Hemodynamic Factors and Perfusion Abnormalities in Early Neurological Deterioration

Josef A. Alawneh, MRCP; Ramez Reda Moustafa, MD, MRCP; Jean-Claude Baron, MD, FRCP, FMedSci

Background and Purpose—Early neurological deterioration (END) is a relatively common unfavorable course after anterior circulation ischemic stroke that can lead to worse clinical outcome. None of the END predictors identified so far is sufficiently reliable to be used in clinical practice and the mechanisms underlying END are not fully understood. We review the evidence from the literature for a role of hemodynamic and perfusion abnormalities, more specifically infarction of the oligemia, in END.

Summary of Review—After an overview of the neuroimaging, including perfusion imaging, predictors of END, we review the putative mechanisms of END with a special focus on hemodynamic factors. The evidence relating perfusion abnormalities to END is addressed and potential hemodynamic mechanisms are suggested.

Conclusions—Hemodynamic factors and perfusion abnormalities are likely to play a critical role in END. Infarction of the oligemic tissue surrounding the penumbra could be the putative culprit leading to END as a result of perfusion, but also physiological and biochemical abnormalities. Further studies addressing the role of the oligemia in END and developing measures to protect its progression to infarction are now needed. (Stroke. 2009;40:e443-e450.)

Key Words: disease progression ▪ imaging ▪ oligemia ▪ penumbra ▪ perfusion ▪ stroke

Early neurological deterioration (END) after anterior circulation stroke (ACS) is observed in 10% to 40% of patients1–3 and often leads to worse clinical outcome.4–8 Its definition, which depends on the clinical scale, cutoff, and time scale used, has varied over time with no formal consensus achieved so far. END usually refers to deterioration that is observed during the first 48 or 72 hours after onset, in contrast to late neurological deterioration, which occurs later. This dichotomy is justified because it reflects 2 largely separate entities with different underlying mechanisms. Thus, END is more likely to be associated with hemodynamic and metabolic causes, whereas late deterioration is most often due to systemic complications such as infection and aspiration or to stroke recurrence. This dichotomy, albeit convenient for research purposes, is nonetheless somewhat arbitrary and there is an overlap between these mechanisms.

One definition for END used in the early literature is an increase ≥1 point on the Canadian Neurological scale during the first 48 hours.6,9 Others used an increase of ≥2 or ≥3 on the motor or speech components of the Scandinavian Stroke Scale, respectively.5,7 The need for an internationally agreed definition has been previously highlighted10 but not fulfilled so far. However, the National Institutes of Health Stroke Scale has been recently widely used to define END with deterioration ≥4 points during the first 48 or 72 hours being almost consistently used.

The current interest in END derives from the potential clinical implication of identifying reliable predictors and tailoring treatment. However, sufficiently reliable predictors of END are not available at this time, which may be due to incomplete understanding of the underlying pathophysiology. Our aim in the present review is to propose that hemodynamic factors play a key role in END after ACS, at least in a large fraction of affected patients, and to present available evidence in support of this hypothesis. To this end, based on a systematic search of the English language literature, we first review the neuroimaging predictors of END in ACS insofar as they relate to hemodynamic factors, such as plain CT, angiography, and diffusion/perfusion-weighted MR. The clinical and biochemical predictors of END, and END secondary to symptomatic intracranial hemorrhage, are not discussed here; the interested reader is referred to topical reviews.13–17 The neuroimaging predictors of malignant middle cerebral artery infarction (MMI), a distinct form of END, is addressed separately. In the second section, we address putative mechanisms of END focusing on perfusion abnormalities. We particularly address the role of perfusion status (and any physiological variable that can influence tissue perfusion such as blood pressure), but also factors that may influence neuronal viability in hypoperfused areas such as biochemical abnormalities and inflammation. We close with comments on the relevance of the presented data and propose a hypothesis on the role of hemodynamic factors in END with suggestions on how to test it in future studies.
Table 1. Plain CT and Angiographic and MR Predictors of END

