Proposal for a Universal Definition of Cerebral Infarction

Jeffrey L. Saver, MD

Background and Purpose—Cerebral infarction is a leading cause of disability and death worldwide but has no uniform international definition.

Summary of Review—Recent diagnostic advances have revised fundamental concepts in cerebral and cardiac ischemia.

Cardiologists, already possessed of a nosologic framework distinguishing myocardial infarction from unstable angina on the basis of tissue state, promulgated a new “universal” tissue definition of myocardial infarction incorporating insights afforded by assays of cardiac troponin, a serum biomarker exquisitely sensitive to myocardial injury. Concurrently, vascular neurologists proposed a new tissue, rather than time, criterion to distinguish transient ischemia attack from cerebral infarction, responding to perspectives provided by diffusion MRI and cerebral blood volume CT, imaging biomarkers highly sensitive to neuronal injury. To complete this conceptual realignment, vascular neurology must now advance a clear, uniform, and operationalizable tissue definition of cerebral infarction. This review proposes cerebral infarction be defined as brain or retinal cell death due to prolonged ischemia. This definition categorizes both pan necrosis and neuronal dropout (“complete” and “incomplete” infarcts in classic neuropathologic terminology) as cerebral infarcts. Making the presence of any neuronal or glial cell death essential yields a definition of cerebral infarction that has high relevance to patients, physicians, and policymakers; is more easily applied in clinical practice; fosters action in acute care; harmonizes with myocardial ischemia classification; and focuses diagnostic evaluation on the cause of brain ischemia and the occurrence of end organ injury.

Conclusions—The term cerebral infarction should be used when there is evidence of brain or retinal cell death due to cerebral ischemia. (Stroke. 2008;39:3110-3115.)

Key Words: cerebral infarct ■ ischemic stroke ■ MRI ■ myocardial infarct ■ transient ischemic attack

Since the turn of the millennium, both vascular neurologists and cardiologists have been revising the fundamental conceptual framework of their disciplines as new diagnostic and therapeutic advances have yielded fresh insights into the nature of cerebral and cardiac ischemia. These conceptual reworkings at first appeared somewhat distinct. Cardiology focused on defining myocardial infarction (rather than unstable angina) and vascular neurology focused on defining transient ischemic attack (rather than cerebral infarction). However, because establishing the boundary for myocardial infarction also defines unstable angina, and establishing the boundary for transient ischemic attack (TIA) also defines cerebral infarction, the nosologic reframings actually shared profound affinities. The historical stage is now set for a final joining of the trajectories of these intellectual quests, because the next necessary step as proposed in this Commentary is for vascular neurologists to advance a redifinition of cerebral infarction that parallels the recent redefinection of myocardial infarction completed by our cardiological colleagues. The same driving forces behind the revisions in cardiovascular and cerebrovascular nosologic classifications that have already transpired now compel the formulation of an updated definition of cerebral infarction.

Recent Developments in the Definition of Myocardial Infarction

In cardiology, thought leaders during the past decade focused their attention on generating new definitions of what constitutes a myocardial infarction (MI). Already possessed of a straightforward tissue, rather than arbitrary time, distinction between MI and unstable angina, cardiologists nonetheless recognized a need to update the tissue definition of MI, driven by remarkable advances in the sensitivity to myocardial tissue injury of serum biomarkers. In 2000, a Joint Committee of the European Society of Cardiology and the American College of Cardiology issued a “reddefinition” of MI. The Committee noted that MI can be defined from a number of different perspectives related to clinical, electrocardiographic, biochemical, and pathological characteristics, and that the term MI also has social and psychological implications. However, the starting point for the new framework was the following revised tissue definition: “Myocardial infarction is defined as myocardial cell death due to prolonged ischemia.”

