Seizures Induces Hypoxia and Hypoxia Induces Seizures. A Perverse Relationship that Increases the Risk of SUDEP

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LETTER

"He uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable" [1].

Hypoxia is a biological stimulus capable of promoting both rescue and survival mechanisms, as well as triggering a sequence of irreversible events that lead to death of cell, tissue and even individual. Brain and heart functions depend critically on adequate energy supply and they are highly susceptible to hypoxic conditions. Adequate oxygen supply is needed for the brain and heart to metabolize glucose as its major energy source. But how many type of hypoxia we know, and how much severe is the hypoxic condition, when more than one type of hypoxia are simultaneously acting? Four types of hypoxia are distinguished in medicine: a- the hypoxemic hypoxia, due to a decrease in the amount of breathable oxygen or cardiopulmonary failure, b- the anemic hypoxia related with decreased amount of functional hemoglobin, c- the stagnant hypoxia, secondary to reduced or unevenly distributed flow of blood distribution to the tissues, and mainly result from heart disease that impairs the circulation; and d- the histotoxic hypoxia, in which the tissue cells are poisoned and are therefore unable to make proper use of oxygen [2].

A highly sensitive and complex mechanism capable of identifying the hypoxic condition was developed by eukaryotic cells, which give rapid responses to rescue or to cell death induction. These ambivalent responses to hypoxia (acute or chronic) is mediated by the transcription factor "Hypoxia Inducible Factor 1-α" (HIF-1α), described originally by Greg L. Semenza, who won the Nobel Prize 2019 for this discovery. HIF-1α plays a master role in the stimulation and/or repression of a large list of genes, which will modify the functionality of the cells that undergo said modifications induced by HIF-1α under hypoxic conditions. Thus, after any hypoxic event, the nuclear translocation of HIF-1α is an unequivocal marker off hypoxic suffering by the affected cell, and it should be related to the increase and loss of expression of the genes up-regulated and down-regulated by HIF-1α respectively [3]. Between these large gene list, erythropoietin and erythropoietin receptor genes, are also up-regulated by HIF-1α [4]. The P-glycoprotein (P-gp) encoded by MDR-1/ABCB-1 gene, is responsible for the multidrug-resistant phenotype and it is also induced by HIF-1α [5].

Normal cerebral oxygenation may be modified during or immediately after a seizure, and inversely brain hypoxia can further increase seizure

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susceptibility. Because O_2 acts as the final electron acceptor in the mitochondrial electron transport chain to generate ATP in eukaryotic cells, during O_2 deprivation (hypoxia), a closely relationship with tissue inflammation will be developed. In this context, it is important to highlight that cerebral hypoxia, either global hypoxia, as well as focal hypoxia due to cerebrovascular accident or stroke may to have heterogeneous characteristics with multiple etiologies, and taken together, brain hypoxia represents the second disease with the greatest cause of sequelae of disability or death in the world [6].

Brain hypoxia triggers molecular processes leading to neuronal damage, where ATP production can falls more than 50%, and neurons lose the ability to maintain the membrane potential and suffering progressive depolarization [7]. This complex mechanism that is involved in the onset of seizures was also observed in experimental apneas [8]. Stroke (ischemic or hemorrhagic) as well as cardiac arrest related brain injury, are two major causative factors for seizure development, however, the underlying pathophysiology of seizure development is not well understood [9].

One important alert is that seizures arising within two weeks of the initial stroke or cardiac event are generally categorized as "early-onset". Early-onset seizures are primarily observed within 24 hours of the initial insult and are considered a medical emergency as life-threatening status epilepticus may development. Similar observations have been reported cases with seizures arising after stroke events. In spite two different types of hypoxia are involved by heart arrest (stagnant hypoxia) and stroke (histotoxic hypoxia) respectively, both conditions can lead to the same consequence: "seizures or status epilepticus" development. Interestingly, the fine mechanisms underlying leading to convulsive episodes are not clearly understood.

Experimentally in aging mice, it was also demonstrated that brain Hypoxia-Ischemia (HI) can induce early-onset seizures, closely associated with severe brain injury and acute mortality; however prophylactic anticonvulsive treatment can inhibit seizures development and improve survival in post-HI aging mice [10].

