Neuropathy and Ankle Mobility Abnormalities in Patients With Chronic Venous Disease

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Chronic venous disease and its complications are an underestimated public health problem in our society. Approximately 7 million people in the United States have chronic venous insufficiency (CVI) at an average cost of $40 000 over a lifetime. The most severe form of CVI is a venous leg ulcer, which is responsible for 70% to 80% of all chronic ulcers of the lower limb. Venous leg ulcers have a high recurrence rate, placing additional financial and treatment burdens on the health care system.

How complications associated with chronic venous disease develop is not clear but likely involves dysfunction of the calf muscle pump. Contraction of the calf and other lower limb muscles propels venous blood from the leg toward the heart through the venous system. Dysfunction of the muscle pump leads to impaired venous return from the lower limbs, development of sustained ambulatory venous hypertension, distention of capillary walls, and extravasation of fluid into the interstitial space. This eventuates into edema, hyperpigmentation and fibrosis of the skin, and ultimately to breakdown of the tissue and development of an ulcer through activation of white blood cells and the formation of pericapillary fibrin cuffs. These cuffs are presumed to impede the exchange of oxygen and other nutrients and trap needed growth factors. Other factors that may contribute to calf muscle pump failure include abnormalities in the calf muscle itself or the nerves that supply the muscle as well as limitation of movement or gait.

The current standard of care for chronic venous disease is directed toward lowering venous hypertension with com-
pression therapy, a standard treatment for venous ulcers that reduces edema, stimulates fibrinolysis, and improves calf muscle pump contraction, all aiding venous return.

Neuropathy
Few studies have identified an association between CVI and damage to peripheral nerves. Reinhardt et al found that patients with CVI had prolonged distal motor latency, reduced vibration threshold, and diminished temperature perception. In a pilot study by Newland et al, patients with CVI had a higher Neuropathy Symptom Score (NSS), a higher Neuropathy Disability Score (NDS), and altered gait, as measured by lower total foot pressure, compared with a matched control group. These clinical findings suggest that abnormalities in nerve function and ankle movement exist in patients with CVI.

Ankle Movement
Mobility and range of motion of the ankle joint are reduced in patients with venous leg ulcers that may be associated with severity of venous hypertension. One study demonstrated that patients with venous leg ulcers have impaired dorsiflexion, which is required for normal function of the calf muscle pump.

Study Aims
We hypothesized that reduced range of ankle movement (ROAM) and worsening neuropathy will be associated with more severe clinical stages of CVI. This hypothesis would demonstrate that a relationship exists between sensory neuropathy and ankle mobility in patients with CVI.

Methods
Patients
After approval by the institutional review board of the University of Miami, a cross-sectional study was conducted between August 2011 and August 2012. Individuals who participated provided written informed consent. A convenience sample of adults with chronic venous disease who were aged 18 years or older who were recruited from the outpatient wound clinic and the wound healing research clinic at the University of Miami Hospital. Classification of each limb was based on the clinical component of the clinical-etiology-anatomy-pathophysiology (CEAP) classification: C1, telangiectasia or reticular veins; C2, varicose veins; C3, edema; C4, skin changes (pigmentation, venous eczema, and lipodermatosclerosis); C5, healed ulceration; and C6, active ulceration. If venous disease was present on more than one limb, each limb was analyzed separately. If the participants’ limbs had different clinical severities of CVI, only the limb with the highest CEAP classification was included in the study.

A complete medical history was obtained to identify and exclude patients with leg ulcers caused by a disease other than CVI as well as patients at risk for peripheral neuropathy resulting from other diseases, such as uncontrolled diabetes mellitus, human immunodeficiency virus, vitamin B12 deficiency, shingles, autoimmune disease, Guillain-Barré syndrome, syphilis, family history of inherited neuropathy or myopathy, and stroke. Other exclusion criteria included Hansen disease, cellulitis, uncontrolled diabetes mellitus (hemoglobin A1C level >7%), body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 40, congestive heart failure meeting New York Heart Association criteria class III or IV, peripheral arterial disease, or an ankle brachial index less than 0.9. Patients with restricted mobility secondary to pain, rheumatoid arthritis, or osteoarthritis or who were immobile and restricted to a wheelchair or bed were also excluded.

