Effect of Carotid Endarterectomy on Patterns of Cerebrovascular Reactivity in Patients With Unilateral Carotid Artery Stenosis

Wolfgang H. Hartl, MD; Ingrid Janssen, BS; Heinrich Fürst, MD

Background and Purpose Patients with unilateral significant carotid artery stenosis present with a variable intracranial hemodynamic status. In the majority of patients, hemodynamics are normal because of sufficient collateral flow. One subgroup shows poor ipsilateral hemodynamics because of a severely reduced blood supply, whereas in another subgroup of patients a steal phenomenon from the contralateral to the ipsilateral hemisphere can be observed during pharmacological provocation. The present study examined the effect of carotid endarterectomy (CEA) on these patterns of cerebrovascular hemodynamics in patients with carotid artery stenosis.

Methods The CO2 reactivity of the cerebral resistance index (CR) was determined with transcranial Doppler sonography in 63 patients with unilateral high-grade to threadlike carotid artery stenosis before and 3 months after CEA and in 37 control subjects. The interhemispheric asymmetry of CR, reactivity of the control group was used to differentiate between normal and abnormal findings.

Results In patients with normal CR, asymmetry (comparable CR, reactivities at both hemispheres, n = 41), CEA did not change hemispheric CR, reactivity. In patients in whom CR, reactivity was absent at the contralateral hemisphere (intracerebral steal during hypercapnia, n = 12), CEA abolished the steal phenomenon by significantly increasing CR, reactivity at the contralateral hemisphere (preoperative, -1.0 ± 2.1 %CR/vol%CO2; postoperative, 5.2 ± 0.7 %CR/vol%CO2; P < .01). Patients who showed severely diminished ipsilateral CR, reactivity, compatible with a significantly reduced perfusion pressure at the poststenotic hemisphere (n = 10), demonstrated an improvement of ipsilateral CR, reactivity after surgery (preoperative, 0.6 ± 0.8 %CR/vol%CO2; postoperative, 3.7 ± 1.1 %CR/vol%CO2; P < .01).

Conclusions Most patients do not respond significantly to CEA. One small subgroup of patients who presented with severely disturbed ipsilateral hemodynamics demonstrated postoperative improvement at the poststenotic hemisphere, whereas in another small subgroup, who showed a steal phenomenon at the contralateral hemisphere, CEA improved contralateral hemodynamics. Determination of preoperative CR, reactivity allowed precise prediction of the effect of CEA on intracerebral hemodynamics. (Stroke. 1994;25:1952-1957.)

Key Words • carotid endarterectomy • carotid stenosis • hemodynamics • ultrasonics

Proposed recommendations for carotid endarterectomy focus on two patient groups, namely, patients who present with complicated plaques and who are therefore at risk for thromboembolic stroke and patients who show hemodynamically significant carotid artery stenosis and who are at risk for cerebral ischemia of a hemodynamic cause.1 It was suggested that abnormal intracerebral hemodynamics (as indicated by increased oxygen extraction fraction, pathologica...
side asymmetry), it is possible to eliminate interindividual variability caused by age as well as by differences in CO2-induced systemic hemodynamic changes, blood viscosity, myocardial contractility, or preexisting extent of arteriosclerosis.7

Subjects and Methods

Subjects

Studies were performed in 63 subjects seeking treatment in our hospital. Carotid artery disease was diagnosed during clinical evaluation or during routine examination in vascular high-risk patients. Thirty-six patients had symptomatic unilateral high-grade to threadlike stenosis of the ICA (age, 65.6±1.0 years; 20 men, 16 women). These patients demonstrated either transient reversible neurological deficits or minor strokes that had occurred at least 12 weeks before the study. None of these patients was suffering from a major stroke. Twenty-seven patients were completely asymptomatic but had unilateral threadlike ICA stenosis (age, 66.6±1.1 years; 12 men, 15 women). According to previous randomized trials,6,8 it is the current policy in our department to perform CEA in symptomatic and asymptomatic patients who have the respective lesions at the ICA as described above. High-grade stenosis corresponds to a maximum percentage reduction in the angiographic diameter of the relevant carotid artery of 80% or more. A threadlike stenosis corresponds to a 99% diameter reduction. All patients underwent careful neurological examinations. Extracranial and intracranial supra-aortic vessels were screened by TCD sonography, duplex sonography, color-flow Doppler imaging, and continuous-wave Doppler sonography. Color-flow Doppler imaging and continuous-wave Doppler sonography have recently been shown to be more than 90% accurate in identifying carotid artery stenosis with a lumen diameter reduction from 80% to 99%.11,12

