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ABSTRACT: Normative data are limited on autonomic function tests, especially beyond age 60 years. We therefore evaluated these tests in a total of 557 normal subjects evenly distributed by age and gender from 10 to 83 years. Heart rate (HR) response to deep breathing fell with increasing age. Valsalva ratio varied with both age and gender. QSART (quantitative sudomotor axon-reflex test) volume was consistently greater in men (approximately double) and progressively declined with age for all three lower extremity sites but not the forearm site. Orthostatic blood pressure reduction was greater with increasing age. HR at rest was significantly higher in women, and the increment with head-up tilt fell with increasing age. For no tests did we find a regression to zero, and some tests seem to level off with increasing age, indicating that diagnosis of autonomic failure was possible to over 80 years of age. © 1997 John Wiley & Sons, Inc. *Muscle Nerve* **20**: 1561–1568, 1997

Key words: sudomotor; cardiovagal; tilt; adrenergic; blood pressure

EFFECT OF AGE AND GENDER ON SUDOMOTOR AND CARDIOVAGAL FUNCTION AND BLOOD PRESSURE RESPONSE TO TILT IN NORMAL SUBJECTS

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Autonomic function can be evaluated using noninvasive autonomic function tests. The best validated are tests of sudomotor, cardiovagal, and adrenergic function.[1,22,23] There is an effect of age on heart rate (HR) and response to deep breathing (HR_{DB}), but uncertainty exists as to whether there is an effect of age on the Valsalva ratio (VR), sudomotor function, and orthostatic blood pressure (BP) and HR, or if there is a gender effect. Recently concerns have also been raised as to whether cardiovascular HR tests will differentiate between normal subjects and those with autonomic failure, beyond the age of 60 years.[5] With the increasing use of autonomic function tests in the United States of America, with an encouraging position article by the Academy of Neurology,[1] and with three new CPT codes, there is the great need for a large normative database.

We report an evaluation of the Mayo Autonomic Laboratory database of 557 normal subjects aged 10–83 years.

MATERIALS AND METHODS

Normal Subjects. A total of 557 normal subjects aged 10–83 years were studied. Subjects were evenly distributed by age and gender for the tests. Subjects were required to be on no regular medication except the oral contraceptive pill. Mayo Clinic history was reviewed and all subjects also completed a questionnaire directed at ruling out peripheral neuropathy and autonomic disorders. They were free of alcoholism, diabetes, malnutrition, obesity, or illnesses known to affect the autonomic nervous system. No food, coffee, or nicotine were permitted for 3 h before the study.

The distribution of the 557 normal subjects by tests are shown below. Distribution by age and gender follows. The number of men and women for age ranges are shown in brackets with male values followed by female values: ≤ 20 (22, 24), 21–30 (54,

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57), 31–40 (49, 56), 41–50 (46, 58), 51–60 (46, 45), 61–70 (39, 28), ≥ 70 (14, 19).

Autonomic Function Tests. All tests were done with the patient supine. All tests were done in the following order: sudomotor, cardiovagal, adrenergic. The sequence ensured that head-up tilt (HUT) studies were done following a minimum of 20 min of supine rest, since there is an influence of rest on orthostatic blood pressure responses.[47] The numbers of subjects used in specific tests were: QSART (quantitative sudomotor axon-reflex test), 357 subjects; QSART subset (left vs. right sides), 39; HR_{DB}, 376; VR, 425; orthostatic BP/HR, 270.

QSART. QSART, which quantitatively evaluates the postganglionic sympathetic sudomotor axon,[26,31] was routinely recorded from four sites: medial forearm site three fourths of the distance from the ulnar epicondyle to the pisiform bone; proximal lateral leg, 5 cm distal to the fibular head; medial distal leg, 5 cm proximal to the medial malleolus; and proximal foot over the extensor digitorum brevis muscle. The stimulus was iontophoresis of 10% acetylcholine solution for 5 min, and the responses were recorded in a compartment of a multicompartmental sweat cell that was separate from the stimulus compartment. The "axon reflex" is mediated by postganglionic sympathetic sudomotor fibers.[30]

HR_{DB} and VR. These tests were performed as previously described.[26,31] HR_{DB} was the HR range in response to forced deep breathing, with the subject breathing rhythmically and maximally at six breaths per minute, in concert with an oscillating bar. Eight cycles were recorded, and repeated after 2 min of rest. Respiration was also monitored using a nasal thermistor.

