Acute Cerebral Venous Thrombosis
Three-Dimensional Visualization and Quantification of Hemodynamic Alterations Using 4-Dimensional Flow Magnetic Resonance Imaging

Florian Schuchardt, MD; Anja Hennemuth, PhD; Laure Schroeder, MD; Stephan Meckel, MD; Michael Markl, PhD; Thomas Wehrum, MD; Andreas Harloff, MD

Background and Purpose—Cerebral venous thrombosis (CVT) affects venous hemodynamics and can provoke severe stroke and chronic intracranial hypertension. We sought to comprehensively analyze 3-dimensional blood flow and hemodynamic alterations during acute CVT including collateral recruitment and at follow-up.

Methods—Twenty-two consecutive patients with acute CVT were prospectively included and underwent routine brain magnetic resonance imaging (MRI) and 4-dimensional flow MRI at 3 T for the in vivo assessment of cerebral blood flow. Neurological and MRI follow-up at 6 months was performed in 18 patients.

Results—Three-dimensional blood flow visualization and quantification of large dural venous sinuses and deep cerebral veins was successfully performed in all patients. During acute CVT, we observed abnormal flow patterns including stagnant flow, flow acceleration in stenoses, and change of flow directions. In patients with complete recanalization, flow trajectories resembled those known from previously published 4-dimensional flow MRI data in healthy adults. There was a trend toward a relationship between occluded segments and cerebral lesions (not significant). Furthermore, patients with versus without cerebral lesions showed increased mean (0.08±0.09 versus 0.005±0.014 m/s) and peak velocities (0.18±0.21 versus 0.006±0.02 m/s) within partially thrombosed left and right transverse sinuses (P<0.05) at baseline.

Conclusions—Four-dimensional flow MRI was successfully applied for the 3-dimensional visualization and quantification of venous hemodynamics in patients with CVT and provided new dynamic information regarding vessel recanalization. This technique seems promising to investigate the contribution of hemodynamic parameters and collaterals in a larger cohort to identify those at risk of stroke. (Stroke. 2017;48:671-677. DOI: 10.1161/STROKEAHA.116.015102.)

Key Words: adult ▪ brain infarction ▪ cause of death ▪ cerebral hemorrhage ▪ headache ▪ hemodynamics ▪ sinus thrombosis

Cerebral venous thrombosis (CVT) affects particularly young adults with an incidence of 1.3 per 100,000 person-years in the general population and is more frequent in young women.1 Diagnosis and treatment of CVT is challenging as clinical signs and symptoms (eg, headache, impaired vision, focal deficit, and seizures) are unspecific. CVT can be complicated by brain infarction and intracranial hemorrhage, and cerebral herniation is the most frequent cause of death.2,3 If untreated, CVT develops an unfavorable course in 15% with a mortality rate approximating 10%.3,4 Thrombosis of the deep cerebral veins, for example, is associated with even worse outcome. Over the past decades, mortality has declined5 because of improved diagnostics resulting in earlier treatment using anticoagulation. Prognostic factors in CVT rely on various symptoms (eg, disturbed consciousness and seizures) and clinical parameters (eg, cerebral hemorrhage and straight sinus thrombosis).6-8

However, little is known about venous hemodynamics in acute CVT, their change during disease, and their impact on prognosis. Routine computed tomographic imaging and magnetic resonance imaging (MRI) lack quantitative hemodynamic information. Conventional digital subtraction angiography provides such data to a certain extent but is invasive and carries the risk of complications and is not recommended for routine imaging.9 Thus, most data on intracranial venous hemodynamics was derived from trancranial duplex sonography,10-13 which requires highly experienced examiners and is restricted to vessel segments assessable through a limited acoustic bone window. By contrast, 4-dimensional (4D) flow MRI has the potential to examine the entire cerebral venous system and thus visualize and quantify hemodynamics in vivo.14-17

In this study, we aimed to demonstrate 4D flow MRI in patients with acute CVT. We sought to comprehensively...
investigate pathological intracerebral venous flow conditions in detail and study hemodynamic changes after recanalization, including collateral recruitment, at baseline and follow-up.

