.

2. Methods

2.1. Subjects

Participants were all registered with the Netherlands Twin Register (NTR). They came from families that participated in a linkage study searching for genes influencing personality and cardiovascular disease risk, which is described elsewhere (Boomsma et al., 2000). Out of the 1332 twins and siblings who returned a DNA sample (buccal swabs) for the linkage study, 816 were also willing to participate in cardiovascular ambulatory monitoring. Reasons for exclusion were pregnancy, heart transplantation, pacemaker and known ischemic heart disease, congestive heart failure or diabetic neuropathy. Of these subjects a total of 65 (20 male, 45 female) were tested twice separated by a minimum of 2 years and 1 month and a maximum of 4 years and 8 months (mean 3 years and 4 months). At the first test day the age ranged from 18 to 62 years (mean = 30.7, S.D. = 9.7). The Ethics Committee of the Vrije Universiteit approved of the study protocol and all subjects gave written consent before entering the study. No payment was made for participation, but all subjects received an annotated review of their ambulatory heart rate and blood pressure recordings.

2.2. Ambulatory recording

Subjects were invited to participate in the study by letter and subsequently phoned by the researchers to receive additional information on the study, and to make an appointment for 24 h ambulatory monitoring. The first ambulatory measurement took place during a representative work day (or a day with representative housekeeping chores for those who were not employed). The second ambulatory measurement day took place during a comparable (work) day for most of the subjects, but 17 subjects would only participate if the repeated measurement was scheduled on a leisure day. On the day preceding monitoring and on the monitoring day itself subjects were asked to refrain from leisure time exercise or heavy physical work. Subjects were visited at home between 7:00 and 10:00 a.m., and fitted with the Vrije Universiteit Ambulatory Monitoring System (VU-AMS46; de Geus et al., 1995; Riese et al., 2003; Willemsen et al., 1996). They received detailed instructions to regularly check the 'all clear' signal of the device (a small blinking light on the side of the device), and how to proceed in case of suspected device malfunction. The VU-AMS produced an audible alarm approximately every 30 min (±10 min randomized) to prompt the subject to fill out an activity diary. They were instructed to write down their physical activity and bodily postures during the last 30 min period in chronological order. Diary prompting was disabled during sleep, but regular beat-to-beat recording of the ICG was maintained throughout the night. The following day the participants were visited again to collect the equipment.

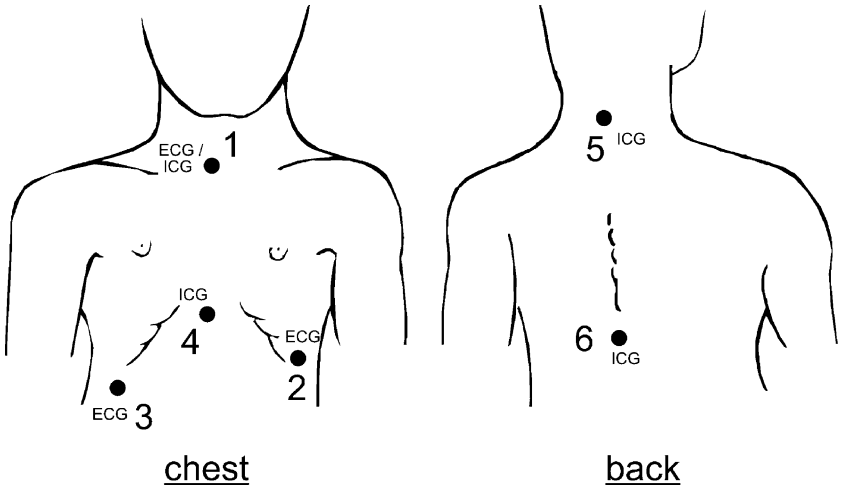

Fig. 1. Location of the six ECG and ICG electrodes. Note that a combined electrode is used for ECG and ICG on the sternum (1).

The ECG and ICG were recorded continuously during a 24 h period (daytime and sleep) using six disposable, pregelled Ag/AgCl electrodes. The first ECG/ICG electrode was placed on the sternum over the first rib between the two collarbones. The second ECG electrode was placed at the apex of the heart over the ninth rib on the left lateral margin of the chest approximately 3 cm under the left nipple. The third ECG electrode is a ground electrode and was placed at the lower right abdomen. A second ICG measuring electrode was placed over the tip of the xiphoid complex of the sternum. The ICG current electrodes were placed on the back over cervical vertebra C4 and between thorax vertebras T8–T9 (see Fig. 1). Electrode resistance was kept low by cleaning the skin with alcohol and rubbing.