For the Valsalva maneuver, the subject, rested and recumbent, was asked to maintain a column of mercury at 40 mmHg for 15 s. The subject was required to repeat the maneuvers until two reproducible beat-to-beat BP recordings were obtained. The Valsalva ratio was the ratio of the maximal (following phases II/III) to minimal HR (occurring within 30 s of phase IV peak).

Orthostatic BP Recordings. BP was recorded using a sphygmomanometer cuff and mercury manometer over the brachial artery. We also recorded beat-to-beat BP using a continuous NIBP Monitor (Finapres Monitor, Ohmeda, Englewood, CO) and input into a computer console which displays systolic (SBP), diastolic (DBP), and mean blood pressure (MBP) continuously.[41,42]

In a separate study, we compared the BP response of HUT (80°) to standing up, to evaluate if the orthostatic stress was similar. For this study we needed a wide range of BP changes, changes that would not be found in normal subjects. We therefore used a subset of patients, selected so that approximately one third would have a large fall in BP (> 30 mmHg systolic BP). For this segment of the study, patients were alternately assigned to HUT or standing up as the initial procedure. A 5-min period of supine rest preceded each of the procedures. BP and HR were recorded supine, and following tilt-up or standing up, at 30 s, 1 min, and 5 min.

Statistical Analysis. For each test, we first evaluated associations with age and gender using stepwise multiple regression analysis, using a stepping up algorithm at the 0.05 level of significance. When age was significant, we tested for nonlinear associations by successively considering higher order terms (quadratic, cubic, etc.), using $P < 0.05$ as the criteria. When both age and gender were significant, we tested for an age by gender interaction. The hierarchical principle was observed: main effects were not deleted from a model if higher order terms or interactions were in the model. Normative percentiles were estimated nonparametrically, using the algorithm described in O'Brien and Dyck.[35] Tests for paired data were compared using the paired *t*-test. Data were expressed as mean ± SD (standard deviation).

RESULTS

QSART. Data were analyzed using stepwise regression analysis. For the forearm, proximal leg, distal leg, and proximal foot sites, the regression coefficients follow, where b_0 is intercept, b_2 is gender, and b_1 is age: Forearm; b_0, 4.191; b_2, −1.520; b_1 = NS; Proximal leg, b_0, 4.098; b_2, −1.058; b_1, −0.0180; Distal leg, b_0, 5.078; b_2, −1.252, b_1, −0.033; Proximal foot, b_0, 3.819; b_2, −1.059; b_1, −0.016. All values listed are significant ($P < 0.001$). b_2 indicates the gender difference, with minus value indicating the reduction in women. For all sites, gender had the largest effect, volumes of women being 1.0–1.5 µl/cm^2 lower than that of men. The effect of age was significant for all three lower extremity sites but not for the forearm. Latency showed no significant differences by either gender or age (not shown). Table 2 summarizes the mean values, 5th and 95th percentiles for men and women, respectively, as applied to the clinical auto-

Table 1. Paired comparison of QSART values of left versus right side.

Variable	*n*	Mean left	Mean right	Δ (L − R)	SD Δ	*P**
QSART FA	39	1.831	1.874	−0.043	0.803	0.741
QSART PL	40	1.451	1.431	0.198	0.569	0.828
QSART DL	39	1.729	1.995	−0.266	0.735	0.030
QSART Ft	37	1.440	1.291	0.148	0.800	0.267

QSART FA, quantitative sudomotor axon-reflex test for forearm site; PL, proximal leg; DL, distal leg; Ft, foot.
**Paired t-tests.*

nomic laboratory at Mayo. For proximal leg, the values could be equally and more simply explained by a bilayered response, with a lower value for subjects older than 45 years. Table 1 summarizes a comparison of QSART values recorded over identical sites on the left and right side. Except for a single site, no significant difference by side was found. We interpret the study as not showing a side-by-side difference, considering the number of comparisons that were made.

