Calf Venous Compliance in Multiple System Atrophy

A. Lipp, M.D.¹; P. Sandroni, M.D.¹; J. Eric Ahlskog, M.D.¹; D. M. Maraganore, M.D.¹;
C. W. Shults, M.D.²; and P. A. Low, M.D.¹*

¹Department of Neurology, Mayo Clinic, Rochester, MN
²Department of Neurosciences, UCSD School of Medicine, San Diego, CA

Mayo Foundation
Autonomic Reflex Laboratory
Department of Neurology
200 First Street SW
Rochester, Minnesota 55905
Phone: 507-284-3375
Fax: 507-284-3133
Email: low@mayo.edu

*To whom correspondence should be addressed
ABSTRACT

In multiple system atrophy (MSA), increased venous compliance with excessive venous pooling is assumed to be a major contributor to orthostatic hypotension (OH); however, venous compliance has never been assessed in patients with MSA.

We evaluate the severity and distribution of adrenergic, cardiovagal, and sudomotor failure in 11 patients with probable MSA (MSA-P), 14 age- and gender-matched control subjects and 8 patients with Parkinson’s disease (PD) but not OH. Calf venous compliance as well as venous filling and capillary filtration were measured using calf plethysmography. Response to directly acting \( \alpha \)-adrenergic stimulation (10 mg midodrine) on calf venous compliance was additionally evaluated.

Contrary to our hypothesis, pressure-volume curves in the legs of MSA patients were flatter than in PD (P<0.05) patients or controls (P<0.001), this indicated reduced calf venous compliance in MSA. The MSA group had reduced venous filling compared to controls (P<0.001) or PD (P<0.001) but normal capillary filtration rate (P=0.73). Direct \( \alpha \)-adrenergic stimulation resulted in a slight but significant reduction of calf venous compliance in controls (P=0.001) and PD (P<0.001) but not in the MSA group. The compliance change in MSA significantly regressed with autonomic failure (composite autonomic severity scale – CASS, \( r^2=0.56 \)) but not with parkinsonism (UMSARS, \( r^2=0.12 \)).

Our data indicate that MSA patients with chronic OH have reduced, rather than increased, venous compliance in the lower leg. We postulate that chronic venous distension that is associated with OH results in structural remodelling of veins, leading to reduced compliance, a change which may protect patients against orthostatic stress.
Key words: veins, compliance, vascular capacitance, orthostatic hypotension, vasoconstriction.
INTRODUCTION

In humans, upright posture induces pooling of 300-800 ml blood in the lower extremities (40) and a subsequent decrease of venous return. Under physiological conditions, these changes are rapidly counteracted by the baroreflex, resulting in an increase in heart rate and in vascular sympathetic nerve activity and peripheral vasoconstriction. In addition, increased arteriolar vasomotor and limb skeletal muscle tone are thought to limit venous pooling during standing (5).

In multiple system atrophy (MSA), degeneration of preganglionic adrenergic neurons prevents baroreflex-mediated vasoconstriction resulting in insufficient total peripheral resistance response to standing. Loss of arteriolar vasoconstrictor tone also increases arteriovenous shunting and intravenous pressure in the lower leg (27). Thus, limb venous pooling is presumed to be increased during standing in MSA, although earlier studies have demonstrated only a modest or negligible rise in calf volume with ganglion blockade (2, 17). Venous compliance is reported to be increased in conditions with reduced orthostatic tolerance, a condition that is different to MSA (13, 34). However, limb venous compliance in MSA has never been directly measured, although recordings in 2 patients with pure autonomic failure showed a 2-3% increase in calf volume (35). In the present study, we tested the hypothesis that calf venous compliance is higher in MSA patients with OH compared to age-matched controls, recognizing full well the antagonistic roles of denervation versus the chronic effects of orthostatic stress on potential venous structural and innervational changes (25).

