Clin Auton Res (2010) 20:3–9
DOI 10.1007/s10286-009-0036-z

RESEARCH ARTICLE

Cognitive performance in hypotensive persons with spinal cord injury

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Received: 21 July 2009 / Accepted: 21 September 2009 / Published online: 16 October 2009

Abstract
Background Due to sympathetic de-centralization, individuals with spinal cord injury (SCI), especially those with tetraplegia, often present with hypotension, worsened with upright posture. Several investigations in the non-SCI population have noted a relationship between chronic hypotension and deficits in memory, attention and processing speed and delayed reaction times.
Objective To determine cognitive function in persons with SCI who were normotensive or hypotensive over a 24-h observation period while maintaining their routine activities.
Methods Subjects included 20 individuals with chronic SCI (2–39 years), 13 with tetraplegia (C4–8) and 7 with paraplegia (T2–11). Individuals with hypotension were defined as having a mean 24-h systolic blood pressure (SBP) below 110 mmHg for males and 100 mmHg for females, and having spent ≥50% of the total time below these gender-specific thresholds. The cognitive battery used included assessment of memory (CVLT), attention and processing speed (Digit Span, Stroop word and color and Oral Trails A), language (COWAT) and executive function (Oral Trails B and Stroop color–word).
Results Demographic parameters did not differ among the hypotensive and normotensive groups; the proportion of individuals with tetraplegia (82%) was higher in the hypotensive group. Memory was significantly impaired ($P < 0.05$) and there was a trend toward slowed attention and processing speed ($P < 0.06$) in the hypotensive compared to the normotensive group.
Interpretation These preliminary data suggest that chronic hypotension in persons with SCI is associated with deficits in memory and possibly attention and processing speed, as previously reported in the non-SCI population.

Keywords Blood pressure · Tetraplegia · Paraplegia · Cognitive testing · Hypotension · Spinal cord injury

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Introduction

The World Health Organization (WHO) defines hypotension as systolic blood pressure (SBP) of less than 100 mmHg for women and less than 110 mmHg for men, without regard to diastolic blood pressure [1]. In contrast to

essential hypertension, essential hypotension is not regarded as a clinically relevant or important medical condition; however, chronically low blood pressure (BP) has been associated with poorer quality of life and wellbeing in large population-based studies particularly among older adults [44, 59]. In addition, although commonly reported symptoms of low BP include fatigue, reduced drive, light-headedness, dizziness, sleepiness, blurred vision and subjective reports of impaired concentration, many individuals with hypotension are clinically asymptomatic.

There is emerging evidence that autonomic cardiovascular dysregulation may be the underpinning of inadequate BP and baroreceptor responsiveness, which results in measurable cognitive deficits in individuals with essential and postural hypotension [19, 22, 35]. Due to partial or complete denervation of sympathetic cardiovascular control, which may or may not relate to the level or completeness of the motor-sensory injury, BP dysregulation is a common clinical observation in persons with spinal cord injury (SCI) [9, 10, 32]. Furthermore, individuals with high cord lesions are prone to systemic hypotension, which is worsened with postural stress [9, 10, 29, 32, 56, 57]. In the non-SCI population, an association between essential hypotension and cognitive impairment has been reported [11, 21, 25, 58]. Specifically, prolonged reaction times and decreased accuracy in sustained attention and working memory are reported in hypotensive compared to normotensive subjects [21, 23, 25].

It is estimated that between 10 and 60% of individuals with SCI have cognitive impairment in the areas of processing speed, attention, memory, and cognitive flexibility [14, 16, 17]. These cognitive deficits may be due to a range of co-morbid conditions including BP dysregulation. Thus, the aim of this study was to quantify cognitive function in individuals with SCI who were normotensive compared to those who were hypotensive over a 24-h BP collection period while performing their routine activities of daily living.

