Advances in Clinical Medicine 临床医学进展, 2022, 12(7), 6097-6105
Published Online July 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.127879

Hans汉斯

基于心率变异性对不同癫痫患者自主神经功能差异的研究进展

陈　娜[1]，李　沛[2*]

[1]青海大学医学研究生院，青海　西宁
[2]青海省人民医院神经内科，青海　西宁

收稿日期：2022年6月4日；录用日期：2022年6月28日；发布日期：2022年7月5日

摘　要

癫痫是一种由于大脑神经元异常放电引起的发作性疾病，除了脑电图之外，研究者们试图通过使用心率变异性参数来预测癫痫发作。在癫痫发作期间，中枢神经系统受影响可导致交感神经和副交感神经出现冲突或抑制改变。由于性别差异、昼夜节律差异、发作类型不同、发作部位不同，癫痫患者的心率变异性及自主神经功能障碍可能不同，本文就其在上述不同方面的比较及其对癫痫发作的预测价值等方面进行综述。

关键词

心率变异性，自主神经功能障碍，癫痫猝死，心因性非癫痫性发作，癫痫预测

Recent Advance of Differences Autonomic Nerve Function in Different Epilepsy Patients Based on Heart Rate Variability

Na Chen[1], Pei Li[2*]

[1]Graduate School of Medicine, Qinghai University, Xining Qinghai
[2]Department of Internal Neurology, Qinghai Provincial People's Hospital, Xining Qinghai

Received: Jun. 4th, 2022; accepted: Jun. 28th, 2022; published: Jul. 5th, 2022

Abstract

Epilepsy is a paroxysmal disease caused by abnormal discharge of brain neurons. In addition to

*通讯作者。

文章引用: 陈娜, 李沛. 基于心率变异性对不同癫痫患者自主神经功能差异的研究进展[J]. 临床医学进展, 2022, 12(7): 6097-6105. DOI: 10.12677/acm.2022.127879

EEG, researchers try to predict seizures by using heart rate variability parameters. During an epileptic seizure, the central nervous system may be affected to cause a conflict or inhibition between the sympathetic and parasympathetic nerves. Because of sex difference, circadian rhythm difference, seizure type and seizure site, the heart rate variability and autonomic nervous dysfunction of epilepsy patients may be different. In this paper, the comparison of the above aspects and its predictive value for epileptic seizures are reviewed.

Keywords

Heart Rate Variability, Dysfunction of Autonomic Nerve, Sudden Unexpected Death in Epilepsy, Psychogenic Nonepileptic Seizure, Prediction of Epilepsy

1. 引言

癫痫是大脑不同部位神经元异常放电导致的发作性疾病，大多数患者会出现自主神经功能(utonomic nervous function, ANS)障碍，90%以上会出现发作性心动过速，心动过缓较少见[1] [2]。Leal 等[3]发现超过 53%患者在发作前 40 min 左右出现心率变异性(HRV)参数变化。Myers 等人将发作时自主神经(ANS)功能障碍与癫痫猝死(SUDEP)联系起来[4] [5]：一方面 HRV 值明显降低，增加了 SUDEP 的风险；另一方面当心动过缓持续 10~30 s 时可能发生心脏停搏，最终导致 SUDEP [2]。虽然通过监测 HRV 数据不能完全准确预测癫痫发作，但可以及时发现心血管系统的相关变化。本文就不同癫痫相关的 HRV、ANS 障碍方面的差异进行综述，以期更深入地了解其病理生理基础。

2. 癫痫患者 HRV 的性别差异

生理状况下男性的心脏比女性要大 25%，心率低于女性[6]。Jafarnia 等人[6]研究发现无论什么类型的癫痫，男性均比女性表现出更高的低频/高频(LF/HF)、低频(LH)、心率(HR)，代表其交感神经活动更活跃，但女性患者发作前更容易出现心衰($P < 0.01$)。由此推测，采取刺激迷走神经的方法治疗癫痫有助于降低和预防男性心律失常和 SUDEP；而女性低频(LH)降低代表交感神经活动减弱，一定程度上可减少心脏病和心律失常的发生。综上，目前文献中关于癫痫患者心率变异性(HRV)的性别差异仍存在争议，一方面可能与实验变量和研究条件不同有关；另一方面癫痫的发作情况、病情控制程度、与其他疾病叠加等都会对 HRV 产生影响。女性患者在发作前期出现更高的心衰风险的病理生理机制目前仍不明确，对于临床医生而言仍然是一个挑战。

3. 癫痫患者 HRV 昼夜节律之间的差异

尽管在 Faria 等[7]的研究没有发现癫痫患者 HRV 昼夜节律的显著差异 LF ($P = 0.010$)，但人们普遍认为其存在着双向关系，可能会影响患者的生活质量[8] [9] [10]。在动物实验中曾报道，癫痫小鼠在受到压力影响时其 HRV 的昼夜节律出现显著差异[11]；其中，Möller 等人[12]发现与黑暗条件下相比，在光亮阶段癫痫小鼠的心率表现出较高水平，光亮对 HRV 的影响更大，昼夜节律改变会对癫痫的 HRV 产生影响；他们还在诱发实验中发现：每日一次的癫痫发作对 HR、HRV 的昼夜节律产生相关影响，而且发作次数越频繁其 HRV 的昼夜节律差异越明显[12]；这一研究证实了二者存在相互作用。综上，

