Ischemic Penumbra: A Personal View

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Abstract

The concept of the ischemic penumbra was defined over 40 years ago by Lindsay Symon and his group and is now an established principle of all acute ischemic stroke therapies. These reperfusion treatments rescue threatened, critically hypoperfused brain tissue and have been proven to improve clinical outcomes.

We have been fortunate to have observed and played a small part in the penumbral story from its beginnings in the 1970s to its pivotal position today. Over this period, we have witnessed penumbral imaging evolve from positron emission tomography through to magnetic resonance imaging and now predominantly computed tomography perfusion, with the advent of automated imaging facilitating case selection for reperfusion therapies.

We and others have conducted clinical trials using penumbral imaging to extend the time window for intravenous thrombolysis and select patients for thrombectomy. Together with the concept of fast- and slow-growing ischemic infarct patterns, this embeds the penumbral principle in everyday clinical management. The opportunity now exists to make penumbral imaging even more portable, affordable, and more widely available using mobile platforms, novel imaging techniques, digital linkage, and artificial intelligence.

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The Beginnings

We both began our training in neurology in 1976. Little did we realize that this was such a pivotal time in the history of stroke which had several thousand years of a history of therapeutic nihilism. When we were interns, stroke was still called “CVA,” appropriately named “confused vascular analysis” by one of the stroke pioneers, Vladimir Hachinski (Fig. 1). The referring doctor in the Emergency Department would apologize for admitting a stroke patient and say that the next one would be “more interesting.” Stroke units were in their infancy with one of the first acute units established at Sunnybrook Hospital in Toronto, Canada, by Norris and Hachinski [1], enabled by a generous philanthropic donation [1, 2].

Computed tomography (CT) started to be introduced as a routine imaging tool in the mid-1970s. Even then, most strokes were looked after by general physicians with little interest or expertise and who did not regard brain imaging as a priority. Indeed, it was not uncommon to be challenged if a CT was ordered for stroke diagnosis “because it will not alter the outcome.”

During our training as neurologists from 1977 to 1980, we first heard of the concept of the ischemic penumbra [3]. This was quite a revolutionary concept that acute stroke was an evolving process, with definition of cerebral blood flow thresholds for reversible and irreversible cerebral ischemia. This dynamic process showed progressive

Fig. 1. John Norris (a) and Vladimir Hachinski (b) who established the world's first acute stroke unit at Sunnybrook, Toronto, Canada, in 1976 [1].

cerebral ischemic damage over an uncertain period of time. Prior to this, the firm dogma was that immediate brain tissue death occurred after stroke onset, with no opportunity for intervention. However, led by Lindsay Symon, a professor of neurosurgery at the National Hospital for Neurology and Neurosurgery in Queen Square, UK, this concept was completely overturned [4] (Fig. 2). He introduced the term “penumbra” which he apparently coined while walking with a colleague, Anthony Strong, across Guildford Street to have lunch at Queen Square [5]. He stated that it was “rather like the area around the centre of a candle flame where there is a small bright zone known as the penumbra.” Astrup and Lassen pointed out that it was also akin to the bright zone around the sun in a total eclipse [5].

Working with other outstanding scientists including visiting neurosurgeons from Denmark, Jens Astrup, and Sweden, Bo Siesjö, he performed pivotal animal experiments to demonstrate the time course of tissue death in relation to perfusion thresholds in baboons [6]. They were able to show that this region of cerebral dysfunction could be monitored by somatosensory-evoked potentials which could be restored to normal with restoration of cerebral blood flow [3]. At around this time, Jones et al. [7] also established the important relationship between thresholds of cerebral ischemia and duration of vessel occlusion in an awake primate model.

Surprisingly, the enormity of their discoveries were not really appreciated at the time; perhaps, in part, this reflected the perception that Lindsay Symon was primarily a neurosurgeon and not actively treating acute ischemic stroke. Furthermore, there was no emergency department at the National Hospital and little management

Fig. 2. Lindsay Symon (a) with his research team (b). Left to right: Neil Branstor, Terry Hope, Robert Harris, Lindsay Symon, Anthony Strong, and Jens Astrup [5].

of acute stroke. Interestingly, another leading neurosurgeon, Thor Sundt at the Mayo Clinic, a friend and colleague of Lindsay Symon, demonstrated reversibility of cerebral ischemia in humans with subarachnoid hemorrhage monitored by changes in somatosensory-evoked potentials [8, 9]. Lindsay Symon and his group prophesized that therapeutic intervention to restore brain perfusion would potentially be based, in the future, on imaging of the penumbra [6].

