History of Stroke Imaging

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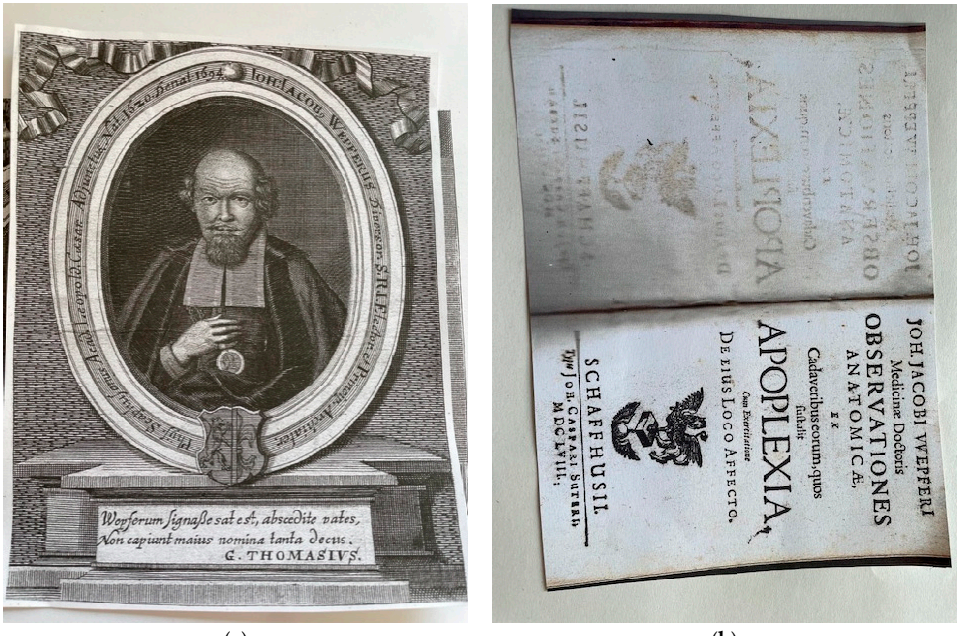
Abstract: This chapter summarizes the history of cerebrovascular brain imaging from its early roots (clinical anatomy) in the 17th century to the first successful technological steps and the application of various brain and vessel imaging procedures in the last two centuries. Today, cerebrovascular ultrasound, cranial computed tomography and magnetic resonance brain imaging all contribute to our current diagnostic management for the best early stroke treatment in the acute phase with high-technology expertise.

1. Early Progress in Understanding Stroke—The Need for Brain Imaging

Although some signs and symptoms of permanent stroke were already known in ancient Egyptian, Greek and Roman times, many were sources of misinterpretation among a wide variety of established knowledge. Hippocrates created the term apoplexy—still misused today even in medical books and scientific writing—for a sudden condition of a disease, later termed as stroke, referring to a sudden or chronic interrupted blood supply to specific areas of the brain. The treatment and prevention of stroke were extremely limited, as written in Galen's *Opera Omina*, published in Venice in 1556: "*It is impossible to cure a severe attack of apoplexy and difficult to cure a mild one*".

Progress in understanding stroke was made in the 17th century. Thomas Willis (1621–1675), an English physician who was born near and practiced in Oxford as a local physician, was known as one of the first pioneers in our present knowledge of the anatomy of the brain and associated brain diseases. Apart from his achievement as the first to describe cerebral circulation, and having the circle of Willis named after his identification, he also described the twelve brain nerves and coined the term *neurology.* Willis discussed many signs and symptoms of behavioral and functional neurological problems which are still known and identified today. In 1658, Johann Jakob Wepfer (1620–1695) (Figure 1), a physician in Schaffhausen, Switzerland, identified the main causes of stroke as ischemia and hemorrhage, based on post-mortem examinations of people who died of the condition.

In spite of the increasing knowledge regarding the pathophysiology of stroke, there remained no means of clinical verification of this condition, especially with respect to etiology. An instrument to assess the cerebral vasculature or to image brain ischemia and hemorrhage was lacking, and this deficit continued for centuries!



(**a**) (**b**)

Figure 1. (**a**) Johann Jakob Wepfer (1620–1695). (**b**) *Observationes anatomicae, ex cadaveribus eorum, quos sustulit apoplexia*. Source: private library of Michael Hennerici.

