Impaired Carotid Baroreflex Control of Arterial Blood Pressure in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS), a progressive neurological disease, can lead to impairments in the autonomic control of cardiovascular function. We tested the hypothesis that individuals with relapsing-remitting MS (n=10; 7 females, 3 males; 13 ± 4 yrs from diagnosis) exhibit impaired carotid baroreflex control of blood pressure and heart rate compared to sex, age, and body weight matched healthy individuals (CON: n=10; 7 females, 3 males). At rest, 5-s trials of neck pressure (NP; +40 Torr) and neck suction (NS; -60 Torr) were applied to simulate carotid hypotension and hypertension, respectively, while mean arterial pressure (MAP; finger photoplethysmography), heart rate (HR), cardiac output (CO; Modelflow), and total vascular conductance (TVC) were continuously measured. In response to NP, there was a blunted increase in peak MAP responses (MS: 5±2 mmHg) in individuals with MS compared to healthy controls (CON: 9±3 mmHg; P=0.005), whereas peak HR responses were not different between groups. At the peak MAP response to NP, individuals with MS demonstrated an attenuated decrease in TVC (MS, -10±4% baseline vs. CON, -15±4% baseline, P=0.012), whereas changes in CO were similar between groups. Following NS, all cardiovascular responses (i.e., nadir MAP and HR and percent changes in CO and TVC) were not different between MS and CON groups. These data suggest that individuals with MS have impaired carotid baroreflex control of blood pressure via a blunted vascular conductance response resulting in a diminished ability to increase MAP in response to a hypotensive challenge.
New and Noteworthy

This study is the first to report carotid baroreflex responsiveness to simulated hypotension and hypertension in individuals with MS. The novel findings of our study are twofold. First, carotid baroreflex mediated increases in blood pressure in response to hypotensive stimuli (NP) were attenuated in individuals with MS. Second, the impaired responsiveness to hypotension appeared to be due to a diminished ability to decrease vascular conductance.


**Introduction**

Multiple sclerosis (MS), the most common disabling neurological disorder of young adults, is a progressive autoimmune disease affecting the central nervous system (9). This disease results in the demyelination of axons leading to slowed or blocked nerve conduction and ultimately axonal loss within the brain and spinal cord. Abnormal nerve conduction resulting from demyelination disrupts communication to, from, and within the central nervous system causing a constellation of neurological clinical signs and symptoms (32, 35).

Because the underlying pathophysiology of MS becomes more severe as areas of disease progression get larger and involve more of the central nervous system, it is likely the autonomic nervous system is affected (32). Case in point, impaired autonomic control of cardiovascular function has been reported in up to two-thirds of individuals with MS (1, 34). The most perilous health-related concern related to this autonomic cardiovascular dysfunction is the prevalence of orthostasis-related symptomology (i.e., orthostatic dizziness and orthostatic intolerance) in greater than 50% of people in this clinical population (2, 27).

Orthostasis-related symptomology is avoided in healthy individuals by the homeostatic regulation of blood pressure. Arterial baroreflex control of blood pressure is essential for short-term (i.e., beat-to-beat) regulation of blood pressure (44, 46). The arterial baroreceptor reflex prevents large fluctuations of arterial blood pressure by providing the central nervous system with continuous information from stretch sensitive baroreceptors originating at the carotid sinus and aortic arch. This classic negative-feedback reflex system is completed by dynamically modulating changes in blood pressure through efferent autonomic neural activity. In its most simplistic form, a decrease in arterial blood pressure elicits decreases in afferent firing of the baroreceptors. This diminished afferent nerve activity, through integration in the nucleus tractus solitareus of the central nervous system, reflexively increases efferent sympathetic nerve activity to the heart and blood vessels and decreases parasympathetic nerve activity to the heart. This results in an increase in cardiac output (i.e., due to increased heart rate), peripheral
vasoconstriction and, ultimately, a corrective increase in blood pressure. In contrast, increases in arterial blood pressure elicit an increase in afferent firing of the baroreceptors reflexively decreasing sympathetic nerve activity to the heart and blood vessels and increasing parasympathetic nerve activity to the heart. This results in a decrease in heart rate and cardiac output, peripheral vasodilation, and ultimately a corrective decrease in blood pressure.