Early Penumbra Imaging Experiences Using Positron Emission Tomography

In the early 1980s, we were both stroke research fellows at the Massachusetts General Hospital working with Robert Ackerman, who had appointments in both the Departments of Radiology and Neurology. The MGH stroke service was the home of C Miller Fisher who is widely recognized as one of the fathers of modern stroke medi-

Fig. 3. Some of the early pioneers of the ischemic penumbra using PET technology. Robert Ackerman (a), Jean-Claude Baron (b), Richard Frackowiak (c), Wolf-Dieter Heiss (d), and Marcus Raichle (e). PET, positron emission tomography.

cine. Ackerman et al. [10] led the positron emission tomography (PET) program at the MGH, one of the early pioneering programs of its type, underpinned by a large NIH grant. The main focus of the research group was acute ischemic stroke (Fig. 3).

They demonstrated that increased oxygen extraction fraction signified potentially salvageable tissue (Fig. 4). There were also other PET programs launched around the same time in St Louis, led by Marcus Raichle [11], and

Fig. 4. Initial PET images at three levels (1, 2, 3) from the Frackowiak Group [13] showing the ischemic penumbra represented by increased oxygen extraction fraction (lower two central panels, white signal), reduced CBF (lower two left panels) and relatively maintained $CMRO_2$ (lower two right panels). PET, positron emission tomography.

in London by Terry Jones and Richard Frackowiak (Fig. 3) [12, 13].

Jean-Claude Baron had been Ackerman's first research fellow at the MGH several years before (Fig. 3). Jim Grotta, another stroke pioneer, was also an early Ackerman research fellow. Upon his return to France, Baron led the PET program in Paris for many years and later in Caen. He coined the term "misery perfusion" as the penumbral signature and the inverse of the concept of "luxury perfusion" devised earlier by Niels Lassen [14] using more basic arterial perfusion measures with $^{133}\text{xenon}$ [15, 16]. He and others showed that penumbral salvage directly predicts neurological recovery [17].

How to reperfuse hypoperfused tissue with a consequent increased oxygen extraction fraction was a topic of debate. An early hypothesis was to increase systemic blood pressure, but this has never been fully explored with large randomized control trials, despite pilot studies confirming feasibility [18]. The more direct idea of recanalization of occluded major arteries was not really on

Fig. 5. Steven Warach (a). A mismatch acutely (b) between the region of hypoperfusion (middle image, larger) and the region of diffusion abnormality (left image, smaller) is predictive of ischemic lesion enlargement (right image), regardless of time from onset [38].

the horizon at this early stage, particularly as early trials of thrombolysis were negative [19]. However, Meyer et al. [20] had attempted surgical embolectomy as early as the late 1970s and early 1980s.

We both recall the excitement of seeing the first images in humans of the ischemic penumbra on PET as defined by reduced CBF and increased oxygen extraction fraction (Fig. 4). To reverse this process seemed to be a pipe dream. Indeed, to even consider that there would be an approved effective therapy during our careers seemed most unlikely. Remarkably, this hypothesis has been now completely validated.

The brain CT scanner was invented 50 years ago by Hounsfield (winning the Nobel Prize) and still remains the workhorse of acute stroke imaging [21]. It is exquisitely sensitive in the distinction between ischemic stroke and intracerebral hemorrhage, the essential substrate before considering thrombolytic therapy. Magnetic resonance imaging (MRI) only became widely available a decade later, invented by Damadian, Mansfield, and Lauterbur, although only the latter 2 were awarded the Nobel Prize amid considerable controversy [22–24]. MRI ushered in the revolution of contemporary penumbral imaging.