NSS and NDS
Symptoms of peripheral sensory neuropathy were determined using the validated NSS and NDS. Patients were asked subjective questions regarding pain and discomfort to calculate the NSS, and specific tests were performed to obtain quantitative objective neuropathic changes to calculate the NDS. The following questions were used as part of the NSS.

- Have you in the last 6 months had any pain or discomfort in your legs and feet when you are not walking? (2 points: yes [burning, numbing, and tingling]; 1 point: yes [fatigue, cramping, and aching]; 0 points: other symptoms or none)
- Is this pain or discomfort felt in the feet (2 points), calves (1 point), or thighs (0 points)?
- Are these symptoms worse during the night (2 points), at various times (1 point), or the day only (0 points)?
- Have these symptoms ever kept you awake at night? (1 point: yes; 0 points: no)
- When you get this pain or discomfort, is there anything you can do to make it feel better? (2 points: yes [walk]; 1 point: no or yes [stand up]; 0 points: yes [all other actions])

As part of the NDS, a 10-g monofilament was used to perform sensory testing of the feet at the apex of the first toe. Vibration perception threshold testing was performed using a 128-Hz tuning fork at the apex of the first toe. Temperature discrimination was tested using the tuning fork placed in a beaker of ice or warm water and applied to the dorsum of the foot. One point was given for each test response showing abnormality, and no points were given if the response was normal. The Achilles tendon reflex was evaluated using a reflex hammer. Two points were given if there was no reflex, and 1 point was given if the reflex was present with reinforcement. No points were given if there was a normal reflex.

Goniometry
The ROAM was measured during plantarflexion and dorsiflexion with the participant sitting on the examination table with his or her knees over the edge of the table, flexed at 90°. The patient’s ankle had to be in a neutral, non–weight-bearing position. For plantarflexion and dorsiflexion, the fulcrum was placed at midpoint of the lateral malleolus and the stationary arm along the fibula. The moving arm was placed parallel to the fifth metatarsal bone. Measurements were taken at maximal plantarflexion and dorsiflexion that the patient could achieve voluntarily. For inversion and eversion, with the pa-
The results of clinical staging and ROAM (plantarflexion-dorsiflexion and inversion-eversion), NSS, and NDS are summarized in Table 1. There was no significant difference in age between the groups (P = .30, analysis of variance). The mean age of the participants was 64 years. There were no patients in the C3 or C4 CEAP classification of CVI recruited for participation. The ROAM, NSS, and NDS values were significantly different between the mild (C1-C2) and severe (C5-C6) CVI groups (P < .001, analysis of variance).

### Results

A convenience sample of 42 adults (28 women, 14 men) with chronic venous disease who were aged 18 years or older were recruited from the outpatient wound clinic and the wound healing research clinic at the University of Miami Hospital. A total of 64 limbs were considered and classified into 4 groups depending on the clinical stage of chronic venous disease as follows: C1, telangiectasias or reticular veins (14 limbs); C2, varicose veins (22 limbs); C5, healed ulceration (4 limbs); and C6, active ulcer (24 limbs).

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**Table 1. Results of Clinical Staging, Range of Ankle Movement, NSS, and NDS**

<table>
<thead>
<tr>
<th>CVI Classification*</th>
<th>No. of Limbs</th>
<th>Mean Age, y</th>
<th>Mean (SD) [SE]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range of Ankle Movement, Degrees</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plantarflexion-Dorsiflexion</td>
</tr>
<tr>
<td>C1</td>
<td>14</td>
<td>61.0</td>
<td>58.35 (18.19) [4.86]</td>
</tr>
<tr>
<td>C2</td>
<td>22</td>
<td>68.5</td>
<td>55.32 (13.39) [2.85]</td>
</tr>
<tr>
<td>C5</td>
<td>4</td>
<td>56.2</td>
<td>33.50 (20.98) [10.49]</td>
</tr>
<tr>
<td>C6</td>
<td>24</td>
<td>63.6</td>
<td>26.71 (13.39) [2.73]</td>
</tr>
</tbody>
</table>

Abbreviations: CVI, chronic venous insufficiency; NDS, Neuropathy Disability Score; NSS, Neuropathy Symptom Score.