2.3. Ambulatory signal scoring

The amount of 60 s ensemble averaged ICG waveforms collected during a typical 24 h ambulatory recording can be up to 1440 complexes for a single subject for a single measurement day. To score 24 h ambulatory SV in large samples, for instance, in our 130 (65 times 2) recordings, this is a very laborious procedure. Unless unlimited resources are available, 60 s ensemble averaging of the ambulatory ICG can be effectively disqualified as a feasible approach in large population studies. To solve this problem, we used the large-scale ensemble average (LSEA) strategy outlined by Riese et al. (2003). This strategy hinges on the idea that most ambulatory studies will ultimately average the results obtained on the smaller time scale (e.g. 60 s averages) over much larger time periods. Consecutive fragments of ambulatory recording are identified in which no significant change occurs in the hypothesized causes of intra-individual variance in impedance-derived variables, for instance, similar posture, type of activity, physical load, social situation, location or the level of self-experienced mental or emotional strain. Signals within these periods are averaged and scored.

Using the activity diary entries in combination with a visual display of the vertical accelerometer signal, the entire 24 h recording was divided into fixed periods coded for posture (lying, sitting, standing, walking, bicycling), physical activity (e.g. desk work, dinner, meetings, watching TV), social situation (e.g. alone, with significant other, with colleagues, with friends) and location (e.g. at work, at home, with family). If fixed periods lasted more than 1 h (e.g. during sleep), they were divided into multiple periods of maximally 1 h. This procedure allowed us to compute temporal stability for specific postures and across comparable levels of physical activity. Based on the reported times of lunch, diner, bedtime and awakening we further aggregated the data into four periods of day: morning, afternoon, evening and nighttime sleep. For the subjects of which the exact time of dinner, lunch, awakening or bedtime could not be extracted from either diary or body movement, the missing time was imputed with the use of the mean times of these events in the rest of the sample.

Fig. 2 plots a typical large-scale ensemble average over a period of 512 ms. The graph shows three vertical lines, representing: (1) upstroke or B-point, (2) $dZ/dt_{(min)}$ and (3) incisura or X-point. The PEP (in ms) is defined as the interval from the R-wave peak, minus a fixed interval of 48 ms (Sherwood et al., 1990; Willemsen et al., 1996) to the B-point, which signals opening of the aortic valves. The LVET (in ms) is defined by the interval between the B-point and X-point, which signals the closure of the aortic valves. $DZ/dt_{(min)}$ (Ω/s) is the difference in amplitude of the dZ/dt waveform at its peak compared to the B-point. Detection of B-point, X-point and $dZ/dt_{(min)}$ was done automatically, but automatic scoring was always followed by interactive visual inspection of all large-scale ensemble averages (see Fig. 2). Scoring of the ICG signals on test and retest data was always done by the same rater (first author).

To compute the SV, the VU-AMS relies on Kubicek's equation (Kubicek et al., 1966):

$$\mathrm{SV} = \rho\left(\frac{L_0}{Z_0}\right)^2 \mathrm{LVET}\frac{\mathrm{d}Z}{\mathrm{d}t_{(\mathrm{min})}}$$

In this formula, ρ is the blood resistivity, which was fixed here at 135 Ω cm, L_0 the average distance between the electrodes (cm) and Z_0 is the basal thoracic impedance (Ω). The SV is multiplied by the average HR obtained from the R-to-R-wave time series to yield the CO. As mentioned earlier, we used two different measures for $dZ/dt_{(min)}$ resulting in two different SV and CO measures, namely

