Neurogenic Disturbances of Cardiac Rhythm

Daniel Loh, Patrick Pullicino

Abstract

Arrhythmias are disturbances of electrical activation of the heart and are commonly encountered clinical conditions. Although typically associated with cardiac pathology, they have also been described in stroke and epilepsy. Two closely related structures, the insula and the temporal lobe, particularly the mesial region, have been implicated. Derangement of central autonomic control appears to be a key driver in neurogenic arrhythmogenesis and both these structures appear to play some role in influencing autonomic activity. Our understanding of this phenomenon is only in its infancy, and more research will be necessary to further it.

Keywords
Stoke, epilepsy, arrhythmias

Cardiac arrhythmias, stroke and epilepsy

Cardiac arrhythmias are disorders of electrical myocardial activation that manifest as abnormalities in the rate and rhythm of contraction. They fall loosely into two categories: tachyarrhythmias and bradyarrhythmias, and are conventionally thought to be phenomena related to cardiac lesions. Rhythm disturbances have, however, also been reported with certain cerebral insults: stroke and epilepsy.

A stroke is an acute episode of neurological deficit of presumed vascular origin persisting ≥ 24 hours. It may be ischaemic or haemorrhagic in nature and both aetiologies have been observed to be arrhythmogenic.

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and diagnosis requires the occurrence of at least one epileptic seizure.

Growing evidence suggests an independent association between these conditions and arrhythmias and this article will review existing research and opinion linking them.

Vascular Insults

Neurogenic involvement in arrhythmogenesis was first proposed in 1930, but until the 1970s little mention was made of this relationship with only isolated case reports implicating subarachnoid haemorrhage. Cardiac causes have been identified as the single largest precipitant of death after stroke. There is collective evidence that the presence of cardiac arrhythmias adversely affects stroke survival and together with the lack of post-mortem findings of cardiac ischaemia or thrombosis, strongly argues for a neurological component to arrhythmias.

Type & Incidence of Arrhythmias

The incidence of arrhythmias of any kind is higher in patients with stroke than without. Exact values vary between studies and type of stroke: Lavy et al. reported a 39% incidence of transient arrhythmias in stroke patients without previous cardiac disease. The sample included both haemorrhagic and ischaemic stroke, and when looking at haemorrhagic stroke alone, the incidence went up to 71%. Norris et al. studied 35 patients each in a stroke vs non-stroke group matched for age and sex that revealed a nearly 3x increased incidence of cardiac arrhythmias. Goldstein found a significantly greater frequency of new QT prolongation (32% vs 2%) and arrhythmias of any type (25% vs 3%) in strokes collectively compared to controls. Atrial fibrillation (AF) was the most common arrhythmia (9% vs 0%), followed closely by ventricular arrhythmias (8% vs 2%). QT prolongation was significantly more frequent in subarachnoid haemorrhage (71%) compared to other stroke types (39%) while new AF was more common in cerebral embolus (50%) than non-embolic
stroke (0%).

The range of conduction disturbances observed runs the gamut from sinus bradycardia or nodal escape to ventricular tachycardia. Studies focus mainly on ventricular arrhythmias as they pose a greater risk. Mikolich et al. observed significantly more cases of ventricular ectopy (50%) in the stroke group compared to controls (15%). More worryingly, catastrophic arrhythmias occurred in 20% of the stroke group, resulting directly in death in at least one patient, while none occurred in the controls. 93% of the strokes were ischaemic. Using 24-hour Holter monitoring, Pasquale et al. found arrhythmias in 90% of their cohort of subarachnoid haemorrhage (SAH) patients. Ventricular arrhythmias were observed in 82%, and 4 patients developed torsades de pointes. More recent studies reveal a lower overall incidence: Bruder et al. reports a 35% incidence after SAH, with 5-8% potentially fatal while Kallmanzner et al. detected arrhythmias in 25.1% of a cohort of 501, of which 92% were ischaemic strokes. Ventricular arrhythmias accounted for 27% and incidence of any arrhythmia was highest in the first 24 hours after admission.

Localisation & Lateralisation of cortex

Attempts were made early on to delineate a relationship between the stroke location and frequency of arrhythmias. Lavy et al. estimated that arrhythmias occurred in 100% of brain stem strokes and only 80.5% of hemispheric strokes. Norris et al. found the reverse to be true, with arrhythmias occurring in 52% of hemispheric strokes compared to 38% of brain stem ones. Among hemispheric strokes, arrhythmias were more prevalent in ischaemic strokes (53% vs 42%) while the reverse was true for brain stem strokes (35% vs 67%). Mikolich et al. observed a predominance of arrhythmias in patients with anterior circulation strokes although the small number of posterior circulation strokes included in the study detracts from its value. In SAH, no correlation was noted between site and extent of haemorrhage and either the frequency or severity of arrhythmias.

