Transhemispheric Diaschisis
A Review and Comment
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We review here the literature in both animal models and humans concerning electrical activity, blood flow, and metabolism in the hemisphere contralateral to unilateral cerebral ischemia. We analyze the data by periods based on the time from initial injury to emphasize the time course of transhemispheric diaschisis. Contralateral electrical activity, such as evoked potential amplitude, is increased in the late stages after unilateral infarction, with the data from the more acute periods being inconclusive. Contralateral blood flow changes probably depend on the magnitude of the ischemic injury, with a larger insult resulting in a decrease not seen with smaller insults. Some studies have shown a decrease in contralateral blood flow over the first week followed by a gradual return toward baseline. Most measures of contralateral metabolism show a time course similar to blood flow, that is, a decrease followed by gradual recovery. The effects of corpus callosum section on transhemispheric diaschisis are not yet established. We provide examples to show that under certain conditions, diaschisis may represent a loss of remote inhibition rather than a loss of remote facilitation, as von Monakow originally suggested. By following the contralateral changes over time, particularly during the first minutes and hours of ischemia, insight will be gained into the brain's responses remote from the focus of ischemic injury. These responses should bear a relation to the brain's defense mechanisms ipsilaterally to the region of ischemia. (Stroke 1991;22:943-949)

Von Monakow\(^1\) coined the term “diaschisis” in 1914 to describe specific changes after focal injury to the nervous system and to distinguish these changes from more widespread or systemic alterations after injury. The latter type of deficit he called apoplectic shock, with its characteristic rapid onset and resolution of general symptoms such as loss of consciousness or muscle tone.

In von Monakow's concept of diaschisis, a loss of facilitating or excitatory input from the area of injury renders specific other regions of the nervous system less responsive to stimuli. He emphasized the sudden onset of the deficit and the neuroanatomic relationship between the insult and the remote regions affected: "...diaschisis represents an 'interruption of function' appearing in most cases quite suddenly... which originates from a local lesion but has its points of impact not in the whole cortex (corona radiata, etc.) like apoplectic shock but only at points where fibres coming from the injured area enter into primarily intact grey matter of the whole central nervous system."

Most data pertaining to diaschisis have been gathered from subacute or chronic studies. Furthermore, most studies of diaschisis have considered the remote changes in terms of local blood flow or metabolic indicators rather than in terms of neurophysiologic or neuroanatomic indicators such as electrical activity or synaptic terminal degeneration. A recent review summarizes a broader definition of diaschisis: "...the term diaschisis is now used in a wider sense to cover all remote effects of acute and chronic cerebral injury."\(^2\)

After briefly considering the various types of diaschisis that have evolved and the importance of time after injury, we will review the data regarding transhemispheric diaschisis to demonstrate that broadening the definition of diaschisis may have actually obscured the study of remote effects of focal cerebral injury. Consideration of both the various measures of remote effects and the time course of the changes helps integrate the seemingly disparate diaschisis literature.

Types of Diaschisis
Von Monakow\(^1\) described several types of diaschisis: diaschisis cortico-spinalis (spread from the motor cortex along the pyramidal tract), diaschisis commissuralis (spread contralaterally via the corpus callosum), and diaschisis associativa (spread intrahemispherically along association fibers).
Kempinsky, the first to test von Monakow's notion of diaschisis in an experimental model, defined diaschisis in his cat model as a series of events resulting from a focal nervous system injury: "The injury was circumscribed; the depressive effect has a neuronal basis; it occurred at a distance from the injury; the fiber tract mainly responsible was identified; and the process was reversible."

Since Kempinsky's restatement of von Monakow's original concept, several types of diaschisis have been recognized: effects on the injured cerebral hemisphere remote from the injury (ipsilateral effects); effects on the opposite hemisphere, especially mirror image to the injury (contralateral effects); and effects on the cerebellum contralateral to the cerebral injury (crossed cerebellar diaschisis).