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Definition of END</th>
<th>Predictors of END</th>
<th>OR (95%CI) or P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davalos, 1990</td>
<td>98</td>
<td>Decrease ≥1 on CNS in first 48 hours</td>
<td>Early CT hypodensity</td>
<td>NS</td>
</tr>
<tr>
<td>Jorgensen, 1994</td>
<td>868</td>
<td>Decrease ≥2 in motor or ≥3 in speech in the SSS in first 36 hours</td>
<td>CT infarct volume (median time Day 8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Toni, 1995</td>
<td>152 (80)*</td>
<td>Decrease ≥1 on CNS</td>
<td>CT early cortical hypodensity</td>
<td>3.81 (1.31–11.1)</td>
</tr>
<tr>
<td>Davalos, 1999</td>
<td>615†</td>
<td>Decrease ≥2 in consciousness, motor or ≥3 in speech in the SSS (baseline to 24-hour evaluation)</td>
<td>ICA siphon occlusion on DSA</td>
<td>21.6 (1.36–342)</td>
</tr>
<tr>
<td>Arenillas, 2002</td>
<td>30</td>
<td>Increase ≥4 points on NIHSS within 48 hours of symptom onset</td>
<td>Acute DWI lesion volume</td>
<td>11.5 (2.31–57.1)</td>
</tr>
<tr>
<td>Weimar, 2005</td>
<td>1964</td>
<td>Increase ≥4 points on NIHSS within 48 hours to 72 hours</td>
<td>ICA occlusion</td>
<td>3.32 (2.0–5.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCA (M1) occlusion</td>
<td>MCA (M1) occlusion</td>
<td>1.92 (1.25–2.95)</td>
</tr>
</tbody>
</table>

*These patients had DSA.
†Study included some patients with posterior cerebral artery stroke.
CNS indicates Canadian Neurological Scale; SSS, Scandinavian Stroke Scale; NIHSS, National Institutes of Health Stroke Scale; HMCA, hyperdense middle cerebral artery; MCA, middle cerebral artery; NS, nonsignificant; DSA, digital subtraction angiography.

Neuroimaging Predictors of END

Table 1 summarizes the published studies on neuroimaging predictors of END. The number of patients included, the definition of END used, and the main results are shown for each study.

Computerized Tomography

CT was among the first modalities used to investigate END. Davalos et al, in one of the earliest studies, found no significant differences in CT variables between the END and stable groups; however, acute hypodensity volume tended to be larger in the former. In another study, the END group had significantly larger infarcts. However, CT was mostly done after the deterioration and intracranial hemorrhages were included.

In a secondary analysis of the European Cooperative Acute Stroke Study 1, Davalos et al divided deterioration into early and late. Early deterioration occurred between baseline and the 24-hour evaluation point; late was from 24 hours to Day 7. On the acute CT, focal hypodensity, the hyperdense middle cerebral artery sign, and brain swelling were more frequent in both the early and late deterioration groups compared with the nondeterioration group. However, only the first 2 variables remained significant predictors for END in a logistic model, whereas brain swelling remained significant only for late deterioration.

In a study investigating patients within 5 hours of ACS, CT was done within 1 hour of admission. Some patients also had digital subtraction angiography (DSA) performed after CT. Deterioration was reported up to 92 hours with the majority (59%) in the first 24 hours. Early cortical and even more corticosubcortical hypodensity, and siphon occlusion of the internal carotid artery (ICA), were identified as independent predictors of END. In a further study, ICA occlusion and middle cerebral artery (M1) occlusion were also identified as independent predictors.