The Penumbral Imaging Revolution

As mentioned earlier, the ^{15}O PET technique was shown to demonstrate the penumbra by an increase in oxygen extraction fraction in animal and human models [13, 16, 25, 26]. Based on their delineation of a reversible ischemic state, potentially amenable to therapy, a number

of investigators suggested that their findings would have important stroke management and selection for therapeutic trials [13, 16, 25, 27]. There were a number of other PET techniques which added to the penumbral story including glucose CBF mismatch, flumazenil/CBF mismatch [28], and ^{18}F -MISO [29]. However, none of these were ever practical in everyday clinical use. As a collective, these studies shed enormous light on the natural history and evolution of the ischemic penumbra over the passage of time. Remarkably, they illustrated the opportunities for acute intervention, but also showed the persistence of the penumbra for prolonged time intervals up to 24–48 h [30–33].

Using single-photon emission CT, earlier studies showed the predictive value of acute hypoperfusion and reperfusion [34–36]. It was possible to evaluate the influence of thrombolytic therapy on regions of depressed cerebral blood flow. However, standard single-photon emission CT techniques such as HMPAO only monitored blood flow and could not image the penumbra *per se*.

The real revolution in practical penumbral imaging came with the advent of MRI [37]. Warach showed that the mismatch between a larger perfusion region and a smaller diffusion core was a useful measure of the penumbra [38] (Fig. 5). A further important step was the introduction of thresholding for cerebral perfusion. Specifically, the accuracy was improved when limits for core and salvageable tissue were introduced. This was important particularly to exclude benign oligemia, a problem with earlier use of $T_{\max} 2\text{ s}$ [39, 40]. Subsequently, $T_{\max} 6\text{ s}$ was shown to optimize the penumbral threshold [41]. This was previously validated against PET [42]. Also, thresholding with acute diffusion coefficient values was

important in defining the damaged ischemic core which was generally irreversible. However, partial salvage of the core defined by acute diffusion coefficient values could be generated by hyperacute reperfusion [43]. Later work by the combined EPITHET and DEFUSE collaborators indicated that sustained, clinically relevant reversal of the acute diffusion lesion was infrequent [44].

We and others described the different patterns of diffusion perfusion match and mismatch on MRI and their potential therapeutic applications [45–47]. Because MR perfusion is more difficult to obtain, there was a push to use the mismatch between clinical stroke severity (NIH Stroke Score and the DWI lesion as a surrogate measure of the penumbra [48, 49]). Interestingly, this concept has been successfully used in recent trials of penumbral selection and reperfusion at later time windows with both CTP and MRI (clinical/core mismatch) [50, 51].

Very quickly after MR became established as a clinically useful means of identifying the penumbra, a return to the earlier described technique of CT perfusion was validated by Wintermark et al. [52–54]. Groups led by Parsons and Campbell performed comparisons between MRI and CTP, showing that the different techniques provided analogous clinical information about core and penumbra [55]. In particular, the infarct core was identified by a thresholded cerebral blood volume and later cerebral blood flow, generally <30% of the homologous region [56]. CT perfusion thresholding mirrored the MRI approach. As per MRI, use of $T_{\max}$ 6 s has been shown to be optimal in definition of the penumbra [57].

A number of studies showed that the information provided by these 2 very different brain imaging techniques was comparable. CTP had the advantage of being more universally available, cheaper, faster, and more user-friendly, although less obvious to the naked eye than DWI [58]. Earlier, some concerns about renal damage from gadolinium were dispelled [59].

CTP remains the most commonly used method for routine penumbral imaging, although some centers still employ acute MRI techniques. Indeed, in many countries, the use of CTP has become a routine part of acute stroke management, often replacing simple noncontrast CT scanning alone (Fig. 6).

The Therapeutic Revolution

The sheer logic of recanalizing major arteries to reperfuse the ischemic penumbra with thrombolytic agents had been considered for some time, particularly influ-

Fig. 6. CTP images showing large ischemic core in the left panel (a) documented by CBF <30% of contralateral side. Right panel (b) shows perfusion lesion thresholded T max 6. There is significant mismatch between a lesion core and perfusion, but uncertainty exists as to whether reperfusion therapies should be used in these circumstances.

enced by the successful cardiac paradigm. Imaging had brought it to the forefront given that a specific ischemic stroke diagnosis could be made. There were early attempts with intra-arterial and intravenous agents, including a number with streptokinases which were unsuccessful [60–62]. The remarkable success with ultra-early intravenous tissue plasminogen activator (tPA) was the breakthrough in 1995 [63]. For the first time, stroke was shown to be treatable and this had a major impact on the prevailing therapeutic nihilism, the proliferation of stroke units, and the movement of stroke management into “prime time.”

