Arterial Function

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Arterial Compliance in Multiple Sclerosis: A Pilot Study

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A reduction in arterial compliance in patients with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus has been previously reported. It is caused by the effect that systemic inflammation has on the cardiovascular system. Multiple sclerosis (MS), an immune-mediated disease that exclusively affects the central nervous system (CNS), has a significant inflammatory component that is limited to that compartment. The potential effects of its inflammatory mediators in the cardiovascular system are largely unknown. *Purpose:* To examine large (C1) and small arterial compliance (C2) in patients with MS and compare them with healthy age-matched controls. To also determine whether any differences in C1 and C2 indices between participants diagnosed with relapsing remitting MS (RR-MS), secondary progressive MS (SP-MS), and controls exist. *Methods:* A total of 26 men and women between the ages of 18 and 64 diagnosed with MS and 25 healthy controls volunteered for this study. Arterial compliance was measured by using pulse contour analysis (PCA), which records and analyzes the blood pressure waveform data from the Arterial Pulse Wave Sensors. *Results:* Significant differences in C1 and C2 were found between young RR-MS and healthy young controls ($P < .05$), with the MS group showing lower arterial C1 and C2 compliance. No significant differences ($P > .05$) were seen for C1 or C2 values between older RR-MS, SP-MS, and healthy controls. *Conclusion:* Arterial compliance is significantly compromised in young individuals with MS, compared with age-matched controls, but not for older individuals, suggesting a systemic effect of an inflammatory process that predominantly affects the CNS.

Keywords: multiple sclerosis; arterial compliance; cardiovascular disease

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory, immune-mediated disease that affects the central nervous system (CNS).[1] Inflammation is an independent cardiovascular disease risk factor that is often associated with endothelial dysfunction[2] and loss of arterial compliance in both large and small arteries.[3] The effects that autoimmune diseases have on the cardiovascular system have been evaluated before but mainly concentrated on rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[4,5] There are few studies done in MS and those have looked almost exclusively at the autonomic system.[6-9] Changes in the peripheral arterial structure and function, such as thickening of the vessel wall, decreased small (C2) and large arterial compliance (C1), and reduction in distensibility of the large arteries,[5] are associated with aging[10-12] even in healthy adults,[13] more seen in women.[14] Arterial compliance is defined as the arteries' ability to expand and recoil along with cardiac pulsation and relaxation.[15] A decrease in arterial compliance is seen with conditions such as diabetes, hypertension, and hypertriglyceremia.[16] Individuals with autoimmune inflammatory diseases such as RA have documented reduction in arterial compliance.[3] Previous research

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has found that RA is associated with an increase in arterial stiffness,[17] particularly in patients with RA having prolonged corticosteroid therapy treatment.[18] Rheumatoid arthritis was also associated with earlier onset of atherosclerosis,[19] and disease duration was correlated with the thickness of carotid intima-media.[20]

To our knowledge, this is the first investigation that examines C1 and C2 in patients diagnosed with MS, providing further insight into cardiovascular parameters associated with this disease. The primary purpose of this study was to examine C1 and C2 in patients with MS and compare them with healthy age-matched controls (C). The secondary purpose was to investigate whether there were any differences in C1 and C2 values between patients with relapsing remitting MS (RR-MS) versus patients with secondary progressive MS (SP-MS) and healthy controls.

Our hypotheses were that healthy controls would have more compliant arteries compared with that of patients with MS and that patients with RR-MS would have better arterial compliance compared to patients with SP-MS.

Methods

Participants

Recruitment. This pilot study involved 51 participants between the ages of 18 and 64; 25 participants served as healthy controls and the remaining 26 participants had a diagnosis of MS, according to modified diagnostic McDonald's criteria.[21,22]

Participants were required to have relapsing remitting or secondary progressive MS. None of the participants were taking hormonal supplements, statins, or antihypertensive drugs, were current smokers, were diabetic, and had history of cardiovascular or peripheral arterial disease (defined by ankle-brachial index [ABI] index ≤ 0.90).[23,24] The participants were volunteers from Mercy Hospital and surrounding areas of Oklahoma City. All participants gave written informed consent prior to participation, and all procedures were approved by the Institutional Review Board at Mercy Hospital.