2. Computed Tomography

The invention and development of computed tomography (CT) is a fascinating story in the history of medicine. It includes one of the 20th century's most important music recording companies and a Nobel laureate in medicine and physiology who never attended medical school or earned a PhD. In the 1960s, Godfrey Hounsfield was employed as an electrical engineer by Electric and Music Industries (EMI), the company that would become better known for recording and selling the Beatles' albums. Hounsfield proposed to his company that he develop a machine that would be capable of imaging the human brain. Although EMI had no experience in manufacturing medical equipment, the company agreed to support Hounsfield's idea to realize a totally new approach to medical imaging with X-rays. The first CT scanner, designed specifically for the examination of the brain, was installed at the Atkinson Morley Hospital in Wimbledon, England. On 1 October 1971, the first CT scan of a human patient revealed a clinically suspected brain tumor. Indeed, Hounsfield's innovation transformed medicine. He shared the Nobel Prize for Physiology or Medicine in 1979 and was knighted by Queen Elizabeth II in 1981.

EMI distributed a number of machines to the United States, the first to the Mayo Clinic. By 1973, Ambrose had already reported on the usefulness of the EMI scanner for the depiction of brain infarction, hemorrhage and edema [1], thus paving the way for new developments in the field of clinical stroke research. Using an EM1 Mark I modified 160 x 160 matrix scanner, neurologists at Harvard reported the visualization

of large confluent petechial hemorrhages and/or hemorrhage within infarcts, noting that sequential CT changes in infarcts correlated well with established pathologic changes [2].

The first EMI scanner was quite slow (5 minutes per image acquisition) and had a low image resolution. It required the use of a water-filled tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. This feature was prohibitive for further developments, especially with respect to whole body scanning. The prototype Automatic Computerized Transverse Axial scanner (ACTA), designed by Robert Ledley at Georgetown University, was acquired by the Pfizer drug company, along with the rights to manufacture it. ACTA produced images in a 256×256 matrix, which only took about 20 seconds to acquire. This whole-body scanner was widely distributed over the next few years.

A major milestone in technological advances of CT was the spiral-CT, invented by Will Kalendar in Germany. The first CT scanner to implement this technique was the Siemens Somatom Plus. Within a short time, all other manufacturers had implemented this technology in their CT machines. Major benefits included a reduced scanning time, multi-slice capability, a reduction in movement artifacts, and isotrope voxels. In 2005, Siemens introduced a dual-source CT which offered a further significant reduction in scan time.

The long-awaited ability to image stroke had finally become a reality. In the following years, the enormous progress made in CT technology allowed physicians to quickly and reliably discern

(a) Whether signs and symptoms were related to ischemic or hemorrhagic stroke;
(b) Whether an ischemic stroke was arterial or embolic;
(c) Which regions of the brain were involved;
(d) Whether structures of the brain were already dead, at risk or not yet involved.

CT provided the first diagnostic platform for making clinical decisions on whether to treat stroke patients with thrombolytic drugs. While CT has a relatively low sensitivity for the detection of brain ischemia, it depicts irreversible tissue damage with high specificity. CT reliably detects brain hemorrhage, a contraindication for thrombolysis. In addition, the extent of CT hypoattenuation is an important positive predictor of thrombolysis-induced brain hemorrhage, the most feared complication of thrombolysis.

Research by the Belgian molecular biologist Desire Collen supported the idea of ischemic stroke treatment in his search for a way to dissolve blood clots. He developed a substance best known today as alteplase recombinant tissue plasminogen activator (rt-PA), which can dismantle the underlying framework of a clot/thrombus and break it down. Clinical trials with rt-PA were undertaken in the early 1980s for coronary and deep vein thrombolysis. Only possible through the CT imaging of suspected acute brain infarction, the first results from multicenter studies of intravenous rt-PA therapy in stroke were reported in 1990 [3]. Today, treatment with rt-PA is standardized not only within 4.5 hours after stroke onset, as initially

approved, but also for wake-up stroke with an unknown time of onset during sleep in MRI-guided stroke evaluation [4].

The addition of *CT perfusion imaging* and *CT angiography* allowed for a positive diagnosis of ischemic stroke versus mimics and for the identification of a large vessel occlusion target for endovascular thrombectomy. CT perfusion imaging can also provide imaging evidence of salvageable brain tissue, thus facilitating decision making in late recanalization strategies.

