History of Cardiac Embolism

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Abstract: From 1742, the first time Gerhard van Swieten postulated that embolism might arise inside the heart chambers and great vessels, another century was needed before that clinicians became accustomed to the concept that an embolism can lead to an occlusion of a brain artery. In fact, in 1875, Gowers described a case of blindness and contralateral hemiplegia in a patient with mitral stenosis. At autopsy, emboli were found in the middle cerebral artery and in the central retinal artery. Specifically, the emboli were found to originate from clots on the auricular appendices. Subsequently, in 1954, Fisher demonstrated that a thromboembolic mechanism underlies most ischemic strokes and that the source of thrombus might be the heart rather than a proximal arterial lesion. He suggested that the embolus might have arisen after myocardial infarction, in the fibrillating atrial appendage. In 1977, a necropsy study provided additional evidence supporting the role of atrial fibrillation as a crucial cause of cerebral embolism which was later confirmed by large epidemiological studies. Finally, in the first part of the 1990's, several studies reported that oral anticoagulants consistently reduced the risk of stroke in patients with atrial fibrillation. Oral anticoagulants currently remain the most powerful stroke prevention strategy available for patients with atrial fibrillation.

1. History of Embolism

Gerhard van Swieten (1742) was a precursor in postulating embolism arising inside the heart chambers and great vessels: "*It has been established by many observations that these polyps occasionally attach themselves as excrescences to the columnae carneae of the heart, and perhaps separate from it and are propelled, along with the blood, into the pulmonary artery or the aorta, and its branches . . . were they thrown into the carotid or vertebral arteries, could disturb—or if they completely blocked all approach of arterial blood to the brain—utterly abolish all functions of the brain*". [1]

Virchow (1847), a century later, observed embolism (a term newly introduced in the medical language by him) in patients with gangrene of the lower extremities as the cause of clots formed in the heart [2]. He proposed that the same phenomenon could be the cause of cerebral softening: "*In contrast to that kind of obliterating clot we find another kind. Here there is either no essential change in the vessel wall and its surroundings, or this is ostensibly secondary. I feel perfectly justified in claiming that these clots never originated in the local circulation but that they are torn off at a distance and carried along in the blood stream as far as they can go*". [3]

Sometime later, William Senhouse Kirkes published one of the first descriptions of infective endocarditis associated with cerebral embolism, thus providing its first extensive clinical and pathological illustration [4].

Within a short period of time, clinicians became accustomed to the concept of embolic occlusion.

Virchow's efforts in the vascular area were continued and crowned by his exceptional student Julius Cohnheim, whose theory of ischemic necrosis and hemorrhagic infarction was based on the experimental evidence of injecting wax emboli into test animal's tongue and observing the damage to the vascular endothelium. In the same years, Carl Rokitansky introduced a novel concept: the close mechanical association between hemorrhagic apoplexy and heart disease. In his four-volume manual published in 1856, he stated that many apoplexies were determined by congestion or dilatation of the right ventricle [3].

In 1875, W.R. Gowers presented a case of blindness and contralateral hemiplegia in a patient affected by mitral stenosis. Postmortem examination revealed the presence of emboli in the middle cerebral artery and in the central retinal artery; it was speculated that the clots arose from the auricular appendage associated with mitral stenosis [5]. In Osler's time (late 19th and early 20th centuries), it became well accepted that brain embolism had its source in diseases of the heart, with particular reference to bacterial endocarditis and rheumatic heart disease with mitral stenosis [6].

2. The Role of Atrial Fibrillation

Atrial fibrillation has been known for decades, but was established as a clinical entity in 1909 by Sir Thomas Lewis, who captured it on an ECG and studied the mechanism of conduction, noting that atrial fibrillation was "contiously and extremely irregular". He called it a "common clinical condition", establishing it as a clinical entity [7].

Around the midpoint of the 20th century, cardiologists started to suggest that atrial fibrillation was an important precursor of cerebral embolism in patients with rheumatic mitral stenosis [8]. Atrial stasis as a result of mitral stenosis, and often in the presence of AF, has long been recognized as a predisposing factor to thrombus formation; investigators begin to question if AF played a role in the occurrence of systemic embolism including stroke [6].