Recently, Keller et al. have demonstrated reduced spontaneous muscle sympathetic nerve activity (MSNA) in individuals with MS compared to healthy controls (28). MSNA is an index to assess the sympathetic outflow of the central nervous system, which is in part orchestrated by arterial baroreceptors (4). It is therefore reasonable to suspect that the autonomic neural regulation of beat-to-beat fluctuations in blood pressure by the arterial baroreflex is altered in individuals with MS. Prior investigations on cardiovascular autonomic dysfunction in MS have mostly been descriptive in nature, failing to provide mechanistic insight (1, 3, 17–19, 34, 38, 41, 43, 45). To our knowledge, there has been only one attempt to assess baroreflex control in individuals with MS. Utilizing dynamic sinusoidal neck suction to induce carotid hypertension, Sanya et al. (2005) demonstrated baroreflex impairments in persons with MS. Although these findings suggest an altered neural regulation of blood pressure in MS, no consideration was given to carotid baroreflex responsiveness to decreases in blood pressure.

With greater than 50% of this clinical population reporting orthostasis-related symptomology, it is therefore critical to more completely understand how MS alters baroreflex control of heart rate and blood pressure, particularly to a hypotensive stress. By using a variable neck pressure collar to manipulate the carotid baroreceptors, we tested the hypothesis that individuals with MS exhibit blunted responses following carotid baroreceptor hypotensive and hypertensive perturbations compared to sex, age, and body weight matched healthy controls. The end goal was to gain a more comprehensive understanding of how MS independently alters carotid baroreflex control of heart rate and blood pressure at rest.
Methods

Subjects

Participants from the following two groups were investigated: 1) individuals with clinically definite relapsing-remitting MS [MS; n=10 (7 females, 3 males)]; and 2) healthy BMI, age, race, and sex-matched controls [CON; n=10 (7 females, 3 males)]. We focused on relapsing-remitting MS because it is the most common disease course with approximately 85% of individuals with MS initially diagnosed with this form of the disease (47). All individuals with MS reported experiencing dizziness to some degree with standing (orthostatic dizziness). However, dizziness was not reported as one of their top three MS-related symptomatic concerns.

No subject had a history or symptoms of cardiovascular or pulmonary disease. There is compounding evidence to show that sex, age, and race influence carotid baroreceptor function (7, 12, 14, 15, 22, 23, 30). Thus, in an effort to minimize these variables, each individual with MS was matched to a healthy control of the same sex, age, race, height, and weight. Two participants with MS were currently on anti-depressive medication at the time of the study. Although no studies have directly examined the effects of anti-depressive medication on responses to acute carotid baroreceptor perturbation, there is evidence to suggest that anti-depressive medication alters sympathetic nerve firing (10). To address this potential cofounding variable, the aforementioned two participants with MS were matched to healthy controls taking the exact same anti-depressive medication. Female participants were not tested in a specific phase of the menstrual cycle due to recent evidence suggesting minimal influences on carotid baroreflex control (29). All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the Institutional Review Board of Southern Methodist University.

Participants provided informed written consent prior to testing.

Experimental Procedures

Neck Suction (NS) and Neck Pressure (NP)
For this study, we focused on the baroreceptors located in the carotid sinus due to their accessibility for noninvasive manipulation. The responsiveness of the carotid baroreflex in the short-term regulation of heart rate and blood pressure can be examined quantitatively by utilizing a variable pressure neck chamber system to selectively load (simulated hypertension via neck suction) and unload (simulated hypotension via neck pressure) the carotid baroreceptors (7, 11, 33). In all familiarization and actual experimental trials, subjects were positioned semi-recumbent (~45°) on a patient table. Five-s pulses of -60 Torr neck suction (NS) and +40 Torr neck pressure (NP) were applied to load and unload the carotid baroreceptors, respectively (7, 11, 13, 30, 36). The neck collar (Physiology Research Instruments LC; Austin, TX) was fitted around the anterior two-thirds of the neck with each NS and NP stimulus being delivered 50 ms after the second consecutive R-R interval that did not vary by >50 ms using customized computer-controlled software as previously described (7, 15, 39). A variable pressure source using a 3-stage vacuum/blower motor (Ametek Lamb; Berwyn, PA) in combination with a computer controlled throttle valve was used to generate the changes in neck collar pressure. To accurately quantify the stimulus applied, a silicon piezoresistive pressure sensor (Freescale Semiconductor; Austin, TX) was connected to a port on the collar. To minimize respiratory-related modulation of HR, the 5-s pulses of NS and NP were delivered to the carotid sinus during a brief 12-15-s breath hold at end expiration phase (8, 14).