In 2010, Klaus Fassender's team at the University Hospital of the Saarland in Germany reported on the first mobile stroke unit using a *mobile CT scanner* from Philips [5]. This unit consisted of an ambulance equipped with the CT scanner, a point-of-care laboratory system for complete stroke laboratory work-up, and telemedicine capabilities for contact with hospital experts. The mobile stroke unit achieved the delivery of etiology-specific and guideline-adherent stroke treatment at the site of the emergency, well before arrival at the hospital. In a departure from current practice, stroke patients could be differentially treated according to their ischemic or hemorrhagic etiology even in the pre-hospital phase of stroke management. The immediate diagnosis of cerebral ischemia and the exclusion of thrombolysis contraindications enabled prehospital rt-PA thrombolysis.

3. Magnetic Resonance Imaging

In the 1990s, magnetic resonance imaging (MRI) emerged as a clinically useful diagnostic modality for stroke and other neurologic disorders [6,7]. In the detection of ischemic stroke lesions, MRI was more sensitive than CT, particularly for small infarcts and in sites such as the cerebellum and brainstem and deep white matter [8].Conventional MRI techniques such as *T1-weighted imaging* and *fluid-attenuated inversion recovery imaging* reliably detected ischemic parenchymal changes beyond the first 12 to 24 hours after onset. These methods were combined with *MR angiography* to noninvasively assess the intracranial and extracranial vasculature. However, MRI could not yet adequately assess the extent and severity of ischemic changes within the critical first 3 to 6 hours, the period of greatest therapeutic opportunity.

The revolutionary development of *diffusion-weighted imaging* (DWI) sequences allowed the imaging of cerebral ischemic events within the first 6 hours from onset [9], thus offering immense potential clinical utility in the early detection and investigation of patients with stroke. Further technical developments such as echoplanar imaging made the diffusion and perfusion of MRI feasible in routine clinical practice. A further milestone was the detection of hyperacute intraparenchymal hemorrhagic stroke using *susceptibility-weighted MRI*, which proved to be comparable to CT [10]. Thus, in combination with MR angiography, a multimodal MRI exam allowed for the detection of the site, age, extent, mechanism and tissue viability of acute stroke lesions in a single imaging study. This revolution in stroke imaging allowed therapeutic and clinical decisions to be based on the physiologic state of cerebral tissue. Moreover,

this new methodology proved capable as a patient selection tool for experimental and interventional therapies, and as a biomarker of therapeutic response in clinical trials.

4. Cerebrovascular Ultrasound

Ultrasound has played an important role in the evaluation of both early and advanced atherosclerotic disease, in the identification of stroke etiology and in the monitoring of stroke patients. From a historical perspective, its relative importance to other stroke imaging modalities, particularly those of CT and MRI, has somewhat declined. This is due predominantly to an emphasis upon new treatment strategies implementing acute endovascular thrombectomy, which is guided by the simultaneous use of brain and vascular imaging techniques. Although European centers continue to stress the need for transcranial Doppler and carotid duplex sonography in the accreditation of stroke units, current American stroke guidelines lack defining indications for these ultrasound techniques. Nevertheless, there remains an additional clinical contribution of neurovascular ultrasound in the post-acute care management of patients with acute ischemic stroke and in preventive and follow-up studies.

Continuous wave (CW) Doppler was the earliest ultrasound technique used to assess carotid stenosis, a common cause of stroke. The Doppler effect is named after Christian Doppler, who in 1842 described the change in frequency of light emitted by moving objects. This effect is familiar to anyone who has stood in one place and listened to a source of sound passing by. The sound rises in pitch as the source approaches the listener and then equally drops off as the source moves away after passing. In clinical applications, this effect is known as the Doppler frequency shift, which is the difference between emitted and received ultrasonography frequency and is proportional to the velocity of moving blood cells.

In 1956, Shigeo Satomura (1919–1960), a physicist at Osaka University, made one of the greatest contributions to the field of diagnostic ultrasound when he discovered that the Doppler principle could be applied to ultrasonic energy [11]. Satomura applied the Doppler effect to develop the 'Ultrasonic Blood Rheograph', which was then manufactured as the first commercial ultrasonic Doppler flowmeter by the Nippon Electric Company in 1959. In collaboration with the neurologist Ziro Kaneko (1915–1997), Satomura distinguished arterial flow into high- and low-resistance vasculatures, and then showed in 1962 that the Doppler signal actually arose from the backscattered energy from the moving blood cells [12].