In 1949, Miller Fisher was among the first academics to imply a role for atrial fibrillation in causing brain embolism, even in the absence of endocarditis or rheumatic heart disease [6]: in his memoirs, Fisher stated "*I had the opportunity to examine the cerebral arteries before slicing 3 brains that had large hemorrhagic infarcts. The basal vessels were empty of thrombus. People were signing out these cases as cerebral artery thrombosis – but pathologically there was no thrombus. Afterwards, I looked up the records on these 3 cases and they had all been in atrial fibrillation and the general autopsy had shown infarcts in the spleen and kidneys. I speculated that they might be cases of embolism from the heart*." [9].

However, the current thinking among cardiologists did not change for more than twenty years: emboli infrequently arose from a fibrillating heart without rheumatic disease, and so AF, in absence of RHD, was considered a benign condition [6,10].

In spite of the common knowledge of that time, the evidence based on pathological, clinical and epidemiological studies kept on accumulating: in 1970, Coulshed et al. recognized the presence of atrial fibrillation as the critical factor that leads to systemic embolism in patients with mitral valve disease. Among the population affected by mitral stenosis, the incidence of systemic embolism (embolic stroke included) was three times higher in those with atrial fibrillation than in those with synus rhythm [11]. Szekely reported that systemic embolism occurred more than seven times as frequently in patients with mitral valve disease who had atrial fibrillation [12].

In 1977, a necropsy study provided additional evidence supporting the role of lone atrial fibrillation as an important cause of embolism. The study took into account 333 autopsy patients with atrial fibrillation associated with different kinds of heart disease: the results displayed a high incidence rate of embolism in patients with AF, irrespective of the presence or absence of mitral valve disease [10].

The very next year, data from the prospective epidemiological Framingham Heart Study became available: Wolf and colleagues compared the incidence of stroke in people with and without chronic atrial fibrillation. In total, 345 documented strokes had occurred after 24 years of follow-up: 27 in subjects with chronic AF, 7 with RHD, and 20 with non-rheumatic AF.

In persons with AF associated with rheumatic heart disease, there was a 17.6-fold increase in the incidence of stroke, and in those with AF in the absence of valvular disease, there was a 5.6-fold increase in stroke incidence, even when age and hypertensive status were taken into account [13].

After a follow-up of 34 years, 572 stroke events had occurred and the presence of atrial fibrillation was associated with a near five-fold increase in the 2-year age-adjusted incidence of stroke compared with its absence. Since cardiac conditions often coexist, even at a subclinical level, the increased risk of stroke associated with atrial fibrillation was also demonstrated in the presence of overt coronary heart disease (more than two-fold excess in men, near five-fold excess in women) and cardiac failure (two-fold excess).

While AF-related risk of stroke increased significantly with age, the attributable risk of stroke derived from other cardiovascular diseases was not affected by age [14].

Those epidemiological data were also supported by a comprehensive study in which 154 patients with anterior-circulation stroke and atrial fibrillation were evaluated for alternative determinants of stroke by carotid angiography or noninvasive carotid imaging; lacunar infarction was excluded by computed tomography. Atrial fibrillation emerged as the sole stroke mechanism in 76% of these cases [15].

3. Anticoagulation

McLean discovered the anticoagulant effect of heparin in 1915 while he was trying to extract a procoagulant from dog liver. It was successfully isolated in the early 1930s and was first administered to people in 1935. By the early 1940s, heparin was effectively used in patients and its efficacy in thromboembolic pathologies was confirmed by clinical trials.

In 1993, while studying a hemorrhagic disease affecting cattle, Link identified dicumarol from spoiled sweet clover hay as the agent responsible for sweet clover disease, a hemorrhagic disorder in cattle [16].

In late 1940 dicumarol was given to human volunteers, and in 1941, Dr. Wright became the first to use dicumarol therapeutically, immediately treating his thrombosis patients with success [17].

In 1994, a metanalysis of five RCTs by atrial fibrillation investigators showed that warfarin consistently reduced the risk of stroke by 68% in patients with atrial fibrillation, without virtually no increase in the frequency of major bleeding; people with lone atrial fibrillation had a low risk of stroke, which increased with advancing age [18].