Methods

Participants

Twenty adult individuals (26–60 years) with chronic SCI (2–39 years) were consented and participated in the study, all except two were right-handed, as determined by subject assertion. The 20 subjects included 7 individuals with paraplegia (T2 and below) and 13 with tetraplegia (C8 and above); for statistical comparison, level of injury was made into a continuous variable by assigning an ascending number to descending level of SCI as such; C1 = 1, C2 = 2,…, T12 = 20, L5 = 25. Subjects were excluded if they carried a current diagnosis of cardiovascular diseases or a psychiatric disorder, or were prescribed medications with known psychoactive or cardiovascular effects. However, oxybutynin chloride (Ditropan), a commonly prescribed anti-cholinergic agent for the treatment of an over-active, neurogenic bladder, which may have deleterious effects on memory, was prescribed in eight of the 20 participants. All subjects were non-institutionalized, chronically wheelchair-bound and not able to independently ambulate. Information regarding a prior history of traumatic brain injury (TBI) was collected in the study group by self-report. This study was approved by the James J. Peters Veteran Affairs Medical Center (JJP VAMC) and the Kessler Institute for Rehabilitation Institutional Review Boards.

Blood pressure assessment

The ambulatory BP monitor (90207 ABPM; SpaceLabs Corp. Troy, MI) was applied to subjects over the brachial artery of the non-dominant arm to record BP over a 24-h period, during which all subjects performed their routine activities; testing was avoided on days in which subjects performed their bowel care regimen. The automated BP device was pre-programmed for each individual based on their usual sleep/wake habits, such that BP measurements were recorded every 20 min during the day/wake hours and every 30 min during the night/sleep hours. Hourly BP values were averaged and provided a summary of SBP over the 24-h period. Subjects were instructed to have a "normal" night of sleep and to stay awake during the day. The BP monitor was removed when the subjects returned to the laboratory the following day. Hypotensive individuals were classified using the WHO definition of an SBP below 110 mmHg for males and below 100 mmHg for females [1]. The number of observations of SBP below these thresholds was determined and was used to calculate the percentage of time each subject spent "hypotensive". Individuals with a mean 24-h SBP below the gender-appropriate value and those who spent $\geq$50% of the total observation time below these thresholds, without regard for postural position, were categorized as hypotensive.

Neuropsychological assessment

All study participants were administered a comprehensive neuropsychological assessment, including the following: *Current intellectual function*—Wechsler Abbreviated Scale of Intelligence (WASI), Vocabulary and Matrix Reasoning subtests [53]; *Pre-morbid intelligence*—Wechsler Test of Adult Reading [55]; *Memory*—California Verbal Learning Test-II (CVLT-II) Standard Form includes short delay, long delay and total recall and recognition [15]; *Language*—Controlled Oral Word Association Test [4]; *Attention and Processing Speed*—Oral Trails A [47]; Wechsler Adult Intelligence Scale-III Digit Span Test [54]; Stroop Word and Stroop Color [28]; *Executive Function*—

Oral Trails B [47]; and Stroop color–word [28]; *Mood*—depression was assessed with the 21-item Beck depression inventory-II (BDI) [3]. All tests were administered and scored by a licensed clinical psychologist.

Data analysis

Demographic and clinical characteristic data are summarized by mean ± standard deviation (SD) and frequencies (%); statistical significance was set at $P < 0.05$. The mean and SD of the raw and standardized scores (from test manuals as well as published scores) for each cognitive test were summarized for the hypotensive and normotensive groups and comparisons were made using unpaired *T*-tests. The number of individuals who scored in the impaired range (≥1.5 SD below published normative *T*-scores data) on each cognitive test was identified in the hypotensive and normotensive groups and comparison of the proportion of impairment was made using a Chi-square non-parametric test. Average memory *T*-score on the CVLT battery (average score among the total, short delay, long delay and recognition tests) was calculated and differences between individual prescribed and those not prescribed Ditropan were examined using unpaired *T*-test. Finally, a stepwise linear regression model was constructed to determine the relationship between average memory *T*-score on the CVLT and 24-h SBP after controlling for age, level of injury (continuous variable) and depression score.

Results

Characteristics of the sample

The study sample included 13 individuals with tetraplegia (cervical levels 4–8) and 7 individuals with paraplegia (thoracic levels 2–11). Of these 20 individuals, 11 were categorized as hypotensive and nine normotensive. Subject demographic data are presented by 24-h blood pressure valuation (Table 1); there were more individuals with tetraplegia in the hypotensive group and, as such, level of lesion as a continuous variable was significantly lower (i.e., higher lesion level) compared to the normotensive group. In addition, although not significant, the hypotensive group tended to be younger and to report more depressive symptoms than the normotensive group.

