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**Estudo das alterações cardíacas ictais:
possível relação com a morte súbita na epilepsia**

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**Estudo das alterações cardíacas ictais:
possível relação com a morte súbita na epilepsia**

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Abreviaturas

AAN	<i>American Academy of Neurology</i>
AES	<i>American Epilepsy Society</i>
AVC	acidente vascular cerebral
AVNN	média dos intervalos RR normais (<i>average interval between normal heart beats</i>)
BNP	peptídeo natriurético do tipo B
CHUSJ	Centro Hospitalar Universitário de São João, E.P.E.
C/F	razão coração/fígado
C/P	razão coração/pulmão
CPM	cintigrafia de perfusão do miocárdio
ECG	eletrocardiograma
EEG	eletroencefalograma
EGI	epilepsia generalizada idiopática
ENV	estimulação do nervo vago
FACE	fármacos anti-crisis epiléticas
FC	frequência cardíaca
FDA	<i>Food and Drug Administration</i>
FDG	Fluorodesoxiglicose
FE	fração de ejeção
FRC	Fatores de risco cardiovascular
GABA	ácido gama-aminobutírico
HF	altas frequências (<i>high frequencies</i>)
[^{99m}Tc]Tc-HMPAO	[^{99m} Tc]Tc-hexametilpropilenoaminoxima
hs	elevada sensibilidade
I.C. 95%	Intervalo de confiança a 95%
ILAE	<i>International League Against Epilepsy</i>
LF	baixas frequências (<i>low frequencies</i>)
ln	logaritmo natural
OMS	Organização Mundial de Saúde
OR	razão de chances (<i>odds ratio</i>)
PCR	proteína C reativa
PET	Tomografia por emissão de positrões
PGES	supressão pós-ictal generalizada do EEG
pNN20	proporção de intervalos RR normais acima de 20 ms
pNN50	proporção de intervalos RR normais acima de 50 ms
ROI	região de interesse
RMN	Ressonância magnética nuclear
SDNN	desvio-padrão dos intervalos RR normais (<i>standard deviation of the intervals between normal heart beats</i>)
SPECT	Tomografia computadorizada de emissão de fóton único
SUDEP	morte súbita e inesperada na epilepsia
TCG	tônico-clônica generalizada
cTnI	troponina cardíaca I
cTnT	troponina cardíaca T
UME	Unidade de Monitorização de Epilepsia
VE	ventrículo esquerdo
VEEG	vídeo-EEG
VFC	variabilidade da frequência cardíaca

Resumo

A morte súbita e inesperada na epilepsia (SUDEP) constitui uma das maiores preocupações nestes doentes, sobretudo quando a epilepsia é refratária, sendo a principal causa de morte diretamente relacionada com a mesma.

Numa tentativa de esclarecer os mecanismos da SUDEP, pretendeu-se estudar as alterações cardíacas que possam ocorrer durante a crise epilética, em doentes com epilepsia farmacologicamente intratável.

Essas alterações podem ser avaliadas através de múltiplos biomarcadores, quer analíticos, quer do ritmo cardíaco, quer imagiológicos.

Analiticamente, as crises epiléticas podem induzir elevação da Troponina I (cTnI), do Peptídeo Natriurético do tipo B (BNP) e da Proteína C Reativa (PCR), o que pode refletir lesões cardíacas, possivelmente associadas à SUDEP.

Por outro lado, estão também descritas alterações autonómicas em doentes com epilepsia, sobretudo refratária, objetivadas numa diminuição da variabilidade da frequência cardíaca (VFC). Esta diminuição está já relacionada, noutras patologias, com um risco aumentado de morte súbita. No contexto da epilepsia e, particularmente, da SUDEP, poderia ter um papel idêntico.

Quanto à vertente imagiológica, não existe qualquer estudo publicado que avalie a perfusão do miocárdio durante as crises epiléticas e tentou-se, nesta tese, preencher essa lacuna.

Com o nosso objetivo em vista, realizámos estudos prospetivos, dos quais resultaram quatro publicações.

No primeiro artigo, pretendemos documentar o perfil analítico da hs-cTnI, do BNP e da hs-PCR após crises epiléticas, em doentes com epilepsia refratária, internados na Unidade de Monitorização de Epilepsia (UME) do Centro Hospitalar Universitário de São João, E.P.E., correlacionando-o com variáveis clínicas e a escala de risco SUDEP-7.

Verificou-se que cerca de um quarto dos doentes teve um aumento significativo da hs-cTnI ou do BNP (25,9% e 23,3%, respetivamente), mas sem associação significativa à escala de risco SUDEP-7. O aumento da hs-cTnI associou-se à presença de crises TCG e outros fatores de risco para SUDEP. Cerca de 5% dos doentes tiveram uma elevação da hs-cTnI acima do percentil 99 do limite superior de referência, subindo para 20%, quando se considerou apenas os doentes com crises TCG. De referir, contudo, que também se documentaram elevações da hs-cTnI após crises não-TCG.