After cardiopulmonary arrest, seizures are a common problem in the intensive care unit, occurring in as many as one-third of these patients during their hospitalization. Furthermore, whether seizures exacerbate global hypoxic-ischemic brain injury in human's remains unclear, which raises uncertainty about how aggressively they should be treated. Some pathological data suggest that anoxic brain injury is worsened by Generalized Tonic-Clonic (GTC) Status Epilepticus (SE). On very important features of these particular situations (hypoxia plus seizures, or seizures during hypoxia), is that Status Myoclonus (SM) in hypoxic-ischemic coma is particularly troublesome, because it can be highly refractory to conventional anticonvulsants and appears to portend an extremely poor prognosis, regardless of its management [11].

Patients with epilepsy often experience acute repetitive seizures or seizure clusters, with negative impact on quality of life, emotional wellbeing, daily function, and productivity of the patients and their caregivers. These seizure cluster, are characterized by more than 2 seizures occurring in periods between 6 to 24 hours [12]. After the pioneer and potential first description sudden death during epileptic crisis by Russell above mentioned, Sudden Unexpected Death in Epilepsy (SUDEP) should be assumed as a very likely *"final chapter of a convulsive-life"* for a group of patients with RE, whom haven not control of seizures under therapy with several recommended Antiepileptic Drugs (AEDs). Some risk factors for SUDEP have been identified, such as repetitive Generalized Tonic–Clonic Seizures (GTCS), male sex, poor compliance with AEDs prescription, youth, early age at seizure onset, or being in bed at the time of death [13]. In these patients, a multidrug-resistant phenotype is usually developed, and brain P-gp over expression is one of more common finding [14].

SUDEP determination excludes sudden cardiac death, as by definition, it does not include known causes of mortality as cardiac co-morbidities [15]. Additionally to the SUDEP definition, the concept of "Epileptic Heart" has been recently reported as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated hypoxemia with increased catecholamines leading to electrical and mechanical heart dysfunction" [16]. This concept was supported by clinical evidences showing a higher percentage of heart disease in patients with chronic epilepsies, as compared with patients without epilepsy story [17]. Interestingly, in these patients with chronic epilepsies, the also chronic therapy with several AEDs should be assumed as not-successful treatment. In this regards,

perhaps the most severe stress related with epilepsy could lead to Takotsubo Syndrome (TKS) development, and its potential relationship with SUDEP was suggested [18]. In two experimental studies of chronic and acute heart hypoxia-ischemia, a significant loss of ^{99m}Tc-2-Methoxyisobutylisonitrile (^{99m}Tc-SESTAMIBI) heart retention in the affected ischemic heart regions with a concomitant high expression of P-gp have been demonstrated to be associated heart stunning [19,20].

In this regards, TKS was included into this spectrum of stress-related cardiomyopathies, where heart stunning was documented [21], and heart hypoxic-ischemia was postulated [22]. Both acute as chronic epileptic seizures can to provoke cardiac ischemia and develop several effects on the heart as impaired heart rate variability, ST-segment depression, cardiac fibrosis, increased heart rate, or severe bradycardia. Transient ischemia in heart can be observed after each seizure but if seizures are frequents, this transient condition could turn to a condition of chronic heart ischemia [23,24].

The intermittent hypoxia is broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia. The actual protocols used experimentally vary greatly in cycle length, the number of hypoxic episodes per day, and the number of exposure days [25]. Chronic Intermittent Hypoxia (CIH) is the most distinct feature of Obstructive Sleep Apnea (OSA), a common breathing and sleep disorder that leads to several neuropathological consequences, including alterations in the hippocampal network and high seizure susceptibility. In this regards, 21 days of CIH increases gamma-band hippocampal network activity and aggravates 4-aminopyridine-induced epileptiform activity adult rats, and these CIH-induced alterations remit after 30 days of normal oxygenation [26]. In an experimental model of Intermittent Hypoxia (IH) during sleep, it was demonstrated the brain up-regulation of both Hypoxia Inducible Factor 1 Alpha (HIF-1α) and the P-glycoprotein (P-gp) [27], which was also detected in the heart of these rats (data not shown).