Under this definition, the term MI encompassed 2 pathological categories of ischemia-induced cell death: (1) arrest of muscles in the relaxed state arising from severe, persistent ischemia (“coagulation necrosis”); and (2) arrest of cells in...
the contracted state resulting from severe ischemia followed by reflow (“contraction band necrosis”) and a wide range of degree of cell necrosis from complete necrosis of all myocardial cells at risk to patchy cell loss.1 This approach fit well with the increase in sensitivity to detection of myocardial cell death afforded by the advent of troponin serum biomarkers, substantially more sensitive than prior biochemical indices. Troponin assays made myocardial infarcts that were only microscopic in extent (focal necrosis) detectable and diagnosable. Moreover, although clinicians could now determine with high sensitivity when myocyte loss had occurred, they remained unable to dependably distinguish whether the underlying pathologic lesion was pan necrosis of a small volume of tissue versus scattered myocyte loss within a larger region. Demarcating any ischemia-related myocyte loss as MI allowed formulation of clear clinical operational definitions of MI and accorded with the fundamental intuitive understanding of physicians and patients that a myocardial infarct is death of heart cells due to low blood flow. The Joint Committee established that MI would be recognized when death afforded by the advent of troponin serum biomarkers, substantially more sensitive than prior biochemical indices. Troponin assays made myocardial infarcts that were only microscopic in extent (focal necrosis) detectable and diagnosable. Moreover, although clinicians could now determine with high sensitivity when myocyte loss had occurred, they remained unable to dependably distinguish whether the underlying pathologic lesion was pan necrosis of a small volume of tissue versus scattered myocyte loss within a larger region. Demarcating any ischemia-related myocyte loss as MI allowed formulation of clear clinical operational definitions of MI and accorded with the fundamental intuitive understanding of physicians and patients that a myocardial infarct is death of heart cells due to low blood flow. The Joint Committee established that MI would be recognized when blood levels of troponin exceeded the 99th percentile of the normal reference range in the appropriate clinical setting.1,2

The new definition of MI, although not without its critics,3,4 met with wide acceptance. The greater inclusiveness of the new definition, due to the incorporation into the concept of MI cases with myocyte loss without pan necrosis, led to a marked increase, typically 25% to 75%, in the number of patients classified as having MI.5–7 In 2007, an international Task Force reaffirmed the revised tissue definition as of patients classified as having MI.5–7 In 2007, an international Task Force reaffirmed the revised tissue definition as the “universal definition” of MI and refined the biochemical, electrocardiographic, and clinical operational definitions indexed to the pathological definition.8

Recent Developments in the Definition of Transient Ischemic Attack
In vascular neurology, dramatic advances in diagnostic sensitivity similar to those in cardiology had also recently occurred, albeit in the domain of imaging, rather than serum, biomarkers. The advent of diffusion-weighted MRI (DWI MRI) vastly increased clinicians’ abilities to determine when brain end organ injury due to ischemia had transpired. The greater sensitivity of diffusion MRI compared with noncontrast CT or even T2-weighted MRI, like that of troponin compared with previously used biochemical markers, precipitated a series of revisions in the fundamental conceptual framework of cerebrovascular disease diagnosis. This reframing was further advanced by the development and widespread deployment of dynamic perfusion CT imaging with its ability to identify end organ injury early after onset with high sensitivity and specificity on cerebral blood volume maps.9

Cerebrovascular nomenclature began from a more primitive starting position than did cardiovascular nomenclature, reflecting in part the greater complexity of the brain versus the heart. The cerebrovascular field still used an arbitrary time, rather than tissue, criterion to distinguish stroke from transient ischemic attack. The reigning categories of brain ischemia classification were formulated in the presectional imaging era of the 1950s and 1960s, when the best guess as to whether tissue injury had occurred was afforded by the crude operational variable of the time duration of clinical deficit. In the 1975 National Institutes of Health classification of cerebrovascular diseases, 3 nosologic categories were advanced: TIA, reversible ischemic neurological deficit (RIND), and completed ischemic stroke.10 A TIA was operationally defined as neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms lasting less than 24 hours or less. A RIND was defined as symptoms lasting between 1 day and 3 weeks. Only events with symptoms lasting more than 3 weeks in duration were confidently felt by the classification document’s authors to represent tissue infarction and considered “completed strokes.”