正常人 HRV 的昼夜节律本身存在差异，夜间主要是迷走神经活动占优势，当癫痫发作时会出现 HRV 改变及 ANS 功能紊乱，可使患者突然从主要的迷走神经优势转变为交感神经活动优势，从而引发致命的心律失常。在这种情况下，动态心电监测能及时了解 HRV，最终可能成为预测 SUDEP 的临床生物标志物。

4. 癫痫患者不同发作类型的 HRV 差异

Myers 等人[4]提及全身性惊厥发作(GCS)可能会引发极端的交感神经刺激及 ANS 恶化，最终导致癫痫猝死。不同的研究一致认为全身性肌阵挛性发作(GTCS)是 SUDEP 的危险因素之一[13] [14]。Faria 等人[15]对于局灶性双侧强直阵挛发作(FBTCS)与非 FBTCS 的研究显示：癫痫发作后期 FBTCS 组的 AVNN、RMSSD、pNN20、LF 和 HF 显著降低，LF/HF 和心率显著升高；而且从发作前到发作后 FBTCS 组别中 ANS 变化更大更明显[16] [17]。尽管，不同类型癫痫引起的心功能变化幅度和 SUDEP 风险仍不确定[18]，但是确实存在与此相关的 ANS 功能障碍及 HRV 改变。综上，由于剧烈癫痫发作而过度激活交感神经系统可能会导致心肺功能障碍[19]，短期 HRV 分析有助于监测 ANS 及窦性心律失常(RSA)等。临床医生可以据此推测出心血管功能障碍的类型，甚至可以预测由于长期癫痫发作导致的 ANS 功能紊乱、SUDEP，在这些损伤出现之前及早采取措施进行干预、规避风险。

5. 大脑不同区域癫痫发作的 HRV 差异

5.1. 大脑不同功能区域癫痫发作的 HRV

中枢自主神经网络(CAN)控制着从大脑传送到心脏的传出信息，与癫痫相关的心脏病的发生密切相关，可加重脑缺氧和脑损伤。尽管 Jeppesen 等人[12]就大脑的不同部位癫痫发作没有发现 HRV 灵敏度的显著差异，但是大多数研究显示致痫区的位置不同时 HRV 也存在很大不同[13] [14] [20]。Chiew [21]等人最近研究的一项涉及癫痫合并重度抑郁症患者的 HRV 数据证实：HRV 降低与前额叶皮质结构的抑制性功能障碍有关[22]。Lacuey [23]等人对行颞叶和/或岛叶切除的癫痫手术患者进行研究，并将患者分为 4 型：0 型(岛叶未受累)、1 型(岛叶边缘受累轻微)、2 型(岛叶受累<25%)和 3 型(岛叶受累≥25%)。结果显示：与 0 型和 1 型岛叶癫痫相比，2 型和 3 型岛叶癫痫患者的 RMSSD (P = 0.025)和 CV (P = 0.008)显着降低；行右侧岛叶切除术的癫痫患者 LF (P = 0.010)和 LF/H (P = 0.017)显著增加，或者是岛叶明显损伤者 HRV 下降也更明显，意味着副交感神经张力下降或功能受损。猜测，右侧或左侧岛叶癫痫患者可出现发作期心动过缓和心脏停搏，也可能出现发作后心律失常。因此，癫痫猝死可能与岛叶致痫区或岛状结构受损导致的致命心律失常有关[24]。Sung-Min Yo [25]分析了 58 名(46 名颞叶癫痫(TLE)和 12 名额叶癫痫(FLE))癫痫患者 309 次癫痫发作期间的心电图(ECG)数据，发现 TLE 和 FLE 患者在发作前、发作期和发作后的时间间隔内具有不同的 HRV 曲线。TLE 患者发作前交感神经或迷走神经活动升高，发作后其升高仍持续一段时间，而 FLE 患者在进入和离开发作期时交感神经张力明显增加和减少。与此相关，Möller 和 van Dijk 等人[2]对 TLE 患者的研究表明 TLE 与脑干结构损伤相关，脑干主要参与控制自主神经系统活动，当 TLE 发作扩散到脑干，或者是脑干损伤引起颞叶神经元放电时，就会发生自主神经活动障碍；尤其是在慢性 TLE 患者中表现出较低的 HRV [26]，且在 TLE 发作前期副交感神经活动减少或增加，发作期副交感神经明显受抑制[27]。

综上，当 MRI 检测到的岛叶、颞叶、额叶等不同大脑部位损伤时，患者可能具有 SUDEP 风险。从癫痫发病灶到 ANS 的连接区域存在潜在的电信号扩散，且具有高度的发作特异性，当癫痫发作时很可能引起某部分大脑皮质结构激活涉，从而影响到 ANS 调节系统；或者是调节反射反应的大脑外周机制被驱动，最终引起心功能改变。