After injection in brain rats of the chemical a hypoxiating compound as $CoCl_2$, nuclear translocation of HIF-1α was detected concomitantly with P-gp expression in neurons and vascular endothelial cells, and also co-expressed with erytrhopoietin receptor, a classic HIF-1α responsive gene [28-30]. Similar results were also observed after repetitive PTZ-

induced seizures, and a relationship with SUDEP was suggested [31]. In this regards, experimental repeated pilocarpine-induced Status Epilepticus (SE), resulted in the HIF-1α nuclear translocation and high P-gp expression in cardiomyocytes, associated to Electrocardiographic (ECG) changes such as QT interval prolongation, bradycardia and a high rate of spontaneous death [32]. Furthermore, in a preliminary experimental study developed under these same above mentioned conditions in rats, an important reduction of ^{99m}Tc-SESTAMIBI heart retention 72 h after pilocarpine-induced SE with a high P-gp expression in cardiomyocytes and associated with high sudden death ratio were observed [33].

Although the mechanism that triggers sudden death is unknown, evidences suggest that SUDEP could be due to heart failure as consequence of a high hypoxic-stress with excessive sympathetic overstimulation triggering a neuro-cardiogenic injury, and affecting the electrical properties of myocardium that lead to heart failure with fatal arrhythmia (bradycardia). All these evidences suggest that the highly accumulated burden of convulsive stress results in a hypoxic heart insult, where P-gp expression play a depolarizing role in cardiomyocytes membranes.

In addition, other molecular regulators of membrane potential in both neurons and cardiomyocytes are the inwardly rectifying potassium channels (Kir), whose genetic variants have been related to both epilepsy and heart dysfunctions. In heart, they control cell excitability by acting towards the repolarization phase of cardiac action potential [34]. Based on this property, it would be logical to assume that dysfunction or absence of Kir channel as a deleterious mechanism which gives more durability to the cardiomyocytes membranes depolarization, induced by hypoxia and favored by the over-expression of P-gp as mentioned above. Effectively, after PTZ-induced repetitive seizures in rats, molecular analyses showed a significant decrease in mRNA and protein expression of cardiac Kir channel [35], associated with a over-expression of HIF-1α in these cardiomyocytes (data not show).

Since erythropoietin receptor (EPO-R) gene is also a hypoxia-inducible gene, it has been suggested that exogenous administration of erythropoietin could have an antiapoptotic and rescue effect not only at the brain level but also at the cardiac level [36,37]. It is important to highlight that P-gp is

normally absent in neurons and cardiomyocytes, and the hypoxic-induced P-gp expressions in these cells, are not only related to its pharmacoresistant property. Pioneer studies have demonstrated that P-gp can modify the resting membrane potential, producing depolarization with values from -70 to -10mV in the expressing cells [37,38]. These specific observations are in total concordance with the mechanistic property of ^{99m}Tc-SESTAMIBI, that bind to mitochondrial membrane but it is released out off the cell by P-gp under membrane depolarization as above mentioned [39]. This depolarization has been also observed yippocampus and neocortex after repetitive seizures induced by PTZ in rats where P-gp was highly expressed [40].

All these data suggest that seizures, induces a hypoxic condition not only at brain, but also in heart, with an increased expression of P-gp and the simultaneously loss of Kir expression in cardiomyocytes. These up and down regulations, play a central combined role to develop a sustained depolarization of cardiomyocytes, leading to a potential fatal heart failure, after a new seizure. This situation can be clearly detected by Single-Photon Emission Computed Tomography (SPECT) images of myocardial perfusion, using ^{99m}Tc-SESTAMIBI, a tracer of P-gp functional expression in cardiomyocytes [41]. Reduced ^{99m}Tc-SESTAMIBI heart retention, is a hallmark of heart depolarization and ischemia, and it can be a noninvasive high risk predictor of SUDEP in patients with RE.

REFERENCES

1. Russell AE. (1906). Cessation of the pulse during the onset of epileptic fits, with remarks on the mechanism of fits. Lancet. 168: 152-154.

2. Pierson D. (2000). Pathophysiology and Clinical Effects of Chronic Hypoxia. Respir Care. 45:39-51.

3. Wang GL, Semenza GL. (1993). General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. Proc Natl Acad Sci U S A. 90: 4304-4308.

4. Wang G L, Semenza GL. (1996). Molecular basis of hypoxia-induced erythropoietin expression Curr Opin Hematol. 3:156-62.

5. Comerford KM, Wallace TJ, Karhausen J, Louis NA, Montalto MC, et al. (2002). Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. Cancer Res. 62: 3387-3394.