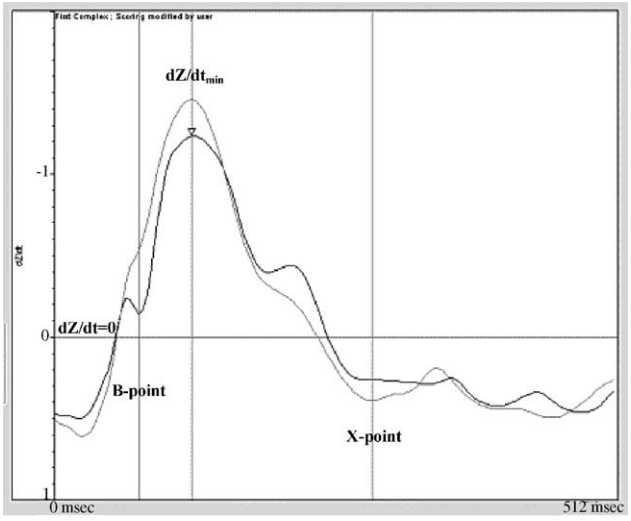

Fig. 2. Graph of a 60 s ensemble averaged ambulatory ICG signal (dark grey), overlaid with the corresponding large-scale ensemble average (light grey). The three vertical bars indicate the B-point, $dZ/dt_{(min)}$ and X-point scored on the large-scale ensemble average.

SV_B and CO_B based on the $dZ/dt_{(min)}$ computed from the dZ/dt amplitude at the B-point to the peak amplitude, and SV_0 and CO_0 computed from the dZ/dt amplitude at the $dZ/dt = 0$ line to the peak amplitude.

2.4. Statistical analyses

Repeated measures ANOVA in SPSS first tested for posture effects (sitting, standing, walking). Next, repeated measures ANOVA was used to test for main effects of measurement day (test, retest) and periods of day (morning, afternoon, evening, sleep). Finally, temporal stability was assessed by intraclass correlation. Intraclass correlations were computed separately for each period of day.

3. Results

The average values for age were 30.7 years (S.D. = 9.7) at the first test day and 34.0 years (S.D. = 9.8) at retesting. Across this time period BMI increased significantly from 24.1 (S.D. = 4.4) to 24.7 (S.D. = 4.8). Repeated measures ANOVA further showed a significant main effect of test/retest day on the average values of L_0 (19.7–17.5) and Z_0 (10.5–9.6) across the measurement days, but basal impedance corrected for the front electrode distance (L_0^2/Z_0^2) was comparable at test and retest days (3.9–4.2).

During the daytime recordings, we expected posture to be an important source of variance, specific to ambulatory recording. Conform this expectation, the three postures (sitting, standing, walking) showed a significant effect on HR, SV, CO, PEP and LVET. As expected, the HR increased significantly from sitting to standing to walking. In parallel, we found a significant linear decrease in PEP and LVET, from sitting to standing to walking. SV_0 was lower during standing than during either sitting or walking. For SV_B, the only significant post hoc contrast was an increase in SV from standing to walking. CO_0 and CO_b increased significantly from sitting to walking and from standing to walking. To avoid confounding by differences in posture and physical activity across measurement days, the ensuing analyses were performed on the averaged periods with sitting activities only. Across both days, an average of 36% of the total awake recording time was spent in sitting activities.

3.1. Test–retest differences across the four periods of the day

Complete data during sitting activities for all daily periods and during sleep on both days was available for 51 subjects. Main source of missing data was signal loss during one of the four periods, mostly at night (12 subjects). Six subjects did not perform any sitting activities during the morning or afternoon. Across both test days, daily periods had a significant main effect on most of the cardiovascular measures (Table 1) with

Table 1
Means and standard deviations for each of the cardiovascular variables, measured at four daily periods, on the test and retest days