5.2. 大脑偏侧化区域癫痫患者的 HRV

大脑左(优势)半球主要控制副交感神经输出，而右(非优势)半球主要控制交感神经输出，前脑岛回和扣带回在这种控制中起着关键作用[21]。尽管，Romigi [28]报告说 TLE 患者发作后 SDNN、RMSSD、LF、HF 和 LF/HF 没有受大脑偏侧化的影响，且 Behbahani 报道[6]在不区分致痫灶大脑偏侧化的情况下，癫痫发作前 5 分钟时心率都增加($P < 0.01$)，但发现在单纯性右侧癫痫患者(男女)中心率、LF、LF/HF、SD2/SD1 增加与 HF 降低更为明显($P < 0.01$)。Shimmura 等人研究[29]提示与左侧癫痫相比，右侧癫痫患者发作后副交感神经活动更高，发作相关的 HRV 基线波动更明显($P < 0.01$) [6]，恰好证明了发作后 ANS 不稳定可能与右半球受累有关。另一方面，Hödl 等[30]发现使用迷走神经刺激术(VNS)治疗癫痫时，无反应的患者 HRV 显著降低($P = 0.005$)，其中左侧癫痫发作组的无反应者占 10/11，右侧癫痫发作组的无反应者占 4/11 [31]；对 VNS 治疗有反应的癫痫发作主要在左侧，包括左丘脑皮层、边缘，以及更大的功能连接网络：左丘脑、岛叶和颞叶[32]；这一发现证明 ANS 控制的心血管活动存在癫痫发作偏侧性差异，HRV 参数的改变与癫痫的部位(颞叶/颞外，左/右或双侧)相关，副交感神经控制的心脏活动在左侧岛叶更占优势。综上所述，HRV 参数尽管能发现致痫区在大脑偏侧化的 ANS 调节的差异性，但关于其具体机制仍不明确。许多癫痫发作早期就传播到对侧半球，目前仍难确定临界值来区分右侧和左侧癫痫发作。由于 SUDEP 与涉及双侧半球的癫痫发作有关[6]，且大多数患者长期服用抗癫痫药、病程较长，癫痫反复发作影响疾病的严重程度，或加强右侧和左侧癫痫发作之间的 HRV 差异，应在未来对此进行探索，以阐明半球偏侧化对 SUDEP 的具体影响。

6. EP、EP/PNES、PNES 患者之间的 HRV

6.1. EP 与 PNES 患者的 HRV 差异

对于一些癫痫患者来说，生活压力(如：身体虐待、性虐待和心理虐待、严重的经济问题或人际关系问题)可能会诱发 PNES；与具有相似人口统计学特征的 EP 患者相比(如：发病年龄、神经精神共病率、死亡年龄、aed 依从性)相比，PNES 可能会增加 SUDEP 风险[31]。Beniczky 等[33]通过 EP 和 PNES 研究的对比发现：EP 和 PNES 患者在发作期间均出现交感神经活动增强，但癫痫发作期间的最大 CSI 值、最大交感神经活动值均高于 PNES ($P = 0.015$)；而 PNES 恢复期时迷走神经张力明显高于癫痫[34]，猜测 PNES 与控制 ANS 活动的大脑皮质及皮层下区域功能失衡有关。与此相同，Jeppesen 等人[32]发现与 PNES 相比，癫痫发作前和发作期交感神经活动更活跃[28] [35]，尤其是在 TLE 中[36]。综上，HRV 分析或许能够区分 PNES 和癫痫的自主神经活动差异，帮助医生提高诊断率，减少对 PNES 的误诊，避免不必要的治疗措施，减轻患者的生活压力及家庭负担。

6.2. EP/PNES 于 PNES 患者之间的 HRV

癫痫合并心因性非癫痫性发作(PNES/ES)的患者约占癫痫的 22% [37]，更容易出现焦虑抑郁障碍和其他精神疾病[38]，HRV 及 ANS 功能障碍更明显，SUDEP 风险也随之增加。Romigi 等人[32]将 PNES 和 PNES/ES 对比研究发现：PNES/ES 发作期间 LF 和 LF/HF、CSI 比值显著增高，交感神经张力显著增加；而在发作后的恢复期 CSI、ApEn 较低，表示迷走神经张力较高($P = 0.01$)。同样，Vandel Krujis [34]描述了在 PNES 发作之后迷走神经张力增加，且发现交感神经和迷走神经的调节张力更敏感[39] [40] [41]。综上，EP/PNES 患者自主神经过度驱动可能受癫痫、PNES 的双重影响：一方面，发作期间出现交感神经过度驱动，另一方面发作后期迷走神经过度活跃。交感神经过度活跃时患者出现心动过速、快速性心律失常；迷走神经过度驱动可导致心动过缓、脑组织或其它器官缺血缺氧，甚至昏迷、心脏停搏。将 HRV 应用于 PNES/癫痫患者中，可以更好的监测心血管系统的态变化，有助于医生及时启动应急方案，减少与发作相关的不良事件。