Methods

Study Population

During a 4-year study period (December 1, 2010, to October 1, 2014), we prospectively identified 41 consecutive suitable patients (age 40.4±16.4 years) admitted to our institution. Inclusion criteria for our study were age ≥18 years and newly diagnosed CVT on computed tomographic angiography, magnetic resonance angiography, or conventional digital subtraction angiography. Exclusion criteria comprised denial of participation, withdrawal of consent, critical illness (eg, mechanical ventilation, signs of acute intracranial hypertension, and severe alterations of conscience), ferromagnetic implants, and pregnancy.

Nineteen out of 41 patients (46.3%) could not be included in the study for the following reasons: claustrophobia (n=4), denial of participation (n=4), severe aphasia (n=3), critical clinical condition (n=2), pregnancy (n=2), ferromagnetic implants (n=3), or spontaneous recanalization of thrombosis in baseline study MRI (n=1). Accordingly, 22 patients were included and underwent baseline study MRI 5.0±3.4 (range, 0–15) days after initial diagnosis of CVT.

Eighteen out of 22 patients (81.8%) completed the follow-up, 17 out of 22 patients (77.3%) ≥6 months later (202±29 days; range, 151–281). One patient suffering progressive CVT received 2 follow-up MRI at 31 and 314 days after baseline. Follow-up was delayed >1 month in 6 patients because of intercurrent chemotherapy (n=1) and scheduling difficulties (n=5). Four patients did not receive follow-up MRI: 2 were lost to follow-up, 1 withdrew consent, and 1 died of urothelial carcinoma.

Demographic data, symptoms at diagnosis, NIHSS score at admission and follow-up, presence of cerebral lesions, and predisposing factors for CVT are given in Table I in the online-only Data Supplement.

The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Routine Brain Imaging

Patients underwent standard brain MRI (3 T MRI; Magnetom Trio Siemens, Erlangen, Germany) using a 32 channel head coil at baseline and follow-up. Contrast-enhanced MRI (Multihance, Bracco, Milan, Italy) was performed in all patients in the absence of contraindications. In addition to 4D flow MRI and 2D time-of-flight venography for anatomic overview of intracranial veins (see below), it comprised the following sequences: susceptibility weighted imaging sequence for the detection of hemorrhage (repetition time (TR)/echo time (TE), 28 ms/20 ms; voxel size, 0.8×0.7×1.2 mm; flip angle, 15°; field of view (FOV), 230×172×127 mm; axial slices; and acquisition time (TA), 6 minutes 0 seconds), 3-dimensional (3D) FLAIR SPACE (fluid attenuated inversion recovery/sampling perfection with application-optimized contrasts using different flip angle evolution) to identify cerebral edema related to venous hypertension (TR/TE, 5000 ms/388 ms; TI, 1800 ms; voxel size, 1×1×1 mm; FOV, 250×250×176 mm; sagittal slab; and TA, 7 minutes 37 seconds), and MPRAEcontrast-enhanced (Magnetization-Prepared Rapid Gradient Echo sequence; TR/TE, 1390 ms/2.15 ms; voxel size, 1×1×1 mm; flip angle, 15°; FOV, 256×256×240 mm; sagittal slab; and TA, 3 minutes 26 seconds) to identify venous thrombosis.

4D Flow MRI of Cerebral Veins

Three-directional velocity encoded, ECG synchronized, and time-resolved 3D phase-contrast MRI (4D flow MRI) data were acquired using a ca. 52×218×290 mm wide sagittal volume covering the superior sagittal sinus (SSS) and deep cerebral veins in its midline and the parenchyma below as far as the medulla oblongata (Figure 1). Pulse

sequence parameters were as follows: TR/TE=72/3.46 ms, velocity encoding=0.4 m/s, spatial resolution=1.3×1.0×1.0 mm, temporal resolution=72 ms, imaging acceleration=factor 3, flip angle=7°, and total scan time=13:48 minutes.

3D Blood Flow Visualization

Analysis of 4D flow MRI data, vessel segmentation, and 3D visualization and quantification using MEVISFlow software were previously described. Qualitative analysis of flow characteristics and patterns was performed by one reader based on animations of time-resolved 3D flow trajectories. Visualization results were compared with a previously examined cohort of healthy adults (age, 24.6±0.8 years; range, 23–36; 9 women).

