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Cardiovascular parameters: sensitivity to detect autonomic dysfunction and influence of age and sex in normal subjects

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In 137 healthy volunteers between 18 and 85 years of age, blood pressure (BP) and heart rate (HR) were measured continuously with the Finapres device during active change of posture (ACP), i.e. standing upright, passive tilt (PT, i.e. head-up tilt), Valsalva manoeuvre (VM), deep breathing (DB), isometric muscle exercise (IME) and a mental arithmetic task (MA). Mean HR activation was attenuated with increasing age in all manoeuvres, but was unrelated to sex. In non-orthostatic challenge procedures like MA and IME mean BP increases were independent of age and sex, despite lower increases in HR in the elderly. This points to a preserved sympathetic efferent activity. Following a forced fall in BP during ACP, PT and VM, the initial responses and maintenance values of BP showed a significant age-related decrease. This finding was strongly related to lower BP values in males compared with females, which became more pronounced with increasing age. Further studies to investigate age-related changes in the activation of the various components of the cardiovascular regulation need to consider the mode of activation of the autonomic nervous system and sex as factors of influence. Normal ranges, and also some new points in time not previously measurable, were calculated for all standard autonomic tests based on the continuous measurement of BP and HR. The minimum length of time necessary to assess the cardiovascular responses during ACP and PT was found to be 60 s. The upper time limits for reaching maximum activation during IME and MA were 3.5 min and 1 min, respectively. Age had a relevant influence on the lower limits of normal of all HR parameters and of some BP measurements during PT, ACP and VM. Sex was found to have no relevant impact on normal ranges. Over 65 years of age the normal values for HR activation during VM and DB hardly exceeded baseline values. The possibility of increasing the sensitivity of detection of autonomic dysfunction by measuring BP continuously must be approached with caution, as sufficient sensitivity was only reached at the lower limits of normal during late phase II of the VM. The initial increase of HR after ACP and the BP values after 60 s standing time proved to be the parameters with the best sensitivity for detecting an affection of the regulation of HR and BP over the whole range of age.

Keywords: autonomic testing; normal ranges; sex

Introduction

Change of posture,[1] Valsalva manoeuvre[2] and deep breathing[3] were initially seen as bedside tests for the neuronal regulation of heart rate (HR) by the autonomic nervous system. Today it is generally accepted that reliable results can be obtained only in the defined setting of a laboratory specialized in autonomic testing. Even so, data on the influence of age and sex on the cardiovascular regulation are inconsistent. While the attenuation of HR activation with increasing age, independent of sex,[4–8] appears to be a constant finding, progress regarding the understanding of age-related changes of blood pressure (BP) responses during autonomic function tests has been hampered by the methodological limitation of sphygmomanometric measurement. The introduction of the Finapres blood pressure monitor (Ohmeda 2300, Ohmeda, Hatfield, UK) allowed the non-invasive continuous recording of BP and HR in a greater population with sufficient accuracy.[9–11] The potential of this method to improve the sensitivity of standard autonomic function tests has not so far been investigated systematically. The aim of this study is to evaluate the benefit of the continuous measurement of BP and HR in a population of sufficient size with particular emphasis on the influence of age and sex and their impact on normative data.

Methods

Protocol and devices employed

A total of 137 healthy volunteers were investigated. All of them gave written informed consent before their participation. Testing took place between 9.00 and 11.00 a.m. for 88 participants, and between 2.00 and 6.00 p.m. for the remaining 49. After emptying the bladder the volunteers lay comfortably in a noise-isolated, temperature-controlled room, held constant at 23°C. Non-invasive continuous recording of HR in beats per minute (beats/min) and systolic (SBP) and diastolic blood pressure (DBP) in mmHg was obtained with a Finapres device (Ohmeda 2300) from the right middle finger, allowing an accurate measurement with a maximum deviation of ±5 mmHg compared with intra-arterial measurement[9,10] and also being representative for aortic and brachial BP during rest and exercise.[11] The parameters were printed continuously with an 8-channel thermoprinter (model Schwarzer-Pickert UD210). Stable baseline values for HR and BP were obtained and controlled by sphygmomanometric measurement. After a resting period in the supine position of two minutes, testing was started. The following manoeuvres were performed in sequence: passive tilt (PT), i.e. head-up tilt up to 70° within 25 s with an electrically driven tilt table; active change of posture (ACP) into a vertical position, i.e. standing upright, with both manoeuvres maintained for 120 s; deep breathing (DB) with a rate of 5 to 6 cycles per minute following verbal commands for inspiration and expiration; Valsalva manoeuvre (VM) maintained for 15 s with 50% of the individually maximum expiratory pressure; isometric muscle exercise (IME) of the left hand with approx. 50% of maximum voluntary handgrip pressure maintained for 120 s; and a mental arithmetic task (MA). The expiratory pressure in the VM and the handgrip pressure during IME were measured and controlled with a modified BP gauge. In between each test a return of the cardiovascular parameters to baseline was waited for. Regular checks of the calibration of the Finapres device were performed to ensure accurate measurement; if there had been technical malperformance, the manoeuvres were repeated. After completing all tests the volunteers filled in a questionnaire to document their latest calorie intake, average physical activity per week and state of health.

Each phase of the manoeuvres performed was assessed. After active and passive change of posture the initial fall and increase and values after 60 s of the cardiovascular parameters were measured. All phases of the VM[12] were analysed separately and the Valsalva ratio calculated from the maximum increase in HR and the subsequent minimum. The variation of BP and HR during DB was derived from the sums of the maximum and minimum values, respectively, during each breathing cycle divided by the number of cycles assessed. Maximum values of BP and HR during IME and MA were measured.

Population

A total of 137 healthy volunteers, 71 males and 66 females, between 18.5 and 85.02 years of age (mean 46.68 ± 17.15) participated in this study. The mean age of males and females showed no difference (46.34 ± 16.50 and 47.06 ± 17.94, respectively). They were recruited from an advertisement in the local newspaper and included no hospital staff, who had been shown to perform differently in comparison to a randomly selected population.[13] Their state of health was documented with a physical examination and a questionnaire. The information given by the participants was confirmed by their general practitioners. None of them was taking any medication or was diagnosed as suffering from a chronic disease. While the age groups between 18–40 and 40–60 years included 52 persons each, the group of volunteers between 60 and 85 years of age had 33 participants.

Statistical analysis

A manual analysis of the continuous print-out of the polygraph was performed. The Statistical Package for Social Sciences (SPSS/PC+) version 4.0 and SAS were employed for statistical analysis. The descriptive statistical parameters were calculated. The lower limits of normal were calculated with a probability of 95%. Either a linear adaptation or a logarithmic transformation was performed to account for the influence of age. The latter was found necessary if the residuals after the linear adaptation showed a skewed distribution. If a significant influence of sex was found, separate normative data were calculated.