HR$_{DB}$ and VR. HR$_{DB}$ was studied in 376 subjects and varied significantly ($P < 0.001$) by age but not by gender. The results were therefore combined. The relationship is expressed by the regression, $Y = 31.1196 - 0.3056X$, where Y is HR range, and X is age in years. It should be noted that the number of points beyond age 60 years was fewer and showed a leveling off of HR variation (Fig. 1). For the results on percentiles, this leveling off phenomenon was taken into account in the clinically applied table (Table 3).

For VR, studied in 425 subjects aged 10–83 years, there was an effect of age and gender. Separate plots were therefore provided (Figs. 2 and 3). The relationship is expressed by the equation, $Y = 1.8454 + 0.0058X_1 - 0.00017X_2 + 0.09515X_3$, where Y is Valsalva ratio; X_1, gender (1 = men; 2 = women); X_2, age; X_3, gender × age. The figures are informative. Men ($n = 205$) have relatively few points beyond 60 years, and the minimal values appear to have flattened out (Fig. 2), and we have expressed our percentiles to reflect that (Table 4). For women ($n = 220$; Fig. 3), little change occurs before age 60 years, followed by a decrement. Hence the data for men and women were described separately (Fig. 3).

Comparison of HUT versus Standing Up. To evaluate whether HUT and standing up resulted in similar orthostatic stress, we compared orthostatic BP sphygmomanometrically recorded over the brachial artery in 39 patients (14 men; 25 women; age 58.9 ± 16.0 years). To ensure a wide range in orthostatic BP reductions, one third (13/39) of the patients had orthostatic hypotension defined as a reduction of SBP by at least 30 mmHg. BP recordings showed a very good correlation between values obtained during HUT and standing (Table 5). The Pearson correlation of BP ranged from 0.79 to 0.95. There was no significant difference for any index at baseline (not shown), 30 s, and 5 min; but there was a significant difference in SBP, MBP, and DBP at 1 min ($P < 0.05$), being lower with tilt.

BP and HR. There was a significant effect of both age and gender on both systolic and diastolic BP. BP was lower for women and increased concomitantly with age (Table 6). On average women had a systolic BP that was 8 mmHg lower and a diastolic BP that was 3 mmHg lower. The fall in BP (both systolic and diastolic) at 1 min increased with age and did not vary by gender. The data are shown in Figure 4 and

Table 2. QSART responses for men (M) and women (W).

	10–29 years			30–39 years			40–49 years			50–59 years			60–69 years		
Sites	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
Forearm M	2.67	0.76	5.06	2.67	0.76	5.06	2.67	0.76	5.06	2.67	0.76	5.06	2.67	0.76	5.06
Forearm W	1.15	0.20	2.78	1.15	0.20	2.78	1.15	0.20	2.78	1.15	0.20	2.78	1.15	0.20	2.78
Proximal leg M	2.67	1.27	4.54	2.49	1.10	4.36	2.32	0.93	4.19	2.14	0.75	4.01	1.97	0.58	3.84
Proximal leg W	1.48	0.36	3.17	1.48	0.36	3.17	1.48	0.36	3.17	1.48	0.36	3.17	1.48	0.36	3.17
Distal leg M	3.28	1.37	5.27	2.91	1.18	4.91	2.55	0.98	4.55	2.19	0.79	4.18	1.83	0.59	3.82
Distal leg W	1.83	0.61	2.85	1.55	0.50	2.57	1.26	0.39	2.28	0.97	0.29	1.99	0.68	0.18	1.70
Proximal foot M	2.58	0.87	4.48	2.37	0.83	4.27	2.17	0.78	4.07	1.96	0.73	3.86	1.75	0.68	3.65
Proximal foot W	1.27	0.23	3.07	1.16	0.20	2.96	1.05	0.18	2.85	0.94	0.15	2.74	0.84	0.12	2.64