Many candidate time criteria were advanced for distinguishing TIA, RIND, and completed stroke, and the final 24-hour and 3-week boundaries were arrived at somewhat arbitrarily.11 Initially, these definitions proved operationally useful, because they provided clinicians with a simple, uniform diagnostic metric. Eventhough, however, advances in basic neuroscience and clinical management made the time-based approach to diagnosis increasingly untenable. With the development of CT imaging in the 1970s, MRI in the 1980s, DWI MRI in the 1990s, and cerebral blood volume CT in the 2000s, the ability to identify the presence or absence of ischemic brain injury clinically became increasingly precise.12,13 These neurodiagnostic studies demonstrated that the 24-hour TIA and 3-week RIND criteria were frequently inaccurate in suggesting presence or absence of brain injury. When the time-based definition of TIA had first been formulated, it was implicitly assumed that transient symptoms disappeared completely because no permanent brain injury had occurred. Subsequent advances in understanding the neurobiology of brain plasticity demonstrated that early clinical resolution of deficits frequently occurred because of rapid brain adaptation and functional reorganization despite permanent injury, not because of complete sparing of brain parenchyma from infarction. MRI studies in patients with clinical symptoms lasting less than 24 hours found diffusion lesions indicating acute cerebral ischemic injury in 30% to 45% of such cases.14–16 Fully one third of patients with classical less than 24-hour TIA events actually harbored imaging signatures of tissue infarction. Moreover, although briefer deficit durations have been proposed as new time criteria for the recognition of TIA, including symptoms lasting one,19 2,20 or 6 hours,17 it has now been demonstrated that no single deficit duration threshold distinguishes patients with and without tissue infarction with high sensitivity and specificity.17

Furthermore, when the time-based definitions of TIA and RIND were formulated, there was no need for urgency in arriving at a syndromic diagnosis because no effective treatments for acute cerebral ischemia existed. The sense of urgency was transformed in the 1990s when thrombolytic therapy emerged as a powerful, effective treatment requiring emergent diagnostic assessment of the patient within the first minutes to hours after onset.

As a result of these advances, the time-based definition of RIND and the term itself were recognized as outmoded and dropped from regular use by most stroke neurologists, and
proposals were advanced to make demarcation of TIA from cerebral infarction tissue-based rather than time-based. In 2002, the TIA Working Group proposed the following revised definition of TIA: “a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction.”1 The new tissue-based definition, although not without its critics,21,22 has met with wide acceptance by thought leaders,23–27 independent scientific consensus committees,28 and multicenter clinical trials.29–31 As the TIA Working Group recognized, any revision in the definition of TIA is also a revision in the definition of cerebral infarction: “The corollary (to the proposed TIA definition) is that persistent clinical signs or characteristic imaging abnormalities define infarction—that is, stroke.”19 Subsequent analysis indicated that the epidemiological impact of the new definition of TIA on the proportion of cases diagnosed as stroke rather than TIA was modest, increasing the proportion of patients classified as having cerebral infarct by 7% (much less than the impact of the revised definition of myocardial infarct).32

Several investigators have proposed further refinements in cerebrovascular nosologic classification to more fully harmonize the definitions of cerebral and noncerebral ischemic syndromes, broadening classification schemas to include terms to label acute cerebrovascular symptoms in patients who have not yet undergone sufficient diagnostic evaluation to be classified as TIA or cerebral infarction. “Acute cerebral ischemia” is the classic term for such symptoms, applied to patients experiencing brain ischemic symptoms whose tissue fate is as yet undecided.33 Similar terms that have been advanced include “acute ischemic cerebrovascular syndrome,” as an analog to the acute coronary syndrome rubric widely adopted in cardiology,34 and “acute cerebrovascular syndrome” to encompass symptoms resulting from either acute cerebral ischemia or acute intracerebral hemorrhage, because patients with brain ischemia and those with brain hemorrhage cannot be fully distinguished by clinical features alone.35 If these terms were deployed fully, then before noncontrast CT or susceptibility-weighted MRI patients would be designated as having acute cerebrovascular syndrome. If hemorrhage is ruled out, then patients would be labeled as having acute cerebral ischemia or acute ischemic cerebrovascular syndrome while awaiting performance of clinical, laboratory, or imaging studies sensitive to acute infarction (such as DWI MRI, cerebral blood volume CT, or observation for prolonged periods of time).