Results

The results of the cardiovascular parameters obtained in the morning and afternoon showed no significant differences. In 68 participants the calories of the last meal before testing were estimated (1360.41 ± 814.69 kcal, which had been consumed 1.9 ± 1.01 h previously). No correlation was found between the amount of calories, time of consumption, average physical activity and the cardiovascular responses. Consequently all results were pooled. The influence of sex was considered separately (see below).

Resting values

The resting values are shown in Table 1. The mean values of SBP, DBP and HR during resting conditions did

	ALL		AGE GROUPS		(years)			
		n=136	18 - 40	n= 51	40 - 60	n= 52	> 60	n=33
parameter	mean	SD	mean	SD	mean	SD	mean	SD
SBP	104,06	15,54	104,16	12,41	105,02	17,60	102,42	16,74
DBP	58,02	10,75	57,10	9,64	60,02	11,79	56,31	10,49
HR	69,78	11,25	69,54	12,43	69,39	9,41	70,76	12,26
HR variation	11,34	7,22	13,89	6,77	10,86	8,42	8,17	3,81

Table 1. Means and standard deviations (SD) of systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) during resting conditions in a supine position in 136 healthy volunteers overall and in defined age groups to demonstrate the influence of age

not show statistically significant correlations with age or sex. The baseline values of SBP, DBP and HR of the resting periods before each manoeuvre correlated statistically significantly with all absolute values during each challenge procedure ($p < 0.001$). The differences to baseline during the manoeuvres were calculated. Only the differences to baseline of the initial falls of SBP and DBP in PT and the drop of SBP during phase II of the VM correlated significantly with their baseline values ($p < 0.001$). All other changes of the cardiovascular parameters during the manoeuvres showed no statistically significant relation to baseline values.

Physiological course of blood pressure and heart rate during standard autonomic tests

The overall mean values of the differences to baseline and their standard deviations of the cardiovascular parameters are shown in Table 2.

Passive tilt and active change of posture. The mean initial fall of BP after change of posture was greater following ACP. In PT, mean changes of less than 3 mmHg were recorded. The subsequent rise was similar in both manoeuvres when compared with baseline, with approx. 17 mmHg for SBP and DBP. The compensatory increase of the HR was more pronounced in ACP compared with PT. Sixty seconds after change of posture, mean BP values showed greater increases in ACP than in PT, while the mean HR accelerations were similar. The initial maximum fall of BP in ACP was reached within a mean of 7.19 ± 1.85 s, the compensatory maximum increase after 18.87 ± 8.94 s.

Valsalva manoeuvre. The mean expiratory pressure was 41 ± 11.61 mmHg (range 15–80 mmHg), representing 50% of the individually possible maximum expiratory pressure. The initial increase of SBP and DBP in phase I was followed by a mean maximum drop of SBP of –25 ± 15.06 mmHg and DBP of –2 ± 10.32 mmHg during phase II (see Figure 1). The end of phase II was characterized by a small amplitude of

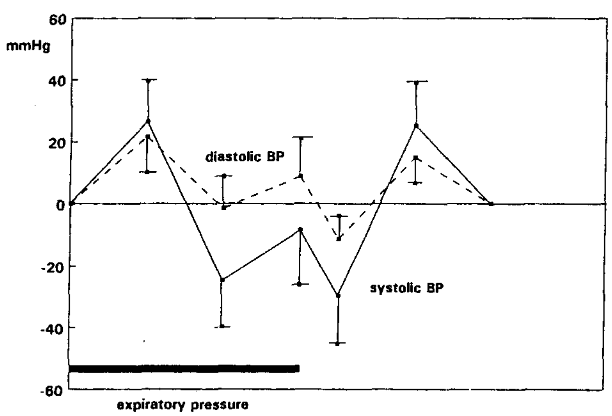

Figure 1. Mean values and standard deviations of blood pressure (BP) during the Valsalva manoeuvre are shown in an idealized curve illustrating the physiological course of the BP response to a mean of 41 mmHg (50% of the maximum individually possible) expiratory pressure over 15 s.

the BP with a mean increase of DBP of 9 ± 12.28 mmHg above baseline and a still lowered SBP of –3 ± 17.66 mmHg. After ending the expiratory pressur,e the BP dropped to the lowest values of the whole manoeuvre in phase III. In phase IV BP reached similar increases as in phase I. The latency to reach the maximum compensatory BP increase during phase IV from the trough of phase III was 4.65 ± 1.24 s.

Deep breathing. The mean duration of one inspiration or expiration was 5.8 ± 1.50 s, which equalled a mean rate of 5.17 complete respiration cycles per minute. The mean variation of HR was 16 ± 7.67 beats/min. Also SBP and DBP showed sinoid changes during the breathing cycles.

Isometric muscle exercise (IME). The mean handgrip pressure was 51 ± 11.63% of the maximum possible pressure tested before the manoeuvre for each individual. The maximum increases of HR and BP were reached after a mean of 91.31 ± 48.40 s and 94.20 ± 51.36 s, respectively.

Mental arithmetic (MA). The mean increases in BP were about 10 mmHg lower compared with IME. The HR reached a similar increment with 20 ± 10.48 beats/min. The mean latency to reach the peak HR and BP was about 20 s.

Influence of age

As shown in Table 1, the resting variation of HR, calculated as the difference between the maximum and the minimum HR during two minutes of supine resting, decreased significantly with age ($p < 0.001$) from about 15 beats up to the age of 30 to about 8 beats over the age of 60. In parallel the variation of SBP, assessed by the standard deviation, increased significantly ($p < 0.001$). The variation of DBP remained unchanged.

The results of the influence of age on the cardiovascular parameters during the manoeuvres are shown as their differences to baseline in Table 3. The total population was arbitrarily divided into three groups covering 20 to 25 years each to demonstrate the changes with age. Mean values, standard deviations of the cardiovascular parameters and significant statistical correlations with age are given.

Regarding methodological aspects, the expiratory pressure in the VM and the handgrip pressure during IME, which were defined as 50% of the maximum individual pressure, decreased significantly with increasing age ($p < 0.01$).

HR activation was significantly negatively correlated with age ($p < 0.001$) in all manoeuvres with the exception of the value 60 s after ACP.