More recently, the insular cortex (which lies beneath the operculum formed from frontal, parietal and temporal lobes) has been implicated in arrhythmogenesis. Stimulation of the insula in humans produced autonomic cardiovascular effects with apparent lateralisation: parasympathetic effects were more frequently produced on left sided stimulation while right insular stimulation showed the reverse. It would be remiss, however, to assume complete lateralisation of autonomic control exists, and the conflict within the literature attests to this: one study involving seven patients with lesions confined mainly to the left insular cortex found a shift toward increased basal sympathetic tone and a corresponding increase in heart rate. Conversely, Lane et al. reported an association between right hemispheric stroke and the incidence of supraventricular tachycardia. Daniele et al. did not observe any hemispheric association with type of arrhythmia, although the data showed arrhythmias occurred more frequently in right compared to left hemisphere strokes. Colivicchi et al. found that ventricular and supraventricular tachycardia was 3.0x and 2.6x respectively more common in right insular stroke compared to left insular stroke. This discrepancy can be explained in part by the existence of inter-hemispheric connections between some insular tracts and by the fact that insular lesions are usually part of a larger infarct, confounding the results. More research is necessary before definite conclusions are drawn.

Pathophysiology of arrhythmogenesis in Stroke

Based on established knowledge of the cardiovascular effect of sympathetic and parasympathetic limbs, initial speculation was that a stroke leads to an autonomic imbalance that favours sympathetic activation, resulting in catecholamine excess which alters the electrical properties of cardiomyocytes, giving rise to arrhythmias.7-8 Recent evidence continues in the same vein: Strittmatter et al. found that plasma noradrenaline and adrenaline levels were significantly elevated in right hemisphere strokes compared to controls at point of admission and throughout the 5 days of monitoring. Regression analysis by Colivicchi et al. revealed that the standard deviation of all normal-to-normal R-R intervals was a significant predictor of the presence of arrhythmias, with lower values (reflecting diminished vagal tone) strongly associated with its presence. Greater age and more neurological deficit from the stroke, leading to more autonomic instability and increased sympathetic tone, were also independently associated with arrhythmias. This theory is now widely accepted, and the term catecholamine storm used to describe it.

Hyperactivation of β-adrenergic receptors is another effect of catecholamine excess, which in turn leads to tonically open calcium channels such that sequestration of intracellular calcium ions necessary for muscle relaxation fails to occur. This ultimately leads to cell death and a characteristic lesion termed coagulative myocytolysis which has the histological features of myofibrillar degeneration and contraction band necrosis. This lesion is predominantly subendocardial and could therefore involve the cardiac conduction system, serving as a substrate for arrhythmogenesis.

Epilepsy

Ictal arrhythmias were first noticed in 1906, with an episode of cardiac asystole at onset of seizure. They have particular relevance with respect to their role in
sudden unexpected death in epilepsy (SUDEP), which has an incidence of 0.099 per 1000 patient-years and accounts for 8-17% of deaths in people with epilepsy. Understanding and controlling these arrhythmias are therefore vitally important.

**Type & Incidence of Arrhythmias**

Variations in heart rate are the most common ictal change reported and tachycardia is the most commonly seen. Zijlmans et al. recorded an increase of more than 10 beats/minute in 93% of patients and more than 20 beats/minute in 80% of patients. Children and adolescents respond similarly; Mayer et al. saw it in 100% of their cohort who were younger than 18 years while 80.6% of seizures observed fulfilled age-adjusted criteria for absolute tachycardia. Onset of tachycardia is usually in the early ictal phase, and can even precede EEG onset. Bradyarrhythmias are significantly less common, Leutmezer et al. documented them in 1.4% of seizures while Rugg-Gunn et al. found them in 0.24% of reported seizures and 2.1% of seizures recorded on an implantable loop recorder. Men are more commonly affected and episodes typically occur in the late ictal phase. The potential for evolution into asystole exists, and this was observed by Schuele et al. in 0.27% of 6825 patients. These periods typically last for 5-10 seconds. Although rare, these events can be serious enough to warrant permanent pacemaker insertion; 21% in the study by Rugg-Gunn et al.

As with stroke, a wide range of arrhythmias have been observed. Nei et al. observed arrhythmias in 39% of patients, the most common of which were atrial premature depolarisations (47%) and sinus arrhythmia (35%). Of the patients with arrhythmias, 20% had potentially serious ones. The authors also noted that longer seizure duration and generalised tonic-clonic seizures rather than complex partial seizures were independent predictors of arrhythmia occurrence. Children are also not spared; Standridge et al. found ictal arrhythmias in 40% of patients, which were potentially serious in 12%. Significant associations with gender were also noted: arrhythmias were more common in boys, and of the potentially serious ones, all those with an abnormal QRS complex and 73% with irregular variable rhythm occurred in boys. Peri-ictal and post-ictal rate changes were more common in girls.