All patients had a preoperative cranial computed tomography. In 9 of these patients, small lacunar infarctions were found at the poststenotic hemisphere. However, cerebral lesions should not have affected the results of our study. An abnormal cerebrovascular reactivity is seen mainly in the acute phase after major stroke.13,14 In patients with minor stroke, a normal CO2 response was found in the chronic phase.15 In more recent studies, poor cerebrovascular reactivity did not correlate with the presence of ipsilateral infarction.16,17

Exclusion criteria included lumen diameter reduction of less than 80% at the extracranial ipsilateral ICA, lumen diameter reduction of more than 50% at the contralateral ICA, tandem lesions of the ICA/MCA, subclavian steal syndrome, vertebral artery occlusion or stenosis, lumen diameter reduction of more than 50% at the common carotid artery, previous ipsilateral or contralateral carotid endarterectomy or extracranial/intracranial bypass, and uncontrolled atrial fibrillation (absolute arrhythmia).

Measurements

Systolic and diastolic blood flow velocity of the MCA in both hemispheres was measured by TCD before surgery and 3 months after surgery as described previously.7 In brief, a 2-MHz TCD sonography transducer (VingMed SD 50, Sonotron) was placed on the "skull window" above the zygomatic arch, and the MCA was studied at the depth of 50 to 60 mm. Average blood flow velocity at peak systole and diastole was transferred to a personal computer (Macintosh II CI, Apple) for further off-line data processing. To evaluate the complete reactivity of blood flow velocity to changes in CO2 concentrations, the arterial CO2 content was changed from normocapnia (CO2 concentration at rest) to hypercapnia and hypocapnia. To produce hypercapnia the subjects were connected through a mouthpiece with a nonreturn valve to a tank containing 5% CO2. Hypocapnia was achieved by having the patient hyperventilate. During the CO2 manipulation, the end-expiratory CO2 content (vol%) was recorded continuously by an infrared CO2 analyzer (Engstrom Eliza, CO2 Analyzer). Mean end-tidal values were used to estimate the arterial CO2 content. Flow velocity in the MCA was recorded when a steady state was reached in end-tidal CO2 and in flow velocity.

Calculations

Each examination yielded values of minimal diastolic and maximal systolic flow velocity (Vd and Vs, respectively) in the MCA in both hemispheres during normocapnia, hypercapnia, and hypocapnia. Flow velocities were used to calculate the relative peak-to-peak velocity (referred to Vd) of the flow velocity wave: (Vs-Vd)/Vd. The relative peak-to-peak velocity represents a measure of cerebral resistance during pulsatile flow and is named cerebral resistance index (CR), which corresponds to Pourcelot's index. Subsequently, we calculated the relative reactivity of CR, to changes in the arterial CO2 content. Total CR, reactivity (%CR,vol%CO2) was quantified as

\[
\frac{CR\text{, at hypocapnia} - CR\text{, at hypercapnia}}{CR\text{, at hypocapnia}} \times 1
\]

CO2 concentration at hypercapnia –

CO2 concentration at hypocapnia

The rationale behind the above formula is described in detail in previous publications6,7 and is based on aspects of interindividual comparison and on the particular interactions between the shape of the flow velocity curve and changes of vascular impedance.