Research design. This study used a cross-sectional design with a control group (C, n = 25), a RR-MS (n = 22), and a SP-MS (n = 4), and all were assessed at 1 time point. Age, sex, and cardiovascular disease risk factors were obtained during medical history questioning. Height and weight of the participants were measured from a stadiometer and a scale, respectively (Detecto scale, MO). Body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressure was measured concurrently with the large and small arterial indices. To avoid potential diurnal variations, all patients were tested in a fasted and rested state in the morning of the visit.

Measurements

Pulse contour analysis. Arterial compliance measurements were obtained in the morning following an overnight fast of at least 8 hours and prior to engaging in any strenuous physical activity. Following approximately 10 minutes of rest in the supine position, large artery (C1) and small artery (C2) elasticity indices were obtained using an HDI/Pulsewave CR-2000 Cardiovascular Profiling System (Hypertension Diagnostic Inc, Eagan, MN). An appropriate-sized blood pressure cuff was placed around the participant's left upper arm, and the right wrist was placed in a rigid wrist brace to prevent the radial artery from moving during the measurements. An Arterial Pulse Wave Sensor was placed on the skin directly over the radial artery at the point of the strongest pulse. The sensor was adjusted to the highest relative signal strength, and the C1 and C2 measures were obtained during 30 seconds of blood pressure waveform collection. A touch screen computer and software was included in the data collection. The averages of the three 30-second trials were used for the analyses after no significant differences were found between the TRIALS using 1-way repeated measures analysis of variance (ANOVA). The measuring tool used (PCA) is a noninvasive instrument that has been proven to be a reliable tool for measuring C1 and C2.

Ankle-brachial index. The ABI was assessed using Doppler ultrasound technique (D.E. Hokanson, Inc, Bellevue, WA). Participants were examined in the supine position after a rest of at least 5 minutes. Systolic blood pressure (SBP) was measured in the right and left brachial artery by the oscillometric method and in the posterior tibial and dorsalis pedis arteries of both legs. The highest brachial systolic pressure and the artery yielding the highest SBP in the more diseased limb was used to calculate ABI

Table 1. Clinical Characteristics for Both Young Groups[a]

Variable	RR-MS (n = 9)	Controls (n = 9)
Age (years)	30.2 (4.49)	34.3 (6.4)
Height (cm)	175.5 (9.9)	173.2 (8.3)
Weight (kg)	79.1 (13.2)	81.2 (19.6)
BMI (kg/m^2)	26.4 (4.4)	27.2 (6.6)
SBP (mm Hg)	120.3 (12.9)	127.5 (12.2)
DBP (mm Hg)	69.7 (5.4)	71.8 (8.5)

NOTES: BMI = body mass index; DBP = diastolic blood pressure; RR-MS = relapsing remitting multiple sclerosis; SBP = systolic blood pressure.
[a] Values are expressed as means (SD).

(ABI = ankle systolic pressure/brachial systolic pressure).[24]

Statistical Analysis

Descriptive analyses are reported as means ± standard deviation (SD) for the dependent variables. Independent *t* tests were used to compare C1 and C2 for healthy controls and patients with MS.

Analysis of covariance (ANCOVA) was used to compare C1 and C2 after adjusting for body surface area. One-way ANOVA was performed to determine whether any significant difference existed between the older RR-MS and the older SP-MS group for C1 and C2 indices. A priori calculation demonstrated that the current study had an adequate sample size, based on previous literature[17] that obtained >80% power. These estimates were based on a population of RA individuals, but used the same technique. The significance level was $P \leq .05$. All statistical analysis was performed by SPSS 16.0 software (Chicago, IL).

Results

There were no significant differences between the 2 young groups for age, height, weight, BMI, SBP, or diastolic blood pressure (DBP), respectively ($P > .05$; Table 1). However, although a significance ($P = .047$) was found for BMI between males and females in the young group with RR-MS, no difference was found between this group and the young control group. The males in the RR-MS group had a significant higher BMI (n = 5, mean = 29.0 ± 8.00 [SD]) compared with that of females (n = 4, mean = 24.8 ± 4.50 [SD]).