Age-related increasing falls and lower activations of BP were seen during PT, ACP and phase II of the VM. The most pronounced influence of age on BP was found in ACP with an approx. 50% lower initial

Table 2. The mean values of the differences to baseline and their standard deviations of the cardiovascular parameters during the autonomic function tests. The points in time during each manoeuvre follow the physiological course of the cardiovascular responses. Relevant influences of age and sex on the normal ranges and their mode of calculation are indicated (see text on methods and statistics). The population of 137 healthy volunteers was arbitrarily divided into three age groups to illustrate the age-related changes of some of the parameters, if they are not shown in figures

	MEAN VALUES		LOWER LIMITS OF NORMAL (n = 137)					
manoeuvre			influence of	influence of	mode of	age	age	age
parameter	mean	SD	age	sex	calculation	18 - 40	40 - 60	60 - 83
PT								
SBP fall	-2	14,22	yes	no	linear	-24	-26	-30
DBP fall	3	11,35	yes	no	linear	-14	-17	-22
SBP rise	17	10,85	yes	male/female	linear	0 / 0	-3 / 0	-6 / 0
DBP rise	17	8,70	yes	male/female	linear	6 / 6	1 / 3	-5 / 1
SBP 60sec	10	10,79	no	no	linear	-8	-8	-8
DBP 60sec	14	7,46	no	no	logarithmic	-4	-4	-4
HR rise	17	8,83	yes	no	linear	5	0	-3
HR 60sec	11	8,19	no	no	logarithmic	0	0	0
ACP								
SBP fall	-19	16,06	no	no	linear	-46	-46	-46
DBP fall	-6	8,29	no	no	linear	-20	-20	-20
SBP rise	17	13,51	yes	male/female	linear	-6 / 1	-10 / -3	-16 / -8
DBP rise	19	7,60	yes	male/female	linear	8 / 10	4 / 8	0 / 5
SBP 60sec	17	11,51	yes	no	linear	**see figure 3**		
DBP 60sec	20	8,13	yes	no	logarithmic	**see figure 3**		
HR rise	29	9,99	yes	no	logarithmic	**see figure 3**		
HR 60sec	14	9,27	no	no	logarithmic	0	0	0
VM								
Pressure	41	11,61						
SBP I	27	13,05	yes	no	linear	6	1	-4
DBP I	22	11,63	yes	no	logarithmic	5	3	0
SBP II	-25	15,06	yes	no	linear	-46	-53	-60
DBP II	-2	10,32	no	no	linear	-19	-19	-19
SBP IIend	-3	17,66	no	no	logarithmic	-5	-5	-5
DBP IIend	9	12,28	no	no	logarithmic	1	1	1
SBP III	-30	15,70	yes	no	linear	-54	-59	-65
DBP III	-11	7,31	no	no	linear	-25	-25	-25
SBP IV	25	13,75	yes	no	linear	**see figure 4**		
DBP IV	15	8,36	yes	no	logarithmic	**see figure 4**		
HR rise	29	12,71	yes	no	logarithmic	**see figure 5**		
HR fall	-10	6,75	yes	no	logarithmic	-23	-20	-19
HR Ratio	2	0,35	yes	no	logarithmic	**see figure 5**		
DB								
sec /cycle	6	1,50						
SBP var.	15	6,04	no	no	logarithmic	6	6	6
DBP var.	9	4,84	no	no	logarithmic	1	1	1
HR var.	16	7,67	yes	no	linear	**see figure 6**		
IME								
Pressure	18	6,33						
SBP rise	29	12,73	no	no	linear	9	9	9
DBP rise	20	9,26	yes	no	linear	9	5	< 3
HR rise	21	10,41	yes	no	logarithmic	**see figure 7**		
MA								
SBP rise	19	10,23	no	no	linear	0	0	0
DBP rise	12	5,57	no	no	linear	0	0	0
HR rise	20	10,48	yes	no	logarithmic	9	6	< 3

SD, standard deviation; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (beats/min); PT, passive tilt; ACP, active change of posture; VM, Valsalva manoeuvre; DB, deep breathing; IME, isometric muscle exercise; MA, mental arithmetic task. Pressure values represent the expiratory and handgrip pressure, respectively, in mmHg. var., variation.

Table 3. The mean values of the differences to baseline and their standard deviations of blood pressure and heart rate during the autonomic function tests. The points in time during each manoeuvre follow the physiological course of the cardiovascular responses. The population of 137 healthy volunteers was arbitrarily divided into three age groups to illustrate the age-related changes of some of the parameters. The *p* values of the statistically significant correlations with age are given

	18-40	n=52	40-60	n=52	>60	n=33	relation to
	mean	SD	mean	SD	mean	SD	age
PT							
SBP fall	1,64	14,02	-1,98	15,23	-6,58	11,61	
DBP fall	6,77	10,67	2,30	11,19	-2,30	10,63	0,01
SBP rise	18,72	10,42	18,03	10,55	12,58	11,12	
DBP rise	20,57	8,38	17,26	7,95	12,51	8,30	0,001
SBP 60sec	10,02	9,76	9,56	11,50	8,93	11,49	
DBP 60sec	16,37	6,91	13,06	7,66	12,75	7,41	
HR rise	20,98	8,99	15,82	8,23	11,83	6,31	0,001
HR 60sec	14,90	9,48	9,03	6,77	9,93	6,08	0,001
ACP							
SBP fall	-18,56	14,48	-20,78	18,88	-18,17	13,94	
DBP fall	-6,65	7,95	-6,42	9,50	-3,36	6,31	
SBP rise	20,17	12,93	17,98	13,21	11,11	13,31	0,01
DBP rise	21,13	7,90	18,69	7,80	15,51	5,42	0,001
SBP 60sec	19,11	10,47	18,14	11,19	10,00	11,38	0,01
DBP 60sec	23,30	8,91	19,70	7,59	15,78	5,04	0,001
HR rise	35,20	9,83	26,52	7,16	21,21	7,28	0,01
HR 60sec	15,73	10,49	11,21	7,46	13,40	9,03	
VM							
Pressure	43,71	10,56	41,58	12,38	35,66	10,44	0,01
SBP I	29,15	13,91	27,54	13,63	18,57	10,00	0,01
DBP I	22,87	12,18	23,14	12,08	16,31	9,41	0,01
SBP II	-14,03	19,21	-19,19	19,37	-29,20	10,40	0,001
DBP II	-2,25	11,72	-0,34	11,19	-2,28	5,15	
SBP IIend	-3,82	17,63	-5,04	17,57	-21,32	10,63	0,001
DBP IIend	6,73	11,48	12,92	13,87	5,01	8,10	
SBP III	-24,58	17,07	-25,12	19,07	-36,28	12,12	0,001
DBP III	-9,12	9,71	-5,90	11,40	-9,04	6,80	
SBP IV	22,20	14,89	28,28	14,90	19,22	13,66	
DBP IV	15,46	7,98	16,12	9,82	10,89	6,65	
HR rise	35,58	12,53	27,69	10,58	19,03	9,47	0,001
HR fall	-10,32	9,02	-9,36	6,08	-6,77	5,31	
HR Ratio	1,85	0,35	1,68	0,31	1,45	0,24	0,001
DB							
SBP var.	12,99	4,98	16,11	6,48	15,46	6,34	
DBP var.	8,81	5,22	10,27	5,64	7,57	3,43	
HR var.	22,07	7,10	13,72	5,10	10,07	4,80	0,001
IME							
Pressure	20,10	7,61	18,09	4,61	15,65	5,50	0,001
SBP rise	27,67	13,18	30,49	12,69	29,92	12,12	
DBP rise	23,48	9,97	19,22	8,40	16,10	7,35	0,001
HR rise	27,56	11,01	19,05	7,47	13,87	6,61	0,001
MA							
SBP rise	16,34	12,19	19,31	10,48	19,59	11,28	
DBP rise	11,40	9,48	12,23	6,32	11,40	5,32	
HR rise	23,90	11,97	20,85	8,64	12,48	5,77	0,001