Blood pressure

Blood pressure characteristics are presented by categorical level of lesion (Table 2). Based on our classification criteria for the determination of hypotension, 53% of our study sample was classified as hypotensive, of which 82% (9 of 11) were individuals with tetraplegia. Mean 24-h SBP was significantly lower ($P < 0.02$) and the number of hours ($P < 0.02$) and percentage of time ($P < 0.02$) spent hypotensive were significantly increased in the tetraplegic compared to the paraplegic group.

Performance on neuropsychological measures

The raw score, normalized *T*-score and the number and percentage of individuals who scored in the impaired range on the cognitive test are compared and presented by group (Table 3). Normalized *T*-scores on measures assessing memory (CVLT) were significantly lower in the hypotensive compared to the normotensive group. There was a trend toward poorer attention and processing speed in the hypotensive compared to the normotensive group as assessed on the Oral Trails A test. Although not statistically significant,

Table 1 Subject characteristics by 24-h SBP

	Hypotensive ($n = 11$)	Normotensive ($n = 9$)	*P* value
24-h SBP	102 ± 7	115 ± 10	<0.0001
24-h DBP	63 ± 6	71 ± 4	<0.01
24-h HR	69 ± 10	79 ± 8	<0.05
Age (years)	39 ± 8	46 ± 10	0.1006
Female # (%)	0	1 (11)	NS
DOI (years)	16 ± 10	18 ± 13	NS
Lesion level	C4–T4	C4–T11	NS
Tetraplegia # (%)	9 (82)*	4 (44)	NS
Lesion level (continuous)	6.09 ± 2.74	10.33 ± 5.29	<0.05
AIS A # (%)	9 (82)	9 (100)	NS
BDI	5.46 ± 5.47	0.64 ± 3.67	0.0878
Level of education (years)	15 ± 3	15 ± 4	NS
Pre-morbid IQ	103 ± 14	103 ± 13	NS
Measured IQ	91 ± 20	98 ± 8	NS
Positive history of TBI # (%)	5 (45)	4 (44)	NS

Data presented as mean ± SD

DBP Diastolic blood pressure, *HR* heart rate, *DOI* duration of injury, *AIS A* American spinal injury scale complete, *BDI* Becks depression inventory, *IQ* intelligence quotient, *TBI* traumatic brain injury

* χ^2 of 0.0831

Table 2 24-h systolic blood pressure in subjects with SCI

Level of				24-h SBP			Hypotensive	
Gender	SCI	AIS	Group	Mean	Min	Max	Episodes	
				mmHg			Hours	%
Tetraplegia								
Male	C4	A	Hypotensive	108	85	127	12	50
Male	C5	A	Hypotensive	99	86	104	24	100
Male	C5	A	Hypotensive	104	94	132	20	83
Male	C5	C	Hypotensive	101	86	118	18	75
Male	C4	A	Hypotensive	106	91	126	14	58
Male	C5	A	Hypotensive	106	89	123	16	67
Male	C5	A	Hypotensive	85	74	96	24	100
Male	C5	A	Hypotensive	102	87	120	19	79
Male	C6	A	Hypotensive	96	87	106	24	100
Male	C8	A	Normotensive	116	93	139	8	33
Male	C5	A	Normotensive	110	93	126	12	50
Male	C4	A	Normotensive	111	89	128	9	38
Male	C5	A	Normotensive	114	95	148	11	46
Mean				104*	88	123	16*	68*
SD				8	5	14	6	24
Paraplegia								
Male	T3	B	Hypotensive	105	93	115	20	83
Male	T4	A	Hypotensive	109	95	133	15	63
Male	T7	A	Normotensive	116	89	130	6	25
Male	T11	A	Normotensive	122	77	161	7	29
Female	T2	A	Normotensive	119	101	140	0	0
Male	T4	A	Normotensive	118	91	139	4	17
Male	T7	A	Normotensive	112	101	127	10	42
Mean				114	92	135	9	37
SD				6	8	14	7	28

C Cervical, *T* thoracic

* $P < 0.02$ versus the paraplegic group

executive function as assessed on the Stroop color–word test was lower in the hypotensive compared to the normotensive group. Average score on the CVLT memory battery did not differ among individuals prescribed Ditropan, compared to those who were not prescribed the medication (51.0 ± 11.1 vs. 50.9 ± 12.1, respectively).

Age and depression score (BDI) did not independently correlate with any cognitive measure among the study cohort. After controlling for group differences in age, level of injury (continuous variable) and depression score, 24-h SBP was a significant predictor of average normalized CVLT memory *T*-score ($r^2 = 0.497$; $P < 0.001$) (Fig. 1).

