Cryptogenic stroke (CS) accounts for ≈25% to 30% of ischemic strokes (IS) in modern stroke registries. One potential stroke mechanism in patients with CS is paradoxical (venous to arterial) embolization through a cardiac defect. Several studies have suggested that the deep lower extremity and pelvic veins might be an embolic source in cryptogenic stroke (CS) patients with patent foramen ovale. The published prevalence of LE and pelvic deep venous thrombosis (DVT) in patients with CS is highly variable, ranging from 3.2% to 65.5%, depending on imaging modality. One large multicenter prospective study, the Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) study, found an 11.6% prevalence of pelvic DVT in IS patients with a disproportionate amount in CS patients. The role of systematic deep venous imaging in the evaluation of patients with IS remains uncertain, especially in the evaluation of patients with CS.

**Background and Purpose**—Paradoxical embolization is frequently posited as a mechanism of ischemic stroke in patients with patent foramen ovale. Several studies have suggested that the deep lower extremity and pelvic veins might be an embolic source in cryptogenic stroke (CS) patients with patent foramen ovale.

**Methods**—Consecutive adult patients with ischemic stroke or transient ischemic attack and a patent foramen ovale who underwent pelvic magnetic resonance venography as part of an inpatient diagnostic evaluation were included in this single-center retrospective observational study to determine pelvic and lower extremity (LE) deep venous thrombosis (DVT) prevalence in CS versus non-CS stroke subtypes.

**Results**—Of 131 patients who met inclusion criteria, 126 (96.2%) also had LE duplex ultrasound data. DVT prevalence overall was 7.6% (95% confidence interval, 4.1–13.6), pelvic DVT 1.5% (95% confidence interval, 0.1–5.8), and LE DVT 7.1% (95% confidence interval, 3.6–13.2). One patient with a pelvic DVT also had a LE DVT. Comparing patients with CS (n=98) with non-CS subtypes (n=33), there was no significant difference in the prevalence of pelvic DVT (2.1% versus 0%, P=1), LE DVT (6.2% versus 10.3%, P=0.43), or any DVT (7.2% versus 9.1%, P=0.71).

**Conclusions**—Among patients with ischemic stroke/transient ischemic attack and patent foramen ovale, the majority of detected DVTs were in LE veins rather than the pelvic veins and did not differ by stroke subtype. The routine inclusion of pelvic magnetic resonance venography in the diagnostic evaluation of CS warrants further prospective investigation. 

**Key Words:** physiopathology ■ thromboembolism

Cryptogenic stroke (CS) accounts for ≈25% to 30% of ischemic strokes (IS) in modern stroke registries. One potential stroke mechanism in patients with CS is paradoxical (venous to arterial) embolization through a cardiac defect. Several studies have suggested that the deep veins of the lower extremity (LE) could be a source of paradoxical thromboembolism in CS patients with patent foramen ovale (PFO). Deep pelvic veins have also been shown to harbor thrombi in patients diagnosed with pulmonary embolism and CS.

The published prevalence of LE and pelvic deep venous thrombosis (DVT) in patients with CS is highly variable, ranging from 3.2% to 65.5%, depending on imaging modality. One large multicenter prospective study, the Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) study, found an 11.6% prevalence of pelvic DVT in IS patients with a disproportionate amount in CS patients. The role of systematic deep venous imaging in the evaluation of patients with IS remains uncertain, especially in the evaluation of patients with CS.

Given the variable DVT prevalence findings and the limited data using pelvic magnetic resonance venography (MRV) to detect pelvic DVT, we sought to evaluate the prevalence of pelvic and LE DVT in patients with PFO after IS or transient ischemic attack (TIA) and in the subset with CS.

**Methods**

**Data Collection**

A retrospective observational cohort study at a single-center was performed from January 1, 2009, to March 1, 2013, with institutional review board approval.