SD, standard deviation; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (beats/min); PT, passive tilt; ACP, active change of posture; VM, Valsalva manoeuvre; DB, deep breathing; IME, isometric muscle exercise; MA, mental arithmetic task. Pressure values represent the expiratory and handgrip pressure, respectively, in mmHg. var., variation.

Table 4. The mean values of the differences to baseline and their standard deviations of blood pressure and heart rate during the autonomic function tests are shown in relation to sex. The points in time during each manoeuvre follow the physiological course of the cardiovascular responses. Significant differences of the Mann–Whitney *U* test (M-W-U-test) between the two groups are indicated with their level of significance and the relation of the values between males and females is given. The M-W-U-test was repeated within the age groups younger and older than 50 years to demonstrate the additional influence of age on the differences between males and females

	Males	n=71	Females	n=66	M-W-U-test	relation	M-W-U-test	
	mean	SD	mean	SD	gender	male/female	< 50	> 50
PT								
SBP fall	-1,71	10,93	-1,76	17,08				
DBP fall	2,51	9,38	3,23	13,16				
SBP rise	15,17	10,06	18,92	11,38				0,05
DBP rise	15,36	8,02	19,54	8,93	0,01	m < f		0,001
SBP 60sec	8,99	10,41	10,21	11,23				
DBP 60sec	13,17	7,29	15,38	7,52	0,05	m < f		0,01
HR rise	16,08	8,66	17,63	9,01				
HR 60sec	11,78	8,07	11,16	8,37				
ACP								
SBP fall	-20,86	15,18	-17,58	16,94				
DBP fall	-6,92	7,50	-4,56	8,97				0,05
SBP rise	14,17	13,31	20,31	13,08	0,01	m < f	0,05	0,05
DBP rise	16,52	6,92	21,33	7,56	0,001	m < f	0,05	0,001
SBP 60sec	14,04	9,78	19,07	12,63	0,05	m < f		
DBP 60sec	18,13	6,59	22,23	9,05	0,01	m < f		0,01
HR rise	28,03	10,07	29,11	9,96				
HR 60sec	12,87	9,85	14,21	8,66				
VM								
Pressure	44,83	11,03	37,20	10,96	0,0001	m > f	0,01	0,01
SBP I	27,54	12,74	24,51	14,32				
DBP I	22,59	11,89	20,27	11,71				
SBP II	-17,05	17,51	-22,25	19,17				
DBP II	-1,48	10,07	-1,52	10,66				
SBP IIend	-7,76	16,90	-8,94	18,56				
DBP IIend	7,34	10,90	10,37	13,49				
SBP III	-28,05	18,02	-26,86	17,08				
DBP III	-10,13	9,32	-5,37	10,03	0,01	m < f		0,001
SBP IV	24,48	12,38	23,34	17,41				
DBP IV	13,84	6,91	15,56	10,25				
HR rise	28,66	11,85	28,72	13,64				
HR fall	-10,09	6,28	-8,14	8,09				
HR Ratio	1,72	0,33	1,66	0,36				
DB								
SBP var.	14,91	6,49	14,63	5,61				
DBP var.	9,52	5,50	8,64	4,69				
HR var.	16,43	7,23	15,62	8,12				
IME								
Pressure	21,12	7,01	15,83	4,24	0,0001	m > f	0,0001	0,05
SBP rise	32,64	13,71	25,98	10,86	0,01	m > f		
DBP rise	22,64	9,43	18,15	8,67	0,01	m > f		
HR rise	22,65	10,68	20,06	10,07				
MA								
SBP rise	17,37	10,69	19,15	11,97				
DBP rise	11,61	5,09	11,85	9,26				
HR rise	20,79	10,86	19,57	10,12				

SD, standard deviation; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (beats/min); PT, passive tilt; ACP, active change of posture; VM, Valsalva manoeuvre; DB, deep breathing; IME, isometric muscle exercise; MA, mental arithmetic task. Pressure values represent the expiratory and handgrip pressure, respectively, in mmHg. var., variation.