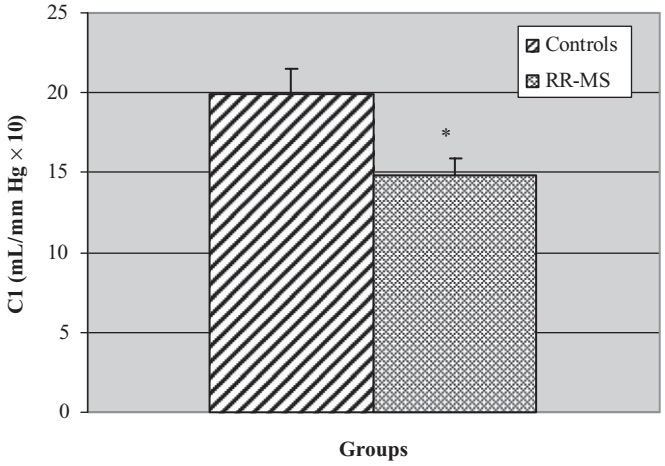

Figure 1. The C1 values for both young groups. *$P < .05$. Values are expressed as means (SE). C1 indicates large arterial compliance; RR-MS = relapsing remitting multiple sclerosis.

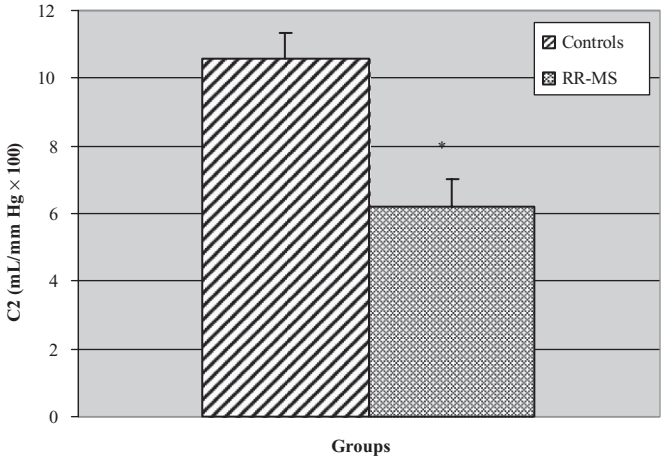

Figure 2. The C2 values for both young groups. *$P < .05$. Values are expressed as means (SE). C2 indicates small arterial compliance; RR-MS = relapsing remitting multiple sclerosis.

Young Group's C1 and C2

Significant differences in C1 and C2 between the 2 young groups ($P < .05$) were found with the MS group having decreased C1 (14.8 vs. 19.9 mL/mm Hg × 10) and C2 (6.1 vs. 10.5 mL/mm Hg × 100) compared with that of healthy controls (Figures 1 and 2, respectively). After adjusting for body surface area in the analysis, there still was a significant difference between the 2 young groups for C1 ($P = .038$) and C2 ($P = .007$) indices.

No differences were found for C1 and C2 indices between genders for the young RR-MS group. However, a significant difference was found for C2 only,

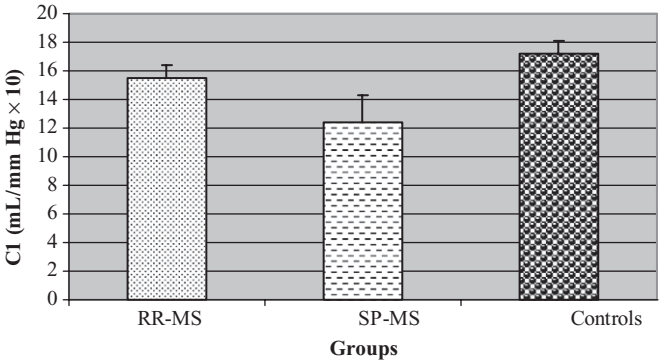

Figure 3. The C1 values for all 3 older groups. Values are expressed as means (SE; $P > .05$). C1 indicates large arterial compliance; RR-MS = relapsing remitting multiple sclerosis; SP-MS = secondary progressive multiple sclerosis.

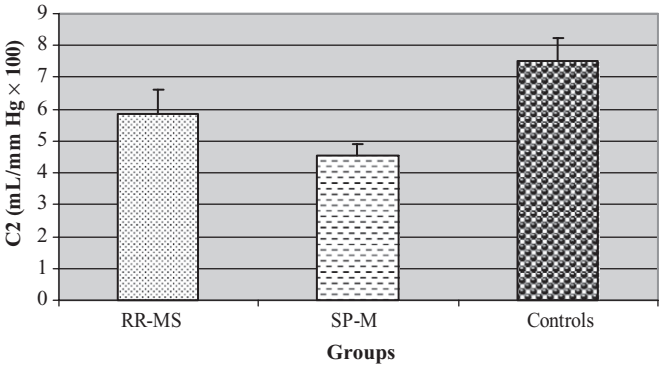

Figure 4. The C2 values for all 3 older groups. Values are expressed as means (SE; $P > .05$). C2 indicates small arterial compliance; RR-MS = relapsing remitting multiple sclerosis; SP-MS = secondary progressive multiple sclerosis.