The electronic medical record was queried to identify consecutive patients who underwent pelvic MRV during hospitalization for IS or TIA. Records were reviewed to extract demographic, clinical, and radiographic data. We included all patients older than 18 years who had a PFO identified by color Doppler or bubble study on
echocardiography and who were initially considered to be cryptogenic (ie, undetermined mechanism). Of 145 consecutive patients who underwent pelvic MRV, 14 were excluded based on these additional criteria (Figure 1).

The Northwestern University Brain Attack Registry, a prospective database that has been active since August 2012, was further queried to evaluate the prevalence of PFO and CS for a 1-year period and provided a comparator to detect potential biases in our case identification.

IS and TIA Classification

The diagnosis of IS required evidence of diffusion-weighted imaging abnormality on brain MRI or focal symptoms or signs persisting ≥24 hours as determined by the treating board-certified vascular neurologist.14 TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia without radiographic evidence of acute infarction also as determined by the treating vascular neurologist.14

We retrospectively applied the previously validated Causative Classification System to all patients who met inclusion criteria for a more nuanced etiologic classification.13,15 Patients were dichotomized into 2 groups: (1) those classified as possible cardioaortic embolism or undetermined (ie, CS subtype) and (2) patients with determined causes of stroke (ie, non-CS subtypes).15 The Causative Classification System was performed using the online software available at http://ccs.mgh.harvard.edu.

MRV Acquisition and Interpretation

Pelvic MRV was performed at 1.5 T or 3 T. For contrast-enhanced scans, a contrast agent was given to acquire a multiphase first pass magnetic resonance angiogram with arterial, early venous, and late venous phases under conditions of suspended respiration. Steady-state MRV was performed after 8 minutes of contrast equilibration using a T1-weighted 3-dimensional (3D) gradient echo acquisition during free breathing with an isotropic 1 mm³ voxel enabling clear depiction of small arteries and veins in the pelvis. Three different types of contrast agents were used: gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals Inc, Whippany, NJ), gadobenate dimeglumine (MultiHance; Bracco Diagnostics Inc, Monroe Township, NJ), and gadoxorset trisodium (Ablavar; Lantheus Medical Imaging, North Billerica, MA). Patients with contraindications to gadolinium containing contrast media underwent unenhanced MRV studies. Noncontrast protocols included multiphase (3D) gradient echo, noncontrast acquisitions.

Pelvic DVT was defined as a filling defect identified on steady-state MRV acquisitions without clear evidence of artifact corresponding to this location on first pass perfusion magnetic resonance angiographic sequences. Centrally located filling defects within the vessel were considered to represent acute pelvic thrombus; eccentric filling defects with mural irregularity were considered to represent chronic thrombus. When contrast was not given, filling defects in the center of the blood vessel were considered to represent acute venous thrombus; laminar defects and defects without T1 hyper-intensity were considered to represent chronic thrombus. Filling defects were considered artifactual if they were not consistently seen on 2 complimentary noncontrast acquisitions.

MRV studies were interpreted by 1 of 2 board-certified cardiovascular and interventional radiologists (J.D.C. or J.C.) with a minimum of 9 years’ experience as part of the normal clinical workflow. Although the clinical indication for the MRV study was available for review at the time of interpretation, no other studies were performed to evaluate the presence of pelvic DVT. Fifty pelvic MRV studies were later reanalyzed in a blinded manner by 2 independent readers (J.B.A. and M.P.F.B.), specialized in cardiovascular imaging, to assess inter-rater reliability.

Statistical Analysis

Means (SD) or medians (interquartile ranges) were reported for continuous variables. We calculated point estimates and 95% confidence intervals (CI) for DVT prevalence overall and among subgroups using the Wald method and compared proportions between groups using the Pearson χ² test or Fisher exact test. We considered type-1 errors <5% (P<0.05) to be statistically significant. Cohen κ coefficient was used to calculate inter-rater agreement of MRV interpretation. Calculations were done using SPSS (IBM Corp Released 2013, Version 22.0., Armonk, NY).

