Cerebral Blood Flow and Internal Carotid Artery Flow During Carotid Surgery

BY GUDRUN BOYSEN, M.D., H. J. LADEGAARD-PEDERSEN, M.D., N. VALENTIN, M.D., AND H. C. ENGELL, M.D.

Abstract:
Cerebral Blood Flow and Internal Carotid Artery Flow During Carotid Surgery

In a series of 17 patients operated on for stenosis of the internal carotid artery, measurement of the blood flow in the internal carotid artery by a squarewave electromagnetic flowmeter was performed simultaneously with measurement of the regional cerebral blood flow (rCBF) by the $^{133}$Xenon injection technique. The measurements were made before and after endarterectomy. On completion of endarterectomy there was significant increase in mean internal carotid artery flow (ICAF), from 133 ml/min to 212 ml/min ($P < 0.05$), whereas mean rCBF remained unaltered.

The ratio ICAF/rCBF gives brain substance in grams supplied by the internal carotid artery. The mean value of this ratio increased significantly from 231 gm to 452 gm after endarterectomy ($P < 0.01$). Thus cerebral hemodynamics tended to the normal postoperatively.

ADDITIONAL KEY WORDS cerebral transient ischemic attacks $^{133}$Xenon electromagnetic flowmetry carotid stenosis

Arterial blood flow measurement during reconstructive vascular surgery is of value in estimating the degree of flow reduction before the reconstruction and in evaluating the effect of the operation. Changes of blood flow through an artery, however, do not necessarily reflect changes in tissue perfusion, unless that artery is the sole supply to the organ or region in question and no arteriovenous shunting takes place at the periphery.

Because the cerebral collateral circulation is abundant, flow changes in an extracranial cerebral artery effected by reconstructive surgery do not necessarily result in changes in brain tissue perfusion.

To determine the effect of carotid endarterectomy on the cerebral hemodynamics, simultaneous measurements of internal carotid artery flow (ICAF) (electromagnetic squarewave flowmeter) and regional cerebral blood flow (rCBF) ($^{133}$Xenon injection technique) were made in a series of patients before and after endarterectomy for carotid stenosis.

Methods
The series comprises 17 patients operated on for severe atherosclerotic stenosis of the internal carotid artery. Concomitant lesions of other extracranial arteries were common (table 1). Six patients presented with a history of transient ischemic attacks. Three patients had had small episodes of cerebral ischemia lasting longer than 24 hours and had slight neurological symptoms at the time of operation. Five patients had suffered a completed stroke and partial remission had taken place before the operation. Three patients were operated on immediately after admission because of progressing stroke; they were, however, all fully conscious and without severe neurological defects. There were no postoperative deaths.

The surgical operations were performed under general anesthesia. After induction with a short-acting barbiturate, anesthesia was main-
### TABLE 1

**Clinical Data in 17 Patients Undergoing Endarterectomy for Stenosis of the Internal Carotid Artery**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Sex</th>
<th>Age</th>
<th>Group</th>
<th>Side of operation</th>
<th>Arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>66</td>
<td></td>
<td>L.</td>
<td>Subtotal occlusion of left internal carotid. Right internal carotid artery normal.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>61</td>
<td>x</td>
<td>R.</td>
<td>Stenosis of right common and internal carotid. Stenosis of both subclavian arteries and stenosis of left vertebral artery.</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>57</td>
<td>x</td>
<td>L.</td>
<td>Stenosis of left internal carotid. Atherosclerosis of both common carotids. Right internal carotid normal at the bifurcation, atherosclerotic at the siphon.</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>67</td>
<td>x</td>
<td>L.</td>
<td>Stenosis of left internal carotid artery. Occlusion of right internal carotid. Filling of the right anterior and middle cerebral arteries from the left internal carotid.</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>66</td>
<td>x</td>
<td>L.</td>
<td>Stenosis of left internal carotid artery.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>69</td>
<td>x</td>
<td>L.</td>
<td>Stenosis of left internal carotid artery.</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>75</td>
<td>x</td>
<td>R.</td>
<td>Subtotal occlusion of right internal carotid. Occlusion of left common carotid. Filling of left anterior and middle cerebral arteries from right internal carotid.</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>65</td>
<td>x</td>
<td>L.</td>
<td>Subtotal occlusion of left internal carotid. Slight stenosis of the right internal carotid. Stenosis of both vertebral arteries.</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>67</td>
<td>x</td>
<td>R.</td>
<td>Stenosis of right common and internal carotid. Atherosclerosis of left carotid at the bifurcation. Stenosis of right vertebral artery.</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>60</td>
<td>x</td>
<td>R.</td>
<td>Stenosis of right internal carotid and of right subclavian artery.</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>51</td>
<td>x</td>
<td>R.</td>
<td>Stenosis of right and left internal carotid arteries. Atherosclerosis of both vertebral arteries.</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>x</td>
<td>L.</td>
<td>Stenosis of left internal carotid artery.</td>
</tr>
</tbody>
</table>
BLOOD FLOW DURING CAROTID SURGERY
tained by halothane in concentrations \( \leq 1.0\% \) in oxygen and nitrous oxide, approximately 50\% of each. The patients were ventilated by a ventilator via a non-rebreathing system. Systemic blood pressure was continuously monitored via a catheter inserted into the radial artery and connected to a Statham pressure transducer and potentiometer recorder.