We will consider the following factors as measures of diaschisis: electrical activity—electroencephalogram (EEG), electrocorticography, and evoked potentials; cerebral blood flow (CBF); and metabolic factors such as oxygen extraction ratio, cerebral metabolic rate for oxygen and glucose (CMRO2, CMRglu), neurotransmitter levels, and protein synthesis. The choice of these three factors stems from the imperfect correlation among them; measuring one or two of them will not always allow one to predict the others. Electrical activity has the advantage that it can be repeatedly recorded bilaterally. Although the relationship between CBF and the threshold for loss of electrical activity has been studied in some detail, the relatively low flow values at which this occurs are not reliably assessed by the noninvasive methods required for use in humans. Particularly in the region of infarction, but also contralaterally, there is variable correlation between CBF on the one hand and CMRO2 or oxygen extraction ratio on the other.45

Recent reviews have summarized both von Monakow's1 and Kempinsky's3 formulations of diaschisis and the literature that has appeared over the last 30 years on the various types of diaschisis.2,67 The ischemic insult in humans usually has been a unilateral infarction, whereas in animal studies a variety of ischemic insults have been used, most often one of the many internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion models. The variation in volume and location of tissue lost in infarction in humans and the variation in ischemic damage depending on the type of insult in the numerous animal models are potential sources of differing results. One technique that is not helpful for assessing transhemispheric diaschisis is the use of asymmetry indexes that assume that the contralateral hemisphere is a reasonable control.810

We limit this discussion to transhemispheric diaschisis, the terms "transhemispheric" or "interhemispheric" being preferable to "transcallosal" because the contralateral effects of a unilateral insult may be mediated by neural pathways other than, or in addition to, the corpus callosum.12 However, relevant findings regarding the callosal contribution to transhemispheric diaschisis have come from callosal section models.31214

Time Course of Diaschisis

Both von Monakow1 and Kempinsky3 noted the importance of recovery of the deficits, or reversibility of the alterations, in diaschisis. Von Monakow wrote that "the effect of diaschisis, just as the effect of any type of shock, is in principle confined to a longer or shorter limited period (in its individual elements) and undergoes gradual regression in well-defined phases." Kempinsky noted that "with time, the duration of which must depend upon the internal organization of the system and its other sources of afferent contributions, the second group of neurons assumes a greater autonomy than before injury and ultimately functions at a level more closely approaching that present initially."

In general, insufficient attention has been paid to noting the time after injury at which the data regarding diaschisis are collected, particularly in the very early periods after injury. This point has been made clearly with regard to blood flow and metabolism in stroke: "The natural history of stroke must be clarified clearly with regard to blood flow and metabolism in stroke: "The natural history of stroke must be clarified in terms of rCMRO2-rCBF balance in the very first hours as well as in the first days after the ictus. This requires a large body of well-documented, individual case studies to build up the overall picture in this physiologically heterogeneous patient population."15

In this review, we have divided the time of data collection from the time of initial cerebral injury into the following categories: 1) hyperacute (<1 hour), 2) acute (1–24 hours), 3) subacute (1–10 days), 4) intermediate (10 days to 2 months), and 5) chronic (>2 months). We chose these time divisions based on changes in electrical activity, CBF, and cerebral metabolism that occur at different intervals after injury.

Most studies in humans involve measures at an intermediate or chronic time period, that is, days to months after injury. Animal studies, on the other hand, usually involve the hyperacute or acute periods, with occasional subacute, intermediate, or chronic data. Given the early time after injury at which the data are gathered in most animal studies, the findings may bear little relation to human studies much farther out from the initial injury. However, in small animal models, it is likely that the time course of diaschisis is considerably more compressed than in humans. It is unlikely that a large body of data in very early human stroke will be obtained with complex techniques such as positron emission tomographic scanning; there are, however, a few examples of data collected within the first few hours after stroke.416

It should be relatively easy in animal models to note carefully the time after insult when the data are collected, with the distinction between the hyperacute and acute time periods being particularly important. Together with this need for precise timing is the need for serial measures in the same model. The research sum-

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marized here is notable for frequent discrepancies or discordant findings, many of which can be resolved by standardizing both timing and methodologies.17

A Review

The following summary is arranged according to the time periods discussed in the previous section. Studies in humans will be considered first in each category.

Hyperacute and Acute Time Periods

Electrical activity. There are no studies in humans that consider electrical activity during the first 24 hours after unilateral ischemic insult. Using primarily unilateral MCA occlusion animal models, a number of researchers have found no change in contralateral electrical activity (EEG or evoked potentials) during the first 24 hours. Others have found some decrease either in EEG power or in evoked potential amplitude. Bo et al27 noted an increase in delta activity contralateral to common carotid artery (CCA) embolization in the rabbit at 1, 4, and 24 hours. However, somatosensory evoked potential (SEP) amplitude increased to 124% and 132%, respectively, during the hyperacute and acute periods. Meyer et al29 also found an increase in contralateral SEP amplitude during both the hyperacute and acute periods, as did Sakatani et al30 for contralateral hind limb SEP. Andrews and Muto (unpublished data, 1990), during the hyperacute period in a miniature swine unilateral brain retraction ischemia model, noted an average increase in contralateral auditory evoked potential or SEP amplitude to 121%.