Results

Among 131 patients included in our analysis, 107 (79.4%) had an IS as opposed to a TIA. The median time from symptom onset to admission was 0 days (interquartile range, 0–1). LE duplex ultrasound was obtained on 126 (96.2%) of the patients. The median time from admission to acquisition of LE duplex ultrasound was 2 days (interquartile range, 2–3) with 79.4% performed within 72 hours of admission. Similarly, the median time from admission to pelvic MRV was 2 days (interquartile range, 1–4) with 74.8% performed within 72 hours of admission (Table 1).

Thirty-three patients (25.2%) had IS/TIA of determinate subtypes and 98 (74.8%) of CS subtype. Ninety-three patients with CS had possible cardioaortic embolism and 5 were categorized as undetermined. Patients with CS were younger (55 versus 62 years; P=0.04), more likely to be evaluated for TIA (23.5% versus 3.0%; P=0.01), and more frequently had LE duplex ultrasound performed (99.0% versus 87.9%; P=0.01) compared with non-CS patients. There were no other significant demographic or clinical differences between the 2 groups. There was a trend toward more CS patients undergoing both transhoracic and transesophageal echocardiograms compared with non-CS patients (54.1% versus 36.4%; P=0.06; Table 1).

Of the 131 pelvic MRVs obtained, 1 study was not interpretable due to incorrect administration of contrast agent and 5 studies were performed without intravenous contrast (all in the CS group; P=0.33). In a sample of 50 pelvic MRV studies, 2 blinded independent radiologists agreed in all cases as to the presence or absence of pelvic DVT (κ=1).

Figure 1. Consecutive patients who underwent pelvic magnetic resonance venography.
Data from our prospective stroke registry revealed that 30 patients with PFO and CS (defined as possible cardioaortic embolism or undetermined by the Causative Classification System) were admitted to the hospital for a 12-month period, a rate of 2.50 patients per month. Our retrospective data, which was collected for 50 months, demonstrated a comparable monthly rate of 1.98 patients with PFO and CS. Consecutive review of patients from August 2012 to March 2013 revealed that 13 of 15 patients (87%) with PFO and CS admitted to the hospital were included in our study; 1 patient had severe claustrophobia and the other refused MRV.

A total of 10 patients were found to have a LE or pelvic DVTs for an overall DVT prevalence of 7.6% (95% CI, 4.1–13.6). Only 2 pelvic DVTs were detected, both acute in appearance. The prevalence of pelvic DVT was 1.5% (95% CI, 0.1–5.8) and that of LE DVT was 7.1% (95% CI, 3.6–13.2). A total of 9 LE DVTs were detected, of which 6 were acute and 3 were chronic (Table 2). One patient with a chronic LE DVT also had clinical evidence of a pulmonary embolus. All patients found to have an acute LE or a pelvic DVT were discharged from the hospital on therapeutic anticoagulation.

When MRV was obtained within 72 hours of admission (n=97), the prevalence of pelvic DVT was 2.1% (95% CI, 1.2–7.7). When LE duplex ultrasound was obtained within 72 hours of admission (n=104), the prevalence of LE DVT was 7.7% (95% CI, 3.7–14.7). In the subgroup of patients <60 years (n=75), the prevalence of any DVT was 4.0% (95% CI, 0.9–11.6; Table 2).

Comparing the CS group with the non-CS group, there were no significant differences in the prevalence of LE or pelvic DVT (7.2% versus 9.1%, P=0.71), pelvic DVT (2.1% versus 0%, P=1), or LE DVT (6.2% versus 10.3%, P=0.43). We did not observe any statistically significant differences in DVT prevalence comparing CS with non-CS groups when subgroups of patients who had MRV studies obtained within 72 hours of admission (n=97), had LE duplex ultrasound obtained within 72 hours of admission (n=104), or were younger than 60 years (n=75) were compared (Table 2).