7. 基于 HRV 对癫痫发作的预测

7.1. 成人基于 HRV 对癫痫的预测

在过去的几十年中，许多研究人员使用 ECG 和 HRV 信号来检测癫痫发作，并且阐述了发作相关的 HRV 特征。ShamiShamim 等人[42]提出了一种使用 ECG 信号检测癫痫发作的新技术：基于线性阈值使用 SVM 器进行分类，结果显示预测癫痫发作的准确率为 94.2%，敏感性为 84.1%，特异性为 4.5%。Moridani 等[43]通过将 HRV 信号分成持续时间 5 分钟为一个片段的方法，检测到的敏感性为 88.32%，特异性为 86.2%。Behbahani 等[44]人提出了一种自适应决策阈值方法，根据发作前期 HRV 的动态变化特征来进行预测，敏感度为 78.59%，每小时阳性率为 0.21。Vandecasteele 等人[45]应用 ECG 和光电容积描记法(PPG)来比较预测作的可行性：其中使用 ECG 装置和 PPG 装置的灵敏度分别为 70%和 32%，相应的每小时误差为(FP/h)为 2.11 和 1.80。Behbahani 等人[46]分析了 170 例发作时间持续为 5 分钟的癫痫患者 HRV 参数，其中 86 例左侧 EP 和 84 例右侧 EP。结果显示：通过 HRV 预测右侧和左侧 EP 的准确率分别为 86.74%和 79.41%。尽管上述很多采用 HVR 来预测癫痫发作的方法都取得了一定成果，但是除了要求预测结果的有效性，还必须考虑心理、疾病、运动、药物等相关因素的影；而且大脑是癫痫发作的起源，心脏是受其影响的第二个器官，HRV 并不对大脑进行预测。因此，当使用 HRV 进行预测时，都是建立在曾经做过 EEG，且明确诊断为癫痫的基础上。

7.2. 新生儿基于 HRV 对癫痫的预测

正如国际抗癫痫联盟(ILAE)文件[47]所述：大多数新生儿 EP 约(85%)与缺氧缺血性脑病(HIE)、中风、感染、代谢和遗传学相关[48]，是引起神经损伤或急性疾病最相关的因素之一[49]。Bersani 和 Statello 研究表明[50] [51]一些新生儿 EP 可直接或间接影响心脏功能，使用 HRV 分析可以提高诊断的准确性，而且除了 EEG 外，利用 Hoter 检测新生儿 EP 优于对其它生物标志物的检测[52]。Stevenson 等人[53]通过对 33 名 EP 患儿和 19 名非 EP 患儿的 HRV 对比分析，同样验证了使用熵指数对新生儿 EP 预测有统计学意义[54] [55]。HRV 的多尺度熵分析不仅能显示 ANS 的不同动态，而且有助于发现或检测患儿的病理状况[56]。所以，用于成人的 HRV 多尺度熵分析方法也同样适用于婴儿和儿童[57] [58]，但是将其应用于 HRV 动力学可能存在一些局限性，比如：HRV 熵指数偏向于预测某些特殊疾病引起的 EP，例如缺氧缺血性脑病或窒息发作[59]，而且在上述研究中并未排除影响脏活动的干扰事件，如婴儿猝死综合征(SIDS) [60]。总之，虽然 ECG 易于使用、侵入性更小、成本更低，且使用 ECG 和 HRV 多尺度熵分析有助于快速识别新生儿 EP 发作，但是还需要进一步阐明新生儿神经血管改变的病理生理机制。

8. 小结与展望

EP 发作的各个时期经常影响大脑网络系统和 ANS 功能，导致 HRV 及其它众多标志物发生改变。本文通过检索相关文献，基于 HRV 关于 EP 患者的 ANS 功能进行了详细阐述。尽管，运用 HRV 评估和预测 EP 具有良好的生物标志物潜能，但是目前仍然面临许多挑战，最常见是区分导致 HR 变化的条件，例如：兴奋、锻炼、行走、药物、毒物、疾病等对 HRV 的影响。在该领域中获得的结果仍然不能与 EEG 的检测结果相比，而且大部分研究都是为了支持其可以预测 EP 发作的假设，需要进一步的研究来提高预测灵敏度。

参考文献

[1] Hammer, D., Scheuer, M. and Fong-Isariyawongse, J. (2021) Pearls & Oysters: Cyclic Seizures and Heart Rate Variability. *Neurology*, **96**, e1694-e1696. https://doi.org/10.1212/WNL.0000000000011317

[2] Möller, C., van Dijk, R.M., Wolf, F., Keck, M., Schönhoff, K., Bierling, V. and Potschka, H. (2019) Impact of Repeated Kindled Seizures on Heart Rate Rhythms, Heart Rate Variability, and Locomotor Activity in Rats. *Epilepsy & Behavior*, **92**, 36-44. https://doi.org/10.1016/j.yebeh.2018.11.034

[3] Leal, A., Pinto, M.F., Lopes, F., Bianchi, A.M., Henriques, J., Ruano, M.G., de Carvalho, P., Dourado, A. and Teixeira, C.A. (2021) Heart Rate Variability Analysis for the Identification of the Preictal Interval in Patients with Drug-Resistant Epilepsy. *Scientific Reports*, **11**, Article No. 5987. https://doi.org/10.1038/s41598-021-85350-y

