Progressive neurological deterioration in patients with recent stroke or transient ischemic attack (TIA) is a distressing and all too common occurrence. Anticoagulation is an important therapeutic consideration for many of these patients. The use of heparin in patients with acute brain ischemia will be reviewed in this paper.

Anticoagulation with heparin is often considered in the following clinical settings: 1) progressing stroke; 2) acute, partial stroke; 3) recent TIA, especially if multiple; and 4) cardioembolic stroke. Anticoagulation is of no value and in fact may be detrimental in completed thrombotic strokes.1

Progressing Stroke

Although progressing stroke (stroke-in-evolution) has been recognized for more than 30 years, no clinical definition is universally accepted.2 Progressing stroke describes an acute ischemic neurological deficit or constellation of deficits that increase in severity, extent, or number in the minutes or hours after onset. The increase may be gradual, stepwise, or fluctuating with periods of improvement.3 Ideally, this progression is observed by a physician, but the patient or family can often provide a compelling account that allows reliable diagnosis.

Progressing stroke is common, occurring in 15–20% of carotid distribution infarcts4–6 and in about 40% of those in the vertebrobasilar circulation.11,12 Vertebrobasilar system strokes may progress for as long as 96 hours, while carotid territory strokes are generally completed in 24–48 hours.2,3 Once a progressive course has declared itself, further deterioration will occur in one third of patients.7,14

A progressive course complicates several different mechanisms of brain ischemia. Large arterial thrombosis is often the first consideration, but distal field or “watershed” infarcts and lacunar strokes due to small, penetrating artery disease frequently present in this manner as well.2,3,5 More than half the intracerebral hemorrhages have a smooth or stuttering course.3 Even cardioembolic strokes, usually characterized by a sudden maximal deficit, have a smooth or stuttering onset about 20% of the time.3 A number of other entities, including tumors, subdural hematomas, infections, intoxications, and even metabolic disturbances such as hypoglycemia, may mimic progressing stroke, emphasizing that accurate diagnosis must precede any consideration of antithrombotic therapy.

Several mechanisms have been proposed to explain the progression of thrombotic strokes. Enlargement of a thrombus can cause further obstruction, or distal–proximal propagation of thrombus can occlude collateral channels.4,5 Thrombus or atherosclerotic debris may also embolize distally. Other, nonthromboembolic causes of clinical worsening must also be considered. Cerebral edema can cause clinical worsening, usually manifested by increasing obtundation several days after large infarcts. Systemic and metabolic factors, such as decreased cardiac output, hypotension, hypoxia, hyper- and hypoglycemia, electrolyte disturbances, and infections, account for at least 25% of progressive impairments in this setting.2,14

Several early clinical studies suggested that heparin benefits patients with progressing stroke.15–17 Although two studies were randomized trials (Table 1), the lack of precise criteria for entry and outcome, the inability to identify small hemorrhages in the pre–computed tomography (CT) era, nonblind observation, and the small number of patients make these studies inadequate by current methodological standards.

In a recent uncontrolled study Haley et al18 reported that 43% of 28 patients with progressing stroke continued to progress despite conventional heparin dosages (partial thromboplastin time, PTT 60–120 seconds). The efficacy of heparin for lacunar strokes has also been questioned recently.19 Nevertheless, at present, progressing infarct (stroke-in-evolution) is a generally accepted, although unproven, indication for urgent anticoagulation.

Acute, Partial Stroke

On initial evaluation it is not possible to determine which stroke patients will have a progressive course. Because of the frequency of progressing stroke (15–40%) and the relative safety of heparin (see below) in nonhemorrhagic infarcts, some advocate administration of heparin to all patients presenting within 24–48 hours of a stroke with submaximal deficit in an attempt to prevent progression.

The preliminary report of a recent randomized, double-blind trial of heparin in 220 patients with acute partial stroke in the carotid or vertebrobasilar distributions indicated that 16% of treated patients pro-
gressed compared with 19% of controls, a nonsignificant difference.4 No hemorrhagic complications occurred. Evaluation of efficacy in stroke subtypes (cardiot versus vertebrobasilar, lacunar versus nonlacunar) awaits full publication of the results. In an uncontrolled study of 136 patients with acute stroke who received heparin, only 3% had progressing or new infarction, but serious bleeding occurred in 4%.20 Pending further data and more effective therapy, on an empirical basis we anticoagulate some patients with partial stroke in the vertebrobasilar system because of the substantial risk (40%) of progression.

**Recent TIA**

TIA stands as one of the most important indicators of impending stroke, with the greatest risk in the weeks following onset of TIA.21 “Crescendo” TIA describes the occurrence of multiple TIAs over a few hours to a few days, often increasing in duration and in severity of deficit. The natural history has not been systematically studied, but anecdotal experience suggests that this pattern of TIA is particularly ominous, frequently heralding imminent brain infarction.22-23

In an uncontrolled, observational study of consecutive patients with acute TIA treated with heparin within 72 hours, 12 (17%) had continued TIAs, and five (7%) subsequently experienced brain infarction.24 However, two of these five strokes were related to anticoagulation in nine patients (13%). Still, in patients with recent or crescendo TIAs, heparin is widely used.

**Cardioembolic Stroke**

About 14% of patients who experience cardiogenic brain embolism will have a second embolism to the brain within 2 weeks of the initial event.2425 The risk of these early, recurrent emboli is similar for most major cardioembolic sources (e.g., atrial fibrillation, ischemic heart disease, mitral stenosis). Early anticoagulation reduces the likelihood of recurrent emboli to about one third of its natural rate.2425 Heparin would seem ideal for these patients in whom intracardiac thrombosis is the presumed culprit.