Using transcallosal stimulation, West et al31 and Graf et al32 found no decrease in the contralateral evoked potential amplitude after a unilateral insult. Kempinsky2 investigated the effect of corpus callosum section on the electrocorticogram and evoked potential amplitude contralateral to both normal and ablated cortex. He found that 1) acutely after corpus callosum section, there was decreased fast activity, and 2) in several unilateral insult models (ablation or MCA occlusion) performed 6 weeks after the corpus callosum section, the evoked potential amplitude decrease noted with an intact corpus callosum was no longer present; that is, there was no consistent change in the contralateral evoked potential amplitude, nor did the electrocorticogram change.

Cerebral blood flow. The only study in humans that considers CBF within the first 24 hours is that of Giubilei et al,26 who reported CBF based on single-photon emission computed tomography within 6 hours of unilateral ischemic stroke in terms of asymmetry indexes rather than absolute flow. There was a relationship between higher asymmetry of flow and larger infarction, based on computed tomography at 1 month.

Contralateral CBF in animal models early after injury may depend significantly on the type of ischemia model used. In small animals with a relatively large insult, for example, gerbil with CCA occlusion33,34 or rat with either ICA embolization35 or MCA occlusion,36 the hyperacute period contralateral CBF has shown a mild decrease (80–90% of control). A slight hyperacute contralateral CBF increase was found in a rat model with a focal photochemically induced cortical infarct37 and in rabbit ICA occlusion and embolization models.38 In cat MCA occlusion models, the hyperacute contralateral CBF has shown variable results—from a slight increase or no change from control11,19,39 to a moderate decrease to 50–90% of control.40 In larger animal models, either no change or a mild contralateral CBF increase over control has been noted: the former in baboon MCA occlusion21 and the latter in both baboon ICA embolization44 and miniature swine unilateral brain retraction (RJ Andrews, RP Muto, unpublished data, 1990). An exception is the dog unilateral brain retraction model of Albin et al,43 in which the ipsilateral and contralateral CBF showed similar decreases during retraction.

Several studies have included serial CBF measurements that permit comparison of contralateral CBF during both the hyperacute and acute periods in the same model. Although the majority of such studies found a decrease in contralateral CBF from the hyperacute to acute periods,11,13,34,37,38 one study noted a persistent slight increase in CBF.19

In summary, CBF contralateral to cerebral injury may show variable changes immediately after the insult: larger injuries in small animal models are more likely to result in a decrease in contralateral CBF, whereas a larger animal model or a more localized insult is more likely to result in no change or a mild increase. With progression to the acute period, it appears that the contralateral CBF is less than that recorded immediately after the insult, based on the few serial studies available.

Cerebral metabolism. Few studies in humans assess cerebral metabolism during the first 24 hours after unilateral ischemic insult. Wise et al40 found the oxygen extraction ratio mirror image contralateral to infarction to be within the normal range.

In animal models also, only a few studies are available. In a rat ICA embolization model, both ipsilateral and contralateral energy stores (e.g., ATP) and intermediate energy metabolites fell immediately after injury, with contralateral recovery in less than 1 hour.35 In a rat MCA occlusion model, contralateral ATP was virtually unchanged at 2 hours, but brain glucose was significantly lower.42 During the acute period, glucose utilization contralateral to injury was decreased to 65–70% of baseline, both in a cat MCA occlusion model43 and in a rat photochemical cortical infarct model.45 In a cat MCA occlusion model, contralateral CMRglu at 2 hours was decreased approximately 20% from controls, considerably less than the 50% decrease in CBF noted contralaterally.28 In a rat MCA occlusion model, no changes
were noted in several cerebral proteins both ipsilaterally and contralaterally at 4 hours after injury.44

**Subacute, Intermediate, and Chronic Time Periods**

Many studies in humans report data together for patients evaluated at various points in these three time periods. Fortunately, there are a few serial studies in humans, as well as animal studies, in which the time from initial insult is retained in the data analysis.

**Electrical activity.** In humans, after unilateral infarction, the EEG has demonstrated both bilateral slowing45 and ipsilateral slowing with no change contralaterally.46 In patients with either a unilateral tumor or stroke evaluated more than 2 weeks after injury (or after diagnosis), the majority showed an increase in contralateral SEP amplitude (N22 component) compared to controls, regardless of whether a sensory deficit was present or not.47 An increase in contralateral SEP amplitude also was found during the intermediate and chronic time periods in patients with either unilateral cortical infarction or intracerebral hemorrhage.48 Patients with subcortical infarction did not show this late contralateral SEP amplitude increase. When measured more acutely (before day 10), the patients with subcortical infarctions demonstrated an SEP decrease, whereas the cortical infarction and intracerebral hemorrhage patients showed no decrease. Thus, both groups showed an increase in SEP amplitude contralateral to injury between the subacute and later time periods.