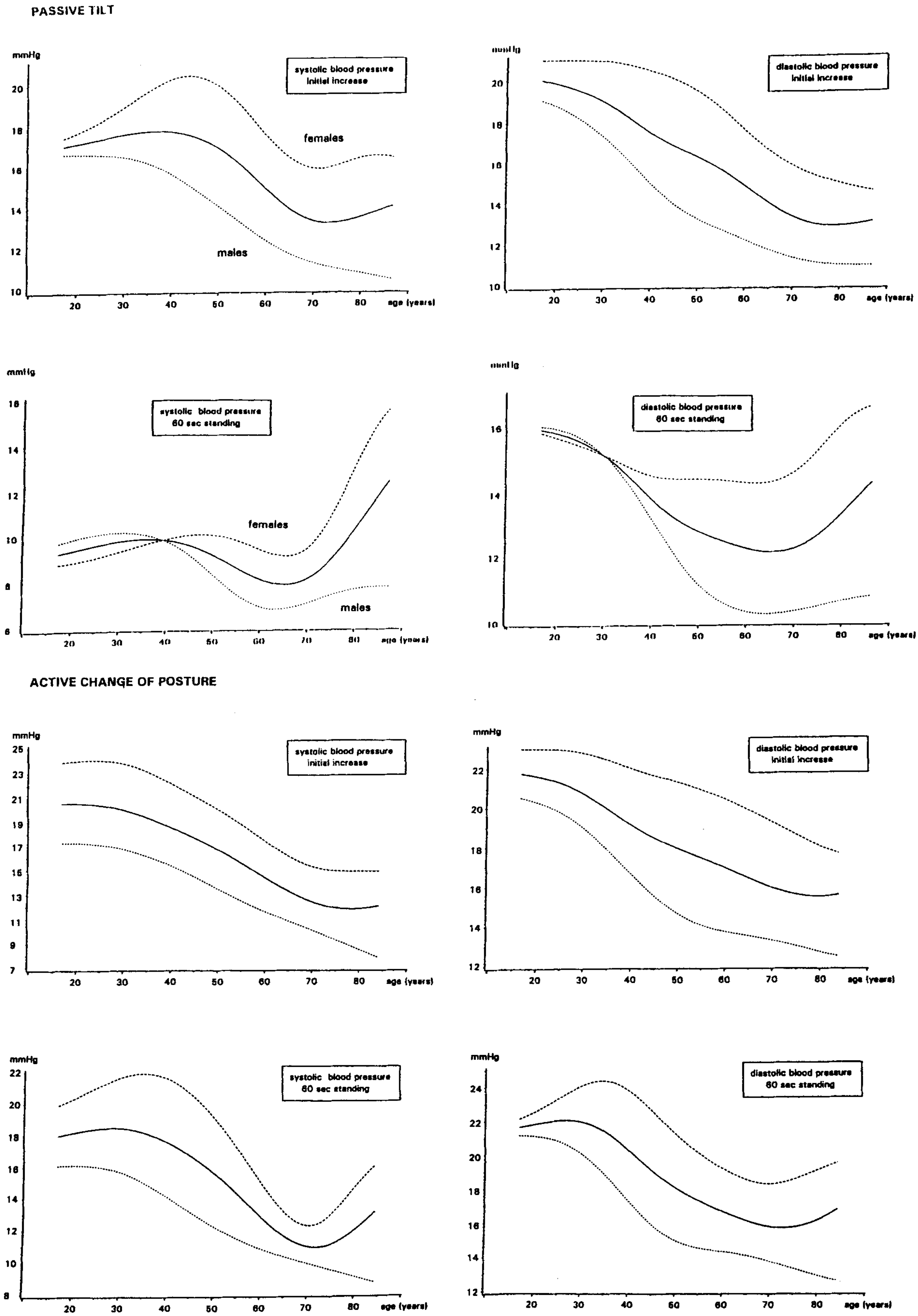

Figure 2. Mean values of the differences to baseline of systolic and diastolic blood pressure are shown for the whole population (thick line) and for males (thin dotted line) and females (thick dotted line). They were measured with the Finapres device at the initial increase in blood pressure after active and passive change of posture and after 60 s standing and in a 70 vertical position, respectively. The statistical model employed considered for the calculation of each value also five mean values before and behind in a weighted manner to smooth curves

increase and value after 60 s for SBP in the oldest compared with the youngest age group. DBP values decreased by about 30%. In PT only the DBP was progressively lowered with age during the initial phase, while values after 60 s were not significantly affected by age. During phase II of the VM the maximum drop of SBP and its value at the end of the expiratory pressure phase decreased significantly with age despite the smaller pressures employed.

Influence of sex
The mean age and the resting values of BP and HR showed no significant differences between males and females. The mean values, standard deviations and the results of the Mann-Whitney-U-test are shown in Table 4. Sex had a significant influence only on changes in BP during PT, ACP and IME. In the latter procedure the higher handgrip pressure of the male participants caused a greater activation of BP. In the orthostatic manoeuvres males showed lower BP values compared with females, being more pronounced during ACP. With increasing age this difference became even more evident (Figure 2).

Normal values
The lower limits of normal of the BP and HR were calculated with a 95% probability employing either a linear or a logarithmic regression model. The statistical model employed and the potential influence of sex and age on normal values are shown in Table 2. If the parameter was either not affected by age or of minor clinical importance, the lower limits of normal are given for each of the arbitrarily defined age groups; otherwise figures illustrate the results. Although age and sex showed a statistically significant impact on some cardiovascular parameters, these correlations did not necessarily have an influence of practical relevance on normal ranges. If the differences between the lower limits of normal in the early third and the ninth decade of life were smaller than 5 mmHg or 5 beats/min, they were considered as having no relevance for the normal values.

In PT, normal values of BP and HR after 60 s were independent of age and sex. The lower limits for the 60 s values of BP during ACP were age related, as was the initial increase in HR (see Figure 3). The ranges of the compensatory increases in BP after the initial fall were found to be relevantly affected by sex and age in these manoeuvres. In PT and ACP the upper limits of normal for the latencies describing the adjustments of cardiovascular parameters were the same for the BP with 38 s, while the maximum increase of HR had to be reached faster in ACP than in PT (34 s and 50 s, respectively).

The minimum normal increases in BP during phase I and IV (see Figure 4) of the VM hardly exceeded baseline values. While the maximum fall of BP within normal range during phase II was considerable, BP at the end of phase II had to return close to baseline to remain within normal limits. The upper limit of normal for reaching the maximum increase in BP after the trough in phase III was found to be 7 s. When the Valsalva ratio and the maximum increase in HR were considered separately, a higher sensitivity of the lower limits of normal were found in the elderly for the latter parameter (see Figure 5). Due to a higher variability the maximum Valsalva ratio or increase in HR out of three VM did not increase the normal values compared with the mean of the three manoeuvres.

The effect of age on the normal values of the HR variation in DB is shown in Figure 6. A minimum normal variation of SBP of 6 mmHg emerged, which was not influenced by age or sex. In IME the lower limit of