To define normal values, a control group of elderly subjects (n=37 [18 men, 19 women]; age, 65±3.5 years) was studied. Details of this group were published recently.7 To determine the normal absolute side-to-side asymmetry, we subtracted arbitrarily right CR, reactivity from left CR, reactivity in control subjects and ignored the signs. Normal absolute side-to-side asymmetry amounted to 1.6±0.2 [1.2] %CR,vol%CO2 (mean±SEM [SD]). The normal range of absolute side-to-side asymmetry was defined as mean±2 SD, and correspondingly, we obtained a normal span for absolute side-to-side asymmetry ranging from 0 to 4.0 %CR,vol%CO2. Then, we determined in all patients the side-to-side asymmetry of total CR, reactivity and differentiated between normal, abnormal positive, and abnormal negative asymmetry of CR, reactivity. Patients with an absolute side-to-side asymmetry of more than 4.0 %CR,vol%CO2 and with a greater CR, reactivity of the affected hemisphere than of the contralateral hemisphere were classified as having an abnormal positive side-to-side asymmetry. Correspondingly, patients with an absolute side-to-side asymmetry of more than 4.0 %CR,vol%CO2 and with lesser CR, reactivity of the affected hemisphere than of the contralateral hemisphere were placed into an abnormal negative side-to-side asymmetry category. All patients with an absolute side-to-side asymmetry of less than 4.0 %CR, vol%CO2 were classified as normal.

Statistics

The differences between means of the two hemispheres and between preoperative and postoperative values were compared with the paired t test. Because means of several variables were compared, the Bonferroni method was applied, taking into account the multiplicity of comparisons. For convenience, a significance level of P=0.01 was used throughout the study.

Results

Preoperative Findings

Normal side-to-side asymmetry of CR, reactivity (<4.0 %CR,vol%CO2), which had been derived from
The remaining patients had an abnormal side-to-side asymmetry (>4.0 %CRj/vol%CO₂) and could be separated into two subgroups: (1) patients in whom CRi reactivity of the affected hemisphere was smaller than that of the opposite hemisphere (group 2, n=10; absolute side-to-side asymmetry=7.1±0.7 %CRi/vol%CO₂; Fig 1) and (2) patients in whom CRi of the affected hemisphere was larger than that of the opposite hemisphere (group 3, n=12; absolute side-to-side asymmetry=8.0±1.4 %CRi/vol%CO₂; Fig 1). In the latter group, corresponding hemispheric CRi reactivities were as follows: ipsilateral, 7.1±1.1 %CRi/vol%CO₂; contralateral, 1.0±2.1 (Figs 2 and 3).

Patients in group 2 (abnormal negative side-to-side asymmetry, ipsilateral CRi reactivity less than contralateral CRi reactivity) demonstrated the opposite situation. CRi reactivities were as follows: ipsilateral, 0.6±0.8 %CRi/vol%CO₂; contralateral, 7.6±0.9 %CRi/vol%CO₂ (Figs 2 and 3).

**Effect of Endarterectomy**

CEA was performed without perioperative morbidity and mortality. When data of all 63 patients were combined, total CRi reactivity was not significantly affected by endarterectomy (hemisphere of ICA stenosis: preoperative value, 4.1±0.5 %CRj/vol%CO₂ and postoperative value, 4.3±0.5 %CRi/vol%CO₂; contralateral hemisphere: preoperative value, 4.2±0.4 %CRj/vol%CO₂ and postoperative value, 4.5±0.4 %CRi/vol%CO₂). However, a significant effect of the surgical procedure was found when changes in CRi reactivity were analyzed depending on the preoperative side-to-side asymmetry. Thus, all patients with an abnormal side-to-side asymmetry of CRi reactivity were categorized into three subgroups that did not differ with respect to age or localization of carotid artery stenosis.

The control group allowed differentiation of our patients into three subgroups that did not differ with respect to age or localization of carotid artery stenosis. Also, the percentage of symptomatic and asymptomatic patients was comparable between these subgroups. The Table shows hemispheric average values of systolic and diastolic flow velocities at different CO₂ concentrations in these subgroups before and after CEA. Most patients (group 1, n=41) demonstrated an absolute side-to-side asymmetry in the normal range (2.3±0.2 %CRi/vol%CO₂; mean±SEM; Fig 1). The corresponding hemispheric CO₂ reactivities were as follows: ipsilateral, 4.2±0.2 %CRi/vol%CO₂; contralateral, 4.3±0.4 %CRi/vol%CO₂ (Figs 2 and 3).