[4] Myers, K.A., Bello-Espinosa, L.E., Symonds, J.D., Zuberi, S.M., Clegg, R., Sadleir, L.G., Buchhalter, J. and Scheffer, I.E. (2018) Heart Rate Variability in Epilepsy: A Potential Biomarker of Sudden Unexpected Death in Epilepsy Risk. *Epilepsia*, **59**, 1372-1380. https://doi.org/10.1111/epi.14438

[5] Myers, K.A., Sivathamboo, S. and Perucca, P. (2018) Heart Rate Variability Measurement in Epilepsy: How Can We Move from Research to Clinical Practice? *Epilepsia*, **592**, 2169-2178. https://doi.org/10.1111/epi.14587

[6] Behbahani, S., Jafarnia Dabanloo, N., Motie Nasrabadi, A. and Dourado, A. (2018) Gender-Related Differences in Heart Rate Variability of Epileptic Patients. *American Journal of Men's Health*, **12**, 117-125. https://doi.org/10.1177/1557988316638733

[7] Faria, M.T., Rodrigues, S., Campelo, M., Dias, D., Rego, R., Rocha, H., Sa, F., Tavares-Silva, M., Pinto, R., Pestana, G., Oliveira, A., Pereira, J., Cunha, J.P.S., Rocha-Gonçalves, F., Gonçalves, H. and Martins, E. (2021) Heart Rate Variability in Patients with Refractory Epilepsy: The Influence of Generalized Convulsive Seizures. *Epilepsy Research*, **178**, Article ID: 106796. https://doi.org/10.1016/j.eplepsyres.2021.106796

[8] Gurkas, E., Serdaroglu, A., Hirfanoglu, T., Kartal, A., Yilmaz, U. and Bilir, E. (2016) Sleep-Wake Distribution and Circadian Patterns of Epileptic Seizures in Children. *European Journal of Paediatric Neurology*, **20**, 549-554. https://doi.org/10.1016/j.ejpn.2016.04.004

[9] Ju, Y.S., Videnovic, A. and Vaughn, B.V. (2017) Come or Bid Sleep Disturbances in Neurologic Disorders. *Continuum* (*Min near Minn*), **23**, 1117-1131. https://doi.org/10.1212/CON.0000000000000501

[10] Quigg, M., Gharai, S., Ruland, J., Schroeder, C., Hodges, M., Ingersoll, K.S., *et al*. (2016) Insomnia in Epilepsy Is Associated with Continuing Seizures and Worse Quality of Life. *Epilepsy Research*, **122**, 91-96. https://doi.org/10.1016/j.eplepsyres.2016.02.014

[11] Thompson, R.S., Roller, R., Greenwood, B.N. and Fleshner, M. (2016) Wheel Running Improves REM Sleep and Attenuates Stress-Induced Flattening of Diurnal Rhythm in F344 Rats. *Stress*, **19**, 312-324. https://doi.org/10.1080/10253890.2016.1174852

[12] Jeppesen, J., Fuglsang-Frederiksen, A., Johansen, P., Christensen, J., Wustenhagen, S., Tankisi, H., Qerama, E., Hess, A. and Beniczky, S. (2019). Seizure Detection Based on Heart Rate Variability Using a Wearable Electrocardiography Device. *Epilepsia*, **60**, 2105-2113. https://doi.org/10.1111/epi.16343

[13] Hampel, K.G., Elger, C.E. and Surges, R. (2017) Impaired Baroreflex Sensitivity after Bilateral Convulsive Seizures in Patients with Focal Epilepsy. *Frontiers in Neurology*, **8**, Article No. 210. https://doi.org/10.3389/fneur.2017.00210

[14] Arbune, A.A., Jeppesen, J., Conradsen, I., Ryvlin, P. and Beniczky, S. (2020) Peri-Ictal Heart Rate Variability Parameters as Surrogate Markers of Seizure Severity. *Epilepsia*, **61**, S55-S60. https://doi.org/10.1111/epi.16491

[15] Faria, M.T., Rodrigues, S., Campelo, M., Dias, D., Rego, R., Rocha, H., Sa, F., Tavares-Silva, M., Pinto, R., Pestana, G., Oliveira, A., Pereira, J., Cunha, J.P.S., Rocha-Gonçalves, F., Gonçalves, H. and Martins, E. (2022) Does the Type of Seizure Influence Heart Rate Variability Changes? *Epilepsy & Behavior*, **126**, Article ID: 108453. https://doi.org/10.1016/j.yebeh.2021.108453

[16] Ryvlin, P., Rheims, S. and Lhatoo, S.D. (2019) Risks and Predictive Biomarkers of Sudden Unexpected Death in Epilepsy Patient. *Current Opinion in Neurology*, **32**, 205-212. https://doi.org/10.1097/WCO.0000000000000668

[17] Sveinsson, O. andersson, T., Mattsson, P., Carlsson, S. and Tomson, T. (2020) Clinical Risk Factors in SUDEP: A Nation Wide Population-Based Case-Control Study. *Neurology*, **94**, e419-e429. https://doi.org/10.1212/WNL.0000000000008741