The internal carotid artery flow was measured by a squarewave electromagnetic flowmeter (Nycotron 372). The flow probes were calibrated in vitro as described by Lauridsen et al.\(^1\) The variation coefficient was 2.6\%. Zero flow reference was established by a brief (5 to 10 sec) occlusion of the artery before every measurement.

The rCBF measurements were made by the isotope clearance technique described by Høedt-Rasmussen, Sveinsdottir and Lassen.\(^2\) After surgical exposure, 0.2 to 0.4 mCi \(^{188}\)Xe, dissolved in 0.2 to 1.0 ml physiological saline, was injected directly into the internal carotid artery. The clearance of the tracer was recorded by a single scintillation detector placed over the temporal region. The detector was connected to a Meditronic ratemeter, and the curve was written out by a potentiometer recorder.

The rCBF was calculated according to the equation

\[
rCBF_{10} = \frac{H - H_{10}}{A_{10}^{(corr)}} \cdot \lambda \cdot 100 \text{ ml/100 gm \cdot minute}
\]

where \( H \) is the initial height of the clearance curve, \( H_{10} \) the height at ten minutes, and \( A_{10}^{(corr)} \) the area below the curve corrected for recirculation and remaining activity from previous injection. \( \lambda \) is the blood-tissue partition coefficient of Xenon for whole brain (1.15). A wide-angle collimation was used, enabling the detector to “see” the whole hemisphere. The rCBF\(_{10} \) thus represents an average flow value for the region of the brain getting its blood supply from the internal carotid artery in question.

Of the 34 pairs of rCBF and carotid artery flow measurements 21 were carried out simultaneously. In ten instances the flowmetry was made one to six minutes before, and in three instances 15 to 38 minutes after the Xenon injection. It was secured that no important change in blood pressure took place during the two examinations. Arterial carbon dioxide tension (\( P_{\text{aco}_2} \)) was measured at each set of flow measurements.

**Results**

In all cases the stenoses were estimated to reduce the cross-sectional area of the internal carotid arteries by 50\% or more. In some cases the lumen was reduced to a threadlike passage.
### TABLE 2