Table 2. Clinical Characteristics for the 3 Older Groups[a]

Variable	RR-MS (n = 13)	SP-MS (n = 4)	Controls (n = 16)
Age (years)	48.8 (6.3)	49.7 (6.6)	48.8 (6.4)
Height (cm)	166.5 (5.5)	159.3 (6.5)	173.7 (9.2)
Weight (kg)	78.6 (15.2)	61.8 (6.9)	90.2 (13.0)
BMI (kg/m^2)	28.3 (5.5)	24.2 (1.6)	29.9 (4.2)
SBP (mm Hg)	129.3 (22.8)	139.0 (15.2)	131.7 (17.5)
DBP (mm Hg)	77.4 (13.4)	76.3 (7.5)	77.0 (10.4)

NOTES: BMI = body mass index; DBP = diastolic blood pressure; RR-MS = relapsing remitting multiple sclerosis; SBP = systolic blood pressure; SP-MS = secondary progressive multiple sclerosis.
[a] Values are expressed as means (SD).

between males and females for the healthy control group ($P = .049$), with men having a lower compliance (n = 13, mean = 9.65 $\pm$ 1.44) compared to that of females (n = 14, mean = 9.70 $\pm$ 2.51), C2 values, respectively.

Older Group's C1 and C2

No significant differences ($P > .05$) were observed for C1 or C2 indices (Figures 3 and 4, respectively), age, BMI, SBP, or DBP between the older RR-MS and SP-MS groups compared with healthy controls (Table 2). Although, not significant, there was a trend for increased arterial compliance in the healthy older control group for C1 at 17.25 (mL/mm Hg × 10) versus older RR-MS at 15.50 (mL/mm Hg × 10) and older SP-MS at 12.36 (mL/mm Hg × 10), respectively. The same was observed for C2, with the control group showing 7.53 (mL/mm Hg × 100) versus RR-MS 5.85 (mL/mm Hg × 100) and SP-MS 4.85 (mL/mm Hg × 100), respectively. No gender differences were found between any of the old groups and BMI, C1, and C2.

Discussion

We examined C1 and C2 in patients with MS, and compared them to healthy age-matched controls. Furthermore, we also wanted to investigate whether any differences in C1 and C2 values between patients with RR-MS, patients with SP-MS, and healthy controls existed. The uniqueness of this study is that we did demonstrate that arterial compliance is significantly compromised in young individuals diagnosed with MS, compared to age-matched healthy controls, suggesting a potential systemic effect of an inflammatory process that is primarily confined to the CNS. This coincides with a study[25] reporting altered endothelial function related to chronic inflammation in young patients with RA that were free of any cardiovascular risk factors and with low disease activity. No significant differences were

observed in SBP and DBP measures between the 2 groups, which are not in agreement with Saari et al who found significant decrease in blood pressure in patients with MS compared to healthy controls.[8] Although, not significant, there was a trend toward better arterial compliance in the healthy older control group for C1 and C2 compared to RR-MS and older SP-MS groups (although not significantly older).

Several studies have previously reported occurrence of up to as much as 90% of cardiovascular autonomic dysfunction in those diagnosed with MS[6-8,26-32] and has been linked to brainstem lesions,[26,31] particularly in the midbrain.[8] Other documented effects include orthostatic intolerance,[27,33] disease duration,[28] increased Expanded Disability Status Score,[26] progression of clinical disability[6,34] as well as severity of MS.[29]

The main limitation of this study is the cross-sectional design, which does not establish a cause and effect relationship between arterial compliance and MS. Another limitation is that the PCA is a noninvasive measure of C1 and C2, and an invasive measure would be more precise.

Conclusions

This study found significant differences of C1 and C2 indices between the young healthy group and the young MS group. This response was not seen in the older groups and raises awareness of potential risk for cardiovascular diseases in young adults with MS who have no other identifiable risk factors.

Future studies are warranted to examine the risk and development of cardiovascular diseases in the population with MS. Early identification of such changes could modify therapies accordingly and have a significant impact on outcome.

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