**Familiarization Sessions**

All subjects participated in at least two familiarization sessions before the actual experimental visit. The initial familiarization session included screening subjects to identify the location of the carotid sinus bifurcation using Doppler ultrasound to ensure that the neck collar fully enclosed the carotid sinuses. Although transmission of NS and NP to the carotid sinus has been shown to be near complete, there is variability in the location of the carotid sinuses that requires consideration (40). Subsequently, all subjects were familiarized with the study procedures and fitted with a collar based on carotid sinus location and observed neck size.
Practice trials of NS and NP were then performed to determine directionally appropriate HR and BP responses. The second familiarization session included additional practice trials of NS and NP to assure subjects were comfortable with the experimental protocol.

**Experimental Protocol**

Subjects refrained from caffeine, alcohol and intensive exercise 24 h before the study day. Upon arrival, subjects were positioned semi-recumbent (~45°) on a patient table in a constant ambient room temperature (23-24 °C) and instrumented for continuous measures of HR and BP. After instrumentation, subjects were fitted with the neck collar for the application of NS and NP and 5 min of baseline data were collected. Carotid baroreflex-mediated changes in HR and BP were then determined by applying random-ordered single 5-s pulses of NS and NP as described above. Ten trials for each NS and NP were performed with a minimum of 45 s of recovery allotted between trials to allow all physiological variable to return to pre-stimulus values. The rationale for performing ten trials of NS and NP was to better characterize individual carotid baroreceptor responses for all cardiovascular variables as previous utilized by Credeur et al (7).

**Experimental Measurements**

Heart rate (HR) and respiratory rhythm (electrical impedance) were continuously monitored using a standard lead II surface ECG (Solar 8000i, General Electric, NY, USA) interfaced with a cardiotachometer (CWE, Ardmore, PA, USA). Beat-to-beat blood pressure was measured by continuous finger cuff photoplethysmography (Finometer, FMS, Amsterdam, The Netherlands) with resting values verified by brachial artery auscultation (SunTech, Medical Instruments Raleigh, NC, USA).

**Data Analysis**

Data including the ECG, arterial BP waveform, neck chamber pressure and respiratory signals were sampled at 100 Hz through a commercial data-acquisition system (Biopac System, Santa Barbara, CA, USA). Cardiac output (CO) was estimated from the arterial BP waveform
using the Modelflow method (TNO-TPD, Biomedical Instrumentation, Amsterdam, Netherlands),
which incorporates age, sex, weight, and height (24, 25, 30). Recently, Fadel and colleagues
validated the use of Modelflow to measure CO during carotid baroreflex perturbations
demonstrating no significant differences between the beat-to-beat CO responses to NS and NP
recorded simultaneously by Doppler echocardiography in comparison to Modelflow (30). Total
vascular conductance (TVC) was calculated as $\text{TVC} = \frac{\text{CO}}{\text{MAP}}$.

Characterization of carotid baroreflex response variables

For all carotid baroreflex-mediated changes, the peak change in HR and BP were
determined in the cardiac cycle (R-R interval) at which the largest change from pre-stimulus
values occurred and compared to the pre-stimulus (3 cardiac cycle average) for each trial of NS
and NP. CO and TVC were calculated from the cardiac cycle at the peak and nadir blood
pressure responses and were analyzed as percent changes from the pre-stimulus value
(%baseline). Changes in HR and BP and percent changes in CO and TVC for each subject were
determined for each trial and averaged across all trials of NS and NP, respectively, to provide
individual mean responses. These individual mean responses were then averaged to provide
group means.

Statistical Analysis

All values are presented as means ± SD. Statistical analyses were conducted using Prism
6 (GraphPad Software Inc., La Jolla, CA). Unpaired $t$-tests were used to compare group
differences in baseline characteristics and cardiovascular responses to NS and NP. Statistical
significance was set at $P<0.05$.

Results

Baseline Subject Characteristics

General baseline characteristics for individuals with MS and matched healthy controls are
summarized in Table 1. All individuals with MS were diagnosed with relapsing-remitting
multiple sclerosis with an average diagnosis duration of $12.6 \pm 4.2$ years at the time of
participating in the study. Disease modifying medications used by individuals with MS included: Avonex (Interferon Beta-1a), n=4; Gilenya (Fingolimod), n=2; Copaxone (Glatiramer Acetate), n=2; Tecifedera (Dimethyl Fumarate), n=2. Individuals with MS and their matched healthy controls were similar in age, height, weight, and body mass index. Furthermore, resting heart rate, mean arterial pressure, cardiac output, and total vascular conductance were not different between groups.