[18] Myers, K.A., Bello-Espinosa, L.E., Symonds, J.D., Zuberi, S.M., Clegg, R., Sadleir, L.G., *et al*. (2018) Heart Rate Variability in Epilepsy: A Potential Biomarker of Sudden Unexpected Death in Epilepsy Risk. *Epilepsia*, **59**, 1372-1380. https://doi.org/10.1111/epi.14438

[19] Suna, N., Suna, I., Gutmane, E., Kande, L., Karelis, G., Viksna, L. and Folkmanis, V. (2021) Electrocardiographic Abnormalities and Mortality in Epilepsy Patients. *Medicina*, **57**, 504. https://doi.org/10.3390/medicina57050504

[20] Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E., *et al*. (2017) Operational Classification of Seizure Types by the International League against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, **58**, 522-530. https://doi.org/10.1111/epi.13670

[21] Chiew, C.J., Liu, N., Tagami, T., Wong, T.H., Koh, Z.X. and Ong, M.E.H. (2019) Heart Rate Variability Based Ma-

chine Learning Models for Risk Prediction of Suspected Sepsis Patients in the Emergency Department. *Medicine* (*Baltimore*), **98**, e14197. https://doi.org/10.1097/MD.0000000000014197

[22] Zhou, H., Dai, Z., Hua, L., Jiang, H., Tian, S., Han, Y., *et al*. (2019) Decreased Task-Related HRV Is Associated with Inhibitory Dysfunction through Functional Inter-Region Connectivity of PFC in Major Depressive Disorder. *Frontiers in Psychiatry*, **10**, Article No. 989. https://doi.org/10.3389/fpsyt.2019.00989

[23] Lacuey, N., Garg, V., Bangert, B., Hampson, J.P., Miller, J. and Lhatoo, S. (2019) Insular Resection May Lead to Autonomic Function Changes. *Epilepsy & Behavior*, **97**, 260-264. https://doi.org/10.1016/j.yebeh.2019.04.035

[24] Lacuey, N., Zonjy, B., Theerannaew, W., Loparo, K.A., Tatsuoka, C., Sahadevan, J., *et al*. (2016) Left Insular Damage, Autonomic Instability, and Sudden Unexpected Death in Epilepsy. *Epilepsy & Behavior*, **55**, 170-173. https://doi.org/10.1016/j.yebeh.2015.12.009

[25] You, S.M., Jo, H.J., Cho, B.H., Song, J.Y., Kim, D.Y., Hwang, Y.H., Shon, Y.M., Seo, D.W. and Kim, I.Y. (2021) Comparing Ictal Cardiac Autonomic Changes in Patients with Frontal Lobe Epilepsy and Temporal Lobe Epilepsy by Ultra-Short-Term Heart Rate Variability Analysis. *Medicina* (*Kaunas*), **57**, 666. https://doi.org/10.3390/medicina57070666

[26] Englot, D.J., Gonzalez, H.F.J., Reynolds, B.B., Konrad, P.E., Jacobs, M.L., Gore, J.C., *et al*. (2018) Relating Structural and Functional Brainstem Connectivity to Disease Measures in Epilepsy. *Neurology*, **91**, e67-e77. https://doi.org/10.1212/WNL.0000000000005733

[27] Pernice, R., Faes, L., Kotiuchyi, I., Stivala, S., Busacca, A., Popov, A., *et al*. (2019) Time, Frequency and in Formation Domain Analysis of Short-Term Heart Rate Variability before and after Focal and Generalized Seizures in Epileptic Children. *Physiological Measurement*, **40**, Article ID: 074003. https://doi.org/10.1088/1361-6579/ab16a3

[28] Romigi, A., Albanese, M., Placidi, F., Izzi, F., Mercuri, N.B., Marchi, A., *et al*. (2016) Heart Rate Variability in Untreated Newly Diagnosed Temporal Lobe Epilepsy: Evidence for Ictal Sympathetic Dysregulation. *Epilepsia*, **57**, 418-426. https://doi.org/10.1111/epi.13309

[29] Shimmura, M., Uehara, T., Ogata, K., Shigeto, H., Maeda, T., Sakata, A., Yamasaki, R. and Kira, J.I. (2020) Higher Postictal Parasympathetic Activity Following Greater Ictal Heart Rate Increase in Right- than Left-Sided Seizures. *Epilepsy & Behavior*, **97**, 161-168. Erratum in: *Epilepsy & Behavior*, 103(Pt A): 106865. https://doi.org/10.1016/j.yebeh.2019.106865

[30] Hödl, S., Olbert, E., Mahringer, C., Struhal, W., Carrette, E., Meurs, A., Gadeyne, S., Dauwe, I., Goossens, L., Raedt, R., Boon, P. and Vonck, K. (2021) Pre-ictal Heart Rate Variability Alterations in Focal Onset Seizures and Response to Vagus Nerve Stimulation. *Seizure*, **86**, 175-180. https://doi.org/10.1016/j.seizure.2021.02.017

[31] Mithani, K., Mikhail, M., Morgan, B.R., Wong, S., Weil, A.G., Deschenes, S., *et al*. (2019) Connectomic Profiling Identifies Responders to Vagus Nerve Stimulation. *Annals of Neurology*, **86**, 743-753.