Leg vein denervation could potentially increase venous compliance and reduce preload, thus aggravating OH (11, 34), although the modest changes with ganglion
blockade suggests that this effect is modest (2, 17). The lack of venous pooling with
denervation may relate to the fact that, in healthy humans, sympathetic innervation of the
veins in the lower leg is scarce and thus does not appear to have a major role in
preventing orthostatic hypotension (8). Likewise, systemic infusion of vasoconstrictor
agents produced a negligible effect on venous tone in the lower leg (7). However, the
function of veins can change in disease states. For instance, local administration of
norepinephrine into the veins of the feet produced a large increase in venous contractile
responsiveness in patients with hyperadrenergic OH (31). In addition, it has been shown
that veins undergo functional changes including increased adrenergic sensitivity in
response to chronically increased transmural pressure (20, 24).

To evaluate further adrenergic control of leg veins in neurogenic OH, our
secondary hypothesis was that calf venous compliance could be decreased by an alpha-
adrenergic agonist (midodrine). To control for the effects of parkinsonism causing
increased skeletal muscle tone, we also tested patients suffering from idiopathic
Parkinson’s disease without OH.
METHOD

Subjects. The study cohort comprised eleven patients with multiple system atrophy of the Parkinsonian type (MSA-P) according to the consensus criteria (10), eight patients with idiopathic Parkinson’s disease, and fourteen age- and sex-matched, predominantly sedentary control subjects. The study was approved by the Institutional Review Board of the Mayo Clinic, and all subjects gave written informed consent before participation. Participants refrained from exercise, alcohol and caffeine for 24 hours and from nicotine at least four hours. All vasoactive medication, including levodopa, was discontinued at least 5 half-lives before the study. Two MSA patients were on fludrocortisones 0.1 mg/day. This was stopped for 2 days prior to the study. Clinical pedal edema to digital indentation was exclusionary. Patients stayed overnight in a hotel within the campus, had an early light breakfast, and underwent plethysmographic study in mid or early morning, at least 2 hours after an early light breakfast. This protocol resulted in only minimal standing time by the study participants to obviate any dependent edema.

Protocol. Subjects were placed in a supine position with the leg slightly elevated above heart level. After a 20-minute period of quiet rest, heart rate (chest ECG), blood pressure (Finometer model 1, FMS, the Netherlands), respiration, and calf volume were continuously recorded for a further 10-minute baseline period.

Venous compliance plethysmography. Changes in calf volume were continuously measured with mercury-in-Silastic strain gauges (model EC6, D. E. Hokanson, Bellevue, WA). The strain gauge was placed around the calf at that point where the largest circumference was measured and electronically calibrated (14). A 0.5% increase of
gauge length or calf circumference is proportional to a 1% rise in calf volume (39) which is expressed in milliliters per 100 milliliter of tissue. Changes in calf volume were induced by venous occlusion. Therefore, a venous occlusion cuff was placed around the thigh proximal to the knee and connected to a custom designed rapid cuff inflator as previously described (12). The cuff inflator also provides a continuous readout of cuff pressure which served as an estimate of intravenous pressure.

Venous compliance was measured by a technique developed by Robinson and Wilson (28) and further adapted by Halliwill (12). Following rapid inflation, pressure in the venous occlusion cuff was maintained for 8 minutes to assure equilibrium of intravenous and cuff pressure. Subsequently, cuff pressure was decreased by 1 mmHg per sec, while changes in calf volume were continuously recorded (Fig. 1, top). The measurement was repeated four times, twice before and twice after the administration of 10 mg midodrine following baseline periods of 10 and 30 minutes, respectively. Thus, each participant provided two sets of data to minimize unusable data due to motion artifacts.

**Data Analysis and Statistic.** Data were recorded at 250 Hz, online averaged, and stored on a computer (LabView, National Instruments, Austin, TX). Data were analyzed off-line using customized signal-processing software.

Compliance was calculated and statistically analyzed by a technique developed by Halliwill (12). Pressure-volume curves were generated from the pressure-volume relationship when the pressure was decreased at 1 mmHg/sec. Data below 10 mmHg were excluded from further analysis. The resulting pressure-volume curves provide an estimate of compliance which was defined as the first derivative of the pressure-volume relationship.
curve (12) (Fig. 1, bottom). Regression models were calculated using GraphPad Prism (GraphPad Prism, Version 3, GraphPad Software, San Diego, CA, USA). Group-wise comparison of the pressure-volume and pressure-compliance data were done using repeated measurement ANOVA and Student’s t-test (SPSS, Version 10, SPSS Inc., Chicago, IL, USA), respectively.