**Hemodynamic Effect of Carotid Endarterectomy in 17 Patients**

<table>
<thead>
<tr>
<th>No.</th>
<th>ICAF ml/min Before</th>
<th>ICAF ml/min After</th>
<th>rCBF&lt;sub&gt;10&lt;/sub&gt; gm/min Before</th>
<th>rCBF&lt;sub&gt;10&lt;/sub&gt; gm/min After</th>
<th>MBP mm Hg Before</th>
<th>MBP mm Hg After</th>
<th>CVR Before</th>
<th>CVR After</th>
<th>Pa&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; Before</th>
<th>Pa&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; After</th>
<th>Halothane conc. per cent Before</th>
<th>Halothane conc. per cent After</th>
<th>ICAF&lt;sub&gt;100&lt;/sub&gt; ml/min Before</th>
<th>ICAF&lt;sub&gt;100&lt;/sub&gt; ml/min After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>200</td>
<td>31</td>
<td>32</td>
<td>114-103</td>
<td>91-80</td>
<td>3.5</td>
<td>2.7</td>
<td>36</td>
<td>33</td>
<td>1.0-0.8</td>
<td>0.5</td>
<td>258</td>
<td>625</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>180</td>
<td>34</td>
<td>38</td>
<td>97-97</td>
<td>97-93</td>
<td>2.9</td>
<td>2.5</td>
<td>30</td>
<td>27</td>
<td>0.2</td>
<td>0.2</td>
<td>265</td>
<td>474</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>145</td>
<td>50</td>
<td>54</td>
<td>95-88</td>
<td>113-97</td>
<td>1.8</td>
<td>1.9</td>
<td>41</td>
<td>44</td>
<td>0.5</td>
<td>1.0</td>
<td>380</td>
<td>269</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>240</td>
<td>34</td>
<td>34</td>
<td>96-103</td>
<td>105-88</td>
<td>2.9</td>
<td>2.8</td>
<td>44</td>
<td>47</td>
<td>0.7</td>
<td>0.5</td>
<td>353</td>
<td>706</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>89</td>
<td>87</td>
<td>41</td>
<td>108-108</td>
<td>83-72</td>
<td>1.2</td>
<td>1.9</td>
<td>54</td>
<td>42</td>
<td>1.0</td>
<td>0.7</td>
<td>111</td>
<td>217</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>500</td>
<td>45</td>
<td>65</td>
<td>85-97</td>
<td>87-75</td>
<td>2.0</td>
<td>1.2</td>
<td>47</td>
<td>54</td>
<td>0.8-1.0</td>
<td>0.8</td>
<td>0</td>
<td>769</td>
</tr>
<tr>
<td>7</td>
<td>114</td>
<td>202</td>
<td>24</td>
<td>35</td>
<td>103-153</td>
<td>153-155</td>
<td>5.3</td>
<td>4.4</td>
<td>58</td>
<td>52</td>
<td>0.1</td>
<td>0.2</td>
<td>475</td>
<td>577</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>93</td>
<td>23</td>
<td>32</td>
<td>112-116</td>
<td>93-111</td>
<td>5.0</td>
<td>3.2</td>
<td>33</td>
<td>33</td>
<td>0.5</td>
<td>0.5</td>
<td>87</td>
<td>291</td>
</tr>
<tr>
<td>9</td>
<td>354</td>
<td>286</td>
<td>86</td>
<td>70</td>
<td>112-100</td>
<td>107-100</td>
<td>1.2</td>
<td>1.5</td>
<td>54</td>
<td>56</td>
<td>0.5</td>
<td>0.5</td>
<td>412</td>
<td>409</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>122</td>
<td>60</td>
<td>90</td>
<td>106-102</td>
<td>102-106</td>
<td>1.7</td>
<td>1.2</td>
<td>60</td>
<td>64</td>
<td>0.5</td>
<td>1.0</td>
<td>100</td>
<td>136</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>242</td>
<td>30</td>
<td>51</td>
<td>97-106</td>
<td>113-110</td>
<td>3.4</td>
<td>2.2</td>
<td>59</td>
<td>57</td>
<td>0.5</td>
<td>0.5</td>
<td>0</td>
<td>475</td>
</tr>
<tr>
<td>12</td>
<td>380</td>
<td>269</td>
<td>104</td>
<td>106</td>
<td>118-120</td>
<td>115-113</td>
<td>1.1</td>
<td>1.1</td>
<td>56</td>
<td>57</td>
<td>0.7</td>
<td>1.0</td>
<td>365</td>
<td>254</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>220</td>
<td>38</td>
<td>41</td>
<td>103-103</td>
<td>93-93</td>
<td>2.7</td>
<td>2.3</td>
<td>43</td>
<td>41</td>
<td>0.3</td>
<td>0.3</td>
<td>79</td>
<td>537</td>
</tr>
<tr>
<td>14</td>
<td>200</td>
<td>213</td>
<td>56</td>
<td>40</td>
<td>87-87</td>
<td>86-86</td>
<td>1.6</td>
<td>2.2</td>
<td>59</td>
<td>58</td>
<td>0.3</td>
<td>0.3</td>
<td>357</td>
<td>533</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>242</td>
<td>39</td>
<td>47</td>
<td>75-70</td>
<td>73-80</td>
<td>1.9</td>
<td>1.6</td>
<td>43</td>
<td>43</td>
<td>0.4-0.25</td>
<td>0.25</td>
<td>87</td>
<td>515</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>154</td>
<td>23</td>
<td>30</td>
<td>92-97</td>
<td>97-102</td>
<td>4.1</td>
<td>3.3</td>
<td>52</td>
<td>-</td>
<td>0.5</td>
<td>0.5</td>
<td>0</td>
<td>513</td>
</tr>
<tr>
<td>17</td>
<td>485</td>
<td>211</td>
<td>81</td>
<td>54</td>
<td>97-85</td>
<td>125-125</td>
<td>1.1</td>
<td>2.3</td>
<td>70</td>
<td>54</td>
<td>0.7</td>
<td>0.6</td>
<td>599</td>
<td>391</td>
</tr>
</tbody>
</table>

Mean 133 212 49.7 50.6 100.9 100.5 2.55 2.25 49.4 47.6 0.54 0.52 231 452

ICAF: Internal carotid artery flow.
rCBF<sub>10</sub>: Regional cerebral blood flow in ml/100 gm/min.
MBP: Mean arterial blood pressure.
CVR: Cerebrovascular resistance in mm Hg/ml/100 gm/min.
Pa<sub>CO<sub>2</sub></sub>: Arterial carbon dioxide tension.
Halothane conc., per cent of the gas mixture administered.
ICAF<sub>100</sub>: The ratio expresses gram brain substance supplied by the internal carotid artery.