Magnetic Resonance Imaging

In recent years, MRI, and in particular diffusion (DWI) and perfusion imaging (PWI), have been used to study END. In one study, 30 patients with intracranial ICA or middle cerebral artery occlusion demonstrated on MR angiography within 6 hours of onset were studied. Proximal occlusion, large initial DWI and PWI volumes, and small PWI–DWI percent mismatch were significantly associated with END in univariate analysis; but only large DWI lesion volume remained an independent predictor of END in a logistic regression model.

Malignant MMI

MMI is a distinct form of neurological deterioration associated with high mortality. It is seen in proximal middle cerebral artery and/or ICA occlusion and involves space-occupying cerebral edema and potentially fatal transtentorial herniation. The time course of clinical deterioration varies, but it usually occurs between Days 2 and 5. Deterioration due to MMI, therefore, does not always fulfill the criteria for END depending on the time scale used. However, it is discussed here because it does often overlap with END; it has devastating consequences; and identifying reliable predictors of MMI has great implications on further management, especially in the context of performing early decompressive surgery.

Early CT predictors of MMI are large hypodensity of the middle cerebral artery territory, the hyperdense middle cerebral artery sign, perfusion deficit >66% of the middle cerebral artery territory, and brain swelling; however, only the first 2 remained significant on multivariate
Pathophysiological Mechanisms of END and Factors Influencing Neuronal Viability

The putative mechanisms of END, although not yet fully elucidated, can be broadly divided into hemodynamic and biochemical. However, as will be seen, the latter may sometimes facilitate the occurrence of END through hemodynamic disturbances or by influencing neuronal viability in hypoperfused areas.

Cerebral Perfusion Pressure

The putative hemodynamic mechanisms of END all involve a reduction in local cerebral perfusion pressure (CPP). Although for obvious reasons directly measuring the CPP in relation to END would be difficult, physiological imaging allows the indirect assessment of CPP, particularly with time-based parameters such as mean transit time and TTP, which are linearly inversely related to CPP.

Studies that directly estimated brain perfusion have consistently suggested that larger and more severe perfusion deficits are associated with END. Mean CBF was lower and the volume of critically hypoperfused tissue larger in the MMI group. Furthermore, 2 MR perfusion studies showed that larger TTP defects were associated with increased occurrence of END as well as MMI.

Factors known to greatly influence local CCP are the location of the arterial occlusion and the state of the leptomeningeal collaterals. Although assessing them does not afford a direct estimate of perfusion, it is clear that proximal occlusions and inadequate collaterals inevitably lead to larger volumes of more severely hypoperfused tissue. Accordingly, proximal occlusion on MR angiography and the hyperdense middle cerebral artery sign have all been associated with a deteriorating course, either MMI or END. In a study that assessed the collateral status on DSA, detectable collateral blood supply was present in 35% of the patients with a deteriorating course and in 63% of those with a nondeteriorating course (P < 0.02).

Further indirect assessment of cerebral perfusion can be obtained by transcranial Doppler. Impaired middle cerebral artery flow (defined as no flow or ≥21% reduction in flow velocity compared with contralateral) within 6 hours after stroke was found to be an independent predictor of END, whereas a normal transcranial Doppler examination was a predictor of early improvement. In another transcranial Doppler study, reduced mean flow velocity and cerebral hemodynamic reserve within the first 24 hours were significantly associated with END. In a transcranial Doppler study of 374 acute patients after thrombolysis, inability to achieve sustained vessel patency correlated with the likelihood of clinical deterioration (defined as an increase in National Institutes of Health Stroke Scale score ≥4 points within 24 hours) with early arterial reclosure as a particularly strong predictor.

Similar results have been reported from a study that assessed the arterial status using variable combination of transcranial Doppler, carotid duplex, DSA, MR angiography, and/or CT angiography in 1093 patients (both anterior and posterior circulation strokes). The presence of stenooctic disease was significantly associated with END in multiple logistic regression, with occlusion more significantly
so than stenosis; the highest adjusted OR was obtained for vertebrobasilar steno-occlusive disease.