These studies have established the role of anticoagulant therapy, which represents the single most powerful stroke prevention measure available. Taking into consideration the aging of the population and the improved survival of patients with heart diseases that predispose to atrial fibrillation (such as congestive heart failure and coronary heart disease), anticoagulation therapy continues to increase in importance in preventing cardioembolic stroke [19].

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References

1. van Swieten, G. *Of the Apoplexy, Palsy and Epilepsy. Commentaries on the Aphorisms of Dr Herman Boerhaave. Translation from Six Volumes (Lugduni Batavorum, J & H Verbeek, 1742–76)*; John & Paul Knapton: London, UK, 1754; Volume 10.
2. Paciaroni, M.; Bogousslavsky, J. Chapter 1 The history of stroke and cerebrovascular disease. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 2008; Volume 92, pp. 3–28.
3. Schiller, F. Concepts of stroke before and after Virchow. *Med. Hist.* **1970**, *14*, 115–131. [CrossRef] [PubMed]
4. Kirkes, W.S. Detachment of fibrinous deposits from the interior of the heart, and their mixture with the circulating blood. *Med. Chir. Trans. Lond.* **1852**, *35*, 281–324. [CrossRef] [PubMed]

5. Gowers, W.R. On a case of simultaneous embolism of central retinal and middle cerebral arteries. *Lancet* **1875**, *2*, 794–796. [CrossRef]
6. Caplan, L.R. Atrial Fibrillation, Past and Future: From a Stroke Non-Entity to an Over-Targeted Cause. *Cerebrovasc. Dis.* **2018**, *45*, 149–153. [CrossRef] [PubMed]
7. Fye, W.B. Tracing atrial fibrillation—100 years. *N. Engl. J. Med.* **2006**, *355*, 1412–1414. [CrossRef] [PubMed]
8. Harris, A.W.; Levine, S.A. Cerebral embolism in mitral stenosis. *Ann. Intern. Med.* **1941**, *15*, 637–643.
9. Fisher, C.M. *Memoirs of a Neurologist, vol 1*; Rutland Vermont, Sharp & Co. Printers: Rutland, VT, USA, 2006.
10. Hinton, R.C.; Kistler, J.P.; Fallon, J.T.; Friedlich, A.L.; Fisher, C.M. Influence of etiology of atrial fibrillation on incidence of systemic embolism. *Am. J. Cardiol.* **1977**, *40*, 509–513. [CrossRef] [PubMed]
11. Dalen, J.E. Atrial Fibrillation and Embolic Stroke. *Arch. Intern. Med.* **1991**, *151*, 1922–1924. [CrossRef] [PubMed]
12. Szekely, P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *BMJ* **1964**, *1*, 209. [CrossRef] [PubMed]
13. Wolf, P.A.; Dawber, T.R.; Thomas, H.E., Jr.; Kannel, W.B. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology* **1978**, *28*, 973–977. [CrossRef] [PubMed]
14. Wolf, P.A.; Abbott, R.D.; Kannel, W.B. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* **1991**, *22*, 983–988. [CrossRef] [PubMed]
15. Bogousslavsky, J.; Van Melle, G.; Regli, F.; Kappenberger, L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: The Lausanne Stroke Registry. *Neurology* **1990**, *40*, 1046–1050. [CrossRef] [PubMed]
16. Gómez-Outes, A.; Suárez-Gea, M.L.; Calvo-Rojas, G.; Lecumberri, R.; Rocha, E.; Pozo-Hernández, C.; Terleira-Fernández, A.I.; Vargas-Castrillón, E. Discovery of anticoagulant drugs: A historical perspective. *Curr. Drug. Discov. Technol.* **2012**, *9*, 83–104. [CrossRef] [PubMed]
17. Wright, I.S. Experiences with dicumarol in the treatment of coronary thrombosis. *Proc. Am. Fed. Clin. Res.* **1945**, *2*, 101. [PubMed]
18. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch. Intern. Med.* **1994**, *154*, 1449–1457.
19. Wolf, P.A. Awareness of the role of atrial fibrillation as a cause of ischemic stroke. *Stroke* **2014**, *45*, e19–e21. [CrossRef] [PubMed]