Measures		Morning mean (S.D.) ($n = 51$)	Afternoon mean (S.D.) ($n = 51$)	Evening mean (S.D.) ($n = 51$)	Sleep mean (S.D.) ($n = 51$)	F_{period}	F_{retest}
$dZ/dt_{(min)}$ (Ω/s)	Test	−1.16 (.35)	−1.19 (.34)	−1.13 (.33)	−1.04 (.30)	**23.18**	2.65
	Retest	−1.13 (.47)	−1.12 (.45)	−1.08 (.39)	−.90 (.32)		
$dZ/dt_{(min)}$ from B (Ω/s)	Test	−1.03 (.45)	−1.00 (.42)	−.92 (.40)	−.93 (.37)	**12.52**	4.22
	Retest	−.96 (.50)	−.90 (.47)	−.85 (.43)	−.73 (.34)		
L_0^2/Z_0^2 (cm/Ω)	Test	3.47 (1.16)	3.66 (1.39)	3.79 (1.45)	3.81 (1.68)	**4.52**	2.39
	Retest	3.32 (1.63)	3.89 (3.19)	4.24 (3.05)	5.08 (4.70)		
SV_0 (ml)	Test	149.93 (44.63)	160.21 (47.41)	166.48 (52.26)	170.56 (49.77)	**16.72**	3.55
	Retest	131.21 (37.95)	140.92 (46.54)	158.06 (60.26)	161.86 (55.55)		
SV_B (ml)	Test	120.98 (47.84)	121.71 (47.64)	121.12 (46.44)	141.86 (56.70)	**12.72**	6.45
	Retest	101.09 (41.99)	102.34 (47.79)	114.07 (56.27)	120.00 (52.75)		
HR (bpm)	Test	85.42 (12.13)	86.94 (11.45)	82.01 (9.92)	64.20 (7.74)	**247.34**	2.91
	Retest	82.74 (8.81)	84.57 (9.59)	79.78 (11.30)	64.32 (7.49)		
CO_0 (l/min)	Test	12.78 (4.13)	13.94 (4.66)	13.66 (4.82)	11.03 (3.87)	**23.15**	5.78
	Retest	10.85 (3.45)	11.86 (4.03)	12.54 (5.08)	10.32 (3.56)		
CO_B (l/min)	Test	10.42 (4.71)	10.60 (4.52)	9.92 (4.08)	9.19 (4.25)	**7.98**	7.89
	Retest	8.42 (3.94)	8.66 (4.29)	9.09 (4.89)	7.64 (3.47)		
PEP (ms)	Test	98.53 (12.79)	96.79 (12.53)	98.40 (11.54)	109.67 (11.88)	**138.75**	.69
	Retest	98.54 (13.78)	97.40 (13.00)	98.86 (12.97)	112.03 (12.88)		
LVET (ms)	Test	278.65 (27.64)	274.54 (27.97)	285.92 (28.67)	327.57 (27.19)	**212.69**	2.78
	Retest	287.39 (30.05)	278.82 (27.53)	293.43 (31.93)	324.51 (26.32)		
$(dZ/dt_{(min)} \times LVET)_0$ (Ω)	Test	−.34 (.09)	−.34 (.09)	−.34 (.10)	−.36 (.09)	.16	1.20
	Retest	−.34 (.14)	−.33 (.12)	−.34 (.12)	−.31 (.10)		
$(dZ/dt_{(min)}\ LVET)_B$ (Ω)	Test	−.28 (.11)	−.27 (.11)	−.26 (.11)	−.30 (.12)	**7.09**	3.47
	Retest	−.27 (.14)	−.24 (.12)	−.25 (.12)	−.24 (.11)		

Significant main effects of period or retest ($p < .01$) are in bold.

the exception of $(dZ/dt_{(min)} \times LVET)_0$, a crucial component of SV_0 calculation.

Post hoc testing of the period main effect revealed that SV_0 was significantly higher during the evening and sleep than during the day. SV_B was significantly higher only during sleep. HR was at comparable levels during the morning and afternoon, but decreased mildly during the evening and strongly at night (on average 20 bpm lower than during daytime recording). CO_0 increased significant from morning to afternoon, stayed at a comparable level during the evening and significantly decreased during sleep. For CO_B the only significant post hoc contrast was between awake periods (morning, afternoon, evening) and sleep. PEP and LVET decreased significantly from morning to afternoon, increased again during the evening and further increased during the sleep.

A main effect of test/retest day was found only on the average 24 h values of CO_B, although SV_B also showed a trend in the same direction. The values were significantly lower on the retest day compared to the first test day. No interactive effects were found between measurement day and daily periods.

3.2. Temporal stability

Table 2 displays the intraclass correlations for the cardiovascular variables per periods of day.

Temporal stability of SV was moderate. Because stability of HR was good, intraclass correlations for CO were slightly higher than for SV. The largest source of instability in SV was the L_0/Z_0 ratio. $dZ/dt_{(min)}$ and LVET proved to be more stable, the LVET even more so than HR. From the impedance-derived measures, best performance was obtained for PEP, with temporal stability across the average period of 3 years and 4 months above .71 during the daytime and .66 at night.