6. World Health Organization (2004). Deaths from stroke and global burden of stroke. In: Mackay J, Mensah GA, Eds. The Atlas of Heart Disease and Stroke. Geneva: World Health Organization. 48-51.

7. Richter F, Bauer R, Lehmenkühler A, Schaible H-G. (2010). The relationship between sudden severe hypoxia and ischemia-associated spreading depolarization in adult rat brainstem in vivo Exp Neurol. 224: 146-154.

8. Jansen NA, Schenke M, Voskuyl RA, Thijs RD, van den Maagdenberg MJM, et al. (2019). Apnea associated with brainstem seizures in Cacna1aS218L mice is caused by medullary spreading depolarization. J Neurosci. 39: 9633-9644.

9. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. (2012). The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation. 83: 840-847.

10. Wang J, Wu C, Peng J, Patel N, Huang Y, et al. (2015). Early-Onset Convulsive Seizures Induced by Brain Hypoxia-Ischemia in Aging Mice: Effects of Anticonvulsive Treatments. PLoSOne. 10: e0144113.

11. Koenig MA, Geocadin R. (2005). Global Hypoxia-Ischemia and Critical Care Seizures. In: Varelas P.N. (Eds) Seizures in Critical Care. Current Clinical Neurology. Humana Press

12. Jafarpoura S, Hirschb LJ, Gaínza-Leina M, Kellinghausd C, Detyniecki K. (2019). Seizure cluster: Definition, prevalence, consequences, and management. Seizure. 68: 9-15.

13. Devinsky O. (2011). Sudden unexpected death in epilepsy. N Engl J Med. 365: 1801-1811.

14. Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, et al (2007). ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. Epilepsia. 48: 140-149.

15. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. (2001). Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology. 56: 519-525.

04

16. Verrier RL, Pang TD, Nearing BD, Schachter SC. (2020). The Epileptic Heart: Concept and clinical evidence. Epilepsy & Behavior. 105: 106946.

17. Zack M, Luncheon C. (2018). Adults with an epilepsy history, notably those 45-64 years old or at the lowest income levels, more often report heart disease than adults without an epilepsy history. Epilepsy Behav. 86: 208-210.

18. Dupuis M, van Rijckevorsel K, Evrard F, Dubuisson N, Dupuis F, et al. (2012). Takotsubo syndrome (TKS): A possible mechanism of sudden unexplained death in epilepsy (SUDEP). Seizure. 21: 51-54.

19. Lazarowski AJ, García Rivello HJ, Vera Janavel GL, Cuniberti LA, Cabeza Meckert PM, et al. (2005). Cardiomyocytes of chronically ischemic pig hearts express the MDR-1 gene-encoded P-glycoprotein. J. Histochem. Cytochem., 53: 845-850.

20. Laguens RP, Lazarowski AJ, Cuniberti LA, Vera Janavel GL, Cabeza Meckert PM, et al. (2007). Expression of the MDR-1 gene-encoded Pglycoprotein in cardiomyocytes of conscious sheep undergoing acute myocardial ischemia followed by reperfusion. J. Histochem. Cytochem. 55: 191-197.

21. Ancona F, Bertoldi LF, Ruggieri F, Cerri M, Magnoni M, et al. (2016). Takotsubo cardiomyopathy and neurogenic stunned myocardium: similar albeit different. Eur Heart J. 37: 2830-2832.

22. Ghadri JR, Bataisou RD, Diekmann J, Lüscher TF, Templin C. (2015). First case of atypical takotsubo cardiomyopathy in a bilateral lungtransplanted patient due to acute respiratory failure. Eur Heart J Acute Cardiovasc Care. 4: 482-485.

23. Tigaran S, Molgaard H, McClelland R, Dam M, Jaffe AS. (2003). Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Neurology. 60: 492-495.

24. Nei M, Sperling MR, Mintzer S, Ho RT. (2012). Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia. 53: e137-140.

25. Neubauer JA. (2001). Physiological and Genomic Consequences of Intermittent Hypoxia Invited Review: Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol. 90: 1593-1599.

26. Villasana-Salazar B, Hernández-Soto R, Guerrero-Gómez ME, Ordaz B, Manrique-Maldonado G, et al. (2020). Chronic intermittent hypoxia transiently increases hippocampal network activity in the gamma frequency band and 4-Aminopyridine-induced hyperexcitability in vitro. Epilepsy Res.166: 106375.