Apenas o BNP se associou à presença de fatores de risco cardiovascular (FRC).

As elevações dos diversos biomarcadores foram independentes.

No segundo e no terceiro artigos, avaliámos parâmetros de VFC, retirados de registos de *Holter* de 48 horas, também em doentes com epilepsia refratária internados da UME. Explorámos as alterações provocadas pelas crises nesses parâmetros e se o tipo de crise teria algum impacto nessas alterações.

Inicialmente, avaliámos a VFC em doentes com crises TCG, e comparámos com uma população saudável de referência.

Encontrámos diferenças nos parâmetros da VFC entre os diversos períodos analisados (interictal, pré-ictal e pós-ictal), especialmente durante o pós-ictal. Todos os parâmetros, exceto o LF/HF sofreram uma redução nesse período.

Posteriormente, avaliámos o impacto do tipo da crise na VFC. Verificámos que as crises TCG tiveram um maior efeito na função autonómica cardíaca, do que as crises não-TCG, provocando uma redução significativa no tónus vagal, o que poderia estar associado a maior risco de SUDEP.

No quarto artigo, após um estudo exploratório que também é descrito nesta tese, quisemos analisar a possibilidade de avaliar a perfusão do miocárdio com um radiofármaco tradicionalmente utilizado para mapear a perfusão cerebral ($[^{99m}\text{Tc}]\text{Tc-HMPAO}$).

Nesse estudo, comparámos imagens cardíacas realizadas, nos mesmos doentes, com $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ e com $[^{99m}\text{Tc}]\text{Tc-Tetrofosmina}$ (o tradicional radiofármaco utilizado na Cintigrafia miocárdica de perfusão).

Os exames foram comparados pixel a pixel, e obtivemos correlações tão altas quanto 0,93.

Este estudo, embora preliminar e com um número insuficiente de doentes, propõe que a tomografia cardíaca com $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ possa vir a ser um método de rastreio de isquemia miocárdica, em doentes com epilepsia refratária, com indicação para o exame cerebral e suspeitos de terem também alterações cardíacas.

Com base nesse pressuposto, avaliámos a captação regional do $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ no miocárdio de doentes com epilepsia refratária, enviados para a realização da SPECT cerebral, nos períodos ictal ou interictal.

Ambos os grupos (ictal e interictal) exibiram um número significativo de defeitos de captação cardíaca do radiofármaco, o que aponta para alterações crónicas, uma vez que, entre os dois grupos, não encontrámos diferenças estatisticamente significativas nas características dos defeitos.

Com esta tese, propomos a introdução de biomarcadores cardíacos específicos para uso na prática clínica, com a intenção de reduzir o risco de SUDEP, incluindo uma nova aplicação para um radiofármaco já estabelecido na avaliação cerebral destes doentes.

Abstract

Sudden unexpected death in epilepsy (SUDEP) is one of the major concerns in patients with epilepsy, especially if refractory, being the main cause of death directly related to epilepsy itself.

In an attempt to clarify the mechanisms of SUDEP, it was intended to study the cardiac changes that would occur during epileptic seizures in patients with pharmacologically intractable epilepsy.

These changes can be evaluated through multiple biomarkers, be they analytical, heart rate related or derived from image examinations.

Analytically, epileptic seizures may induce elevation of Troponin I (cTnI), natriuretic peptide type B (BNP) and C-Reactive Protein (CRP), which may reflect cardiac lesions, which may, in turn, be associated with SUDEP.

On the other hand, autonomic changes are also described in patients with epilepsy, especially refractory, consisting of a decrease in heart rate variability (HRV). This decrease is already associated, in other pathologies, with an increased risk of sudden death. In the context of epilepsy and, particularly, SUDEP it could play an identical role.

Regarding the imaging aspect, there is no published study evaluating myocardial perfusion during epileptic seizures and this thesis has attempted to fill that gap.

With our objective in view, we conducted prospective studies, which resulted in four publications.

In the first article, we intended to document the analytical profile of hs-cTnI, BNP and hs-PCR after epileptic seizures in patients with refractory epilepsy, admitted to the Epilepsy Monitoring Unit (EMU) of the Centro Hospitalar Universitário de São João, E.P.E., correlating it with clinical variables and the Risk Scale SUDEP-7 inventory. We found that about a quarter of patients had a significant increase in hs-cTnI or BNP (25.9% and 23.3%, respectively), but without significant association with the SUDEP-7 risk scale. The increase in hs-cTnI was associated with the presence of generalized convulsive seizures (GCS) and other risk factors for SUDEP. About 5% of patients had an increase in hs-cTnI above the 99th percentile of the upper reference limit, rising to 20% when considering only patients with GCS. It should be noted, however, that hs-cTnI elevations were also documented after non-GCS. Only increased BNP was associated with the presence of cardiovascular risk factors (CRF).