In 17 subjects, retesting was on a different type of day than testing on the first day (i.e. a work day and a leisure day). To test whether this affected temporal stability, we repeated the analyses after excluding those 17 subjects. The temporal stability of PEP and LVET was largely unchanged. In contrast, an increase was found for the SV and CO measures in the morning and afternoon. In addition, differences of the averaged values across test–retest day were no longer significant.

In contrast to our expectation, SV and CO calculated from the B-point, which at times was ambiguous in visual scoring, led to better results than SV and CO calculated by using the dZ/dt baseline, particularly in the evening and during sleep. This suggests that the theoretically more sound measure of SV is also the most useful measure in repeated measurement designs. We proceeded with values based on the B-point only in two further analyses that looked at: (1) the effect of the duration of the test–retest interval on the temporal stability and (2) the use of relative changes in SV and CO rather than absolute levels.

Table 3 displays separate intraclass correlations for a shorter and a longer time interval. By effectively halving the sample size, significance of the correlations is compromised in

Table 3
Intra-class correlation for the cardiovascular variables across the four daily periods

Measures	Time between test and retest day (years)	Morning	Afternoon	Evening	Sleep
Number of subjects	2–3.2	32	33	34	28
	>3.2	29	29	31	25
SV_B (ml)	2–3.2	**.33**	.28	**.44**	**.52**
	>3.2	.25	**.48**	**.48**	**.35**
HR (bpm)	2–3.2	**.63**	**.61**	**.56**	**.73**
	>3.2	**.39**	**.39**	**.47**	**.59**
CO_B (l/min)	2–3.2	**.33**	.23	**.44**	**.50**
	>3.2	**.35**	**.41**	**.48**	**.39**
PEP (ms)	2–3.2	**.75**	**.76**	**.63**	**.65**
	>3.2	**.89**	**.91**	**.82**	**.68**
LVET (ms)	2–3.2	**.70**	**.83**	**.41**	**.73**
	>3.2	**.56**	**.71**	**.68**	**.62**

Separate correlations are given for short (2–3.2 years) and long (>3.2 years) test–retest intervals. Correlations that are significant at $p < .05$ are in bold.

Table 2
Intra-class correlation for the cardiovascular variables across the four daily periods

Measures	Periods of day			
	Morning (n = 61/45)	Afternoon (n = 62/46)	Evening (n = 65/48)	Sleep (n = 53/39)
$dZ/dt_{(min)}$ (Ω/s)	**.44/.57**	**.50/.62**	**.52/.59**	**.63/.72**
$dZ/dt_{(min)}$ from B (Ω/s)	**.37/.48**	**.45/.53**	**.58/.61**	**.58/.66**
L_0^2/Z_0^2 (cm/Ω)	**.56/.62**	**.36/.37**	**.37/.36**	.05/.14
SV_0 (ml)	**.33/.46**	**.37/.46**	**.41/.36**	.11/.24
SV_B (ml)	**.29/.42**	**.39/.46**	**.46/.42**	**.41/.46**
HR (bpm)	**.50/.57**	**.50/.54**	**.52/.53**	**.68/.76**
CO_0 (l/min)	**.29/.39**	**.31/.37**	**.38/.38**	.17/.26
CO_B (l/min)	**.34/.45**	**.33/.43**	**.46/.48**	**.43/.50**
PEP (ms)	**.80/.81**	**.81/.83**	**.71/.77**	**.66/.79**
LVET (ms)	**.62/.52**	**.76/.77**	**.55/.45**	**.70/.67**
$(dZ/dt_{(min)} \times LVET)_0$ (Ω)	**.46/.56**	**.53/.62**	**.42/.48**	**.54/.64**
$(dZ/dt_{(min)} \times LVET)_B$ (Ω)	**.32/.44**	**.44/.52**	**.50/.53**	**.54/.62**

Correlations are given for the entire sample and after excluding subjects with one measurement on a work day and one on a leisure day. The column before the slash (/) reports on the entire sample. The column after the slash (/) on subjects with either two work days (n = 45) or two leisure days (n = 3). Correlations that are significant at $p < .05$ are in bold.