The definitions of TIA and ischemic stroke advanced by the TIA Working Group are not constrained by the geographic availability or the technological limitations of DWI MRI, cerebral blood volume CT, or any other imaging sequence or modality. The definition of cerebral infarction is tissue-based like that of other diseases in medicine such as herniated discs, sinusitis, and aortic dissection. Like with these and other conditions, the histopathologic diagnosis of brain infarction typically must be inferred based on clinical, laboratory, and imaging data rather than directly proven by microscopic tissue examination. The reliability of the diagnosis will increase when more sophisticated diagnostic technologies are used, but diagnosis based on history and physical examination alone will often be accurate, and diagnoses may be rendered even when advanced technologies are not available. Sometimes even advanced diagnostic technology will not provide definitive findings; the entity of “diffusion-negative” cerebral infarction is well known, often involving brainstem strokes.36 The most appropriate clinical, laboratory, and imaging modalities to support the diagnosis of transient ischemia versus cerebral infarction will evolve over time as diagnostic techniques advance. Specific operational criteria for the clinical diagnosis of brain infarction will also evolve just as the criteria for the diagnosis of MI evolved when new serum markers were identified. However, the definition of the underlying disease states will not vary; ischemic stroke is cerebral infarction and TIA is symptomatic ischemia with no evidence of infarction.

The New Definition of Cerebral Infarction
Implementing a tissue, rather than time, definition of TIA has been a major accomplishment of 21st century vascular neurology. However, it has been little noted that this advance mandates clarification of the tissue definition of cerebral infarction. The potential of a tissue definition of TIA to provide a more reliable foundation for clinical and societal handling of stroke can only be realized if a clear, uniform, and operationalizable tissue definition of cerebral infarction exists. At present, unfortunately, definitions of cerebral infarction are nonuniform, outmoded, and nonoperationalizable. For vascular neurology nosology to advance, cerebral infarction (CI) must now be redefined in the same manner as has MI.

It is a remarkable fact that the major intersocietal classification documents that attempted to systematize understanding of cerebrovascular disease in the past generally avoided proffering a definition of cerebral infarction. In the United States, the 1958 initial National Institutes of Health Classification of Cerebrovascular Diseases and the 1975 revision of the National Institutes of Health Classification both failed to offer any definition of cerebral infarction.10,37 The latest World Health Organization classification of cerebrovascular disease, of 1980, similarly fails to advance any definition of cerebral infarction.38

Presumably, the nature of cerebral infarction was felt to be so elemental and widely agreed-on as to make any interdisciplinary committee definition superfluous. The definition of cerebral infarction was laid out in basic neuropathologic textbooks and needed no attention. However, a glance at modern neuropathologic texts reveals such an assumption to be faulty. Mainstream neuropathologic textbooks contain divergent and imprecise tissue definitions of cerebral infarction. One text, for example, defines cerebral infarct as “an area of coagulation necrosis that develops as a result of an ischemic event, secondary to an arterial occlusion,”39 whereas another defines it as “a well-circumscribed area of necrosis in the distribution of a specific vascular territory and results from occlusion or severe hypoperfusion in the feeding artery.”40 These definitions are contradictory; one requires an arterial occlusion, the other only hypoperfusion through a feeding artery; one specifically requires coagulation necrosis,
the other merely necrosis. Both texts’ definitions are operationally imprecise; neither specifies how large a volume of tissue needs to be injured at the microscopic level to qualify as cerebral infarction nor exactly how distinctly circumscribed the lesion must be.

Even more importantly, many neuropathologic texts also recognize the tissue entity of “incomplete infarction” characterized as selective neuronal necrosis due to hypoperfusion through an arterial feeding artery analogous to selective vulnerability in global brain ischemia. Selective neuronal necrosis and brain parenchymal pannecrosis exist on a continuum of severity of ischemic end organ injury, similar to selective and contraction band myocyte necrosis and myocardial pannecrosis.

Vascular neurology must now decide whether to adopt a narrow tissue definition of cerebral infarction that includes only regions of complete pannecrosis with tissue collapse or a broad definition that also encompasses regions of neuronal dropout with preservation of some supportive tissue. We must decide if clinical cerebral infarction will be defined to include both “complete” and “incomplete” or only “complete” tissue infarction.

For many reasons, it is preferable to follow the example of our cardiology colleagues and adopt a broad tissue definition of cerebral infarction that includes both types of cerebral ischemic injury. The following revised tissue definition of cerebral infarction is proposed: Cerebral infarction is defined as brain or retinal cell death due to prolonged ischemia. Under this definition, both “complete” and “incomplete” neuropathologic infarcts are cerebral infarcts.