The remaining patients had an abnormal side-to-side asymmetry (>4.0 %CRj/vol%CO₂) and could be separated into two subgroups: (1) patients in whom CRi reactivity of the affected hemisphere was smaller than that of the opposite hemisphere (group 2, n=10; absolute side-to-side asymmetry=7.1±0.7 %CRi/vol%CO₂; Fig 1) and (2) patients in whom CRi of the affected hemisphere was larger than that of the opposite hemisphere (group 3, n=12; absolute side-to-side asymmetry=8.0±1.4 %CRi/vol%CO₂; Fig 1). In the latter group, corresponding hemispheric CRi reactivities were as follows: ipsilateral, 7.1±1.1 %CRi/vol%CO₂; contralateral, 1.0±2.1 (Figs 2 and 3).

Patients in group 2 (abnormal negative side-to-side asymmetry, ipsilateral CRi reactivity less than contralateral CRi reactivity) demonstrated the opposite situation. CRi reactivities were as follows: ipsilateral, 0.6±0.8 %CRi/vol%CO₂; contralateral, 7.6±0.9 %CRi/vol%CO₂ (Figs 2 and 3).

**Effect of Hypocapnia and Hypercapnia on Hemispheric Peak Systolic Flow Velocity and on Peak Diastolic Flow Velocity at the Middle Cerebral Artery in Patients With Unilateral Carotid Artery Stenosis Who Presented With Normal, Abnormal Negative, or Abnormal Positive Side-to-Side Asymmetry in Cerebral Resistance Index Reactivity**

<table>
<thead>
<tr>
<th></th>
<th>Abnormal Negative Side-to-Side Asymmetry (n=10)</th>
<th>Normal Side-to-Side Asymmetry (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td></td>
<td>Ipsi</td>
<td>Contra</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_syst, m/s</td>
<td>0.80±0.10</td>
<td>0.90±0.07</td>
</tr>
<tr>
<td>V_diast, m/s</td>
<td>0.35±0.04</td>
<td>0.41±0.03</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_syst, m/s</td>
<td>0.51±0.08</td>
<td>0.63±0.07</td>
</tr>
<tr>
<td>V_diast, m/s</td>
<td>0.22±0.03</td>
<td>0.19±0.02</td>
</tr>
</tbody>
</table>

V_syst indicates systolic flow velocity; V_diast, diastolic flow velocity. Velocities were determined at the hemisphere ipsilateral (Ipsi) and contralateral (Contra) to carotid artery stenosis before carotid endarterectomy and 3 months thereafter. Patients whose ipsilateral CRi reactivity was abnormally low compared with the contralateral CRi reactivity were classified as having an abnormal negative side-to-side asymmetry. Positive side-to-side asymmetry refers to patients in whom the ipsilateral CRi reactivity was abnormally high compared with the contralateral CRi reactivity. Normality was based on the side-to-side asymmetry in 37 age-matched, healthy control subjects. Values are mean±SEM.

![Fig 1](http://stroke.ahajournals.org/). Bar graph shows effect of carotid endarterectomy on the side-to-side asymmetry of CRi (cerebral resistance index) reactivity (%CRj/vol%CO₂) in patients with carotid artery stenosis depending on the preoperative quality of the side-to-side asymmetry. I indicates Group 1 (ipsilateral CRi reactivity in the range of normal side-to-side asymmetry, n=41); II, group 2 (ipsilateral CRi reactivity abnormally low compared with the CRi reactivity at the unaffected hemisphere [abnormal negative side-to-side asymmetry, n=10]); and III, group 3 (ipsilateral CRi reactivity abnormally high compared with the CRi reactivity at the unaffected hemisphere [abnormal positive side-to-side asymmetry, n=12]). *P<.01 vs side-to-side asymmetry before surgery.
Abnormal Positive Side-to-Side Asymmetry