The elevation of one biomarker did not compel the elevation of any other.

In the second and third articles, we evaluated HRV parameters, taken from 48-hour Holter, also in patients with refractory epilepsy hospitalized in the EMU. We explored the changes caused by epileptic seizures and whether the type of seizure would have any impact. Initially, we evaluated HRV in patients with GCS

and compared them with a healthy reference population. We found differences in HRV parameters between the different periods analyzed (interictal, preictal, and postictal), especially during the postictal one. All parameters except LF/HF were reduced during this period. Later, we evaluated the impact of the type of seizure on HRV. We found that GCS had a greater effect on cardiac autonomic function than non-GCS, causing a significant reduction in vagal tone, which could be associated with a higher risk of SUDEP.

In the fourth article, after an exploratory study also described in this thesis, we wanted to analyze the possibility of evaluating myocardial perfusion with a radiopharmaceutical traditionally used to map brain perfusion (^{99m}Tc -HMPAO). In that study, we compared cardiac images performed in the same patients with ^{99m}Tc -HMPAO and ^{99m}Tc -Tetrofosmin (the traditional radiopharmaceutical used in myocardial perfusion scintigraphy). The tests were compared pixel by pixel and we obtained correlations as high as 0.93. This study, although preliminary and with an insufficient number of patients, proposes that cardiac SPECT with ^{99m}Tc -HMPAO may be a method of screening for myocardial ischemia in patients with refractory epilepsy with the indication for a brain scan and suspected of also having cardiac changes.

Based on this assumption, we evaluated the regional uptake of ^{99m}Tc -HMPAO in the myocardium of patients with refractory epilepsy sent to perform brain SPECT, in the ictal or interictal period. Both ictal and interictal groups exhibited a significant number of uptake defects of ^{99m}Tc -HMPAO, which points to chronic alterations since we did not find statistically significant differences in the characteristics of the defects between the two groups.

With this thesis, we propose the use in clinical practice of specific cardiac biomarkers that may reduce the risk of SUDEP, including a novel use for a radiopharmaceutical already established in the brain evaluation of these patients.

1. INTRODUÇÃO

'The immediate cause of death in epilepsy is a matter which is not always easily solved, and one which is not often discussed in works on medicine, most probably from lack of information.

...

If we read in the Registrar-General's Report for 1864 that 2406 deaths were due to epilepsy, we get no definite idea as to the real cause of death, and cannot tell whether the patients died directly from the fit or in quite a different manner. Indeed, the only proper conclusion to be drawn is that an individual who was epileptic, amongst other faults, is dead.

Surely we might get a nearer approximation to truth than this!

G. MACKENZIE BACON, in The Lancet, 1868

Ao longo da História, foi sendo conhecido o risco de uma crise epilética levar à morte (1, 2) e já no século XIX encontramos publicações científicas que denotam preocupação por não existir uma causa clara para a morte súbita e inesperada em doentes com epilepsia (SUDEP) (3).

Mais de 150 anos volvidos, a SUDEP mantém-se um motivo global de preocupação, atraindo recursos para esta investigação – muita ainda por fazer. Múltiplos doentes morreram já, sem o benefício do conhecimento ou conselho acerca dos riscos associados à epilepsia (2).

Com caminhos trilhados em variadas direções e muitas conclusões diferentes, continuamos na busca da(s) causa(s) da morte súbita em doentes com epilepsia, sendo provável que a causa seja multifatorial (4, 5).

Este é o meu contributo para esta procura, explorando diferentes vertentes das alterações cardíacas durante as crises epiléticas.

A. Morte súbita e inesperada na epilepsia (SUDEP)

1. Definição

A necessidade de criar uma definição para a SUDEP adveio da inconsistência e imprecisão dos certificados de óbito, da falta de definições concordantes, e da existência de diferentes terminologias ou interpretações distintas das mesmas terminologias. Existindo uma definição única e globalmente aceite, seria possível uma análise correta da incidência, a comparação entre estudos, a monitorização das tendências, em suma: o avanço da investigação (4-6).