Calculation of venous filling and capillary filtration was based on the change in calf volume that occurred while the collection cuff pressure was increased to and maintained at 60 mmHg for 8 minutes (Fig. 1, middle). Within that period, the volume curve can be separated into an initial exponential segment and a subsequent linear component, reflecting venous filling and capillary filtration, respectively (9).

One source of error with this approach in the calculation of capillary filtration is the determination of the transition point on the time-volume curve where the steeper filling segment evolves into a more linear filtration segment. Even a modest shift in the transition point can substantially alter the slope of the regression line used to calculate capillary filtration. In the present study, we have developed an approach that minimizes transition point errors by considering the curve as a whole, instead of two arbitrary portions. In response to venous occlusion, the volume of the calf rises in proportion to the applied occlusion pressure and thus, can be expressed by equation 1 (xe = blood volume flowing into the occluded vein; xa = whole calf volume).

\[ xa(t) = K_{\text{filling}} \times xe(t) \]  

The subsequent volume increase is caused by fluid transudation thru the capillary wall. This process is time dependent and can be described by equation 2.

\[ xa(t) = K_{\text{filtration}} \times \int xe(t) \times dt \]
Since the sequential changes of calf volume do not follow cuff pressure immediately but with a brief delay, the behaviour of the volume change resembled a delayed proportional-integrative (PI) system (first order PI system, equation 3).

\[ \frac{dx(t)}{dt} + x_a(t) = K_{\text{filling}} * x_e(t) + K_{\text{filtration}} * \int x_e(t) \, dt \]  

In our study, the three constants defining a PI system correspond to venous filling, capillary filtration and the delay of the volume response. Thus, in the present study, fitting of the time-volume curve to a PI-system allowed assessment of both venous filling and filtration independent of a transition point, since the whole curve was considered in the analysis (equation 4).

\[ \text{Volume}_{\text{calf}} = K_{\text{filtration}} * t + (K_{\text{filling}} - K_{\text{delay}} * K_{\text{filtration}}) * (1 - \exp(-t / K_{\text{delay}})) \]  

Fitting of individual plethysmographic data was performed using nonlinear least square analysis (Curve-Fitting Toolbox, Matlab, Version 7, Mathworks Inc, Natick, MA, USA). Venous filling (K_{\text{filling}}) and capillary filtration (K_{\text{filtration}}) are based on percentage volume changes and thus expressed in ml * 100 ml\(^{-1}\) of tissue and ml * 100 ml\(^{-1}\) * min\(^{-1}\), respectively. Furthermore, the reported values are specific for a step-wise increase in venous pressure (collection cuff pressure) of 60 mmHg. Coefficients for filtration(K_{\text{filtration}}) and filling (K_{\text{filling}}) were compared using paired and non-paired t-test for differences regarding the effects of treatment and diagnosis, respectively (GraphPad Prism Version 3, GraphPad Software, San Diego, CA, USA). Differences were considered significant when P < 0.05, values are reported as mean ± SD.
RESULTS

Clinical characteristics of patients and control subjects are summarized in Table 1. All MSA patients exhibited parkinsonism, which was unresponsive or only minimally responsive to levodopa treatment. Autonomic impairment (combined cardiovagal, adrenergic, sudomotor failure), scored using the Composite Autonomic Severity Scale (CASS) (16), was significantly higher in MSA, matching the criteria for probable MSA-P (10). PD patients were slightly older than the two other groups, whereas MSA and control subjects did not differ. The severity of parkinsonism of MSA and PD patients were matched, although the score on Unified MSA Rating Scale (UMSARS) (38) was significantly higher in MSA than PD patients; this reflects the fact that UMSARS measures additional deficits like oculomotor and cerebellar impairment in addition to extrapyramidal dysfunction.

Pressure-volume relationship and venous compliance

During baseline conditions, pressure-volume curves in controls and PD patients were steeper than those of MSA patients indicating reduced calf venous compliance in the MSA group (Fig. 2, top). This becomes even more evident when the slopes of the group-average pressure-compliance lines are compared, showing a significantly reduced slope only in the MSA group (P < 0.01, ANOVA; MSA vs. control: P < 0.01, MSA vs. PD: P < 0.05, Tukey’s post hoc analysis) (Fig. 2, bottom; Table 2).