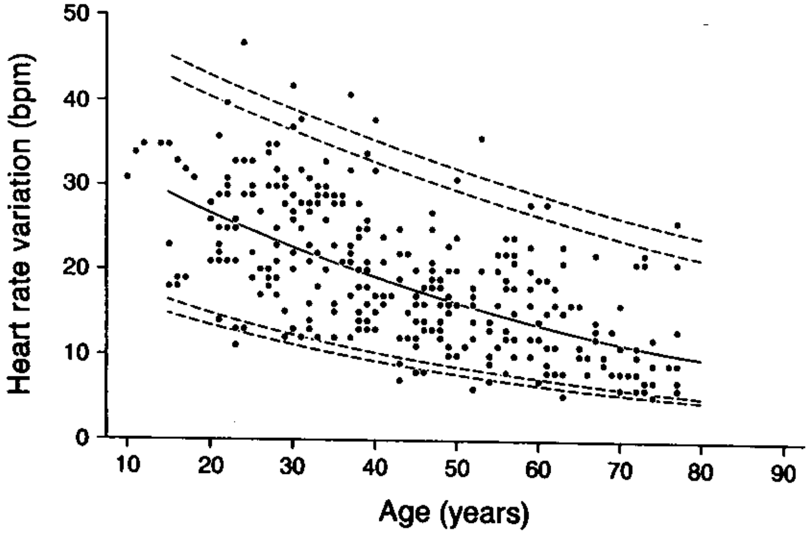

FIGURE 1. Heart rate variation to deep breathing as a function of age. Lines show 2.5th, 5th, 95th, and 97.5th percentiles. There is a reduction with age.

Table 7. By 5 min significant correction had occurred. The 97.5th percentile of systolic BP decrement for the ages of 20, 40, 60, and 80 years exemplifies the large age effect. The values were: 21, 24, 26, and 29 mmHg respectively (Table 7).

HR at rest showed a significant gender effect (Table 6, higher in women). The HR increment with HUT showed an age but not a gender effect (Table 7).

DISCUSSION

QSART. The main findings of the QSART data are that men have approximately double the mean evoked sweat volume of women, that there is side-to-side symmetry of the sweat response, and that the leg sites (proximal leg, distal leg, and proximal foot) but not the arm site (forearm) demonstrate a progressive reduction with age. The lower value in women confirms earlier studies.[24,26,31,32] Sweat gland density is not different between men and women, but the latter have a smaller evoked sweat volume per gland.[20] The greater influence of age on the longer unmyelinated fibers is of interest, and confirms an earlier observation from our laboratory, based on a smaller number of controls.[24] A similar pattern of somatic sensory unmyelinated fiber function, as thermal thresholds, has been reported by Dyck et al.,[9] where changes in the lower extremity are more pronounced than those of the upper extremity.

Table 3. Heart rate response to deep breathing: 2.5th, 5th, 95th, and 97.5th percentile values.

Percentile	10–29 years	30–39 years	40–49 years	50–59 years	60–69 years
2.5th	13	11	9	8	7
5.0th	14	12	10	9	7
95.0th	41	37	33	31	27
97.5th	43	38	36	32	29

HR_{DB}. All studies involving large numbers of normal subjects have revealed a progressive reduction with age in HR_{DB}.[5,12,18,31–33,37,50,51] All large studies have either demonstrated a linear or log-linear relationship[18,51] to age, with similar slopes to ours.[17,18,33] Recently, the value of HR_{DB} in subjects older than 60 years has been questioned, since the values approach zero.[5] It is, however, likely that this conclusion goes beyond the evidence. The number of data points beyond age 60 is usually small. What seems to have been unappreciated is the leveling off of values beyond age 60, evident in Braune et al.[5] Figure 6 and in our Figure 1.