There are no studies in animals that consider electrical activity after the first 24 hours following unilateral ischemic insult.

**Cerebral blood flow.** In humans, a number of studies assess CBF changes ipsilaterally and contralaterally over the first 7–10 days after a unilateral infarction.8,15,49–65 These studies have principally used xenon-133 with scintillation counters, single-photon emission computed tomography (15O or 18F). Several studies have reported a decrease in contralateral CBF, particularly mirror image to the region of infarction, with a gradual increase in contralateral CBF, with a lesser increase in ipsilateral CBF, which has been found. In the late chronic time period (many months after injury), the contralateral CBF has returned to normal or near-normal levels, whereas the ipsilateral CBF usually has been found to remain slightly decreased.

Few animal studies have been carried out through the subacute time period and later. In a monkey MCA occlusion model, at day 1 to day 20, only one of six animals evidenced a contralateral CBF decrease.22 Serial measurements in both a baboon ICA occlusion model and a rat photochemical cortical infarction model37 showed the same decline in contralateral CBF over the first 5–7 days, followed by an increase to near baseline paralleling that found in humans, that is, greater contralateral CBF recovery than ipsilateral.

**Cerebral metabolism.** In a number of studies in humans using 15O or 18FDG positron emission tomography to assess CMRO2, oxygen extraction ratio, and CMRglu, it has been found that both CMRO2 and CMRglu are decreased in the hemisphere contralateral to infarction to a level between the decrease noted in the ipsilateral hemisphere and the level of normal controls.4,5,15,58,59,66,67

In animal models, only CMRglu has been studied in detail more than 24 hours after injury. Little change in contralateral CMRglu has been found 24 hours after MCA occlusion in the rat,68 at day 5 after photochemically induced infarction in the rat,44,69 and at day 7 after cortical ablation in the macaque.70 In a baboon model with a unilateral lesion of the nucleus basalis of Meynert, CMRglu contralaterally was decreased at day 4, day 11, and day 25, with the largest decrease at day 4, but not at day 39 or day 88.71 In a rat MCA occlusion model in which no changes were noted during the acute period in several cerebral proteins both ipsilaterally and contralaterally, it was found that at 72 hours these cerebral proteins decreased significantly, ipsilaterally more so than contralaterally.44

Recent studies by Yamaguchi et al12,14 with baboons after section of the anterior corpus callosum showed that the callosal section procedure itself led to a significant decrease in CMRglu bilaterally at day 11 and day 18 compared with sham-operated controls, with complete recovery not being noted until day 98.14 Three callosotomized animals underwent unilateral lesion of the nucleus basalis of Meynert over 4 months after callosotomy. A decrease in CMRglu bilaterally, ipsilateral greater than contralateral, was noted at day 4, with no significant resolution through day 39 and only a trend for recovery of the hemispheric asymmetry.12 The authors, commenting on such a unilateral lesion, noted that the contralateral metabolic effects operate through extracallosal mechanisms and that an intact corpus callosum is important for recovery of CMRglu after insult, at least for recovery as rapidly as with an intact corpus callosum. However, Meyer et al13 found in baboons 24–48 hours after corpus callosum section that bilateral CBF was not decreased by the corpus callosum section alone. Furthermore, the contralateral decrease in CBF several hours after ICA embolization seen with an intact corpus callosum was lost with prior corpus callosum section.13 These findings, plus those of Kempinsky3 on electrical activity after callosotomy discussed above, indicate that to date, the data regarding the effects of corpus callosum section on electrical activity, CBF, and cerebral metabolism are not entirely consistent.

**A Comment**

A concept that may help reconcile some of the seemingly disparate findings in the diaschisis literature is that of disinhibition (or facilitation), as well as inhibition, occurring remote from the ischemic region. Remote disinhibition may result with types of
ischemic insults different from those leading to remote inhibition. As noted in the “Review,” the size of both the ischemic injury and the animal model, as well as the nature of the insult (e.g., ligation versus embolization),\textsuperscript{35} may be important in whether diaschisis inhibition or disinhibition results. We present examples below of disinhibition involving transhemispheric diaschisis in the hyperacute stage and in cortical versus subcortical injury.