To gain insight into the mechanism of compliance change, we regressed compliance in MSA patients against parkinsonism (UMSARS) and severity of autonomic failure (CASS). Correlation analysis did not reveal a significant dependency of
compliance on UMSARS ($r^2 = 0.12$) within this group. In contrast, correlation analysis between autonomic impairment (CASS) and compliance was highly significant in MSA patients ($r^2 = 0.56$, Fig. 3).

**Venous filling and capillary filtration**

Although venous filling is mainly determined by venous compliance, increased capillary leakage would decrease intravascular volume and, thus, might further contribute to OH. Thus, we additionally studied venous filling and capillary filtration (Fig. 4).

The groups did not differ in their filtration rate ($P = 0.82$, ANOVA) indicating no alterations in capillary leakiness. According to the venous compliance results, there was a marked and highly significant decrease in venous filling in MSA patients ($P < 0.001$, ANOVA). Individual data are presented in Fig. 4.

**Influence of direct $\alpha$-adrenergic stimulation on calf venous compliance**

The effect of the directly acting $\alpha_1$-agonist, midodrine, on venous compliance was estimated by the slope of the pressure-compliance lines. In control subjects, $\alpha$-adrenergic stimulation induced a slight but significant reduction of calf venous compliance ($P < 0.001$, paired t-test) indicating the presence of venous $\alpha_1$-adrenoreceptors. The consequent increase in venomotor tone resulted in a significant decrease in venous filling (Table 2; $P < 0.001$, paired t-test) and a trend towards lower capillary filtration (Table 2; $P = 0.063$).

Similar results were obtained within the Parkinson group; both venous compliance slope and venous filling were significantly reduced by direct $\alpha$-adrenergic
stimulation (Table 2; \( P < 0.001 \) and Table 2; \( P = 0.007 \), respectively; paired t-test). Capillary filtration remained unchanged in the PD group (Table 2; \( P = 0.87 \), paired t-test).

In five MSA patients, administration of midodrine was contraindicated due to resting supine hypertension. In six remaining patients, midodrine attenuated the volume-pressure curves, but the change in the slopes of the pressure-compliance lines did not reach statistical significance (\( P = 0.246 \), paired t-test). However, direct \( \alpha \)-adrenergic stimulation led to a minor but significant decrease in venous filling (Table 2; \( P < 0.034 \); paired t-test) whereas filtration was not changed (Table 2; \( P < 0.82 \); paired t-test).
DISCUSSION

The major finding of our study is the novel observation that resting calf venous compliance is significantly reduced in MSA patients with chronic neurogenic OH compared with controls and Parkinson patients (Fig. 2). In MSA, the reduction in venous compliance was accompanied by diminished venous filling, whereas capillary filtration was not altered.

Sympathetic adrenergic denervation, present in all cases of MSA, results in markedly reduced arteriolar tone. This in turn leads to increased capillary pressure and increased transmural pressure. In MSA, venous pressure may be additionally augmented by hypervolemia due to increased salt and fluid intake and mineralocorticoid therapy (4). The finding of reduced venous compliance is a surprise. A reduction in venous compliance would tend to counteract venous pooling and protect against the decrease in venous return that can lead to OH. Although the present study was not designed to address the mechanism of reduced compliance, we hypothesize that it may reflect chronic adaptive changes in dependent veins of MSA patients in response to chronic distension.

It is known that a persistent increase in venous pressure and volume can cause venous remodeling (24, 29). Chronic venous hypertension can lead to structural changes including intimal hyperplasia due to smooth muscle cell replication and migration (1) as well as fibroblastic remodeling (24). Structural remodeling has been reported in conditions with increased venous pressure (arterialization of veins) and with chronic orthostatic stress (25, 32), and it is known to limit graft function in aortocoronary and femoropopliteal bypass procedures (1, 3, 24). In addition, stressed veins show functional changes including altered adrenergic sensitivity (20, 24), altered endothelium-dependent
vasodilation (26), and switch to serotonergic sensitivity (20). Taken together, these reports indicate that veins adapt to chronic increased pressure with structural and functional changes, directed to decrease mechanical wall stress and thus venous compliance. Our present data suggest that these changes might help to limit orthostatic intolerance in the face of chronically impaired reflex sympathetic vasoconstriction. In this context, it would be of interest to compare these changes to alterations that occur in patients with acute OH.