VR. The effect of age on VR is controversial. Some workers have reported a lack of variability with age,[12,49] while others have observed a difference[6,13,28,31,34,36] (Table 1). Reported slopes have been similar. Ingall et al.[18] reported a slope of 0.01 per year, which is very similar to ours.[28] The less consistent effect of age on VR than on HR_{DB} likely relates to the smaller change and greater complexity of the maneuver. Whereas HR_{DB} is a relatively pure test of cardiovagal function, many factors, including blood volume, antecedent period of rest,[47] cardiac sympathetic and peripheral sympathetic tone, and

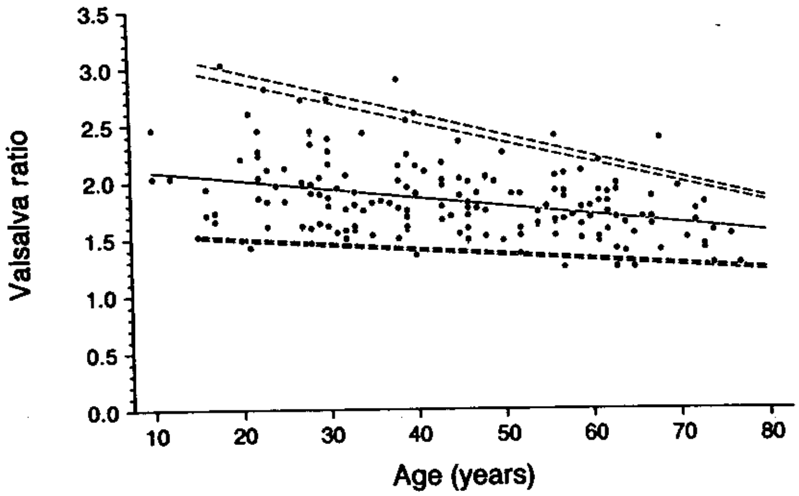

FIGURE 2. Valsalva ratio as a function of age for males. Lines show 2.5th, 5th, 95th, and 97.5th percentiles.

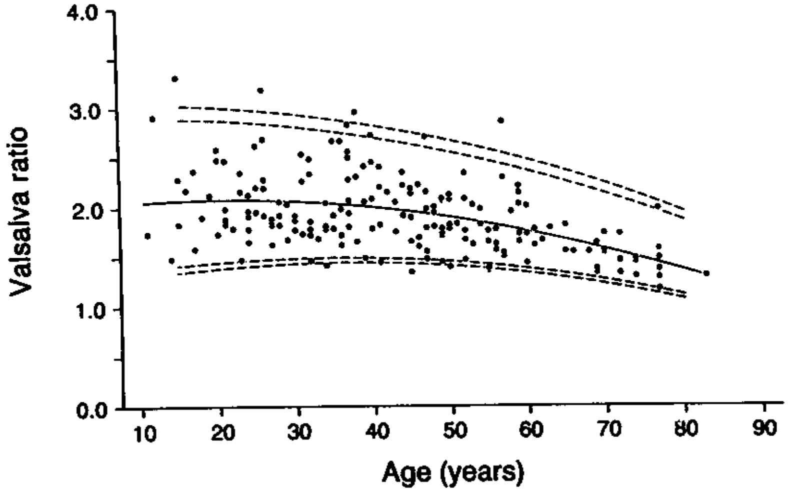

FIGURE 3. Valsalva ratio as a function of age for females. Lines show 2.5th, 5th, 95th, and 97.5th percentiles.

Table 4. Valsalva ratio: 2.5th, 5th, 95th, and 97.5th percentile values by age and gender.

	10–29 years		30–39 years		40–49 years		50–59 years		60–69 years	
Percentile	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
2.5th	1.51	1.41	1.43	1.46	1.36	1.47	1.28	1.43	1.21	1.36
5.0th	1.59	1.46	1.52	1.50	1.44	1.51	1.36	1.47	1.29	1.39
95th	2.87	2.73	2.70	2.71	2.52	2.65	2.35	2.55	2.18	2.41
97.5th	2.97	2.97	2.78	2.95	2.60	2.89	2.41	2.79	2.23	2.65

Table 5. Comparison of blood pressure on HUT versus standing up.