This definition of cerebral infarction encompasses both symptomatic and silent events. Unlike transient ischemic attacks, which must be symptomatic, cerebral infarcts may be either symptomatic or silent. Symptomatic ischemic strokes occur when central nervous system infarction produces clinical signs of focal or global cerebral, spinal, or retinal dysfunction. A silent or covert ischemic stroke is a documented central nervous system infarction that was asymptomatic. The proposed definition also recognizes both white and gray matter infarcts. Infarcts confined to white matter are characterized by glial cell death due to ischemia, often accompanied by axonal injury. Gray matter infarcts are characterized by neuronal cell death.

Implementing such a broad tissue definition of cerebral infarction offers many advantages, among which a few are here briefly noted:

(1) Greater relevance to patient, physician, and societal decision-making: Individuals, in making their personal healthcare choices, and policymakers, in formulating societal healthcare decisions, are interested in protecting the brain from injury. Their key goal is to avoid neuronal and glial loss that impairs cerebral function. This perspective supports a broad tissue definition of cerebral infarction, because both neuronal dropout and pannecrosis can permanently impair brain activity, whereas there is no compelling evidence that ischemia without neuronal necrosis produces permanent functional impairments.

(2) Greater operationalizability in clinical practice: DWI MRI sequences and perfusion CT cerebral blood volume maps are extraordinarily sensitive to cerebral tissue injury. Of particular relevance is that DWI MRI shows abnormality in regions of neuronal and glial dropout as well as regions of pannecrosis. Follow-up scans in patients with clinical deficits lasting less than 24 hours show that most regions evidencing diffusion abnormality acutely will evolve a T2-weighted abnormality suggesting pannecrosis on late follow-up imaging, but 0% to 21% of patients experience reversal of the DWI abnormality without evident T2 abnormality. Studies in animal models demonstrate that cerebral regions experiencing early, reversible diffusion change without a final T2-weighted signature of injury neuropathologically exhibit neuronal dropout. Consequently, DWI MRI abnormality is a good biomarker for the occurrence of neuronal cell death and not a good demarcator of pannecrosis from neuronal dropout.

(3) Fosters action rather than inaction among patients and healthcare providers in the treatment of acute cerebral ischemia: A demarcation that categorized neuronal dropout as TIA rather than cerebral infarction would encourage clinicians to wait until follow-up MRI or CT imaging was available, days after presentation, before rendering their diagnosis of the ischemic syndrome. If the classification of a patient as having CI or TIA is to be made at the time of presentation, rather than days later, then CI must be demarcated as neuronal death of any degree, not pannecrosis. The proposed definition of cerebral infarction facilitates rapid response to acutely presenting patients in standard practice of recanalization therapy and in acute stroke treatment trials.

(4) Harmonization with cardiac injury definitions: The distinction between angina and MI is based on myocyte cell death, not coagulative necrosis. Making the distinction between TIA and cerebral infarction similarly based on neuronal and glial cell death rather than coagulative necrosis would harmonize cerebrovascular and cardiovascular nosology.

(5) Focus diagnostic evaluation on the cause of brain ischemia and the presence or absence of end organ injury: A definition of CI confined to pannecrosis would squander resources and physician attention on making a distinction between pannecrosis and neuronal dropout that is of little relevance to patient management. The key diagnostic issues in patients who have a cerebral ischemic event are the vascular cause of the brain ischemia and whether cerebral injury has occurred. The broad tissue definition of CI appropriately focuses evaluation on identifying the vascular genesis of brain ischemia and rapid implementation of acute and secondary prevention therapies.

Conclusion

Clinicopathologic correlation is the hallmark of modern medical diagnosis. The former foundation offered by a tissue rather than time criterion for cerebrovascular diagnosis can only be fully realized if a clear, uniform pathological definition of CI is established in relation to which clinical, imaging, serum biomarker, clinical trial, epidemiological, and public policy case definitions can be...
refined. The updated tissue definition of CI advanced here is neuropathologically sound, fosters best clinical practices, and is convergent with the approach undertaken in allied disciplines. It would be helpful to science, society, and our patients for an intersocietal working group to adopt this or a similar definition as the “universal definition” of CI.

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