Taken together, these studies suggest that perfusion pressure abnormalities play an important, and perhaps critical, factor in END. However, a change in perfusion pressure at the time of deterioration has not been directly demonstrated. Establishing this, as well as defining the actual cause(s) leading to the changes in perfusion, would be paramount, albeit admittedly difficult.

**Systemic Blood Pressure**

Because CPP is directly related to the difference between systemic blood pressure (BP) and cerebral venous pressure (which reflects intracranial pressure), it is not surprising that BP has been extensively investigated in END. The role of BP becomes particularly important whenever a large volume of hypoperfused but still viable tissue, susceptible to changes in systemic BP, is present. Indeed, in this case, any drop in BP cannot be compensated for by autoregulatory mechanisms, which can in turn lead to tissue infarction.

Early studies looked mainly at cross-sectional BP values and not changes in BP over time. They yielded conflicting results, ie, both hypertension and hypotension have been associated with clinical deterioration. In a subsequent study, a U-shaped relationship was found, with a higher risk of END at either low or high BP. However, when the changes in systolic BP during the first day were taken into account in a logistic regression, patients with a decrease in systolic BP >20 mm Hg showed significantly increased odds of END, whereas systolic BP values on admission lost significance.

As mentioned, however, the role of BP drops in END might be important in only a subgroup of patients, namely those with large hypoperfused areas. Other mechanisms for END would play a more important role in other patients, which could explain why not all studies looking at BP in END have found a significant relationship.

**Biochemical and Biological Mechanisms**

**Excitotoxicity**

It is believed that glutamate, which is massively released by injured neurons, can cause END by its neurotoxic effects on surrounding tissue. Plasma and cerebrospinal fluid glutamate have been found to be independently and significantly associated with END with higher concentrations of glutamate sustained for more hours in the END group. It is, however, not clear why excitotoxic factors would affect only some patients who deteriorate and not the stable patients. Genetic polymorphism in the excitatory amino acids carriers has been suggested as one potential mechanism. Another possibility is that the role of excitotoxic factors is important in determining the fate of hypoperfused tissue surviving on perfusion levels just above the penumbral threshold. Indeed, excitation of this tissue will have detrimental effects, because any increase in energy metabolism would not be sustained by increased oxygen supply due to autoregulation failure, whereas oxygen extraction fraction is already maximal.

**Inflammation**

Several studies have suggested that inflammation may play a role in END. Plasma and cerebrospinal fluid interleukin-6, one of the proinflammatory cytokines, was found to be independently associated with END in all ischemic stroke subtypes as well as in cortical and subcortical infarctions. On the other hand, plasma interleukin-10, an anti-inflammatory cytokine, was found to be significantly lower in patients with END. However, interleukin-10 reduction was a statistically significant independent factor for subcortical and lacunar strokes, but not for cortical ones. The precise mechanisms underlying END mediated by inflammation are uncertain but could involve neurotoxicity, particularly in conditions of local hypoxia.

**Hyperthermia**

Hyperthermia has been found to be independently associated with END. This association was statistically significant, even independently of inflammatory factors. Increased temperature possibly stimulates cerebral oxygen consumption and may quickly deprive hypoxic neurons from their energy reserves. However, the precise mechanisms leading to END due to hyperthermia are still unclear.

**Edema**

The importance of vasogenic edema in END has been a subject of debate. Brain swelling has been found to be more frequent in END and MMI on univariate but not on multivariate analysis. It is generally agreed that edema plays a major role in MMI in which the swelling around the large infarct acts as a space-occupying lesion, leading to a gradual increase in intracranial pressure and further reductions in CPP. This could cause oligemic, or even potentially normally perfused but autoregulated tissue, to be recruited into the penumbra and eventually into the final infarct. This vicious cycle may in turn lead to massive infarction and thus to further increases in intracranial pressure and death from herniation. By interrupting this cycle, early hemicraniectomy reduces mortality and improves outcome in this group of patients (see above). In other words, this procedure could improve outcome by preventing recruitment of oligemic areas into the core. Whether similar mechanisms, but on a smaller scale, play a role in non-MMI END is still not known but is an attractive hypothesis.