The results in four of the patients (cases 1, 2, 3 and 4) have recently been published. ⁹
The ICAF showed great variations before as well as after the endarterectomy (table 2). In three cases there was no measurable flow before the endarterectomy. In case 16 the flow decreased from 50 ml/min to zero during the measurement. In cases 6 and 11 the occlusion probably took place during manipulation of the vessel, as angiography one and ten days preoperatively had shown some patency and no thrombosis of the peripheral part of the artery was found at operation. For the group as a whole the mean blood flow in the internal carotid artery increased significantly from 133 ml/min before to 212 ml/min after the operation, P < 0.05 (Wilcoxon's test for pair differences). The difference was not caused by changes in systemic blood pressure or in PaCO₂ as the mean values of these parameters were unchanged after endarterectomy.

In seven cases rCBF increased significantly and in four cases a decrease occurred. For the group as a whole the mean value of rCBF before was 49.7 ml/100 gm • minute before and 50.6 ml/100 gm • minute after the endarterectomy. The difference is not significant, P > 0.1.

As the measured rCBF can be taken as a mean value for the whole region supplied by the internal carotid artery, the ratio of ICAF/rCBF gives an expression of the weight of the brain tissue fed by this artery. The mean values of these ratios were 231 gm before and 452 gm after the endarterectomy. The difference is significant, P < 0.01.

Following the operation the cerebrovascular resistance calculated as the mean arterial blood pressure divided by rCBF was slightly reduced, from 2.55 to 2.25 (P > 0.05).

**Discussion**

Arterial blood flow measurements as well as rCBF measurements are beset with inaccuracies. Based on a variation coefficient of 4.8% on the rCBF measurement and a variation coefficient of the flowmetry of 2.6%, the calculated variation coefficient of the ratio of ICAF/rCBF was 5.3%. Consequently, a change of the ratio in any individual case should be in the order of 15% to be significant.

The anesthetic agent, halothane, used for these operations is a cerebral vasodilatator, and the effect is dependent on the concentration. This means that the rCBF increases with increasing halothane concentration provided the blood pressure is kept constant, and that rCBF becomes pressure dependent to a greater degree than normally. The reactivity of the brain vessels to carbon dioxide has been found to be preserved during halothane anesthesia, and also in patients with cerebral atherosclerosis. In cases of severe cerebrovascular insufficiency, however, a permanent vasodilatation may impede further increase of rCBF when hypercapnia is added.

The mean rCBF value of 50 ml/100 gm • minute found in this material is not representative of the “normal” rCBF level among these patients, but should be considered in context of the elevated PaCO₂ and the halothane anesthesia.

Several authors have found hypercapnia to be of value during carotid endarterectomy, the beneficial effect being attributed to an increase in cerebral blood flow. In spite of hypercapnia critical low rCBF values, i.e. 30 ml/100 gm • minute or less, were found in some of our cases (7, 11, and 16), which were the cases with the most severe occlusive lesions of the extracranial arteries. In these cases the vascular bed might have been maximally dilated because of local CO₂ accumulation, and the additional hypercapnia was probably not beneficial. This method of rCBF measurement does not demonstrate whether the phenomenon known as intracerebral steal contributes to the low flow values. Further studies of rCBF under varying PaCO₂ levels are necessary to determine the value of hypercapnia in carotid surgery.

Flowmetry after endarterectomy showed an increase of the ICAF in 11 patients, and insignificant changes or reduction of the flow in six patients. In case 5, where the carotid artery flow was virtually unchanged, the significant decrease in rCBF can be explained by a decrease in PaCO₂, blood pressure, and halothane concentration. In spite of the unaltered carotid artery flow a greater part of the brain was thus supplied from this artery.