Deranged flow within the SSS or straight sinus (SIs) and transverse sinus was defined as nonlaminar and nonhelical, nonforward moving circular flow (Figure I in the online-only Data Supplement), sudden changes of flow direction (Figure 2D; Figure II and Movie I in the online-only Data Supplement). Criteria for stenosis were >50% reduction of vessel diameter (Figure 2D; Figure III in the online-only Data Supplement) or color change of pathlines (Figure 2C; Figure IV in the online-only Data Supplement) indicating local flow acceleration. Retrograde perfusion/flow reversal was defined as flow opposed to physiological draining directions (Figure I and Movies I and III in the online-only Data Supplement). Closure of sinus was indicated by absence of pathlines/upstream flow reversal despite presence of the vessel segment in other MRI sequences (Figures IV and V in the online-only Data Supplement). Partial recanalization at follow-up was defined as flow trajectories bathing filling defects, that is, intraluminal clearance of flow trajectories measuring over twice the width of the vessel segment in cases, where the entire vessel diameter was distinguishable (Figure 2A and 2B).

Blood Flow Quantification

Whenever flow was detectable, we quantified blood flow using 10 standardized cross-sections in four vessels of interest (Figure 1). Seven cross-sections were inserted equidistantly along the SSS, with plane 1 (P1) beginning in the frontal segment to P7 located twice the diameter of the SSS above the sinus confluence, one in the middle segment of the depicted part of the left and right transverse sinus (LTS and RTS) and in the middle of SIs. In extensive thrombosis, we inserted cross-sections in the remaining patent vessel segments. Hemodynamic parameters of the individual cross-sectional regions (maximum, mean, and minimum blood flow velocity and volume) were automatically calculated by the software.
**Statistical Analysis**

Descriptive statistical analysis included calculation of maximum, mean, and minimum blood flow velocity and volume. Student t test was used to evaluate differences between independent (hemodynamic parameters, presence of brain lesions) and dependent variables (baseline versus follow-up). Pearson correlation coefficient investigated the correlation between the number of occluded segments and presence of cerebral lesions. Odds ratios were calculated to assess the influence of hemodynamic parameters on the frequency of brain lesions. \( \chi^2 \) Tests were performed to identify significant differences between these variables. All significance measures were 2-sided, the significance level was 5%. Analyses were performed using the SPSS statistical package (version 22).

**Results**

**Localization of Thrombosis**

The following veins were affected by CVT: SSS 13 out of 22 patients (59.1%), LTS 14 out of 22 patients (63.6%), and RTS 11 out of 22 patients (50%); left sigmoid sinus 11 out of 22 patients (50%), left internal jugular vein 8 out of 22 patients (36.4%), and right internal jugular vein 2 out of 22 patients (9.1%). Two patients (9.1%) with StS thrombosis showed a progressively improving level of conscience until baseline MRI coinciding with recanalization of the vein of Galen and StS. However, the LTS remained partially occluded in one and the LTS, left sigmoid sinus, and internal jugular vein completely occluded in the other.

**3D Visualization of Venous Flow Alterations**

**Healthy Adults**

Flow patterns in previously examined healthy adults showed laminar flow trajectories within the SSS and StS, changing at the sinus confluence into a predominantly spiral, forward moving helical flow pattern, which propagated into the transverse sinus. Zero out of 15 healthy adults (0%) showed deranged flow.

**CVT Baseline**

Abnormal or complex flow patterns (nonlaminar flow, lateral deviation or lack of central flow trajectories, flow acceleration, flow reversal, or stagnant flow) were present in 18 out of 22 patients (81.8%) during the acute phase (Figure 2; Figures II through VII in the online-only Data Supplement). Patients 1 and 7 showed reversal of flow directions in SSS during acute thrombosis (Figure II and Movie I in the online-only Data Supplement). Functional stenosis, that is, local flow acceleration within partially thrombosed segments, occurred in 7 patients (dorsal SSS, n=2 [Figure 2A and 2D; Figure IC in the online-only Data Supplement]; LTS, n=1 [Figure 2C]; RTS, n=2 [Figure IV in the online-only Data Supplement]; StS, n=1; SSS and StS, n=1). Patient 20, suffering progressive thrombosis of the SSS because of heparin-induced thrombocytopenia, showed rapid collateralization via her inferior sagittal sinus (Figure 3).