[32] Romigi, A., Ricciardo Rizzo, G., Izzi, F., Guerrisi, M., Caccamo, M., Testa, F., Centonze, D., Mercuri, N.B. and Toschi, N. (2020) Heart Rate Variability Parameters during Psychogenic Non-Epileptic Seizures: Comparison between Patients with Pure PNES and Comorbid Epilepsy. *Frontiers in Neurology*, **11**, Article No. 713. https://doi.org/10.3389/fneur.2020.00713

[33] Jeppesen, J., Beniczky, S., Johansen, P., Sidenius, P. and Fuglsang-Frederiksen, A. (2016) Comparing Maximum Autonomic Activity of Psychogenic Non-Epileptic Seizures and Epileptic Seizures Using Heart Rate Variability. *Seizure*, **37**, 13-19. https://doi.org/10.1016/j.seizure.2016.02.005

[34] Van der Kruijs, S.J.M., Vonck, K.E.J., Langereis, G.R., Feijs, L.M.G., Bodde, N.M.G., Lazeron, R.H.C., *et al*. (2016) Autonomic Nervous System Functioning Associated with Psychogenic Non Epileptic Seizures: Analysis of Heart Rate Variability. *Epilepsy & Behavior*, **54**, 14-19. https://doi.org/10.1016/j.yebeh.2015.10.014

[35] Valenza, G., Romigi, A., Citi, L., Placidi, F., Izzi, F., Albanese, M., *et al*. (2016) Predicting Seizures in Untreated Temporal lobe Epilepsy Using Point-Process Nonlinear Models of Heart Beat Dynamics. *IEEE Engineering in Medicine and Biology Society*, Orlando, 16-20 August 2016, 985-988. https://doi.org/10.1109/EMBC.2016.7590867

[36] Romigi, A. and Toschi, N. (2017) Cardiac Autonomic Changes in Epilepsy. In: Barbieri, R., Scilingo, E.P. and Valenza, G., Eds., *Complexity and Nonlinearity in Cardiovascular Signals*, Springer International Publishing, Cham, 375-386. https://doi.org/10.1007/978-3-319-58709-7_14

[37] Kutlubaev, M.A., Xu, Y., Hackett, M.L. and Stone, J. (2018) Dual Diagnosis of Epilepsy and Psychogenic Non Epileptic Seizures: Systematic Review and Meta-Analysis of Frequency, Correlates, and Outcomes. *Epilepsy & Behavior*, **89**, 70-78. https://doi.org/10.1016/j.yebeh.2018.10.010

[38] Myers, L., Trobliger, R., Bortnik, K., Zeng, R., Saal, E. and Lancman, M. (2019) Psychological Trauma, Somatization, Dissociation, and Psychiatric Comorbidities in Patients with Psychogenic Nonepileptic Seizures Compared with Those in Patients with Intractable Partial Epilepsy. *Epilepsy & Behavior*, **92**, 108-113. https://doi.org/10.1016/j.yebeh.2018.12.027

[39] Zsom, A., Tsekhan, S., Hamid, T., Leivn, J., Truccolo, W., LaFrance, W.C., *et al*. (2019) Ictal Autonomic Activity Recorded via Wearable-Sensors plus Machine Learning Can Discriminate Epileptic and Psychogenic Non Epileptic Seizures. *IEEE Engineering in Medicine and Biology Society*, Berlin, 23-27 July 2019, 3502-3506. https://doi.org/10.1109/EMBC.2019.8857552

[40] Forte, G., Favieri, F. and Casagrande, M. (2019) Heart Rate Variability and Cognitive Function: A System a Tic Review. *Frontiers in Neuroscience*, **13**, Article No. 710. https://doi.org/10.3389/fnins.2019.00710

[41] Laborde, S., Mosley, E. and Thayer, J.F. (2017) Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research-Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Frontiers in Psychology*, **8**, Article No. 213. https://doi.org/10.3389/fpsyg.2017.00213

[42] Shamim, G., Khan, Y.U., Sarfraz, M. and Farooq, O. (2017) Epileptic Seizure Detection Using Heart Rate Variability. 2016 *International Conference on Signal Processing and Communication* (*ICSC*), Noida, 26-28 December 2016, 250-254. https://doi.org/10.1109/ICSPCom.2016.7980585

[43] Moridani, M.K. and Farhadi, H. (2017) Heart Rate Variability as a Biomarker for Epilepsy Seizure Prediction. *Bratislavske Lekarske Listy*, **118**, 3-8. https://doi.org/10.4149/BLL_2017_001

[44] Behbahani, S., Dabanloo, N.J., Nasrabadi, A.M. and Dourado, A. (2016) Prediction of Epileptic Seizures Based on Heart Rate Variability. *Technology and Health Care*, **24**, 795-810. https://doi.org/10.3233/THC-161225