The important discovery by Satomura led to the development of continuous wave (CW) Doppler systems, which use two transducers, one of which emits while the other receives ultrasound continuously. CW Doppler of the ophthalmic artery was one of the earliest methods used as an indirect test for the detection of significant carotid artery stenosis [13]. This periorbital technique provided information about the existence of collateral pathways. In the presence of severe stenosis or the occlusion of the internal carotid artery (ICA), retrograde blood supply from the external

carotid artery via the ophthalmic anastomosis was easily detected using CW Doppler. However, with sufficient collateralization from the contralateral carotid artery or the vertebrobasilar systems, the orthograde perfusion of the ophthalmic artery could occur. Thus, this indirect test could not detect hemodynamically significant ipsilateral carotid obstruction in up to 20% of patients.

CW Doppler ultrasound for the direct detection of ICA stenosis was reported in 1968 [14]. Although this method detected a broad range of changes in flow velocity associated with carotid stenosis, it provided only limited information on the actual origin of the ultrasound reflecting source. Later, *pulsed-wave (PW) Doppler* systems, in which ultrasound is both emitted from and received by a single piezoelectric crystal in the transducer, were able to provide a depth estimate of the site being insonated [12].

Duplex ultrasonography was a significant imaging milestone in the history of stroke imaging. It combined integrated PW Doppler spectrum analysis and *B-mode scanning*, which displays the morphologic features of normal and diseased vessels. The B-mode image served as a guide for the placement of the PW Doppler sample volume. The Doppler spectrum analysis provided criteria for evaluation of hemodynamics and for the categorization of ICA stenoses.

Although both CW and PW Doppler techniques were simple, inexpensive screening procedures for the detection of stenoses and occlusions in the extracranial arteries, they were largely replaced by *color Doppler flow imaging (CDFI)*, which preserved the advantages of duplex ultrasonography and superimposed color-coded blood flow patterns onto the gray-scale B-mode image. With the use of a defined color scale, the direction and the average mean velocity of moving blood cells within the sample volume at a given point in time were encoded, thus allowing the real-time visualization of hemodynamics. CDFI provided an excellent evaluation of extracranial arteries and was later adapted in transcranial applications. Special transducers were developed to assess the distal extracranial lesions of the ICA, such as carotid dissections, fibromuscular dysplasia, and atypically located atherosclerosis [12,15].

Pioneer studies by Hennerici et al. in 1981 provided ultrasound documentation of the incidence of asymptomatic carotid stenosis [16]. Further work resulted in the first report of the natural history of carotid stenosis [17]. Numerous studies reported on the use of ultrasound to identify symptomatic or vulnerable carotid artery plaques. Parameters for classification included echogenicity, surface structure, and ulcerations [12].

An important milestone in stroke prevention was the demonstration that the first morphological abnormalities of arterial walls can be visualized by B-mode ultrasonography. In 1986, Pignoli and coworkers characterized a “double-line” pattern of the normal carotid artery wall with B-mode ultrasonography [18]. They described the first echogenic line on the far wall to represent the lumen–intima interface and the second line to correspond to the media–adventitia interface.

Significantly, they demonstrated that the distance between these two echogenic lines correlated highly with measurements of intima-media thickness (IMT) in tissue specimens from common carotid arteries. Pignoli's initial report on the measurement of IMT with B-mode scanning was later validated in vitro [19] and was shown to enable good intra-observer and inter-observer reproducibility [12,20].

In the following years, technological advances in B-mode ultrasonography led to a high-resolution, noninvasive technique that offered an excellent method for the detection of early stages of atherosclerotic disease. This success was based upon its simple nature, wide availability, and capacity to depict arterial wall structures with better resolution than other imaging techniques (e.g., MRI or CT). Accordingly, many studies consequently used high-resolution ultrasonography to establish associations between common carotid IMT, cardiovascular risk factors, and the prevalence of cardiovascular disease. The importance of common carotid IMT is reflected by its use as a surrogate endpoint [12]. Important guidelines for the standardization of carotid IMT measurements and the classification of early atherosclerotic lesions were offered by the Mannheim carotid intima-media thickness and plaque consensus meetings from 2004 to 2011 [21].

In 1982, Aaslid et al. described noninvasive *transcranial Doppler (TCD)* for depicting flow velocities in the basal cerebral arteries [22]. TCD later evolved into applications for the detection of intracranial stenosis and occlusion (the sensitivity for the detection of MCA occlusion by TCD was about 80% with a high specificity [15]), the evaluation of intracranial collateral circulations, the detection of vasospasm in subarachnoid hemorrhage (SAH), the assessment of cerebral autoregulation, and for the surveillance of intracranial hemodynamics during stroke therapy.