**Hyperglycemia**

Early studies found an association between high blood glucose and END, whereas others found an association between history of diabetes and END. When both variables were considered together, serum glucose did not predict END after adjusting for history of diabetes. Several mechanisms have been suggested to explain the association of diabetes and/or hyperglycemia with END. Diabetic microangiopathy leading to impaired vasoreactivity and hence cerebral dysregulation within the occluded middle cerebral artery and neighboring territories has been proposed, but hyperglycemia per se may increase lactate production in the penumbra and oligemia, leading to intracellular acidosis, which may be an important contributing factor. The latter is supported by a
study\cite{55} that explored the association of hyperglycemia with final infarct size and functional outcome in patients with or without PW/DWI mismatch. The association of hyperglycemia with tissue lactate levels (measured by MR spectroscopy) and penumbral salvage in the patients with mismatch was studied too. In this latter group, acute hyperglycemia independently correlated with reduced salvage of mismatch tissue from infarction, greater final infarct size, and worse functional outcome. Furthermore, higher acute blood glucose in the mismatch group was associated with greater lactate production, which, in turn, was independently associated with reduced salvage of mismatch tissue.\cite{45} Other studies too found an association between hyperglycemia and both infarct expansion\cite{46} and worse functional outcome,\cite{37} but none of these studies investigated END proper.

**Hypoxia**

Hypoxia plays a major role in ischemic injury after stroke. However, its role in END has not been looked at as extensively as the previously mentioned biological predictors. Oxygen saturation was rarely reported in studies looking at predictors of END. One abstract\cite{48} only was identified that looked at levels of oxygen saturation and END; it reported significantly higher occurrence of deterioration in patients with saturated $O_2 < 90\%$ compared with patients with saturated $O_2 > 90\%$.

Hypoxia, on the other hand, has been associated with worse clinical outcome\cite{49} in patients with acute stroke. Treatment with normobaric oxygen has been found to improve aerobic metabolism and preserve neuronal integrity in ischemic brain tissue.\cite{50} It was suggested that it improves clinical deficits in acute stroke,\cite{51,52} and has been found to reduce infarct size\cite{53} and extend the time window for effective reperfusion in experimental models.\cite{54} Any positive effect of oxygen is likely to be due to its protective effect on the penumbral as well as oligemic tissues surrounding the infarct core.

In one study that used positron emission tomography with $^{18}$F-fluoromisonidazole, believed to map the hypoxic viable tissue but not the normally perfused or the already necrotic tissue,\cite{55} increased likelihood of neurological deterioration occurred if a large proportion of the hypoxic tissue subsequently progressed to infarction.\cite{56} However, concomitant perfusion studies were not reported, and to what degree the hypoxic tissue defined with $^{18}$F-fluoromisonidazole represents only penumbra is still not clear.\cite{55}

**Comments and Hypothesis**

END is an operational concept, i.e., substantial neurological deterioration occurring within 48 to 72 hours of ACS. As mentioned and apparent in Table 1, there are marked differences in the actual criteria used to define END among published studies. If progress in understanding, treating, and preventing this unfavorable course after stroke is desired, it will be important in future research that a single definition is adopted, e.g., \geq 4 National Institutes of Health Stroke Scale points within 48 hours.

Such a strict definition of END may not, however, cover all sorts of clinical scenarios and situations in which deterioration occurs after stroke. For instance, deterioration could be less than 4 National Institutes of Health Stroke Scale points but still be clinically meaningful if it occurs in the context of rapid recovery, e.g., after reperfusion. Likewise, transient deteriorations may last a few hours only, which would not formally count as END but may have the same underlying pathophysiology, e.g., hemodynamic impairment? Also, the National Institutes of Health Stroke Scale gives considerable weight to motor functions but does not reliably reflect the volume of tissue involved in nonmotor areas such as language or neglect.\cite{57} Despite these issues, an operational definition as discussed here would help address the most pressing issues about END, at least in a first approach.