[45] Vandecasteele, K., De Cooman, T., Gu, Y., Cleeren, E., Claes, K., Paesschen, W.V., *et al*. (2017) Automated Epileptic Seizure Detection Based on Wearable ECG and PPG in a Hospital Environment. *Sensors* (*Basel*), **17**, pii: E2338. https://doi.org/10.3390/s17102338

[46] Behbahani, S., Dabanloo, N.J., Nasrabadi, A.M. and Dourado, A. (2016) Classification of Ictal and Seizure-Free HRV Signals with Focus on Late Ralization of Epilepsy. *Technology and Health Care*, **24**, 43-56. https://doi.org/10.3233/THC-151072

[47] Pressler, R.M., Cilio, M.R., Mizrahi, E.M., Moshe, S.L., Nunes, M.L., Plouin, P., Vanhatalo, S., Yozawitz, E., deVries, L.S., Vinayan, K.P., *et al*. (2021) The ILAE Classification of Seizures and the Epilepsies: Modification for Seizures in the Neonate. Position Paper by the ILAET Ask Force on Neonatal Seizures. *Epilepsia*, **62**, Article ID: 615628. https://doi.org/10.1111/epi.16815

[48] Pisani, F., Spagnoli, C., Falsaperla, R., Nagarajan, L. and Ramantani, G. (2021) Seizures in the Neonate: A Review of Etiologies and Outcomes. *Seizure*, **85**, 4856. https://doi.org/10.1016/j.seizure.2020.12.023

[49] Cabon, S., Poree, F., Simon, A., Rosec, O., Pladys, P. and Carrault, G. (2019) Video and Audio Processing in Paediatrics: A Review. *Physiological Measurement*, **40**, 02TR02. https://doi.org/10.1088/1361-6579/ab0096

[50] Bersani, I., Piersigilli, F., Gazzolo, D., Campi, F., Savarese, I., Dotta, A., Tamborrino, P.P., Auriti, C. and Di Mambro, C. (2021) Heart Rate Variability as Possible Marker of Brain Damage in Neonates with Hypoxic Ischemic Encephalopathy: A Systematic Review. *European Journal of Nuclear Medicine and Molecular Imaging*, **180**, 1335-1345. https://doi.org/10.1007/s00431-020-03882-3

[51] tatello, R., Carnevali, L., Alinovi, D., Pisani, F. and Sgoifo, A. (2018) Heart Rate Variability in Neonatal Patients with Seizures. *Clinical Neurophysiology*, **129**, 2534-2540. https://doi.org/10.1016/j.clinph.2018.10.001

[52] Behbahani, S. (2018) A Review of Significant Research on Epileptic Seizure Detection and Prediction Using Heart Rate Variability. *Turk Kardiyoloji Dernegi Arsivi*, **46**, 414-421. https://doi.org/10.5543/tkda.2018.64928

[53] Stevenson, N.J., Tapani, K., Lauronen, L. and Vanhatalo, S. (2019) A Data Set of Neonatal EEG Recordings with Seizure an Notations. *Scientific Data*, **6**, Article ID: 190039. https://doi.org/10.1038/sdata.2019.39

[54] The Math Works, Inc. (2020) MATLAB and Statistics and Machine Learning Toolbox Release. The Math Works, Inc., Natick.

[55] Frassineti, L., Barba, C., Melani, F., Piras, F., Guerrini, R. and Manfredi, C. (2019) Automatic Detection and Sonification of Nonmotor Generalized Onset Epileptic Seizures: Preliminary Results. *Brain Research*, **1721**, Article ID: 146341. https://doi.org/10.1016/j.brainres.2019.146341

[56] Humeau-Heurtier, A. (2020) Entropy Analysis in Health Informatics. In: Ahad, M.A.R. and Ahmed, M.U., Eds., *Signal Processing Techniques for Computational Health Informatics*, Springer, Cham, Volume 192, 123-143. https://doi.org/10.1007/978-3-030-54932-9_5

[57] Frassineti, L., Parente, A. and Manfredi, C. (2021) Multi Parametric EEG Analysis of Brain Network Dynamics during Neonatal Seizures. *Journal of Neuroscience Methods*, **348**, Article ID: 109003. https://doi.org/10.1016/j.jneumeth.2020.109003

[58] Nardelli, M., Lanata, A., Bertschy, G., Scilingo, E.P. and Valenza, G. (2017) Heart Beat Complexity Modulation in Bipolar Disorder during Day Time and Nighttime. *Scientific Reports*, **7**, Article No. 17920. https://doi.org/10.1038/s41598-017-18036-z

[59] Buchanan, G.F. (2019) Impaired CO_2-Induced Arousal in SIDS and SUDEP. *Trends in Neurosciences*, **42**, 242-250. https://doi.org/10.1016/j.tins.2019.02.002

[60] Locatelli, A., Lambicchi, L., Incerti, M., Bonati, F., Ferdico, M., Malguzzi, S., Torcasio, F., Calzi, P., Varisco, T. and Paterlini, G. (2020) Is Perinatal Asphyxia Predictable? *BMC Pregnancy Childbirth*, **20**, 186-188. https://doi.org/10.1186/s12884-020-02876-1