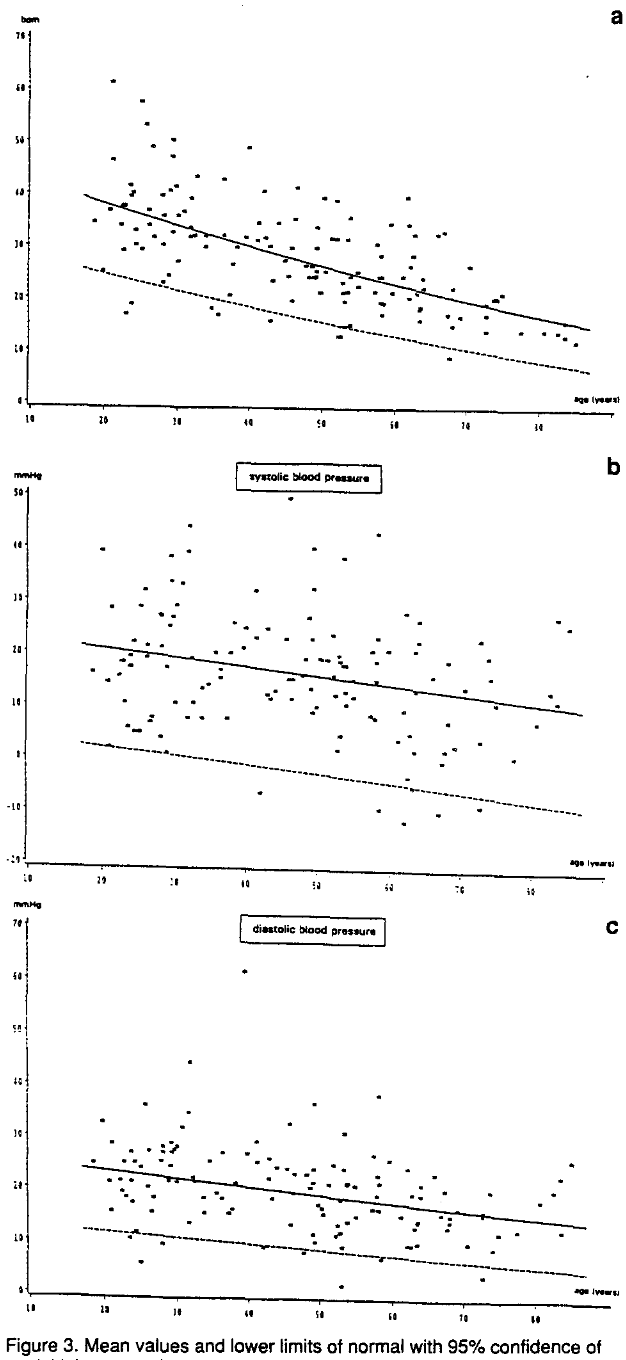

Figure 3. Mean values and lower limits of normal with 95% confidence of the initial increase in heart rate and systolic and diastolic blood pressure 60 s after active change of posture are shown in relation to age

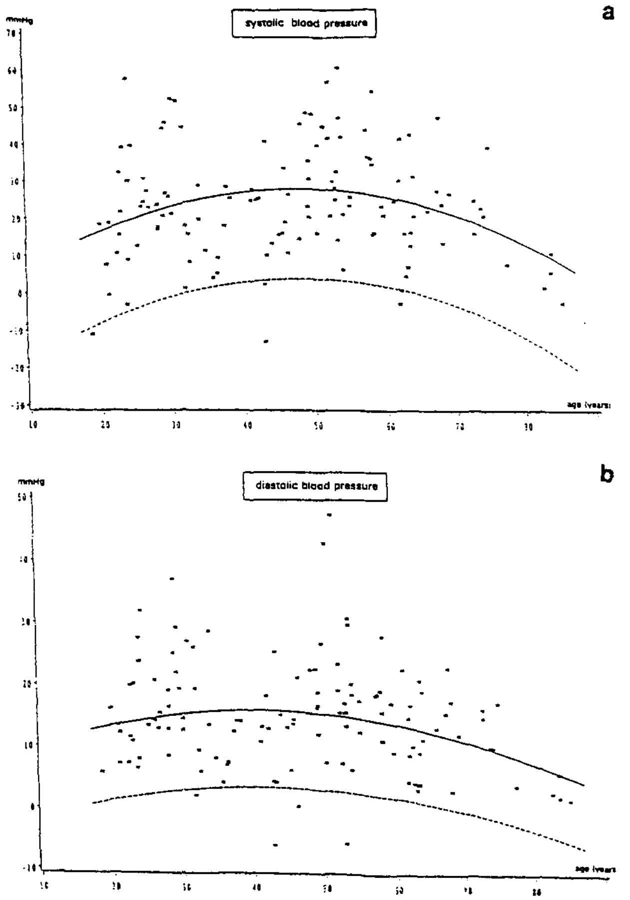

Figure 4. Mean values and lower limits of normal with 95% confidence of systolic and diastolic blood pressure in mmHg during phase IV of the Valsalva manoeuvre are shown in relation to age

normal for SBP was +9 mmHg independent of age and sex. The normal values for DBP and HR decreased with age in parallel with the decreasing handgrip pressure (see Figure 7). In MA the normal values of BP did not exceed baseline. The minimum normal increases of HR were slightly lower in the younger population but similar in the elderly compared with IME.

Discussion

Influence of age and sex on cardiovascular regulation

The resting values of HR and BP in healthy subjects showed no significant influence of age. In line with previous observations[6,7] the resting HR variation, calculated as the difference between maximum and minimum values, decreased with age. It was suggested that a lowered vagal tone in elderly subjects may contribute to this development.[14] In parallel the resting variation of the SBP, represented by the standard deviation, increased. This might be related to the increase in the resting muscle sympathetic nerve activity (MSNA) with age,[15,16] which shows a considerable inter-individual variability.[17]

There is general agreement in the recently published literature, that HR activation and variation during the standard tests of the ANS decline with increasing age in a linear relationship (for review see ref. 18). Our results support these data. HR activation decreased with age in all manoeuvres, with the exception of the HR values 60 s after ACP and PT. One potential reason might be an age-related decreasing β-adrenergic sensitivity of the heart.[19] It should be mentioned with regard to the comparison of results from various laboratories, that in the VM and IME

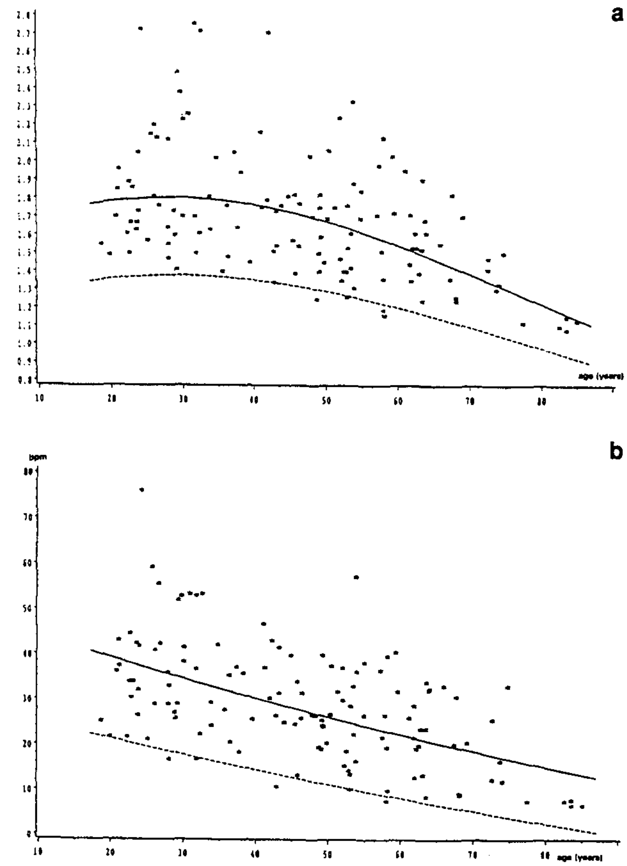

Figure 5. Mean values and lower limits of normal with 95% confidence of the Valsalva ratio (upper part) and the maximum increase in HR (lower part) during the Valsalva manoeuvre are shown in relation to age. The manoeuvre was performed in 137 healthy volunteers with a mean of 41 mmHg expiratory pressure over 15 s