Baroreflex Responses to Simulated Carotid Hypotension (Neck Pressure)

Representative beat-to-beat HR and MAP tracings during NP for an individual with MS and a matched control are presented in Figure 1. Peak HR and MAP responses for both groups are presented in Figure 2. In response to selective baroreceptor unloading (NP; +40 Torr), increases in MAP were blunted in subjects with MS compared to healthy controls ($P=0.005$; Figure 2, panel B). However, increases in HR in subjects with MS were not statistically different compared to healthy controls ($P=0.28$; Figure 2, panel A). In response to NP, percent changes in CO and TVC from baseline at the time of the peak MAP response in individuals with MS and matched healthy controls are presented in Figure 3. Percent changes in CO from baseline were similar between groups ($P=0.44$; Figure 3, panel A). However, individuals with MS demonstrated a significantly reduced percent decrease in TVC from baseline ($P=0.012$; Figure 3, panel B) compared to healthy controls.

Baroreflex Responses to Simulated Carotid Hypertension (Neck Suction)

Individual beat-to-beat MAP and HR tracings during NS from a representative individual with MS and a matched healthy control are presented in Figure 4. Nadir HR and MAP responses for both groups are presented in Figure 5. In response to selective baroreceptor loading (NS; -60 Torr), nadir decreases in MAP and HR were not statistically different between groups (MAP: $P=0.38$; HR: $P=0.36$; Figure 5). In response to NS, changes in CO and TVC at the time of the nadir MAP response in individuals with MS and matched healthy controls are presented in Figure 6. Similar to the HR and MAP data, there was no significant difference between groups in
Discussion

To the authors’ knowledge, the present study is the first to demonstrate the independent influence of MS on carotid baroreflex mediated responses to simulated hypertension and hypotension (i.e., carotid baroreceptor loading and unloading); as well as determine the influence of the heart (CO) and peripheral vasculature (TVC) at the time of the peak BP responses. The novel findings of our study are twofold. First, carotid baroreflex mediated increases in MAP in response to hypotensive stimuli (neck pressure) were reduced in individuals with relapsing-remitting MS. Second, causes of this reduced corrective increase in MAP in response to a hypotensive stimulus appeared to be due to a diminished decrease in TVC. In contrast to NP, carotid baroreflex responses to simulated hypertension (neck suction) were similar in MS and matched healthy controls.

Recently, the interplay between autonomic dysfunction and the pathogenesis and progression of multiple sclerosis has gained traction (5). There is accumulating evidence that MS affects cardiovascular function. The incidence of orthostatic dizziness is as high as 50% in individuals with MS (1, 16, 28, 41). The findings of this study not only provides evidence that MS abnormally influences carotid baroreflex control of blood pressure to a hypotensive stimulus; but more importantly gives implications on how this impairment may factor into the orthostatic related symptomology.

One of the advantages to utilizing the application of brief, sustained periods of neck pressure/suction is the ability to quantify the influence of cardiac output and total vascular conductance to carotid baroreflex-mediated changes in arterial pressure. With this quantification, further insight into the influence of MS on short-term blood pressure control was gained. Prior studies have demonstrated that compensatory blood pressure responses to carotid baroreceptor perturbation were predominantly attributable to changes in peripheral vascular tone (i.e. total...
vascular conductance) (30, 36, 37). In this regard, the primary finding of a significant reduced peak blood pressure response after hypotensive perturbations suggests impairments in vasomotor adjustments in MS potentially due to abnormal sympathetic modulation of blood vessels. This notion is supported by the current findings that the percent decrease from baseline in TVC to NP is significantly lower in the MS group compared to healthy controls.

Corroborating this conjecture of altered sympathetic blood pressure regulation, our lab has recently observed low MSNA at rest in persons with MS (28). Given the involvement of MSNA in blood pressure regulation, reductions in MSNA in individuals with MS, taken together with the current findings, indicate an impaired sympathetic modulation of the vasculature in MS in response to hypotensive stimuli. Given that women are two to three times more likely to be diagnosed with MS along with strong evidence that suggest vasoconstrictor responsiveness is blunted in young women, the impact of reduced baroreflex-mediated vasoconstriction may be compounded (21, 26, 31, 48). Furthermore, men living with MS progress more rapidly which may lead to greater carotid baroreflex dysfunction (20). Therefore, more studies are needed to further investigate mechanism(s) impairing the baroreflex control of BP to hypotension in MS with attention on potential sex differences.