**CVT Follow-Up**

Local flow alterations (partial recanalization, persistent occlusion, or complex flow) persisted in 14 out of 18 patients (77.8%) until follow-up (Figure 2), with 2 patients showing >1 alteration. After complete recanalization, bridging veins, SSS, and StS demonstrated linear parallel flow trajectories in their proximal parts and a helical forward moving pattern in the dorsal SSS, distal StS, sigmoid sinus, and jugular veins as in the healthy control group. Flow reversal during acute thrombosis
in SSS of patient 7 normalized at follow-up (Movie II in the online-only Data Supplement). After incomplete recanalization, 3 patients retained filling defects in the middle and dorsal SSS. In 3 patients, flow pattern at the sinus confluence normalized, although LTS remained obstructed and RTS served as collateral. In patient 9, the predominant drainage via LTS during acute RTS thrombosis was reversed after recanalization of RTS (Figure 2D). The partially thrombosed LTS demonstrated retrograde perfusion after recanalization in patient 19 (Movie III in the online-only Data Supplement). Color coding of flow trajectories indicated velocities as observed in healthy controls despite partially recanalized vessel segments in 8 patients (SSS n=6; LTS n=3; and RTS n=2). Single patients showed >1 partially recanalized vessel segments. Therefore the sum of the vessel segments is higher than 8. Because of incomplete recanalization of SSS in patient 20, the collateral blood flow via the inferior sagittal sinus to the deep cerebral veins persisted >11 months (Figure 3). Net changes of volume and velocity for patient 20 are given in Figure VII in the online-only Data Supplement.

Quantification of Venous Blood Flow
Hemodynamic data of CVT patients at baseline and follow-up are given in detail in Table II in the online-only Data Supplement and Figure 4. We observed an increase of mean blood flow velocity/volume from rostral to dorsal SSS both at baseline and at follow-up. At baseline, there was a broad range of velocity and volume because of zero flow in 53 out of 220 vessel segments (24.1%; n=1–8) in 16 out of 22 patients (72.7%). Compared with acute CVT, at follow-up, flow parameters in 76 previously thrombosed vessel segments revealed significantly (P<0.001) increased mean and peak velocity (+266±120%; +200±93%, not shown) and mean volume (+333±166%). The 104 permanently patent vessel segments showed significantly (P<0.001) lower mean velocity, peak velocity (~85±125%; ~85±100%, not shown) and mean volume (~84±80%), respectively (Table II in the online-only Data Supplement). At follow-up, no flow persisted in 17 out of 180 segments (9.4%; 1–6/patient) of 5 out of 18 patients (27.8%). Hemodynamic parameters of previously published, non–age-matched healthy adults17 are given in the Table II in the online-only Data Supplement.

Hemodynamic Differences Between Patients With/Without Brain Lesions
Eleven out of 22 patients (50%) showed parenchymal damage at baseline as detected by FLAIR or susceptibility weighted imaging: 5 out of 22 patients (22.7%) had venous infarcts, 7 out of 22 patients (31.8%) had intracranial hemorrhage, and 2 out of 22 patients (9.1%) had combined lesions. Table III in the online-only Data Supplement compares flow parameters in frontal, middle, dorsal, deep, and lateral draining vessel sections in patients with versus without brain lesions (infarction or bleeding). Differences of flow parameters between both groups did not reach significance. In patients with thrombosed transverse sinus with cerebral lesions versus without lesion mean (0.08±0.09 versus 0.005±0.014 m/s; +160±57%) and peak (0.18±0.21 versus 0.006±0.02 m/s; +3000±4000%) velocities were significantly (P<0.05) higher at baseline. There