Unfortunately, cardioembolic brain infarctions have a special predisposition to undergo hemorrhagic transformation (Figure 1).2627 Distal migration of embolic fragments from their initial site of obstruction allows reperfusion of the infarcted tissue, often with multifocal capillary bleeding into the infarct. Usually, such secondary bleeding is minimal and seldom results in clinical worsening. In patients receiving anticoagulants, however, massive brain hemorrhage and clinical deterioration can occur. The clinical dilemma pits the risk of recurrent embolism without heparin against the risk of accentuated hemorrhage with anticoagulation.

A key determinant in the safety of anticoagulation is the timing of reperfusion. Virtually all hemorrhagic transformations occur after 6 hours but before 48 hours from stroke onset and generally involve large infarcts.2426 Hence, it is prudent to delay anticoagulation for 24-48 hours in cardioembolic strokes and even longer in massive cardioembolic infarcts to avoid potentiation of hemorrhagic transformation.

**Heparin Therapy**

Heparin is generally started as an intravenous bolus of 5,000-10,000 units followed by a continuous intravenous infusion at 1,000 units/hr initially and adjusted thereafter to maintain the PTT at 2-2½ times control.

In patients with recent cardioembolic stroke, anecdotal experience suggests that bolus dosing should be avoided and the infusion started at 1,000 units/hr.24 The risks of short-term anticoagulation with heparin are relatively low (1-4%) depending on the specific clinical setting (Table 2).

**Recommendations**

Before an antithrombotic agent can be considered in acute stroke patients, it is essential that nonischemic causes of the neurological deficit be excluded. When the nature of the stroke syndrome cannot be reliably defined, the risk of anticoagulation exceeds any potential benefit.

Anticoagulation of selected patients with acute ischemic stroke syndromes is often recommended to prevent further brain injury. At present, these recommendations are based on anecdotal observations or marginal clinical studies. Particularly in patients with recent, single TIA or acute partial stroke, the efficacy of heparin has been seriously questioned by recent

**Table 1. Heparin for Progressing Stroke: Randomized Trials**

<table>
<thead>
<tr>
<th></th>
<th>Carter (1961)15</th>
<th>National study (1962)16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>Controls</td>
<td>38</td>
<td>67</td>
</tr>
<tr>
<td>Further progression</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>Fatal hemorrhage</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>All deaths</td>
<td>18%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Figure 1. Hemorrhagic transformation of cardioembolic strokes is postulated to occur when distal migration of embolic fragments allows reperfusion of infarcted tissue (reprinted from Toole,7 with permission).**
studies. If careful attention is given to proper diagno-
sis, administration of heparin is relatively safe. It is our
current practice to heparinize patients with progressing
stroke and those with multiple crescento TIA's if
there are no contraindications. In patients with car-
dioembolic stroke, we administer heparin as outlined
(Figure 2). In patients with partial stroke in the
vertebrobasilar system, we sometimes employ heparin
empirically because of the substantial (40%) risk of
progression. In all of these situations, the efficacy of
heparin is unproven by strict methodological standards.
The largely empirical use of heparin should not be
presumed need for anticoagulation does not justify
is CT mandatory prior to anticoagulation of acute
stroke patients? In most instances the answer is yes.
While clinical features usually allow differentiation
between ischemic and hemorrhagic stroke, most neu-
rologists have been proven wrong by CT. With the use
of CT, small intracerebral hemorrhages, previously
missed due to misdiagnosed as subcortical infarcts, are readily
detected. Well-documented instances of subdural hema-
toma presenting with multiple TIA-like events have
also been reported. About 30% of patients who are
initially diagnosed as having a progressing infarct are
found with CT to have another cause contraindicating
anticoagulation.3,10,32 Not surprisingly, the risk of brain
hemorrhage complicating anticoagulation of acute stroke patients has fallen by two thirds since the advent
of CT.36
Although there is no unanimity of opinion,33,34 we
do not recommend lumbar puncture routinely prior
to heparinization if CT is nonhemorrhagic in patients
with no suggestion of primary subarachnoid hemor-
 rhage. If lumbar puncture is performed, heparinization
should be delayed 4-6 hours to reduce the chance of
lumbar epidural hematoma.35 Patients with acute stroke
often develop transient hypertension. Lowering blood
pressure acutely in these patients may itself cause
worsening.35 Given the unproven benefit of heparin, the
presumed need for anticoagulation does not justify vigorous attempts to lower blood pressure.

**Table 2. Risk of Heparin in Acute Brain Ischemia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Complication</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA patients</td>
<td>CNS hemorrhage</td>
<td>1% (0-2.3%) — refs 20, 22, 28, 29, 30</td>
</tr>
<tr>
<td></td>
<td>Non-CNS hemorrhage</td>
<td>3% (2.5-4.1%) — refs 20, 22, 28, 29</td>
</tr>
<tr>
<td>Acute partial stroke</td>
<td>CNS hemorrhage</td>
<td>1% (0-2%) — refs 7, 8, 20, 29</td>
</tr>
<tr>
<td></td>
<td>Non-CNS hemorrhage</td>
<td>2% (0-4%) — refs 8, 20, 29</td>
</tr>
<tr>
<td>Progressing stroke</td>
<td>CNS hemorrhage</td>
<td>3% (0-6%) — refs 15, 16, 18, 28, 30</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>CNS hemorrhage</td>
<td>4% (0-14%) — refs 24, 25, 28</td>
</tr>
</tbody>
</table>

*In most studies computed tomography (CT) was done prior to anticoagulation.*

**References**

1. Cerebral Embolism Task Force: Cerebral embolism. *Chest* 1986;89(suppl):82-96
Heparin anticoagulation in acute brain ischemia.
V T Miller and R G Hart

*Stroke.* 1988;19:403-406
doi: 10.1161/01.STR.19.3.403

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 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/19/3/403.citation

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/