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsl</td>
<td>Contra</td>
</tr>
<tr>
<td></td>
<td>0.86±0.05</td>
<td>0.64±0.06</td>
</tr>
<tr>
<td></td>
<td>0.39±0.03</td>
<td>0.33±0.03</td>
</tr>
<tr>
<td></td>
<td>0.62±0.03</td>
<td>0.58±0.06</td>
</tr>
<tr>
<td></td>
<td>0.21±0.02</td>
<td>0.21±0.02</td>
</tr>
</tbody>
</table>

absolute side-to-side asymmetry responded to the surgical procedure significantly. In patients in whom ipsilateral CR, reactivity was lower than contralateral CR, reactivity (group 2), ipsilateral CR, reactivity rose significantly after surgery in all patients (preoperative value, 0.6±0.8 %CR,vol%CO2; postoperative value, 3.7±1.1; P<.01; Fig 2). CEA did not alter contralateral CR, reactivity. In patients in whom ipsilateral CR, reactivity was higher than contralateral CR, reactivity (group 3), contralateral CR, reactivity rose significantly after surgery (preoperative value, -1.0±2.1 %CR,vol%CO2; postoperative value, 5.2±0.7; P<.01; Fig 3). Postoperative ipsilateral CR, reactivity in group 3 showed a tendency toward lower values but was not significantly different from preoperative findings (preoperative value, 7.1±1.1 %CR,vol%CO2; postoperative value, 3.9±1.1; P=.04; Fig 3). Ipsilateral and contralateral CR, reactivity remained unchanged in group 1 (patients with normal absolute side-to-side asymmetry, Figs 2 and 3). CEA normalized the pathological absolute side-to-side asymmetry in group 2 (preoperative value, 7.1±0.7 %CR,vol%CO2; postoperative value, 1.3±1.4; P<.01; Fig 1) and in group 3 (preoperative value, 8.0±1.4 %CR,vol%CO2; postoperative value, 1.2±1.4; P<.01; Fig 1). Side-to-side asymmetry in patients of group 1 (normal side-to-side asymmetry) did not change after surgery.

Discussion
The present study confirms results of a previous study in completely asymptomatic patients with unilateral high-grade to threadlike ICA stenosis.6 Corresponding to the latter study, we could identify three different patterns of hemispheric CR, reactivity as well as side-to-side asymmetry in patients with symptomatic ICA stenosis. Because relative frequency of the hemody-
namic patterns was comparable between symptomatic and asymptomatic patients, we combined hemodynamic data of all patients to analyze the effect of carotid endarterectomy. The majority of patients (n=41, group 1) demonstrated a normal side-to-side asymmetry of CR, reactivity (Fig 1). This normal finding results from an adequate CR, reactivity at the poststenotic hemisphere, although baseline hemodynamics (poststenotic perfusion pressure) were previously found to be slightly abnormal in this subgroup. Complete equilibration of perfusion pressure through collaterals only occurred in patients of group 3 (n=12, abnormal positive side-to-side asymmetry with ipsilateral larger than contralateral CR, reactivity). In this subgroup, baseline hemodynamics (cerebral perfusion pressure and peripheral resistance) were comparable between both hemispheres.

This subgroup demonstrated a marked hyperreactivity to CO₂ at the poststenotic hemisphere. This strong hyperreactivity was mainly the consequence of an increased dilatory response of peripheral cerebral vessels to hypercapnia and surmounted the corresponding CRi reactivity in group 1 (Fig 2). The exaggerated dilatory response apparently generated a steal phenomenon from the contralateral to the ipsilateral hemisphere, explaining the missing CRi reactivity at the contralateral hemisphere.