As summarized in the “Review,” during the hyperacute stage many experimental models have shown an increase in contralateral evoked potential amplitude. Contralateral CBF has been more variable, with an increase both in large animal models and in small animal models in which the ipsilateral insult was relatively minor. Disinhibition during the hyperacute stage can account for these changes, with the greatest effect expected in contralateral regions having direct (e.g., transcallosal) connections with the ischemic region. The increase in evoked potential amplitude and CBF probably occurs in the context of a transient contralateral increase in metabolism.

A greater reduction in gray matter blood flow than in white matter blood flow contralateral to stroke has been shown.\textsuperscript{72} Nakashima et al\textsuperscript{73} found that a subcortical infarction led to a mild decrease in SEP amplitude contralaterally during the intermediate stage followed by no change during the chronic stage, whereas a cortical infarction led to no change in contralateral SEP amplitude during the intermediate stage followed by a mild increase during the chronic stage. In the former situation of subcortical infarction, it is likely that the transient decrease in blood flow predominated, with a concomitant hypometabolism and decrease in electrical activity. In cortical infarction, on the other hand, the loss of contralateral cortical input had a long-term facilitative effect.

Although the notion of disinhibition or facilitation is contrary to the original view of von Monakow that the remote effect of cerebral injury is inhibitory, there is evidence that diaschisis can be facilitative rather than inhibitive. Regarding intrahemispheric diaschisis, prefrontal injury recently has been shown to result in increased amplitude of both the somatosensory and auditory primary cortical evoked potentials.\textsuperscript{74,75} There is also evidence supporting the facilitative effect of unilateral infarction on contralateral neuronal activity. In the “Review” above, we noted patients with a unilateral tumor or stroke to have an increased contralateral SEP amplitude.\textsuperscript{47} In brain slice preparations from the caudate-putamen after rat MCA occlusion, spontaneous discharges were increased not only ipsilaterally, but more so contralaterally, compared to controls and sham-operated animals.\textsuperscript{76} Furthermore, increased seizure activity contralateral to the infarcted hemisphere has been described in a rat ICA embolization model.\textsuperscript{35} It is very likely that the effect of a stroke on electrical activity in the contralateral hemisphere is dependent not only on the size of the infarction but also on both its location (e.g., subcortical versus cortical) and the time after injury at which the contralateral electrical activity is assessed.

Callosal section models may be informative regarding contralateral facilitation or inhibition. None of the models reported to date, however, has assessed both corpus callosum section plus ischemic insult during the hyperacute stage. By the acute or subacute stages after a unilateral insult such as MCA occlusion, there is transcallosal inhibition with synaptic degeneration in the contralateral cortex.\textsuperscript{67} Meyer et al\textsuperscript{13} measured CBF bilaterally after ICA embolization in baboons that had undergone callosal section 1–2 days previously. However, the CBF was measured 2–3 hours after the middle cerebral artery occlusion, not immediately. Kempinsky performed most of his insults and electrical activity recordings weeks after callosal section.\textsuperscript{3} Recent work by Yamauchi et al.,\textsuperscript{12,14} summarized in the “Review,” measured glucose utilization with positron emission tomography in baboons after section of the anterior corpus callosum\textsuperscript{14} and after section of the anterior corpus callosum plus unilateral lesioning of the nucleus basalis of Meynert several months later.\textsuperscript{12} They performed the measurements days after the lesions were made; thus, these studies do not provide information regarding diaschisis in the very early period after insult. There is a need for serial measures of the same parameters bilaterally, preferably including electrical activity, CBF, and cerebral metabolism, in a corpus callosum section model, with postischemic data collection beginning in the hyperacute stage.

The study of transhemispheric diaschisis may have relevance both for understanding the etiology of ischemic injury and for therapeutic interventions, because the mechanisms by which the contralateral hemisphere reacts to remote injury may be related to the defense mechanisms and reparative processes occurring ipsilaterally after injury. Transhemispheric diaschisis has certain advantages over intrahemispheric diaschisis: 1) the greater distance involved from the site of ischemic injury than in intrahemispheric diaschisis lessens resolution problems when one uses noninvasive monitoring techniques, such as those used to measure regional CBF and cerebral metabolism; and 2) one can assess the same parameter both in the ischemic region and in the identical (mirror-image) region contralaterally, for example, SEPs and MCA distribution CBF. Careful attention to the time sequence of changes in electrical activity, CBF, and cerebral metabolism bilaterally after unilateral focal ischemic insult, particularly in the very early stages after injury, plus the increased use of serial measures in the same model, should yield significant insights into the brain's responses to focal ischemic injury.

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