Table 4
Intra-class correlation for the change scores for the cardiovascular variables across the three daytime periods

Measures	Periods of day		
	Morning (n = 50/36)	Afternoon (n = 51/37)	Evening (n = 53/39)
SV_B (ml)	.16/.19	**.40/.45**	**.27**/.24
HR (bpm)	**.39/.35**	.16/.28	**.32/.35**
CO_B (ml)	.12/.14	**.33/.45**	**.31/.31**
PEP (ms)	**.32/.49**	**.38/.54**	**.33/.50**
LVET (ms)	**.29/.28**	**.30/.43**	.03/.00

Correlations are given for the entire sample and after excluding subjects with one measurement on a work day and one on a leisure day. Correlations that are significant at $p < .05$ are in bold.

comparison to Table 2, but the point estimates of temporal stability appear very comparable for shorter and longer test intervals. We repeated these analyses with three intervals using 2.8 and 3.5 years intervals as cut-points. Again, no evidence was found for a reduction in temporal stability across longer test–retest intervals.

It has been suggested that absolute SV values obtained from impedance cardiography are less reliable than the within-person changes in SV. Therefore, we also computed percentual change scores for each individual on test and retest days, using the awake periods as the ''active'' state and sleep levels as the resting state. This approach was previously used by Vrijkotte et al. (2004) to show substantial short-term reliability for ambulatory PEP. At all three daytime periods temporal stability of the within-subject changes was comparable to the temporal stability of the absolute levels (see Table 4).

4. Discussion

The present study tested the temporal stability of ambulatory SV and CO measured with impedance cardiography across an average time span of 3 years and 4 months. The pattern of SV and CO values obtained across the 24 h ambulatory recording period generally confirm the validity of this method. During daytime, CO increased from sitting to standing to walking with a parallel decrease in PEP. Cardiac output fell mildly below its daytime levels due to the strong bradycardia at night. The net increase in PEP during sleep repeats a similar finding in previous studies (Burgess et al., 1997; Lechin et al., 2004; Trinder et al., 2001; van Eekelen et al., 2004). As expected, there was a significant increase in SV during supine sleep. Changes in posture affected both SV and CO during the daytime, which may reflect the complex balance of the effects of increased cardiac sympathetic activity paired to opposing effects from changes in preload and afterload. We reduced our analyses of temporal stability to these periods to avoid confounding by differences in posture and physical activity across the two measurement days.

For SV the most reliable and stable measure was SV_B, i.e. SV calculated with $dZ/dt_{(min)}$ relative to the B-point, as suggested by Doerr et al. (1981), Mohapatra (1981) and Debski et al. (1993). By taking the dZ/dt magnitude from the B-point instead of the zero baseline, the respiratory influences on dZ/dt waveform, confounding the absolute value of $dZ/dt_{(min)}$, are eliminated (Debski et al., 1993; Doerr et al., 1981; Mohapatra, 1981). In a previous comparison of interactive scoring by seven different raters, it was found in a few subjects that interrater agreement on the location of the B-point was very low (Riese et al., 2003). As an alternative point for $dZ/dt_{(min)}$, we scored $dZ/dt_{(min)}$ in relation to the $dZ/dt = 0$ baseline (Sherwood et al., 1991). The lower temporal stability of this alternative SV_0 measure, particularly at night, however, argued against its further use in ambulatory designs.

Intraclass correlations, computed separately for sleep and daytime waking recordings, were acceptable for SV_B (.29–.46) and CO_B (.33–.46) measured during sitting activities during the daytime. These findings did improve when we excluded subjects who were measured on a different type of day (leisure versus work) on the second occasion. The intraclass correlation for SV_B and CO_B generally increased, most strongly during the morning and afternoon. That retesting across a work and a leisure day yields lower stability than retesting across two similar days probably reflects the effects of emotional and mental stressors, which may be more frequent on a work day than on a leisure day.

Our findings are comparable to those found in laboratory studies across a similar time span, e.g. Matthews et al. (2002) reported correlations for composite task change scores of .36 for SV and .40 for CO across 3 years. Barnes et al. (2004) found in his ambulatory study of 35 adolescent African Americans, who were measured twice across a time span of 2 months, test–retest correlations for SV and CO ranging from .45 to .56 over 24 h. In a previous study, Barnes et al. (2002) found test–retest correlation across a time span of 4 months of .52 for daytime CO and .47 for nighttime measures of CO. The slightly higher test–retest correlations most likely reflect the shorter time span, i.e. 2–4 months in their study versus 2–4 years in the present study.