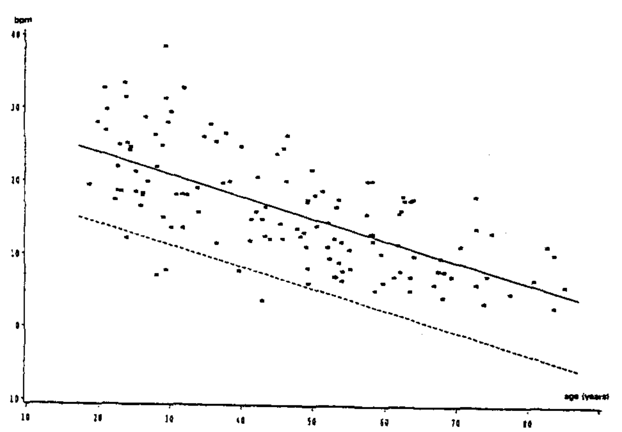

Figure 6. Mean values and lower limits of normal with 95% confidence of the heart rate variation during deep breathing are shown in relation to age. The manoeuvre was performed with a mean of 5.17 complete breathing cycles per minute in 137 healthy volunteers

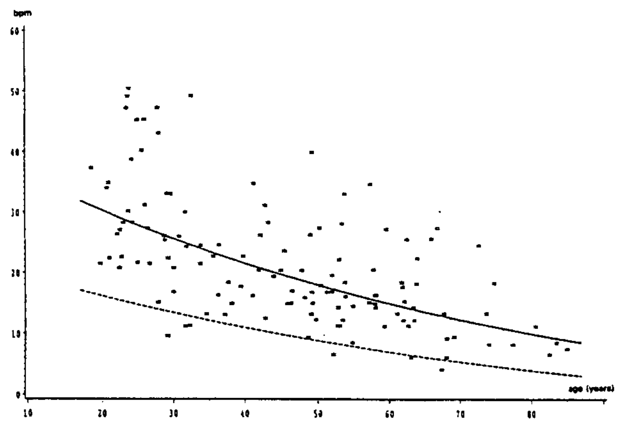

Figure 7. Mean values and lower limits of normal with 95% confidence of the heart rate activation during isometric exercise are shown in relation to age. The manoeuvre was performed with 50% of the maximum individually possible handgrip pressure

the expiratory and handgrip pressure, respectively, also decreased with age and both showed a statistically significant positive correlation with HR.

So far results on the influence of age on BP responses in autonomic function tests were inconsistent. The measurement of BP was limited to predefined points in time. Most protocols included only up to three challenge procedures with varying standards of performance. In IME most authors found no influence of age.[6,7,20,21] The question of an age-related change of the BP response after change of posture remains controversial.[6,7,19,21–24] The phase IV BP response of the VM, measured intra-arterially, was found to be reduced with increasing age.[21] The functional relevance of these findings remained unclear. It was suggested that ageing affects all components of the baroreflex, i.e. receptors, afferent and efferent fibres and the sino-atrial node.[18] In our data the increases of BP in IME, MA and during phase IV of the VM showed no significant influence of age, despite the significantly reduced increases in HR. Only the increase in DBP in IME decreased significantly with age, but was also related to the decreasing handgrip pressure. In these manoeuvres, where either baroreflex activation is not involved, i.e. in IME and MA, or non-baroreflex afferent pathways are activated in addition to a centrally generated stimulation, as in phase IV of the VM, age did not seem to have a functionally relevant impact on efferent sympathetic activity to the vasoconstrictor and capacity vessels. In fact, similar increases in BP were reached with a smaller acceleration of HR in these manoeuvres with increasing age. These findings are in line with previous reports, which indicate that during pharmacologically-induced baroreflex activation and cold-pressor tests the sympathetic outflow and vascular responses are well maintained in elderly healthy subjects.[15] Other authors have reported an age-related increase in plasma norepinephrine responses to mental stress[25] and isometric exercise,[26] providing some possible explanation for the preserved BP response in these manoeuvres in the elderly.

During manoeuvres with a forced decrease of BP as the characteristic stimulus, i.e. PT, ACP and phase II of the VM, increasing age was associated with greater falls and smaller compensatory increases of BP, although the pattern varied. After change of posture the DBP was significantly related to age either alone, as in PT, or its correlation with age was more pronounced compared with SBP ($p < 0.001$ vs. $p < 0.01$), as in ACP. Regarding the non-orthostatic fall of BP in the VM, only the SBP decreased significantly with age in phase II regarding the maximum drop and its compensatory increase. Our data suggest that the BP responses to orthostatic(-like) stressors are attenuated with increasing age in contrast to the preserved BP activation during non-orthostatic challenges. Also the mode of induction of the fall in BP appeared to influence the responses. The reasons for these different impacts of age on BP regulation remain to be identified. The postulated reduction of baroreflex sensitivity in the elderly[21,27–30] is based predominantly on the decreasing HR activation with age and provides no comprehensive model. As MSNA during PT[31,32] showed no decline with age, other co-factors of potential influence need to be considered.

The BP responses during active and passive change of posture showed significant differences between males and females (see Figure 2). The age-related decreasing BP values during ACP and PT were found to be strongly related to the progressively smaller BP activation in the male population. In contrast to previous reports[33,34] our data showed no significant impact of sex on BP and/or HR during the VM and DB or any other manoeuvre and do not support the hypothesized lower baroreceptor sensitivity in females.[21] The differences during IME were related to the significantly higher handgrip pressure in men compared with women and did not appear to be influenced by sex *per se*, which is in line with previous reports.[6,21] In accordance with the literature,[4–8] HR activation and variation was not influenced by sex.

These results do not support the assumption of an overall reduction in sympathetic outflow in all efferent components with increasing age. It was shown in animals and humans, that not only parasympathetic and sympathetic outflow but also different vascular beds, like splanchnic, renal and limb perfusion, and MSNA[15,35] are affected in a non-uniform pattern by age. In this study different modes of activation of the ANS also seemed to induce different age-related shifts within these various contributions to BP regulation. As BP and HR allow only the assessment of the aggregate effect of the various afferent inputs, central processing and efferent activity of the ANS, the contribution of the different components to the results remains unclear. It can be assumed that afferent and efferent structures of the ANS are affected by age in a variable way, with sex being one parameter of influence identified, and that in addition compensatory shifts within the system take place to alleviate age-related deficits. Future studies on the influence of age on baroreflex control should consider sex as an additional factor of influence.