Discussion

These results suggest that subjects with SCI who are hypotensive over a 24-h observation period have significantly reduced memory and have moderately reduced attention and processing speed, as assessed by the Oral Trails A test, and executive function, as assessed by the Stroop color–word test, when compared to normotensive subjects with SCI. Even after controlling for age and depression, the hypotensive group had significantly poorer performance on memory scores.

Studies on cognitive function in persons with SCI report that between 10 and 60% of the population exhibit some degree of cognitive impairment in the domains of attention, concentration, memory, problem solving, abstract reasoning, new learning and high-level cognitive skills [14, 16, 40]; concomitant TBI is most often reported as causal to these deficits [14, 16, 17, 40]. In the current data set, there were no differences in the self-reported incidence of TBI among the hypotensive and normotensive groups. We do acknowledge, however, that the memory deficits reported herein may have skewed our assessment of the true incidence of concomitant TBI and further work is needed to determine the influence of hypotension on cognitive function independent of TBI in the SCI population.

Although little clinical import is given to the treatment of low blood pressure, several studies in the non-SCI population have documented an association between hypotension and impaired cognitive function [11, 21, 25, 39, 58], particularly among older individuals [2, 39, 48]. It is of additional interest to us that the hypotensive group tended to be younger than the normotensive cohort, albeit not statistically significant, because much of the work on hypotension and cognitive impairment suggests that advancing age may be a co-contributor [45, 52]. Analogous to the findings reported in the non-SCI population, it is reasonable to consider that persistent or intermittent hypotension may contribute to impaired memory and cognitive function in individuals with SCI.

There is speculation that the diminished cognitive performance reported in hypotensive compared to normotensive individuals is the result of long-standing cerebral hypoperfusion due to the chronically low blood pressure [24]. Cerebral vasculature autoregulation acts to maintain adequate cerebral perfusion pressures within a "normal range" of systemic blood pressures (i.e., mean arterial pressures between 60 and 150 mmHg) [30]; there is controversy, however, regarding the theoretical lower limit. Recent evidence suggests that the lower threshold (i.e., 60 mmHg) may be higher than previously assumed [6, 18, 26, 33, 41, 42]. Because relative hypotension is a common clinical feature in persons with SCI, particularly those with tetraplegia, studies designed to address the probable association between decrements in cerebral blood flow and cognitive function are warranted.

In addition, autonomic cardiovascular dysregulation, per se, may contribute to the cognitive deficits reported in individuals with SCI. There is evidence which suggests an

Table 3 Raw and Normative Cognitive Scores and prevalence of impairment

	Raw scores		*T* scores			Impaired	
	Mean ± SD		Mean ± SD		*P* value	*N* (%)	
	Hypo	Normo	Hypo	Normo		Hypo	Normo
Memory (CVLT)							
Total recall	44.1 ± 10.5	55.2 ± 7.6	46.0 ± 10.4	59.7 ± 7.0	<0.01	2 (18)	0
Short Delay	8.8 ± 3.6	12.3 ± 2.7	44.1 ± 11.8	58.9 ± 8.6	<0.01	2 (18)	0
Long delay	9.5 ± 4.2	12.9 ± 3.5	45.0 ± 12.6	59.4 ± 9.4	<0.02	2 (18)	0
Recognition	13.7 ± 1.8	15.5 ± 1.4	43.6 ± 13.1	56.3 ± 5.2	<0.02	2 (18)	0
Attention and processing							
Oral Trails A	7.9 ± 2.0	6.6 ± 0.9	34.2 ± 19.6	48.9 ± 8.9	<0.06	6 (55)	2 (22)
Digit Span Total	14.1 ± 4.0	16.4 ± 5.6	43.7 ± 9.1	49.3 ± 13.3	NS	2 (18)	1 (11)
Stroop Word	87.9 ± 14.2	86.4 ± 8.3	37.8 ± 10.1	37.5 ± 6.5	NS	6 (55)	4 (44)
Stroop Color	60.1 ± 7.4	57.8 ± 5.7	35.3 ± 5.7	34.0 ± 4.9	NS	8 (73)	5 (56)
Language							
COWAT	37.5 ± 12.6	34.9 ± 11.1	45.3 ± 9.6	44.6 ± 9.4	NS	3 (27)	2 (22)
Executive function							
Oral Trails B	32.3 ± 15.1	35.1 ± 14.6	41.4 ± 14.5	40.4 ± 10.8	NS	3 (27)	3 (33)
Stroop Color Word	29.8 ± 7.4	32.8 ± 5.7	36.8 ± 6.9	41.5 ± 4.9	0.1194	4 (36)	1 (11)