Figure 3. Sagittal 3-dimensional visualization of intracerebral veins and sinus of patient 20 presenting with headache because of acute thrombosis of the superior sagittal sinus (SSS). A, Yellow arrow heads indicate partially thrombosed SSS at baseline. B, Visualization of the same patient 31 d after presentation. Her symptoms worsened because of heparin-induced thrombocytopenia with progressive SSS thrombosis. The inferior sagittal sinus served as collateral for drainage via deep cerebral veins and shows increased filling and blood flow velocities compared with baseline. C, Follow-up after 11 mo on anticoagulant therapy revealed extensive residual SSS thrombosis and persistent drainage via inferior sagittal and an occipital transosseous collateral.
was a trend (r=0.32) toward a relationship between occluded segments and cerebral lesions, which was not significant.

Discussion

To date, this is the first prospective and longitudinal assessment of intracranial hemodynamics in patients with acute CVT using 4D flow MRI. We investigated patients at disease onset and 6 months later and compared flow patterns to previously described healthy controls.17 Average age, female predominance, frequency, and distribution of the vessels affected by CVT are in line with previous reports, except for the low frequency of StS thrombosis.7,8 This can be explained by the frequent association of StS thrombosis with decreased consciousness.7,18 Such patients, however, were excluded because of the inability to give informed consent.

4D flow MRI provided unique and detailed insight into disturbed macrocirculation, alterations of hemodynamics, recruitment of collateral pathways, and normalization of flow conditions after vessel recanalization. Especially, visualization of 3D blood flow and quantification of hemodynamics of the SSS, the most frequently affected vessel in acute CVT,7,8 could be reliably executed and reproduced. In addition, we were able to visualize and quantify redistribution of blood from superficial to deep cerebral veins serving as collaterals in CVT (Figure 3; Figure VII in the online-only Data Supplement). To date, this comprehensive information on intracranial venous hemodynamics is not obtainable with other imaging techniques. 4D flow MRI enables monitoring of hemodynamic changes during the recanalization process and renders its dynamics measurable. The technique overcomes the missing hemodynamic information of standard magnetic resonance and computed tomographic angiography and the restriction to a sonographic bone window, which hinders the ultrasound examination of intracranial veins.12,13 In contrast to 2D cine phase-contrast imaging, 4D flow MRI offers 3-dimensional spatial information.

Recanalization in CVT usually occurs during the first 4 months of anticoagulant treatment.19 Similarly, Stolz et al20 described normalization of transcranial Doppler ultrasound examination in 50% of CVT patients within 2 months. In only partially recanalized veins, we frequently observed complex blood flow patterns, whereas flow patterns were physiological in completely recanalized vessel segments. Interestingly, we were able to identify collaterals and observe functional stenoses showing elevated flow velocities (Figure 2). In addition to 4 distinct collateral pathways in CVT described by Stolz et al,20 we visualized a previously undescribed intracranial collateral via the inferior sagittal sinus (Figure 3).

Hemodynamic parameters have been studied in different animal models of CVT and demonstrated the important collateral function of bridging veins in induced thrombosis for preventing cerebral dysfunction and tissue damage.21,22 However, only little is known about the prognostic value of hemodynamic alterations and the role of collaterals in CVT in humans. In our cohort, drainage in acute CVT was mainly achieved by increased outflow via existing vessels. Flow within previously thrombosed segments increased after recanalization and, accordingly, decreased in patent segments. The increase of flow velocity and volume (Figure 4) from rostral to dorsal SSS at baseline and in recanalized thrombosis is comparable to findings in healthy adults.17 Normal transcranial duplex sonography examination at baseline and rapid normalization of venous ultrasound were associated with a favorable outcome.20 In contrast, high blood flow velocities in the cerebral veins/sinuses in transcranial ultrasound correlated with decreased consciousness31 and poor prognosis.6,8,18 In our cohort, increased flow velocity within partially thrombosed transverse sinuses was
significantly associated with a higher prevalence of stroke. Furthermore, a rising number of occluded vessel segments showed a trend toward cerebral lesions. Possibly, clear and significant correlation of further factors was missed because of the small sample size.