Normal values of cardiovascular parameters during standard autonomic function tests

Since the introduction of autonomic function tests in the late 1960s, a heterogeneity of methods and assessments has accumulated, in particular regarding cardiovascular regulation. Recently various attempts have been made to establish methodological and diagnostic standards. Most previous reports on normative data referred to absolute values of cardiovascular parameters, which appeared to be significantly related to their baseline values in our study. The differences to baseline of the cardiovascular parameters were statistically independent from baseline values in all challenge procedures. So far this independence has been reported for HR parameters during ACP, VM and DB[24,36] and for BP during ACP and IME.[37] The use of the differences to baseline of BP and HR instead of absolute values appeared to narrow the normal ranges by reducing the standard deviations. It also supports the comparison of data between various laboratories, because the differences are assumed to be independent from the technical variability of the various methods of measuring cardiovascular parameters.

In agreement with many previous studies, the lower limits of normal of the HR increased and variation, respectively, declined in all manoeuvres with age with the exception of the values 60 s after active and passive change of posture. Unfortunately, the latter did not exceed baseline values at any age, preventing a positive proof of dysfunction of cardiac innervation with these parameters. Over the age of 60 this problem was found for many of the challenge procedures tested, which was previously reported in part also by Piha.[24] Over 65 years of age the minimum normal HR variation in DB did not exceed 1 beat/min. The lower limits of normal of the Valsalva ratio (VR) as the mean value of three manoeuvres were below 1.2 over 60 years and less than 1.1 over 69 years of age. When only the maximum of the three tests was considered the mean value of the VR increased by about 10% but no shift to a higher age limit of the test sensitivity was achieved due to a higher inter-individual variability. The maximum increase in HR during the VM appeared to be more useful with a minimum normal acceleration of 9 beats/min compared with baseline at the age of 60. This makes the sole assessment of the maximum increase in HR more sensitive, in particular in the elderly, without loss of information, because neither the Valsalva ratio nor the maximum increase in HR allow for a discrimination between the contributions of the vagal and sympathetic efferent activity.[38] Slightly lower normal limits for HR activation were found during IME (7 beats/min at 60 years of age) and MA (6 beats/min at 60 years of age). The best activation of HR also in the elderly was achieved during the initial phase of ACP after the initial drop in BP. At the age of 60 the lower limit of normal was 13 beats/min, at the age of 70 still an increase of 10 beats/min was necessary to remain within normal range (see Figure 3).

Reports on the advantages of the continuous non-invasive monitoring of BP and HR with the Finapres device have so far been limited to the observation of its usefulness to monitor the correct performance of the VM.[12] To our knowledge no systematic investigation has been performed, which addresses other potential areas of improvement of standard autonomic function tests with this method, for example monitoring of performance or improvement of the sensitivity to detect early autonomic failure.

Little is known about the minimum length of time, during which the cardiovascular parameters need to be assessed in standard autonomic tests. In the VM a duration of the expiratory pressure of 15 s was shown to be necessary to assess the whole course of BP changes.[12] In other manoeuvres no data are available. The continuous monitoring of the cardiovascular parameters enabled the assessment of the relevant latencies. The mean values of the latencies to reach stable increases in HR and BP in ACP and PT were less than 20 s with upper limits of normal of between 34 and 49 s. Therefore an observation period of 60 s after active or passive change of posture appeared to be sufficient to detect potential autonomic dysfunction. Of course, testing for vasovagal syncope must be excluded from this guideline. The 95% confidence ranges of the latencies to reach maximum activation of the cardiovascular parameters in MA and IME suggested that the manoeuvres can be limited to one minute and to 3.5 minutes, respectively. These time limits should contribute to a reduction of false negative results in patients showing no cardiovascular activation during these manoeuvres. The clinical usefulness and sensitivity of the upper limit of normal of 7 s for the latency between the minimum BP in phase III of the VM and the maximum BP in phase IV remain to be established in patients with autonomic failure.

In addition to the VM,[12] also during DB the continuous measurement of BP allowed the monitoring of the correct performance of the manoeuvre. Here a sinoid rhythm of the SBP and DBP was observed in parallel to the variation of HR. The lower limit of normal for the SBP variation was 6 mmHg independent of age, while for the DBP the limit of 1 mmHg appeared not to be of practical relevance.

The continuous measurement of BP raised hopes that the sensitivity of autonomic function tests could be improved. So far the assessment of BP has been limited to fixed points in time during IME[39] and

MA,[40] which cannot be expected to coincide with the maximum activation of sympathetic efferent activity. But when using the true maximum BP values, positive proof of dysfunction also appeared to be difficult, because the lower limits of normal were either low, (less than 10 mmHg for SBP and DBP in IME) or virtually zero (in MA). However, if positive evidence of centrally generated sympathetic activation can be obtained, this can contribute to the discrimination between an afferent or efferent/central localization of dysfunction in autonomic failure in routine testing. Also caution must be advised in expecting more sensitive BP parameters during the early phase after change of posture and during the VM. The lower limits of normal for the initial fall of BP in PT and ACP were found to be between 14 and 46 mmHg. In phase II of the VM the limit for SBP was between 46 to 60 mmHg depending on age. These great falls in BP within normal ranges did not point to the sensitivity of these parameters being sufficient to detect an early impairment of orthostatic regulation. Also the normal range of the compensatory increase of BP in phase IV of the VM, hardly exceeded baseline values. The BP in late phase II appeared to be more promising. To remain within normal range SBP and DBP had to return close to baseline values at the end of phase II independent of age. Overall the best BP parameters to detect autonomic failure were the 60 s values of ACP and PT and the late phase II of the VM. Out of this group only the normal limits of the BP 60 s after ACP were significantly affected by age.

Although BP responses during PT, ACP and phase II of the VM were significantly influenced by sex (see above), the normal ranges for BP differed only for the increases after the initial drop during ACP and PT (see Table 2) with lower values in males compared with females. As this point in time is not used for routine assessment in most laboratories, sex appeared not to be a relevant co-factor for the day-to-day assessment of BP and HR during standard autonomic tests.

Our data demonstrate that although sex and age are relevant factors influencing cardiovascular responses during autonomic function tests, they do not necessarily have an impact on all lower limits of normal used in clinical routine. As the tests investigated activate various afferent and efferent components of the ANS, the sensitivity, in particular for changes in HR activation and variation, varies between the different tests and in daily routine some patients are not able to perform all manoeuvres adequately. More than one test appears to be necessary to allow a reliable assessment; a minimum program should encompass ACP, VM and DB.

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