Both patients found to have a pelvic DVT were in the CS group, both classified by the Causative Classification System as possible cardioaortic embolism. One patient was a 22-year-old woman with a history of multiple sclerosis and depression who presented with aphasia and was found to have a left insular IS. An acute clot in the right gonadal vein with extension into the inferior vena cava lumen was detected on her pelvic MRV (Figure 2). The other patient was a 74-year-old woman...
with a history of diabetes mellitus, chronic kidney disease, and remote renal cancer treated via nephrectomy alone who presented following a transient episode of right hand numbness. She was found to have an acute thrombus in her right internal iliac vein on pelvic MRV and a chronic left LE DVT on duplex ultrasound.

Discussion

In a large single-center study of the utility of deep pelvic venous imaging in the diagnostic evaluation of paradoxical embolic source in IS/TIA patients with PFO, we observed that few patients (1.5%) have pelvic DVT. Our findings contrast with those of earlier studies and suggest that routine pelvic MRV screening in patients with PFO following IS/TIA is low yield.7,11,12 Notably, we observed nearly a 10-fold lower prevalence of pelvic DVT in CS patients than the PELVIS study (2.1% versus 20.0%).11 Even among CS patients in whom pelvic MRV was obtained within the first 72 hours of admission, the prevalence of pelvic DVT in our study only improved to 2.9% (95% CI, 0.20–10.6). Despite this difference in the prevalence of pelvic DVT, the prevalence of LE DVT in our study is comparable to that seen in other studies of CS patients.6,8

A possible reason for our lower prevalence of pelvic DVT compared with the PELVIS study may be differences in imaging modalities. The PELVIS study exclusively used time of flight MRV, a noncontrast imaging technique that depends on flow directionality and rate to generate vascular signal.11 Although time of flight MRV has been found to be equally sensitive as conventional x-ray contrast venography,18 it has known limitations with slow (ie, venous), reversed (ie, venous stenosis with collaterals), and complex turbulent (ie, mixing) flows which may contribute to poor inter-rater performance.11

In our study, nearly all (96%) of our patients had contrast-enhanced MRVs enabling robust high-resolution pelvic

Table 2. Deep Venous Thrombosis Prevalence Overall, by Stroke Subtype, by Mode and Timing of Imaging, and by Age

<table>
<thead>
<tr>
<th></th>
<th>CS (n=98)</th>
<th>Non-CS (n=33)</th>
<th>Total (n=131)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity or pelvic deep venous thrombosis, n (%)</td>
<td>7 (7.2)</td>
<td>3 (9.1)</td>
<td>10 (7.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Pelvic deep venous thrombosis, n (%)*</td>
<td>2 (2.1)</td>
<td>0</td>
<td>2 (1.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pelvic deep venous thrombosis on magnetic resonance venography obtained in ≤72 h, n (%)†</td>
<td>2 (2.9)</td>
<td>0</td>
<td>2 (2.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lower extremity deep venous thrombosis, n (%)‡</td>
<td>6 (6.2)</td>
<td>3 (10.3)</td>
<td>9 (7.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Chronic lower extremity deep venous thrombosis, n (%)‡</td>
<td>3 (3.1)</td>
<td>0</td>
<td>3 (2.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lower extremity deep venous thrombosis on duplex ultrasound obtained in ≤72 h, n (%)§</td>
<td>5 (6.5)</td>
<td>3 (11.1)</td>
<td>8 (7.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Lower extremity or pelvic deep venous thrombosis among patients age &lt;60 y old, n (%)</td>
<td></td>
<td></td>
<td>3 (5.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

CS indicates cryptogenic stroke.
*CS (n=97) as 1 magnetic resonance venography study was uninterpretable, non-CS (n=33), overall (n=130).
†CS (n=69), non-CS (n=28), overall (n=97).
‡CS (n=97), non-CS (n=29), overall (n=126).
§CS (n=77), non-CS (n=27), overall (n=104).
||CS (n=61), non-CS (n=14), overall (n=75).