The importance of time in the therapeutic equation was emphasized by our own Australian streptokinase trial and the early tPA trials including NINDS and the ECASS trials [63–67]. This led to the concept that “time is brain” proposed by Camilo Gomez and readily explained by studies showing that the frequency of the ischemic penumbra diminishes with time [31, 68]. It is important to emphasize that all these earlier trials relied on clinical criteria and noncontrast CT alone.

Interestingly, there was a “mismatch” between our evolving understandings of the duration of the ischemic penumbra, probably up to 24–48 h in some cases versus the relatively short 4.5-h window for thrombolytic therapy [31–33, 69]. A similar developmental sequence occurred with thrombectomy as with tPA, early failure followed by spectacular success. The turning point was the advent of much better intra-arterial clot retrieval devices, the first of which was the Solitaire stent retriever. We recall the excitement at the World Stroke Congress in Istanbul in 2014 when the MR CLEAN results were presented to a standing ovation, a phenomenon never experienced

Fig. 7. Greg Albers (a). Image on left (b) shows MRI DWI lesion and on right (c) thresholded perfusion image ($T_{\max} > 6$) using RAPID¹ software (iSchemaView). The DWI lesion reflects the mostly irreversible ischemic core, and the mismatch with the larger perfusion lesion reflects tissue at risk. MRI, magnetic resonance imaging.

in our careers [70]. There were 5 initial strongly positive thrombectomy trials which led to rapid change in clinical guidelines worldwide [70–74]. The most positive results were seen in those trials employing penumbral selection to enrich the trial population to those most likely to respond [73]. However, debate has continued concerning the role of penumbral selection given that thrombectomy was also shown to be positive in the trials using CT angiography and simple noncontrast CT selection criteria [70]. With a number needed to treat 2.6 to reduce disability based on the meta-analysis of the pivotal thrombectomy trials, it is obvious that thrombectomy is one of the most powerful interventions in medicine [75]. These initial trials generally used a 6-h time window based largely upon the efficacy of intravenous therapy up to almost this time.

The stage was set to extend the time window using multimodal imaging. However, this only became feasible with the advent of automated techniques.

Automated Imaging

Real-time imaging of the ischemic penumbra with thresholded values was pioneered by the Stanford group using their RAPID software [76, 77] (Fig. 7). A number of others followed, using a color-coded system which made interpretation simple, rapid, and generalizable [78]. This imaging allowed urgent assessment of the amount of salvageable tissue and the size of the ischemic core.

Meta-analysis of the thrombectomy trials showed that large ischemic cores predicted worse clinical outcome, although benefit was still achieved at upper limits even with core sizes of over 100 mL [79]. The benefits and risks of reperfusion of patients with large core sizes remain controversial and under investigation in a number of clinical trials.

Selection for Therapy and Extended Time Windows

Intravenous Thrombolysis

The disparity between the short 4.5-h therapeutic time window shown in the intravenous thrombolytic therapy trials and the longer duration of the ischemic penumbra in some patients set the scene for imaging selection to be used in later time windows. Rocha and Jovin, and later Albers (Fig. 7), popularized the concept of fast- and slow-growing infarct cores which had been previously demonstrated with PET [27, 80, 81]. This explained the disparity and fitted well with the overall penumbral hypothesis.

We conducted the first randomized controlled trial (EPITHET) to extend the time window beyond 3 and then 4.5 h using tPA [40]. Automated imaging had not yet been introduced, and we therefore retrospectively tested our hypothesis of penumbral selection for treatment responders. Although it did not reach significance, we showed that in patients with the penumbra using MRI, reperfusion was strongly associated with improved clinical outcomes. Further, in patients with co-registered images or using the $T_{\max}$ 6 threshold (rather than $T_{\max}$ 2 employed in the trial) post hoc positive results were obtained [82].

This set the scene for our extended time window trial (EXTEND) using automated imaging selection of patients with adequate penumbra using either MRI or CT [77, 83]. We aimed to double the time window to 9 h and include “wake-up” stroke patients. The positive result further validated the penumbral hypothesis with prolonged time windows and in patients with an uncertain time of onset. It further prompted the question, “should even longer time windows be considered”? Whether the penumbral concept could be applied to stroke of uncertain time of onset, including wake-up stroke, also needed to be determined. Another approach, not specifically penumbral selection, used the concept of mismatch of DWI-FLAIR. This alternative approach identified patients within 4.5 h and was substantiated in the WAKE-UP trial [84].