**Location & Lateralisation of Cortex**

It was noticed early on that the degree of ictal tachycardia depended largely on the volume of cerebral structures involved in the seizure, with heart rate (HR) increase directly proportional to the regions recruited. This is corroborated by work from Opherk et al. who found that sinus tachycardia was more common in generalised than non-generalised seizures (100% vs 73%). Absolute values both ictally (mean 186 vs 162) and postictally (mean 159 vs 117) were also greater. In the non-generalised seizures, neither hemisphere nor region of onset influenced the ictal HR. The authors did note that left hemispheric seizures more commonly caused benign arrhythmias and noticed a non-significant trend suggesting that mesial temporal sclerosis was linked to serious arrhythmias. Rugg-Gunn et al. also found no evidence for seizure lateralisation in tachycardia, although by contrast, three of the four patients with episodes of prolonged asystole had left hemispheric seizures.

The temporal lobes are well known to be involved in arrhythmogenesis, with the mesial temporal lobe particularly implicated. Leutmezer et al. reported that the absolute increase in ictal HR was significantly greater in patients with mesial temporal lobe seizures (TLS) compared to nonlesional and extratemporal TLS. Lateralisation of onset was also apparent; absolute and relative increases in HR were significantly greater in right compared to left hemisphere onset. Standridge et al. noted that the right hemispheric localisation was significant only in TLSs with ictal sinus tachycardia while Mayer et al. found that early and high HR increases were principally associated with right mesial TLSs. HR changes were more frequently found in mesial TLSs compared to lateral/neocortical TLSs (56 vs 13). Within the mesial TLSs, HR changes were more prominent in right than left (36 vs 20). Furthermore, HR changes at the extremes of the spectrum were nearly exclusively associated with right mesial TLSs. Ictal bradyarrhythmias are also associated with TLSs but do not appear to demonstrate any lateralisation. Britton et al. found that 52% of ictal bradyarrhythmias were bitemporal in onset, accounting for nine of the 13 patients studied. The presence of contralateral insular activation via transcallosal connections was not ruled out however, and this may be an avenue worth exploring.

**Pathophysiology of arrhythmogenesis in epilepsy**

There is evidence to suggest that the mechanisms involved in the stroke pathway also play a part in epilepsy. Myocytolysis has been demonstrated in SUDEP patients, indicating direct catecholamine activity on the heart. Basal autonomic control also appears to be deranged, and this dysfunction increases the more severe the epilepsy is. Decreased heart rate variability, reflecting a loss of vagal tone, has also been reported in epileptics and is associated with an increased risk of lethal arrhythmias.

A separate mechanism by which arrhythmias may be generated is called the lock-step phenomenon in which cortical epileptiform discharges directly influence postganglionic activity at the heart such that synchrony between seizure and cardiac autonomic activity exists, inducing lethal bradyarrhythmias or asystole.
Sudden Unexpected Death in Epilepsy

Besides fatal arrhythmias, SUDEP is also commonly attributed to two other pulmonary conditions: central apnoea and neurogenic pulmonary oedema. Although mechanistically dissimilar, there appear to be several risk factors that operate irrespective of aetiology. Nearly all witnessed cases of SUDEP occur in the context of a generalised tonic-clonic seizure. Seizure frequency was found to be the strongest risk factor, while early onset of epilepsy and a longer duration of the condition are also independent risk factors. The risk of SUDEP appears correlated to severity of epilepsy; it is higher in those with refractory epilepsy (reflected by anti-epileptic drug polytherapy) as well as patients with epilepsy who are not receiving treatment and highest in patients deemed suitable for epilepsy surgery or those who continue to suffer even after surgery. Genetic channelopathies have become the focus of late, and mutations in KCNQ1, SCN1A and RYR2 among others have been identified in several studies.

Concluding Remarks

It is certain that stroke and epilepsy can give rise to arrhythmias. Intuitively, it might appear that these conditions are two sides of the same coin: one causes hypofunction, the other hyperfunction, both of which lead to autonomic imbalance. Unfortunately, the truth is rarely so simple and this is not completely borne out by experimental evidence; the complex interconnections between different regions and hemispheres of the brain almost certainly part of the reason. Further work examining these regions, particularly in the limbic system, with which the insula and mesial temporal lobe approximately, broadening awareness of clinicians to the arrhythmogenic potential of stroke and epilepsy is the earliest, and arguably a key, step in improving patient outcomes: appropriate cardiac monitoring in the context of telemetry monitoring or in HASUs could be potentially life saving while also providing incontrovertible data for future research.

References