A decrease of rCBF following endarterectomy was observed in four cases. In all of them rCBF decreased from very high levels. In cases 5 and 17 the decrease could be explained by a lowering of PaCO₂ and/or blood pressure, while no explanation could be given in cases 9 and 14. In six cases rCBF remained largely unchanged after the endarterectomy. An increase in rCBF was seen in seven cases (6, 7,
8, 10, 11, 15, and 16). They all had very low flow rates in the internal carotid artery before the endarterectomy, except case 7, in which the opposite internal carotid artery was occluded. The five patients in whom a critical low rCBF was found (cases 1, 7, 8, 11, and 16) all had neurological defects at the time of operation, and their symptoms may have been due to the reduced rCBF rather than to embolic episodes. The mean rCBF for the group as a whole was unaltered by the operation, which is in accordance with the findings of O'Brien et al., who, using the Xenon inhalation technique, found the rCBF unaltered postoperatively in a group of ten patients. Likewise, Adams, Smith and Wylie (1962), using the Kety-Schmidt nitrous oxide technique, found the cerebral blood flow unaltered in a series of 17 patients.

Comparison of two rCBF measurements in the same patient is meaningful only when all the factors influencing rCBF are kept constant, as there is no reliable way of quantitating the additive effect of changes in these factors. However, as a rule, these factors will have the same relative influence on the blood flow in the internal carotid artery as on the rCBF, and in simultaneous measurements the ratio of the two parameters will be independent of variations in these factors. Therefore, a comparison of the ratio before and after endarterectomy becomes valid in spite of changes in blood pressure, PaCO₂, and halothane concentration. Thus the hemodynamic effect of the operation can be expressed by the ratio ICAF/rCBF, which gives the amount of brain substance in grams supplied by the internal carotid artery.

In this study increase in the brain mass supplied by the operated artery was registered in 13 of 17 cases. In case 9 the ratio ICAF/rCBF was unchanged. In three cases (3, 12, and 17), all with relatively high flow rates in the internal carotid artery before the endarterectomy, a reduction of the ratio was found. In these cases an increased resistance might have been created at the site of the suture line.

It has been shown by several authors that the cross-sectional area of the normal carotid artery has to be severely reduced before a reduction of flow takes place. The major peripheral resistance is localized to the arterioles and precapillaries, and alterations of the diameter of the carotid artery give no measurable flow alterations until the cross-section is reduced below 5 sq mm (Brice, Dowsett and Lowe). In most of our cases the stenoses have constituted a critical resistance, which has been demonstrated indirectly by the increase of ICAF following the endarterectomy. This did not result in an increase of the mean rCBF, but in an increase of the brain mass supplied by this artery. Consequently, this must have led to a proportionate reduction of the blood flow through the other extracranial arteries. Model studies of the circle of Willis have shown that in the presence of occlusion of one internal carotid artery there is a pressure difference of about 10 mm Hg in the circle of Willis from the side of the open internal carotid artery to the occluded. The flow reduction in the other extracranial arteries following endarterectomy is probably the result of a pressure equalization of the two sides of the circle of Willis.

Quantitative data about the blood flow in the internal carotid artery in normal man are not available. Internal carotid artery blood flow studies in patients in whom the artery was exposed for ligation or who had injection of antitumor drugs or radical operations in the neck have shown mean values varying from 164 ml/min to 364 ml/min. Assuming a brain weight of 1400 gm, an rCBF of 50 ml/100 gm • minute and that the two internal carotids and the basilar artery each supply one-third of the total cerebral blood flow, the mean blood flow for one internal carotid artery would be 230 ml/min, supplying 450 gm of brain substance. In this material the operation resulted in change toward normal of the mean values of the ICAF as well as of the ratio ICAF/rCBF. When comparing the ratios in table 2 with the arteriogram findings in table 1, it will be seen that in six of eight cases where the ratio surpasses 500 gm there is arteriogram evidence of occlusive lesions in the other carotid and/or vertebral arteries.

The pathogenic mechanism of brain ischemia in patients with stenosis of extracranial arteries is a subject of debate. The theory of distal embolization originating from the rough surface of the atheromatous plaque is opposed to the theory of a reduced cerebral blood supply due to the stenosis itself. In this material the mean rCBF was unaltered by the endarterectomy, which speaks in favor of emboli as the most frequent pathogenic
BLOOD FLOW DURING CAROTID SURGERY

mechanism. This, however, does not exclude hemodynamic factors playing a concurrent role in some cases. In the four cases of this series, where the rCBF before the endarterectomy was critically low and increased after the operation, the symptoms might have been due to the compromised blood supply.

Acknowledgment
This work was aided by a grant from the Danish Medical Research Council.

References


Cerebral Blood Flow and Internal Carotid Artery Flow During Carotid Surgery
GUDRUN BOYSEN, H. J. LADEGAARD-PEDERSEN, N. VALENTIN and H. C. ENGELL

Stroke. 1970;1:253-260
doi: 10.1161/01.STR.1.4.253

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/1/4/253

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/