Thrombectomy at Extended Time Windows

A further major change in clinical practice then occurred following the positive results of 2 pivotal extended time window thrombectomy trials, based on penumbral selection. DAWN used a clinical/core mismatch selection criteria to show efficacy of clot retrieval to 24 h [51]. Likewise, DEFUSE-3 showed efficacy up to 16 h using the classical DWI/PWI mismatch technique [50]. Further validating penumbral selection as a principle, these trials showed that the benefits of reperfusion in late time windows were at least as great as those treated earlier. Indeed, small series have even suggested the use of thrombectomy beyond 24 h in patients with persisting penumbra [85]. Clinical trials are likely.

Where to Now?

Based on our understanding of the temporal evolution of the ischemic penumbra, the proportion of penumbral tissue after stroke onset rapidly declines from near 100% to lower levels depending on factors such as collateral supply and the consequent speed of growth of the ischemic core. The classic time-efficacy curve of tPA commenced at 1 h because very few patients were treated in the first 60 min [86]. This relationship was emphasized by the greater benefit shown among the initial 90-min cohort of the NINDS trial than in the subsequent 90–180 cohort [63]. This led to the later concept of pre-hospital stroke treatment and the “golden hour,” the first hour after stroke onset [87]. The prehospital mobile stroke unit (MSU) paradigm was pioneered by Faßbender, with Walter, in Homburg, Germany [88–90], later by Audebert and Ebinger et al. [91] in Berlin, and Grotta in the USA [92]. Initial studies including our own Melbourne MSU showed that a 10-fold greater number of patients could be treated within the “golden hour” [93]. Further, this approach was found to be cost-effective [94]. This has now translated into proven increases in clinical outcomes in 2 pivotal phase 3 clinical trials in Europe (B_PROUD) and the USA (BEST-MSU), which should lead to change in clinical guidelines worldwide [95, 96].

The weight of current CT scanners used in MSU limits their deployment. To date, for example, although there is no aircraft application, plans are underway in Australia [97–99]. Nearly, all metropolitan MSUs around the world deploy a half-ton CT scanner and currently do not utilize penumbral imaging. There is an opportunity to develop lighter weight and more sophisticated CT imaging devices capable of giving penumbral measures useful for therapeutic intervention [100].

While CT and MR with perfusion capability remain the standard imaging technique for penumbral selection, there are a number of newer imaging techniques which may provide similar information. These have the potential advantages of being extremely lightweight, hence highly portable and much more affordable. Examples include electromagnetic radiation and new MR techniques [101].

Coupled with the aforementioned developments in new imaging techniques may be more sophisticated artificial intelligence approaches to interpreting the prognostic value of penumbral signatures [100]. These could prove invaluable in more remote settings where there will be reliance on telemedicine. The opportunity for prolonged real-time penumbral monitoring may also exist.

Telemedicine is transforming the triage and management of acute stroke patients, particularly in nonmetropolitan settings [102–104]. Penumbral imaging may well become an integral component of “telestroke.” Linking these technologies is another exciting development, telerobotic thrombectomy [105]. This addresses the critical shortage of expert interventional neuroradiologists outside of comprehensive stroke centers in cities. An integral component of this will be an online assessment of penumbral status as a part of the thrombectomy process.

In conclusion, we have been fortunate to have been witness to and played a small part in what could be termed the penumbral revolution [106, 107]. The prediction of Lindsay Symon that the penumbra could be imaged in real time and form the basis for therapeutic intervention has been thoroughly validated. There is no doubt it will continue to form the basis of therapeutic decisions in acute ischemic stroke. The digital revolution will take imaging of the penumbra to another level; who knows what the next 40 years will bring!

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Statement of Ethics

Written informed consent was obtained for the use of all images, except Figure 2, of Lindsay Symon who is deceased and whose next of kin is unknown. The image provided is a true and accurate representation of Lindsay Symon.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Both authors contributed equally to the manuscript.

Data Availability Statement

All relevant data are freely available upon request.

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