At time intervals longer than 2 years temporal stability seems to stabilize. We did not find a reduction in intraclass correlations for SV and CO as a function of the test–retest interval, although the power of these analyses, which were done in smaller subsamples, may have been too low to detect subtle differences. Inadequate power also precluded a test of whether stability differed across sexes. Since there were only 20 males with valid retest data (17 at night), we could not meaningfully examine sex differences. In view of the evidence of sex differences in many cardiovascular signals and the potential impact of fluctuations within the menstrual cycle on stability (Girdler et al., 1990, 1993), this issue remains to be addressed by future studies.

A main source of measurement error was introduced by the L_0/Z_0 ratio. The same fixed anatomical points were used for electrode placement on both of the measurement days but we did not attempt to completely standardize L_0 or Z_0 because we felt that temporal stability of SV should be robust to realistic variation in the exact electrode position. Only minor changes in front electrode distance and basal impedance were found. The unreliability of the L_0/Z_0 ratio, therefore, may reflect two

fundamental limitations inherent in our spot electrode approach. The first is that the original Kubicek SV equation applies to a band electrode configuration. Its application to signals recorded using spot electrodes, where Z_0 values are typically much lower and electrode-skin-resistance is more critical, may lead to wider distribution of SV values (Sherwood et al., 1990). A second, related limitation is that we positioned the upper recording electrode at the height of the clavicle. Raaijmakers et al. (1998) showed that small shifts in the position of the neck electrode resulted in large changes in impedance and SV (127–82 ml) when using the Kubicek equation. Because placement at the neck–thorax transition will cause inhomogeneities in the current density and potential distribution, they strongly recommend placement of the upper recording electrodes at least 6 cm above the clavicula (Raaijmakers et al., 1998). Our choice to place spot electrodes relatively low in the neck was completely given in by practical reasons. To be useful in epidemiologically scaled studies, it is essential that normal subjects, not just highly motivated medical students, can tolerate these measurements for prolonged periods. Neither band electrodes nor highly placed visible spot electrodes on the neck are conducive to these goals. A recent alternative to spot electrodes uses a hybrid spot and band configuration with Mylar bands around the base of the neck as recording electrodes but a single spot electrode behind the ear and two on the abdomen, as current electrodes (Sherwood et al., 1998). The one group to address temporal stability using this alternative strategy found results encouragingly comparable to ours (Barnes et al., 2002, 2004).

It has been suggested that part of the measurement error in impedance-based SV, introduced, e.g. by between subject differences in thorax shape, intrathoracal tissue composition, heart and aorta dimensions and structure and blood resistivity, may be negated by using relative within subject changes in SV rather than absolute SV values (Sherwood et al., 1990; Willemsen et al., 1996). To obtain change scores we used a strategy employed previously for PEP and HR (Vrijkotte et al., 2004) computing percentual change scores for each individual, using the awake periods as the ‘‘active’’ state and sleep levels as the resting state. Temporal stability of these change scores was lower compared to those of the corresponding absolute levels. A more focussed computation of reactivity scores may be required, for instance, by looking at the response to specific work-related stressors. This, however, would require repeated measurement in more homogenous populations that are subjected to comparable stressors at the two measurement days.

Stroke volume is only one of the targets of ambulatory impedance cardiography. This method also yields the systolic time intervals LVET and PEP, which may be used to index beta-adrenergic drive to the heart (Rasmussen et al., 1975; Weissler et al., 1968). High test–retest reliability across a few days was reported before by Vrijkotte et al. (2004) for ambulatory PEP. In the present study, intraclass correlations for the PEP across a much longer period were very good (.66–.83). This is as good as the stability of PEP obtained under standardized laboratory conditions. Test–retest correlations from .45 to .88 were found for baseline and stress-task levels of PEP across retest intervals ranging from 28 days to 3 years (Burleson et al., 2003; Matthews et al., 2002; Willemsen et al., 1998).

Ambulatory recording of hemodynamic regulation can further our understanding of how repeated or chronic cardiovascular activation in response to naturalistic events can contribute to cardiovascular disease processes. Although the temporal stability across a time span of more than 3 years was only moderate, it must be kept in mind that tracking coefficients for BP itself are also not much higher than .5 (Palti et al., 1988; Hottenga et al., unpublished data; Woelk, 1994). With this in mind, 24 h ambulatory SV and CO measured by impedance cardiography can be a meaningful addition to the research on blood pressure regulation.

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