Parkinson patients exhibited calf venous compliance that was not different from controls suggesting that motor disability due to muscle rigidity has only a minor impact on calf venous compliance. PD and MSA patients were well-matched in severity of muscle rigidity ($P = 0.4$). Furthermore, autonomic impairment (CASS), but not UMSARS, was highly correlated with reduction in compliance in MSA patients ($r^2 = 0.56$ and $r^2 = 0.12$, respectively; Fig. 3), supporting the notion that autonomic failure rather than immobility/rigidity underlies changes in calf venous compliance in these patients. Nevertheless, considering the strong positive correlation between aerobic capacity and calf venous compliance as reported by Monahan et al. (22), influence of deconditioning onto the observed changes in venous compliance cannot be ruled out.

Midodrine led to a comparable decrease of venous compliance in subjects without neurogenic OH (PD and controls) and thus demonstrates that there is adrenergic innervation of the veins in the lower leg although the vasomotor effect is modest compared to that of arterioles (21, 33). Thus, our data are in good accordance with previous work, reporting a decrease in calf venous compliance in response to sympathoexcitation (23). Midodrine induced a reduction of arteriolar inflow and could
potentially contribute to the observed reduction in calf venous compliance. However, reduced arteriolar flow would primarily delay venous filling rather than reduce the total change in calf volume. To minimize the effects of delayed venous filling, a venous occlusion time of eight minutes was chosen. The finding that MSA patients did not undergo a significant change in compliance with midodrine supports the view that these veins are denervated and implies that there is no denervation hypersensitivity, as would be expected in a preganglionic lesion (37). Whether denervation supersensitivity would occur in a postganglionic lesion in disorders such as autoimmune autonomic neuropathy (36) or pure autonomic failure (30) would be of interest. The present study is sufficiently powered to demonstrate major changes between MSA and controls. It is possible that more modest effects of midodrine would be seen in larger groups or certain subgroups of MSA patients.

In the present study, calf venous compliance was assessed by measuring pressure dependent changes in calf volume. However, blood pooling in response to orthostatic stress occurs in multiple compartments such as thighs and abdomen (6) and only to about 10% within the calves. Hence the total venous adaptive changes could have a major effect on regulation of blood pressure.

We have attempted to minimize other confounding variables. In MSA, edema could limit changes in calf volume. Considerable effort was made to prevent this confounding variable. We excluded patients with overt pedal edema, so that we are confident these patients did not have clinical calf edema. Patients were admitted to a nearby hotel within Mayo campus the night before the study and the study was undertaken in early or mid-morning, with a schedule that minimized standing.
Additionally, the measured limb was rested above heart level for 30 minutes before the first compliance measurement (20 min. rest and 10 min. baseline). The leg was rested a further 10 minutes before the second compliance measurement. The fact that changes in calf volume did not differ between the two measurements provides further support for the absence of leg edema. However, we cannot totally exclude a contribution of subclinical edema. It has been hypothesized that even modest fluid accumulation can function as a “water jacket” around veins and reduce compliance (18, 19). A repeat study before the patient gets out of bed compared with one at the end of the day would be of interest.

An elevated resting venous pressure and/or a residual venous filling could also lead to an underestimation of venous compliance and filling. Since venous pressure is mainly determined by hydrostatic pressure while upright, in the present study all experiments were performed in a supine position with the limb elevated above heart level. Venous pressure is further determined by capillary pressure, which ranges in supine position from 38 to 10-24 mmHg at the arterial and venous capillary pole, respectively (15). In MSA patients, capillary and venous pressure become increasingly affected by arterial blood pressure due to the attenuated effect of peripheral resistance vessels; however, a resting venous pressure exceeding 10 mmHg in the elevated leg was not likely since the volume-pressure relationship was linear at lower cuff pressures (10 to 30 mmHg). Furthermore, compliance analysis was limited to a pressure range (60 to 10 mmHg, Fig. 1, bottom) where a good correlation between intravenous and venous collection cuff pressure was previously demonstrated (12).