27. Aviles-Reyes RX, Angelo MF, Villarreal A, Rios H, Lazarowski A, et al. (2010). Intermittent hypoxia during sleep induces reactive gliosis and limited neuronal death in rats: implications for sleep apnea. J Neurochem. 112: 854-869.

28. Lazarowski A, Caltana L, Merelli A, Rubio MD, Ramos AJ, et al. (2007). Neuronal mdr-1 gene expression after experimental focal hypoxia: a new obstacle for neuroprotection?. J Neurol Sci. 258: 84-92.

29. Caltana L, Merelli A, Lazarowski A, Brusco A. (2009). Neuronal and glial alterations due to focal cortical hypoxia induced by direct cobalt chloride (CoCl$_2$) brain injection. Neurotox Res. 15: 348-358.

30. Merelli A, Caltana L, Girimonti P, Ramos AJ, Lazarowski A, et al. (2011). Recovery of motor spontaneous activity after intranasal delivery of human recombinant erythropoietin in a focal brain hypoxia model induced by CoCl2 in rats. Neurotox Res. 20: 182-192.

31. Auzmendi J, Merelli A, Girardi E, Orozco-Suarez S, Rocha L, et al. (2014). Progressive heart P-glycoprotein (P-gp) overexpression after experimental repetitive seizures (ERS) associated with fatal status epilepticus (FSE). Is it related with SUDEP? Molecular & Cellular Epilepsy. 1: e66.

32. Auzmendi J, Buchholz B, Salguero J, Cañellas C, Kelly J, et al. (2018). Pilocarpine-Induced Status Epilepticus Is Associated with P-Glycoprotein Induction in Cardiomyocytes, Electrocardiographic Changes, and Sudden Death. Pharmaceuticals. 11: 21.

33. Auzmendi J, Salgueiro J, Canellas C, Zubillaga M, Men P, et al (2017). Pilocarpine-induced Status Epilepticus (SE) induces functional and histological P-glycoprotein overexpression in cardiomyocytes, heart dysfunction and high ratio of sudden death in rats. In Proceeding of the

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SCIENTIFIC LITERATURE

Annual Meeting of American Epilepsy Society, Washington, DC, USA, 1-5 December 2017.

34. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. (2014). Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nat Rev Neurol. 10: 271-282.

35. Akyüz E, Mega Tiber P, Beker M, Akbaş F. (2018). Expression of cardiac inwardly rectifying potassium channels in pentylenetetrazole kindling model of epilepsy in rats. Cell Mol Biol (Noisy-le-Grand). 64: 47-54.

36. Auzmendi J, Puchulu MB, Rodríguez JCG, Balaszczuk AM, Lazarowski A, et al. (2020). EPO and EPO-Receptor System as Potential Actionable Mechanism for the Protection of Brain and Heart in Refractory Epilepsy and SUDEP. Curr Pharm Des. 26: 1356-1364.

37. Merelli A, Ramos AJ, Lazarowski A, Auzmendi J. (2019) Convulsive Stress Mimics Brain Hypoxia and Promotes the P-Glycoprotein (P-gp) and Erythropoietin Receptor Overexpression. Recombinant Human Erythropoietin Effect on P-gp Activity. Front Neurosci. 13: 750.

38. Wadkins RM, Roepe PD. (1997). Biophysical aspects of P-glycoproteinmediated multidrug resistance. Int Rev Cytol. 171: 121-165.

39. Piwnica-Worms D, Kronauge JF, Chiu ML. (1990). Uptake and retention of hexakis (2-methoxyisobutyl isonitrile) technetium (I) in cultured chick myocardial cells: mitochondrial and plasma membrane potential dependence. Circulation. 82: 1826-1838.

40. Auzmendi JA, Orozco-Suárez S, Bañuelos-Cabrera I, González-Trujanod ME, González EC, et al. (2013). P-Glycoprotein Contributes to Cell Membrane Depolarization of Hippocampus and Neocortex in a Model of Repetitive Seizures Induced by Pentylenetetrazole in Rats Current Pharmaceutical Design. 19: 6732-6738.

41. Auzmendi J, Akyuz E, Lazarowski A. (2019). The role of P-glycoprotein (P-gp) and inwardly rectifying potassium (Kir) channels in sudden unexpected death in epilepsy (SUDEP). Epilepsy Behav. 106590.

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