This overview of the literature suggests END is probably almost always underlain by multifactorial pathology that involves hemodynamic as well as metabolic factors. This pathophysiological heterogeneity probably in turn explains the difficulties faced so far in both identifying reliable predictors and understanding underlying mechanisms. Although it seems intuitive that the mechanisms discussed all eventually lead to infarction of further brain tissue manifesting as clinical deterioration, even this has not yet been documented. No study so far has investigated whether extra tissue in addition to the initial penumbra proceeds to infarction in patients who experience END. Fundamental here would be whether any such secondary infarction involves only longlasting penumbral areas or if it also includes oligemic areas, e.g., with CBF above this threshold. This is key because, in principle, the penumbra being already dysfunctional, its infarction is not expected to lead to clinical deterioration, whereas on the other hand, the “benign” oligemia is not at risk of infarction and does not normally contribute to the clinical picture.\cite{58} Infarction of the oligemic tissue would therefore stand as an attractive hypothesis to explain END. Documenting this hypothesis would have significant clinical implications.

Extensively searching the literature for any evidence directly supporting this hypothesis revealed only a few anecdotal case reports in which tissue beyond the initially hypoperfused borders progressed to infarction.\cite{59}\textendash\cite{61} A brief description of these cases follows.

In a longitudinal MR study,\cite{59} 2 of 21 patients who had perfusion imaging within 7 hours of onset had final infarct volumes (T2-W approximately 30 days) much larger than the acute perfusion volumes. Perfusion lesions were identified by visual inspection of the TTP maps. Patient 6, an 84-year-old woman, had a right middle cerebral artery distribution lesion and received tissue plasminogen activator treatment. Her National Institutes of Health Stroke Scale score acutely was 14 and at approximately Day 30, her score was 4. Final infarct volume was 100 cm$^3$, whereas the acute perfusion lesion was 53 cm$^3$. Patient 8, an 82-year-old man, had a left posterior cerebral artery territory stroke; his acute and follow-up National Institutes of Health Stroke Scale scores were 10 and 5, respectively. Final infarct volume was 95 cm$^3$, whereas the acute perfusion lesion was 33 cm$^3$. It was not reported whether these patients had END.

In another MR study,\cite{60} 13 patients underwent PWI within 8 hours of onset and a follow-up DWI after 4 to 7 days; PWI
abnormalities were defined as Tmax >2 seconds. Patient 11 had a cardioembolic stroke with baseline National Institutes of Health Stroke Scale score of 18; the follow-up lesion volume was much larger than the acutely hypoperfused volume (240 versus 157 mL). Again, whether END occurred is not reported because this was not part of the study’s objectives.

A third study observed the validity of CT perfusion imaging within 6 hours of stroke onset in predicting final infarction on 24-48 hour CT. Perfusion volumes were derived from TTP maps generated using the manufacturer’s software, and regions of interest were drawn manually around the margins of regions with prolonged TTP. Based on their Figure 5, one of the 17 cases had a final infarct much larger than the initial TTP lesion together with a deterioration of approximately 8 points on the National Institutes of Health Stroke Scale between baseline and 24 hours.

Despite the lack of details provided in the original articles, these anecdotal observations provide some support to the hypothesis that oligemic tissue can be recruited into the penumbra and progress to infarction, causing END and a worse outcome. Recruitment of the oligemia into the infarct is likely to happen as a result of the mechanisms discussed in previous sections. This scenario now needs to be formally documented in prospective studies.