Hypo Hypotensive group, *Normo* normotensive group

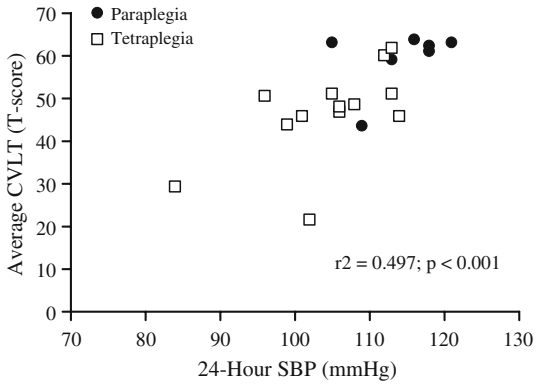

Fig. 1 The relationship between 24-h SBP and the average normalized *T*-score on the CVLT memory test; open squares are subjects with tetraplegia, closed circles are subjects with paraplegia. The relationship between average normalized CVLT *T*-score and 24-SBP was significant after controlling for age, level of lesion (continuous) and BDI depression score

association between the autonomic responses to arousing stimuli and the long-term recall of that stimulus [7, 8, 22, 46, 50]. Adrenergic blockade, compared to placebo, significantly reduced long-term memory of emotionally arousing stimuli [8, 46], whereas post-viewing epinephrine injection improved the long-term recall in healthy volunteers [7]. Therefore, chronic adrenergic denervation among the cervical and high paraplegic (above T6) subjects (91% of the hypotensive cohort) may have influenced the cognitive performance, specifically the memory deficits reported herein.

Final consideration

Increased reliance on the renin–angiotensin–aldosterone system (RAAS) for blood pressure maintenance is a well-documented physiological adaptation to sympathetic vascular denervation in persons with tetraplegia [31, 36–38, 56]. The role of angiotensin II in the development of atherosclerotic disease independent of BP can be inferred from clinical trials in which angiotensin converting enzyme (ACE) inhibition (ACEi) significantly lowered the incidence of ischemic heart disease without lowering blood pressure [12, 60]. Moreover, a direct effect of angiotensin II in the promotion of atherosclerotic lesions has been documented in an animal model of hyperlipidemia, in the absence of hemodynamic influences [13]. In addition, a recent report suggests poorer cognitive performance in persons with high ACE activity [43] and improvements in memory and mental task performance following ACEi [51]. Although speculative, changes in cognitive performance in hypotensive individuals with SCI may be a consequence of increased dependence on the RAAS and the associated vascular degeneration compared to the normotensive cohort.

Study limitations

There is an increased prevalence of sleep apnea in persons with tetraplegia [34] resulting in episodic oxygen desaturation and hypoxemia [5, 27]. Impaired cognitive performance in association with sleep apnea-related hypoxemia

has been reported in persons with tetraplegia [49]. There were a disproportionate number of individuals with tetraplegia in the hypotensive group, which may have contributed to the cognitive findings. In an attempt to minimize the effects of medication use on cognitive performance, we excluded individuals on the most commonly prescribed medications known to affect central nervous system function. Hence, the use of other medications with central nervous system action may have influenced the cognitive deficits reported herein.

Conclusions

There is evidence in the non-SCI population that chronic hypotension is associated with cognitive deficits, and this is the first report to suggest a similar association between low systemic blood pressure and cognitive impairment in the SCI population. Although there is evidence in the non-SCI population of improved cognitive performance following pharmacological elevation in blood pressure [20], to date, there has been surprisingly little attention or consideration given to the treatment and clinical management of hypotension in persons with SCI. Thus, investigations aimed at improving our appreciation of this condition and increasing our clinical armamentarium for the safe and effective treatment of hypotension in the SCI population appears necessary.

Acknowledgments This research was supported by the Veterans Affairs Rehabilitation Research and Development Service (#B3346V, #B4723H and #B4162C), the National Institute of Health (#P50AG005138).

Conflict of interest statement We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated and, if applicable, we certify that all financial and material support for this research (e.g., NIH or NHS grants) and work are clearly identified.

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