	0.5 min			1 min			5 min		
BP	Standing	HUT	Pearson correlation	Standing	HUT	Pearson correlation	Standing	HUT	Pearson correlation
SBP	123.4 ± 27.9*	120.5 ± 24	0.81	122.7 ± 28.3	118.5 ± 25.9†	0.94	119.6 ± 26.8	119.4 ± 26.2	0.95
MBP	90.4 ± 15.8	88.6 ± 17	0.83	89.9 ± 19.5	87.0 ± 18.8†	0.91	89.1 ± 19.9	88.1 ± 19.2	0.94
DBP	73.9 ± 12.3	74.1 ± 12.6	0.79	75.4 ± 13.6	73.1 ± 13.7†	0.88	75.8 ± 13.9	74.4 ± 13.5	0.90

*Mean ± standard deviation.
†$P < 0.05$, paired t-test.*

Table 6. Table of regressions on *Y* against age, gender, and age × gender.

Y	Intercept	Age	Gender	Age × gender	Age^2
Supine SBP	128.44*	0.26*	−7.88*	ns	0.01†
Supine DBP	59.95*	0.49*	2.93	−0.19‡	ns
Supine HR	57.08*		3.69*		
Effect of HUT: absolute values					
1 min SBP	139.48*	−0.73†	−9.46*	ns	0.01‡
1 min DBP	87.87*	ns	−6.10*	ns	ns
5 min SBP	117.53*	0.44*	−11.74*	ns	ns
5 min DBP	82.59*	0.13*	−6.64*	ns	ns
1 min HR	87.10*	−0.21*			
5 min HR	88.94*	−0.20*			
Effect of HUT: reduction in BP					
1 min SBP	1.68	−0.15*	ns	ns	ns
1 min DBP	22.28*	−0.63*	ns	ns	0.005‡
5 min SBP	2.36	ns	−3.46‡	ns	ns
5 min DBP	8.76*	−0.09†	ns	ns	ns

For gender, negative value indicates a lower value for women.

$^*P < 0.001$.

$^\dagger P < 0.05$.

$^\ddagger P < 0.01$.

norepinephrine response, affect the Valsalva maneuver. Age may affect different components of the Valsalva maneuver in different directions.

Comparison of Tilt-Up versus Standing Up. Most published studies on orthostatic hypotension were based on the effect of standing up. However, recent studies have been done in autonomic laboratories, where orthostatic tolerance is evaluated using the tilt table. Studies have been done comparing the physiology of standing up with tilt-up.[4,46] However, we were unaware of published comparisons of tilt versus standing up in patients with orthostatic hypotension. There is good general concordance between values of blood pressure and their change between HUT and standing up, the orthostatic reduction being greater for tilt-up than for standing, the difference reaching statistical significance at 1 min, but the difference is relatively small (< 5 mmHg) even in a group where 1/3 had orthostatic hypotension. These findings suggest that there the use of either the tilt table or standing up are interchangeable.

Orthostatic BP Response and Aging. Orthostatic reduction in BP increases with increasing age. The definition of orthostatic hypotension has been variable. A Consensus Statement[2] has recommended a consistent reduction of 20 mmHg at 3 min indicates orthostatic hypotension. By this definition, orthostatic hypotension is not uncommon in patients beyond the age of 70 years, occurring in about 14–20% of patients.[19,39,45] Although the fall in BP is typically mild or asymptomatic,[38] these patients may become symptomatic under conditions of increased orthostatic stress, as with exercise, after a meal, or with increased ambient temperature.[25]

The alterations have been analyzed in detail.[45] They have, compared to younger subjects, in the upright posture, lesser increments of HR and diastolic pressure, but no significant differences from younger age groups in the response of thoracic blood volume, cardiac output, or total vascular resistance. The basis of the orthostatic hypotension of old age is likely to be multifactorial, since several components of the cardiovascular system are affected by aging.[8,24] First, there is a 5–8% attrition of preganglionic neurons per decade beginning in early adulthood[29]; this becomes symptomatic