TCD detection of *high intensity transient signals (HITS)* entering the cerebral circulation was first reported in 1986 [23]. This important discovery led to studies showing how this technique could be used to identify microembolic signals in patients who may be at increased risk for stroke. HITS corresponding to both gaseous and solid microembolic materials were reported during angiography, carotid angioplasty, open heart surgery, and carotid endarterectomy, as well as in patients with TIAs or stroke, asymptomatic carotid stenosis, heart valve prosthesis, and intracranial arterial disease [12].

Because *brain perfusion imaging* may detect ischemic lesions earlier than CT and may distinguish the stroke subtype and severity of cerebral ischemia, there was great interest in the use of perfusion imaging to predict recovery, differentiate stroke pathogenesis, and monitor therapy. Advanced contrast-specific ultrasound imaging technologies were developed for the assessment of brain perfusion in stroke patients [12,24].

Most studies of cerebral perfusion with ultrasound imaging applied a high mechanical index (MI) after the injection of microbubbles (MBs) as a contrast agent. The MI is a measure of acoustic output. Since MBs are destroyed in the cerebral microcirculation with high MI imaging, a triggered pulsing sequence was

implemented to allow for the replenishment of new MBs in the ultrasound scan plane. Accordingly, most early studies of cerebral perfusion were performed with triggered harmonic gray scale imaging techniques (conventional, power modulation or pulse-inversion) analyzing the bolus kinetics in healthy subjects to determine the best method for the detection of MBs in the cerebral microcirculation [12].

Sophisticated *low-MI real time perfusion* techniques were later introduced, which allowed the detection of MB in the cerebral microcirculation without destruction, as compared to the high MI-imaging. This allowed the application of a high frame rate, which led to a better time resolution of bolus kinetics. Low-MI ultrasound imaging was used to monitor MB replenishment in real time following the application of destruction pulses at high MI [25]. The behavior of the refill kinetics was assessed with an exponential curve fit, which provided parameters for the analysis of cerebral blood flow.

Since individual MBs could be depicted flowing through small vessels in the brain with low MI imaging, it was possible to track these bubbles and map perfusion over time. Dynamic microvascular MB maps provided a demarcation of MCA infarctions and impressive displays of low velocity tissue MB refill following destruction with high mechanical index imaging.

A highly interesting development in the history of ultrasound was the discovery that it might not only be effective for imaging, but also for stroke therapy. Indeed, in vitro experiments and animal studies indicated that ultrasound together with thrombolytic therapy, *sonothrombolysis*, improved the recanalization of occluded intracerebral vessels [26]. Moreover, it was later shown that ultrasound together with microbubbles alone could foster recanalization, thus opening the possibility for a new approach to clot lysis without thrombolytic drugs [12].

CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA) [27] was a multi-center randomized clinical trial of patients with acute ischemic stroke due to MCA occlusion. Target patients received, along with tPA, 2-MHz, pulsed wave transcranial Doppler monitoring for a duration of two hours. A complete reperfusion or dramatic clinical recovery was observed for 49% of the patients in the target group (tPA+US) and for only 30% of the control group. The TRUMBI trial (Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia) was stopped prematurely because of the occurrence of a higher number of intracerebral hemorrhages after tPA treatment combined with transcranial sonication at 300 kHz [28]. Unfortunately, later large-scale studies implementing ultrasound at clinical monitoring frequencies were unable to confirm a positive effect of sonothrombolysis.

Any history of stroke imaging would be incomplete without acknowledging how stroke conferences served to shape and nurture imaging modalities for clinical applications. This was not only true for the fertilization of concerted research activities, but also for developing standards for stroke imaging in diagnosis, follow-up and prevention. Meetings of the American Stroke Association and

the European Stroke Conference set the stage for regular scientific exchange among clinicians and researchers interested in the pathophysiology, diagnosis and treatment of cerebrovascular diseases throughout the world. These conferences were instrumental in promoting international dialogue, and served as platforms for the communication of various stroke organizations and, importantly, for the initiation of many international research activities. Key speakers were often well-known imaging experts, and stroke imaging sessions were highlights of these conferences, which led to the rapid communication of state-of-the-art imaging procedures [29].

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