Increasing thrombus load might progressively reduce the compensation capability to acquire collaterals, subsequently leading to locally disturbed circulation in distal vein branches. Patients without brain lesions seem to achieve sufficient recruitment of collaterals (via eg, vein of Trolard and Labbé, petrosal sinus, and deep neck veins), which was indicated by lower flow volume and velocity of the SSS, StS, and transverse sinuses. In contrast, patients with cerebral lesions seem to depend on drainage via their partially thrombosed outflow tract, which is supported by the observation of higher mean/peak flow velocities, that is, functional stenosis within partially thrombosed transverse sinuses.

The study was designed to show hemodynamic changes during recanalization of CVT. Overall, at follow-up, mean flow velocity of the CVT cohort was in range and mean volume was lower than that in the previously described control group.17 The differences in flow volumes might result from partial recanalization in some CVT patients who still depend on drainage via collaterals that were not captured. As the groups were not age matched and flow velocities are known to decrease with rising age,10,13 a direct group comparison was not performed.

Taken together, these results support the hypothesis of lesions being a consequence of locally rather than generally disturbed circulation. By guaranteeing sufficient drainage, adequate collateralization seems to be crucial to preserve venous infarcts and hemorrhage and discriminates between compensated versus complicated courses of CVT.

Limitations

Our study cohort inherits a selection bias toward less severe CVT courses, as critically ill patients were excluded. Thus, the hemodynamic situation of patients with seriously decreased levels of consciousness, a factor related to an unfavorable course of CVT6–8,18 could not be investigated. In 5 patients, baseline MRI was performed >7 days after diagnosis of CVT and start of anticoagulant therapy with already partial recanalization of some venous sinus segments. The limited FOV focusing on parasagittal veins hindered the investigation of important lateral and basal collateral pathways (eg, vein of Labbé into lateral sinus or petrosal veins into sigmoid sinus) and venous drainage types.20 Moreover, the spatial resolution of ≈1 mm³ per voxel currently impedes the analysis of smaller cerebral veins such as parts of the basal veins of Rosenthal. Furthermore, although the cavernous sinus was identifiable in some cases, it might have been missed in patients falling below the critical velocity threshold. The limited cohort size limits the value of statistical analysis and might explain nonsignificant results.

Outlook

For a more thorough analysis of venous hemodynamics, future studies should optimize the MRI protocol to reduce scan time, cover the entire cerebral venous vasculature, and allow quantifying hemodynamics of even smaller parenchymal veins. Alternative strategies might include susceptibility weighted imaging to quantify venous filling or complementary approaches such as local perfusion imaging. Future clinical studies should include a larger number of patients and investigate radiological imaging findings in relation to the onset of the disease process to improve the understanding of clinical presentation and outcome.

The identification of quantifiable hemodynamic parameters that are predictive of a poor outcome is of high relevance to the 15% of patients suffering severe CVT. In consideration of the findings observed in this proof-of-principle study, 4D flow MRI could help to develop a pathophysiology-based treatment approach considering sufficient versus insufficient collateralization. The technique might serve as a screening tool in the early disease, especially in the subgroup with a functional deficit. It might guide therapeutic decisions and result in a more aggressive approach in selected patients. For example, in patients with insufficient intracranial collaterals, it might display the most favorable side for decompressive hemicraniectomy2 and identify target vessels for interventional venous thrombolysis or thrombectomy.24

Acknowledgments

We thank Hansjörg Mast for performing magnetic resonance imaging examinations.

Sources of Funding

Dr Harloff and Dr Henneimuth received funding from Deutsche Forschungsgemeinschaft (DFG HA 5399/3-1, FR 2795/2-1). Dr Meckel received a grant from Bracco (unrelated to this study).

Disclosures

None.

References

Acute Cerebral Venous Thrombosis: Three-Dimensional Visualization and Quantification of Hemodynamic Alterations Using 4-Dimensional Flow Magnetic Resonance Imaging
Florian Schuchardt, Anja Hennemuth, Laure Schroeder, Stephan Meckel, Michael Markl, Thomas Wehrum and Andreas Harloff

*Stroke.* 2017;48:671-677; originally published online February 8, 2017;
doi: 10.1161/STROKEAHA.116.015102
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
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/48/3/671

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2017/02/08/STROKEAHA.116.015102.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/