* A C1 classification indicates telangiectasias or reticular veins; C2, varicose veins; C5, healed ulceration; and C6, active ulcer.

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The accuracy of the chosen measurement was validated in the same position on the examination table and the ankles in a neutral position with zero degrees of inversion and eversion, the fulcrum of the goniometer was placed midway between the medial and lateral malleoli. The stationary arm was placed in line with the tibia of the lower leg. The moving arm was placed in line with the second metatarsal bone. The knee was stabilized to maintain landmarks during measurements. One research assistant (E.Y.) carried out all measurements and procedures.

### Statistical Analysis

Data were inserted into a commercial software database (SPSS, version 19; SPSS Inc) and analyzed. All participants met the criteria for either group C1-C2 or group C5-C6 classification; the C3 and C4 categories were excluded because no patients had edema or skin changes and hyperpigmentation. Data were analyzed by comparing means, one-way analysis of variance, Pearson correlation coefficients, cross tabulations, and χ² tests. For ROAM, the groups were categorized according to whether their combined plantarflexion and dorsiflexion was less than 47° or greater than or equal to 47° (normal non–weight-bearing range of movement of the ankle joint has been reported to be 47° to 69° for total plantarflexion and dorsiflexion).

For inversion and eversion, groups were categorized according to whether their combined inversion and eversion was less than 20° or greater than or equal to 20° (normal values for total inversion and eversion have been reported to range from 20° to 55°). A χ² test was done to compare groups between each other to evaluate ROAM, NDS, and NSS. Analyses were carried out for all affected limbs, but sensitivity analyses were performed on a single selected limb from each affected patient that had the best achieved measurements.
χ² test for ROAM. For plantarflexion-dorsiflexion, 25 of the participants (89%) with severe CVI had reduced ROAM compared with 11 participants (31%) with mild CVI. For inversion-eversion, 22 patients (79%) in the severe CVI group had reduced ROAM compared with 4 patients (11%) in the mild CVI group.

Neuropathy

The NSS and NDS were significantly higher in patients with severe CVI compared with the scores in patients with mild CVI (P < .001). In addition, limbs with reduced ROAM (<47°) for combined plantarflexion and dorsiflexion had significantly higher NSS (P < .002) and NDS (P < .01) values. Limbs with reduced inversion-eversion (<20°) also scored higher on the NSS (P < .001) and NDS (P < .002) scales. Correlation analysis showed a negative correlation with increasing ROAM, NSS, and NDS. For ROAM plantarflexion-dorsiflexion, the Pearson correlation coefficient was r = −0.66 for NSS and −0.70 for NDS. For ROAM inversion-eversion, the Pearson correlation was r = −0.63 and −0.54 for NSS and NDS, respectively. As part of a sensitivity analysis, when one limb was studied per patient, both NSS and NDS remained significantly different between the mild (C1-C2) and severe (C5-C6) CVI groups (NSS, P = .005; NDS, P = .01).

Discussion

In a population of patients with venous disease, we found that limbs with severe CVI had significantly reduced ROAM, both in plantarflexion-dorsiflexion and inversion-eversion, as well as increased NSS and NDS values. In addition, there was a negative correlation between ROAM and neuropathy. This suggests that clinical severity of CVI is related to decreased ROAM and the presence of neuropathy. This is consistent with the results of previous studies that found reduced ROAM to be related to the clinical severity of chronic venous disease. Dix et al demonstrated in a sample of 47 limbs that all grades of chronic venous disease, from simple varicose veins to venous ulceration, were associated with venous hypertension and significantly reduced ROAM compared with limbs without CVI. Although these studies suggest that there may be a mechanism by which venous hypertension may lead to limited ankle movement, our study also considered the involvement of peripheral nerve damage in patients with CVI, similar to neuropathic ulcers in patients with diabetes mellitus.