Arterial blood pressure, which was significantly higher in MSA patients (in supine position, Table 1) could potentially confound the measurement of venous
compliance. Systemic arterial and venous compliance are known to be reduced in sustained essential hypertension (29). The supine hypertension and high nocturnal blood pressure could be contributory, especially as many of these patients take the α-agonist midodrine and fludrocortisones. This effect is offset by the OH present during most of the day.

Although the proposed technique of analyzing venous filling and capillary filtration minimizes subjectivity, it still assumes a linear increase of capillary filtration over time. In humans, this holds true for only a limited period of venous occlusion, since increasing interstitial pressure will restrict further capillary filtration. By limiting venous occlusion time to eight minutes we did not observe such ceiling effects in any of our recordings.

What are the implications of these findings for our understanding of OH in conditions such as MSA? Venous filling and volume expansion with increased fluids and salt ingestion are still essential, since patients with neurogenic OH cannot respond to any fall in venous return due to impaired baroreflex function. Our present data also imply that aggressive volume expansion may worsen supine hypertension (4) and should be avoided. The focus of treatment should shift to the enhancement of total peripheral resistance (21), preferably using agents that improve OH without aggravating supine hypertension.

In summary, our data suggest that calf venous compliance does not contribute to orthostatic hypotension in chronic neurogenic OH. In contrast to our original hypothesis, a decrease in venous compliance might represent a venous adaptation to overcome chronic high levels of venous pressure in these patients. Important areas of enquiry for
the near future include a definition of tissue alterations in chronic neurogenic OH, and
definition of a time course of development of the changes in compliance.
ACKNOWLEDGMENTS

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FIGURE LEGENDS

**Figure 1:** Time course of cuff pressure and calf volume (top). Venous filling and capillary filtration were calculated by fitting individual changes in calf volume during the first 8 minutes of venous occlusion to a first order PI system (middle). Data for venous compliance analysis were obtained during the last 60 seconds when cuff pressure was reduced from 60 to zero at a rate of 1 mmHg/sec. Resulting pressure-volume curves (bottom) were compared by means of a quadratic regression model (12).

**Figure 2:** Change in calf volume (top) and venous compliance (bottom) for control subjects (○), PD (Δ), and MSA-P patients (●) under resting conditions. Pressure-volume curves were generated after venous occlusion at 60 mmHg for eight minutes. Graphs express mean values ± SEM of 28 measurements in 14 control subjects, 14 measurements of 7 PD patients, and 19 measurements of 11 MSA patients. P = 0.0002 (ANOVA).

**Figure 3:** Correlation analysis between autonomic impairment (CASS) and slope of compliance in MSA patients. With increasing autonomic impairment, individual slope of compliance lines becomes smaller. ● individual data; — regression line; $r^2 = 0.56$

**Figure 4:** Capillary filtration (left) and venous filling (right) for control subjects (○), PD (Δ), and MSA patients (●) under resting conditions. Pressure-volume curves were generated when venous occlusion cuff was inflated to and maintained at 60 mmHg for eight minutes. Graphs represent individual data of 26 measurements in 13 control
subjects, 10 measurements of 5 PD patients, and of 19 measurements in 11 MSA patients; the solid bars indicate mean values. Filtration: $P = 0.83$; Filling: $P < 0.001$ (ANOVA).
References


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Table 1: Patient characteristics; Values are means ± SD; * P < 0.01 (MSA vs. PD); † P = 0.02 (PD vs. control/MSA); N, number of subjects; BMI, body mass index; UMSARS, unified MSA rating scale; CASS, composite autonomic severity scale; MAP, mean arterial pressure; HR, heart rate

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<td>69 ± 7.1†</td>
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**Table 2:** Group-wise comparison of calf venous compliance (slope of compliance lines), venous filling and capillary filtration; * P < 0.05 (compared to control, post hoc ANOVA); † P < 0.05 (compared to PD, post hoc ANOVA); ‡ P < 0.05 (compared to baseline, paired t test)

<table>
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<th>capillary filtration [V%/min]</th>
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