As discussed previously, during hemispheric steal the contralateral hemisphere tries to increase hypercapnic blood flow up to the level of the poststenotic hemisphere. This equilibration is achieved by vasodilation of contralateral large cerebral vessels, which compensates the extreme CO₂-induced vasodilation of peripheral vessels at the poststenotic hemisphere. The particular qualities of CR, make it possible to identify patients with interhemispheric steal during pharmacological provocation. According to the physiology of pulsatile flow, CR, not only reflects changes in peripheral wave reflection or resistance (input impedance) but is also determined by the state of the vessel where CR, is measured (characteristic impedance). Opposite changes of wave reflection and characteristic impedance (vessel elasticity) can cancel each other, leaving CR, unchanged. Such a situation can be observed at the contralateral hemisphere in group 3 during hypercapnic steal from the opposite to the poststenotic hemisphere. The strong ipsilateral response despite limited inflow capacity (significant ICA stenosis) generates the steal phenomenon, which leads to reduced cerebral perfusion pressure at the contralateral hemisphere and to interhemispheric imbalances in blood flow and volume. Subsequently, compensatory dilation of the contralateral MCA takes place. Thereby, characteristic impedance at the site of TCD measurement falls. This phenomenon cancels the effect of diminished wave reflection on CRi. Hypercapnic CRi remains essentially unchanged in comparison to normocapnic CRi, and the strong CR, reactivity at the poststenotic hemisphere is combined with an almost missing CRi reactivity at the contralateral hemisphere.

Finally, the third subgroup (group 2) had an extremely poor CR, reactivity at the poststenotic hemisphere. This subgroup has been identified by various other techniques (positron emission tomography, single-photon emission computed tomography) in the past and is characterized by a critical reduction of ipsilateral perfusion pressure caused by insufficient collaterals. All patients were scheduled for CEA. Indication for surgery in patients with unilateral high-grade to thread-like symptomatic ICA stenosis is no longer controversial. The benefit of CEA in asymptomatic patients still awaits definitive confirmation. Currently, it is our policy to perform CEA in asymptomatic patients with thread-like ICA stenosis and low perioperative risk who simultaneously have complicated plaques at the ICA origin according to color-flow duplex sonography. Recent studies in patients with asymptomatic ICA disease showed a significant association between certain plaque morphologies (such as ulceration) and the frequency of silent cerebral infarction and of future neurological events.

The hemodynamic effect of CEA varies and depends on the preexisting hemodynamic status. When data from all patients are combined, a significant hemodynamic effect of CEA is not evident. Also, the majority of patients (group 1, normal side-to-side asymmetry) did not respond to CEA either at the poststenotic or at the contralateral hemisphere (Figs 2 and 3). Correspondingly, side-to-side asymmetry remained unchanged. A clear effect of the surgical procedure could be identified when patients were analyzed according to their preoperative side-to-side asymmetry. Thus, all those patients who had an abnormal side-to-side asymmetry with the ipsilateral CR, reactivity ipsilateral to ICA occlusion or CEA apparently removed the hypercapnic steal phenomenon, thereby normalizing not only the
contralateral CR, reactivity but also the pathological side-to-side asymmetry (Figs 1 and 3). Ipsilateral CR, reactivity of these patients was reduced after surgery. However, this effect was not significant, presumably because the number of subjects studied was small.

Postoperative disappearance of hypercapnic steal cannot be explained by equilibration of perfusion pressure, since such an equilibration already existed before surgery in this group.6 A postoperative attenuation of the exaggerated ipsilateral CR, reactivity may have contributed to the observed normalizations of side-to-side asymmetry. Apparently, the poststenotic hemisphere "noticed" the improved inflow capacity after CEA. Such a situation could have occurred under conditions in which systemic blood pressure dropped and in which, without CEA, ipsilateral perfusion pressure would have otherwise fallen to critical values.

In conclusion, determination of CR, reactivity and its side-to-side asymmetry by TCD sonography can identify patients with inadequate intracerebral collateralization and with interhemispheric steal in association with significant carotid artery disease. Determination of preoperative CR, reactivity allows precise prediction of the effect of CEA on intracerebral hemodynamics. Our study does not address the clinical outcome of the patients. However, identification of abnormal hemodynamics may help to find the appropriate therapy for patients in which indication for operative or conservative therapy is still controversial (eg, patients with significant asymptomatic ICA disease). Future prospective studies will have to show whether CEA is of benefit in patients with poor cerebrovascular reactivity or with interhemispheric steal.

References


Effect of carotid endarterectomy on patterns of cerebrovascular reactivity in patients with unilateral carotid artery stenosis.

W H Hartl, I Janssen and H Fürst

doi: 10.1161/01.STR.25.10.1952

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/25/10/1952

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/