The combined plantarflexion and dorsiflexion for mild CVI had a mean ROAM of 56.50° (2.54°), which falls within the reference range (47°-69°) described for ankle movement. The ROAM in limbs with severe CVI was significantly lower, at 27.68° (2.72°) (P < .001). For combined inversion and evasion, ROAM was 34.78° (2.20°) in limbs with mild CVI, falling within the normal range between 20° and 55°.11 In our study, these particular movements were significantly reduced in the severe CVI group, with a mean ROAM of 14.75° (2.47°) (P < .001). Nearly 80% of patients with severe CVI had reduced inversion-eversion ROAM compared with 11.1% of those with mild CVI. In addition, we found evidence of worsening ROAM, even within the mild CVI group, with C2 ROAM for both plantarflexion-dorsiflexion and inversion-eversion significantly lower than normal limits.
that of C1 (P < .001), indicating that changes in ROAM occur early in chronic venous disease. Poor calf pump function may contribute to decreased ROAM. Another contributor may be prolonged inactivity, possibly leading to muscle atrophy and weakness. Pain with ankle motion, which we did not study, could also cause a decrease in voluntary ankle flexion. Other factors that could cause a decrease in ankle movement are edema and lipodermatosclerosis, which were seen in some of the patients with severe CVI.

In our study, patients with severe CVI were more likely to report higher NSS and NDS values. Our results showed that the clinical severity of CVI is related to worsening neuropathy demonstrated by higher NSS and NDS values. Participants with mild CVI had mean NSS and NDS values of 0.33 and 1.00, respectively, compared with those with severe CVI (1.86 and 4.96, respectively). Also, our study showed a negative correlation between ROAM and neuropathy. It is possible that patients with active ulcers (C6) have pain despite a higher NSS, which may affect ROAM. An increase in the NDS and NSS may be explained by CVI leading to venous microangiopathy and peripheral tissue damage as seen in venous leg ulcers. Peripheral nerve ischemia can lead to a decrease in nerve conduction, vibration threshold, and pinprick sensitivity as well as diminished temperature perception. Similar to patients evaluated by Reinhardt et al,8 participants in our study had reduced vibration sense as well as warm and cold perception, suggesting neural ischemia that is probably due to venous microangiopathy. Leu et al16 reported that patients with moderately severe CVI had a higher degree of cutaneous microangiopathy at the medial ankle. Similar results were seen by Reinhardt et al,8 which suggested that CVI-associated neuropathy may be a cofactor in the development of venous leg ulcers.

There are several limitations of the present study. First, we were unable to recruit patients who could be classified into the C3 or C4 CVI categories. In addition, despite testing more than 60 limbs in 42 patients, a larger sample size may demonstrate different results. We used goniometry to determine ankle motion, but we did not assess gait (pedal pressures) as has been done in prior work.10 Goniometry was measured with the patient’s legs hanging over the examination table, so each limb or patient had different neutral starting points compared with those in other studies that began measurements at 90° of the ankle joint while the patient was supine. Diagnosis of chronic venous disease was based on clinical presentation, and venous studies were not performed to further classify the disease. Finally, we did not evaluate patients in a longitudinal fashion to determine the role of edema or edema reduction as a contribution to the observed findings.

Conclusions

Patients with decreased ROAM are more likely to have abnormalities in neuropathy and more severe CVI based on clinical staging of CEAP classification. Management of the care of patients with CVI should include testing for neuropathy and improving ankle mobility. Physical therapy that targets increased ankle motion may have a therapeutic role in regaining calf pump function, improving venous return, and reducing venous hypertension.

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Conflict of Interest Disclosures: None reported.

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REFERENCES