In the current study, nadir heart rate and blood pressure responses to simulated baroreceptor loading (i.e. neck suction) were not different between the two experimental groups. In 2005, Sanya et al. reported baroreflex impairments in persons with MS subjected to only neck suction compared to healthy controls (42). While the exact reason for the differences with the findings from the present study are not clear, contrasting methodologies may be involved. Sanya et al. utilized dynamic sinusoidal neck suction stimulation (0 to –30 mmHg at 6 cycles/minute and 12 cycles/minute) compared to the five-s static stimulation utilized in our study. Furthermore, they utilized spectral analysis to separately evaluate the cardiac and blood pressure responses to the baroreceptor stimulations. Nevertheless, despite these differences, the interpretive conclusions of their study are complimentary to ours in that there appears to be an
imPAIRment in baroreflex responsiveness in MS individuals. Future studies quantifying full
carotid baroreflex stimulus response curves are warranted to gain further insight into baroreflex
function in MS.

In regards to clinical implications, presently there is a lack of consensus regarding a clear
definition of cardiovascular autonomic dysfunction in persons with MS, making diagnosis and
treatment more difficult (41). The current results provide experimental evidence demonstrating
the inability of individuals with MS to reflexively increase their blood pressure in response to a
hypotensive stimulus. This leads to a possible mechanistic explanation of why this clinical
population often experiences orthostatic related symptomology. Indeed, our findings emphasize a
potentially deleterious aspect of the disease that likely impacts these individuals on a daily basis.
As such, the carotid baroreflex abnormalities observed in this study highlight the importance for
recognition and continued research of this dysfunction as it relates to daily activities in this
relatively understudied patient population.

A potential limitation of the study that requires consideration is that all individuals with
MS that participated in our study were on disease modifying therapies. According to the 2015
consensus paper by the Multiple Sclerosis Coalition on the use of disease modifying therapies,
FDA-approved disease-modifying treatment is recommended and should be continued
indefinitely (6). Taking persons with MS off of their disease-modifying medication would be
impractical and not suggested by treating clinicians. In light of this circumstance, it is difficult to
distinguish with certainty that the abnormal carotid baroreflex responses were due to the disease
process itself, the sequela of using disease-modifying therapies, or a combination of both.
Regardless, physicians and health care providers need to be aware of this clinical feature that
affects the majority of individuals with MS.

Conclusion

In conclusion, individuals living with MS demonstrate a diminished ability to increase
blood pressure in response to a hypotensive stimuli compared to healthy controls. Furthermore,
this diminished ability to increase blood pressure can be attributed to a blunted vascular response.

Our findings suggest that carotid baroreceptor control of blood pressure is compromised in this clinical population that may be contributing towards orthostasis-related symptomology associated with MS.
Acknowledgments

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).
### Table 1. Baseline Subject Characteristics

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Values are mean ± SD.
Figure 1. Individual beat-to-beat tracings in heart rate (panel A) and mean arterial (panel B) in response to selective carotid baroreceptor unloading (+40 Torr, neck pressure) for a representative person with MS (MS) and a matched healthy control (CON).

Figure 2. Group and individual summary data showing mean peak heart rate responses (panel A) and mean peak blood pressure responses (panel B) elicited by selective baroreceptor unloading (NP; +40 Torr) in individuals with MS (MS) and matched healthy controls (CON). *Significantly different from healthy controls (P<0.05).

Figure 3. Group and individual summary data showing percent changes from baseline in cardiac output (panel A) and total vascular conductance (panel B) at the time of the peak MAP response elicited by selective baroreceptor unloading (NP; +40 Torr) in individuals with MS (MS) and matched healthy controls (CON). *Significantly different from healthy controls (P<0.05).

Figure 4. Individual beat-to-beat tracings in heart rate (panel A) and mean arterial responses (panel B) in response to selective carotid baroreceptor loading (-60 Torr, neck suction) for a representative person with MS (MS) and a matched healthy control (CON).

Figure 5. Group and individual summary data showing mean nadir heart rate responses (panel A) and mean nadir blood pressure responses (panel B) elicited by selective baroreceptor loading (NS; -60 Torr) in individuals with MS (MS) and matched healthy controls (CON).

Figure 6. Group and individual summary data showing percent changes from baseline in cardiac output (panel A) and total vascular conductance (panel B) at the time of the nadir MAP response elicited by selective baroreceptor loading (NS; -60 Torr) in individuals with MS (MS) and matched healthy controls (CON).


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Figure 1.

A

Δ HR (bpm)

Time (s)

+40 Torr

B

Δ MAP (mmHg)

Time (s)

+40 Torr
Figure 2.

A

Δ Heart Rate (bpm)

CON

MS

B

Δ MAP (mmHg)

CON

MS
Figure 3.
Figure 4.
Figure 5.
Figure 6.