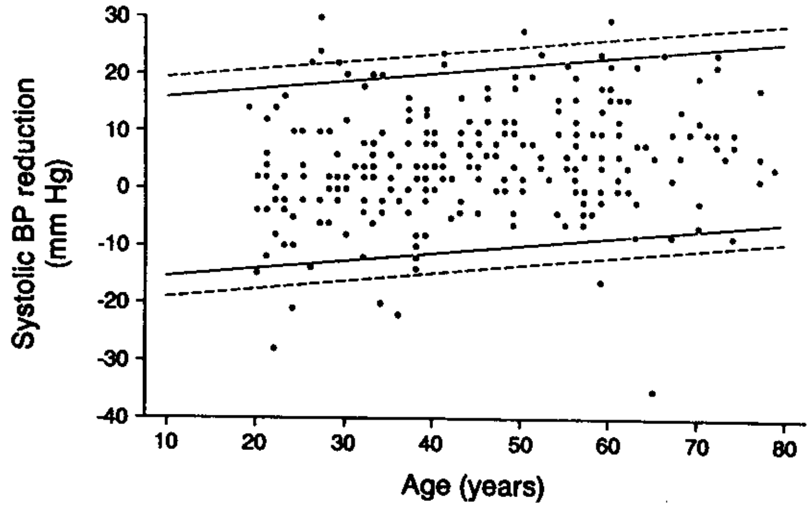

FIGURE 4. Reduction in systolic BP as a function of increasing age. Lines show 2.5th, 5th, 95th, and 97.5th percentiles.

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Table 7. The 95th and 97.5th percentiles of systolic blood pressure decrement and heart rate increment after 1 min HUT.

Percentile	10–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
SBP: 95th; 97.5th	17; 21	19; 22	20; 24	22; 25	23; 26	26; 29
HRM: 95th; 97.5th	24; 40	32; 38	30; 36	28; 34	26; 32	23; 29
HRW: 95th; 97.5th	31; 34	29; 32	27; 30	25; 28	23; 26	21; 24

M, men; W, women.

when about 50% of neurons are lost.[21] Excellent concordance was found in preganglionic neuron counts with preganglionic myelinated fiber counts in ventral spinal root and rami communicantes of the same level at autopsy.[27] Second, aging is associated with baroreflex impairment, involving the receptor, afferent, and efferent fibers and the sinoatrial node.[10,16,44] Third, α_2- and possibly α_1-adrenoreceptors exhibit reduced potency with aging.[8,11] Fourth, β-adrenoceptor-mediated cardioacceleration and inotropic response are reduced in older humans.[43,48] Fifth, older patients are often on diuretics which significantly reduce blood volume. Even recommended doses of diuretics may result in severe orthostatic hypotension in older patients. Sixth, there is an increase in supine BP with age, and the fall in BP on standing is significantly dependent on supine BP.[14] Seventh, the tendency toward orthostatic hypotension in the elderly is also due to the structural and functional changes in the circulation itself, and to an impaired skeletal muscle pump.[45] Increasing age is associated with a decline in total muscle mass.[3,15] There is an approximately 40% reduction in muscle area between the second and seventh decades of life.[40] The maintenance of orthostatic normotension may be different in the elderly. Arginine vasopressin (AVP) has been found to participate in BP maintenance, especially when other pressor systems are endogenously or pharmacologically impaired. Elderly, like subjects with autonomic failure, have a greater reliance on vasopressin, as indicated by the greater fall in BP following the use of vasopressin antagonists.[7]

In conclusion, postganglionic sudomotor function, measured with QSART volumes, is approximately double in men that of women, and lower but not upper extremity sites become progressively reduced with increasing age. Cardiovagal function, measured as HR_{DB}, undergoes progressive reduction with age. VR shows a different pattern in men and women. Men have lower values with increasing age. Women have a more complex pattern, peaking at the ages of 30–40 years, with lower value above and below these ages. There is a progressive increase in orthostatic BP reduction and decrease in HR increment with increasing age. The impairment in function with increasing age appears to level off beyond age 60 years, best seen with HR_{DB} and VR for men.

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