Figure 2. Contrast-enhanced pelvic magnetic resonance venography. A, Acute thrombosis in the right gonadal vein, extending into the inferior vena cava. The white arrow is directed toward the thrombosis. B, Normal magnetic resonance venography depicting widely patent internal iliac veins bilaterally.
vascular imaging which has a favorable sensitivity for DVT whether blood pool contrast agents\textsuperscript{19,20} or nonblood pool contrast agents are used.\textsuperscript{21,22}

We could demonstrate no difference between the prevalence of DVT in our CS patients compared with the non-CS group, even when assessing a variety of subgroups. This lack of correlation between stroke subtypes and pelvic or LE DVT prevalence was seen in a prior single-center study\textsuperscript{8} and is somewhat supported by the PELVIS study.\textsuperscript{11} Although the PELVIS study found that CS patients were significantly more likely than non-CS to have pelvic DVTs, when only patients with PFO or atrial septal aneurysm were examined, the increased number of pelvic DVTs detected in the CS group was not statistically significant.\textsuperscript{11} One previous study did find a significantly higher prevalence of DVT in CS patients with PFO compared with non-CS patients using conventional venography in 17 patients.\textsuperscript{7}

A key limitation of our study is the potential for selection bias insofar as we do not know the characteristics or percentage of patients with CS and PFO who were admitted to our center but did not undergo pelvic MRV during the study period. However, the practice of obtaining pelvic MRV on patients with presumed CS and PFO was standard during the study period. As noted in the audit of the last 7 months of the study period, 87% of CS patients with PFO completed pelvic MRV studies. As 10% of patients in our prospective registry have MRI contraindications (ie, pacemakers, claustrophobia), comparable to other published rates,\textsuperscript{23} we estimate that only 10% to 20% of patients were excluded from our study, primarily due to MRI contraindications or refusal.

There are several other limitations to our study. First, although 3 quarters of patients were scanned within 72 hours of admission and few were treated with tissue-type plasminogen activator (n=5) or on anticoagulation at the time of admission (n=5), it is possible that some patients in our study had DVTs that resolved prior to pelvic MRV or LE duplex ultrasound completion. Additionally, all patients were treated with DVT prophylaxis per American Heart Association/American Stroke Association guidelines on admission which may have lead to a decrease in our overall DVT prevalence compared with prior studies. Second, differences in techniques and definition of DVT by MRV may have led to strict inclusion of only definite DVT in our study while more liberal definitions including probable DVT were used in other studies.\textsuperscript{11}

We may, therefore, have underestimated the actual prevalence of DVT in our population. Third, as our electronic medical record did not systematically document whether the patients in our study had clinical risk factors for DVT such as prolonged travel, clinical symptoms suggestive of DVT such as calf pain, or laboratory testing suggestive of a prothrombotic states, we cannot exclude the possibility that targeting IS/TIA patients at high risk for DVT would have increased the utility of pelvic MRV or LE duplex scanning. Finally, although surveillance bias is an issue when practitioners perform tests based on clinical intuition rather than protocol and find a much higher prevalence than expected, our data argue against this confounding influence as the overall prevalence of DVT was lower than expected.

Conclusions

We observed a 1.5% prevalence of pelvic DVT in patients with PFO who had pelvic MRVs following IS/TIA, with no significant difference between CS versus non-CS patients. Despite being a retrospective study, our findings, in the context of the high cost of MRV\textsuperscript{18} and the low recurrent stroke risk (1%–2% per year) in CS patients with PFO who are managed medically,\textsuperscript{24–26} imply that the role of pelvic MRV in the diagnostic work up of CS is uncertain and warrants further prospective investigation.

Disclosures

Dr Bernstein speaks on behalf of and is a consultant for Medtronic. The other authors report no conflicts.

References


Diagnostic Yield of Pelvic Magnetic Resonance Venography in Patients With Cryptogenic Stroke and Patent Foramen Ovale

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Stroke. published online June 17, 2014;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2014/06/17/STROKEAHA.114.005539

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