One issue illustrated in these cases is the variability in perfusion variables (eg, time-based maps such as TTP, Tmax, and mean transmit time, but also CBF and cerebral blood flow), imaging techniques, and thresholds used to assess the at-risk tissue. Any research prospectively testing the hypothesis that infarction of the oligemia underlies END will require as clearly defined and strongly validated thresholds and perfusion parameters as possible. Although at this time no definite consensus exists among specialists, several recent studies have provided reasonably well-defined perfusion thresholds. For example, tissue with cerebral blood volume <2 mL/100 g on CT perfusion is likely to represent core and an affected-to-contralateral mean transit time ratio of 1.45 may best represent the penumbra threshold. Also, MR-based studies, including some that directly compared MR to gold standard positron emission tomography, suggest that the mean transit time-delay penumbra threshold lies between 6 and 8 seconds. These findings are summarized in Figure 1.

It should be noted here that although the oligemia is usually regarded as the tissue surrounding the penumbra, theoretically, islands of oligemic tissue could exist within areas of the penumbra, in which case distinguishing these 2 compartments could be challenging.

Establishing what actually causes the demise of the oligemia may prove even more challenging. One key difficulty in establishing the mechanisms of END is the pathophysiological heterogeneity seen in this patient population. Toward resolving this issue, we propose here an operational classification of END that might be of help in future research. Based on this literature review and experience of the authors, this classification distinguishes 3 pathophysiological patterns. These are detailed in Table 2. Illustration of these 3 patterns in relation to the penumbra, oligemia, and final infarct are shown in Figure 2.

This classification primarily aims to sort patients into single categories, because the mechanisms underlying each category are likely to differ. However, it is acknowledged that in individual patients, END may have multiple mechanisms, and in addition, there are a few additional situations that do not belong to these categories, eg, deterioration after improvement or with reocclusion after early partial recanalization. As discussed, deterioration in these cases may not exceed the initial clinical deficit and thus may not classify as END. Thus, the classification proposed here should not be

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**Table 2. Operational Classification of END After Anterior Circulation Stroke**

<table>
<thead>
<tr>
<th>Group</th>
<th>Acute Imaging</th>
<th>Acute NIHSS</th>
<th>Imaging After END</th>
<th>Possible Underlying Pathology</th>
<th>Possible END Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>END-A</td>
<td>Very large symptomatic penumbra; usually large DWI; relatively small oligemia</td>
<td>High</td>
<td>Further enlargement of DWI lesion into both previously hypoperfused tissue and normal tissue, vasogenic edema</td>
<td>Complete occlusion of proximal vessels</td>
<td>Vasogenic edema, excitatory/depolarization waves; tissue surrounding penumbra becomes symptomatic</td>
</tr>
<tr>
<td>END-B</td>
<td>Large asymptomatic oligemia; relatively small penumbra and DWI</td>
<td>Mild-to-moderate</td>
<td>Extension of DWI into previously oligemic tissue</td>
<td>Partial occlusion and/or good collaterals</td>
<td>Progression of occlusion or secondary events (eg, hypotension), previously oligemic tissue becomes symptomatic</td>
</tr>
<tr>
<td>END-C</td>
<td>Any of the above but usually small or moderate-sized matched penumbra and DWI</td>
<td>Any depending on extent of ischaemia</td>
<td>New perfusion/DWI lesion adjacent or remote from initial lesion</td>
<td>New occlusion (eg, cardioembolic)</td>
<td>New ischemic event—previously healthy tissue becomes symptomatic</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale.
considered inclusive of all END scenarios, but rather a step toward facilitating future research aiming to determine reliable END predictors, preventive measures, and treatment.

To conclude, END is a relatively common occurrence after ACS with detrimental consequences. Several important predictors of END have been identified but very few are so reliable as to be useful in clinical routine. There has recently been better understanding of the underlying mechanisms of END, but several key questions still remain. Perfusion abnormalities are likely to play a critical role in END. Further research into this topic is warranted to develop preventive measures and treatments for END.

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Disclosures

None.

References


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