No início dos anos 90 do séc. XX, a *Food and Drug Administration* (FDA) dos Estados Unidos da América e a *Burroughs Wellcome* criaram um comité consultivo para determinar a ocorrência de SUDEP em ensaios clínicos. Os seus critérios foram publicados por Annegers (7), em 1997, e estabeleciam que:

1. *A vítima sofria de epilepsia, definida como crises não provocadas recorrentes*
2. *A vítima morreu inesperadamente, gozando de um estado de saúde razoável*
3. *A morte ocorreu repentinamente (em minutos), quando conhecido esse facto*
4. *A morte ocorreu durante atividades normais (ex.: na ou perto da cama, em casa, no trabalho) e em circunstâncias benignas*
5. *Não foi encontrada uma causa médica óbvia para a morte*

Estes critérios visavam excluir mortes acidentais provocadas por crises epiléticas, mas incluíam mortes com ou sem evidência de uma crise próximo da hora da morte.

1. Temkin O. *The falling sickness: a history of epilepsy from the Greeks to the beginnings of modern neurology.*

2. Panelli RJ. *SUDEP: A global perspective.*

3. Bacon GM. *On the modes of death in epilepsy.*

4. Nashef L, So EL, Ryvlin P, Tomson T. *Unifying the definitions of sudden unexpected death in epilepsy.*

5. Nashef L, Sander JW. *Sudden unexpected deaths in epilepsy--where are we now?*

6. Nashef L. *Sudden unexpected death in epilepsy: terminology and definitions.*

7. Annegers JF. *United States perspective on definitions and classifications.*

A SUDEP era classificada como:

- SUDEP definitiva: cumpria todos os critérios e com autópsia
- SUDEP provável: cumpria todos os critérios, mas sem dados de autópsia
- SUDEP possível: não podia excluir-se a hipótese de SUDEP, mas a evidência era insuficiente, tendo em conta as circunstâncias da morte, e sem dados da autópsia
- SUDEP pouco provável/ não-SUDEP: causa da morte claramente estabelecida ou as circunstâncias tornavam a hipótese de SUDEP altamente improvável

Quase simultaneamente, no Reino Unido, Lina Nashef foi também uma das primeiras pessoas a definir SUDEP, como sendo *a morte súbita, inesperada, testemunhada ou não, não traumática e não por afogamento, em doentes com epilepsia, com ou sem evidência de crise epilética e excluindo estado de mal epilético documentado, em que a autópsia não revela uma causa toxicológica ou anatômica para a morte* (6).

Posteriormente, Nashef propôs a unificação das duas definições (4). Esta última proposta é globalmente aceite e é a que se encontra atualmente em uso pela *International League Against Epilepsy* (ILAE).

Partindo da definição publicada por Annegers (7), foram subdivididas algumas categorias, sendo a alteração mais importante o acréscimo da categoria SUDEP definitiva *Plus*. Segundo a autora, há situações em que existe evidência de que uma condição pré-existente pode ter contribuído para a morte, que, de outro modo teria sido classificada como SUDEP (ex.: doença coronária ou síndrome do QT longo, em casos de morte súbita associados a uma crise epilética habitual, mas cuja autópsia não revela enfarte do miocárdio nem qualquer outra causa estrutural para a morte). Essas situações seriam classificadas nesta nova categoria, uma vez que as condições previamente existentes não foram a causa clara da morte, mas podem ter sido contribuidores essenciais (4).

A investigação em doentes com epilepsia, sobretudo sobre SUDEP, tem vindo a aumentar exponencialmente, como atesta o número crescente de artigos indexados, por exemplo, na Pubmed. Dessa investigação, principalmente na última década, verificou-se que existe uma associação entre a epilepsia refratária de longa duração e o desenvolvimento de doenças cardíacas (8-11).

Ao ser criada a categoria SUDEP definitiva *Plus*, torna-se possível investigar a contribuição dessas comorbilidades para a SUDEP e saber se é viável, com intervenções terapêuticas, diminuir o risco dessas mortes. A classificação nesta categoria não implica a presença de uma crise próxima ao momento da morte. Não deverão ser categorizadas como SUDEP definitiva *Plus* situações em que está documentado que uma dessas comorbilidades, por si só, causou a morte, como por exemplo, uma arritmia ventricular primária, que teve como base uma síndrome do QT longo. Este exemplo deverá ser categorizado como não-SUDEP. Por outro lado, se uma crise provocar uma arritmia fatal, num indivíduo com síndrome do QT longo, essa situação já deverá ser classificada como SUDEP definitiva *Plus* (4).

8. Zack M, Luncheon C. 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.

9. Bardai A, Lamberts RJ, Blom MT, Spanjaart AM, Berdowski J, van der Staal SR, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population.

10. Selassie AW, Wilson DA, Martz GU, Smith GG, Wagner JL, Wannamaker BB. Epilepsy beyond seizure: a population-based study of comorbidities.

11. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy.

Definição e classificação de SUDEP atualmente aceites (4):

1. *SUDEP definitiva^a: morte súbita, inesperada, testemunhada ou não, não traumática e não por afogamento, ocorrendo em circunstâncias benignas, num indivíduo com epilepsia, com ou sem evidência de crise epilética e excluindo estado de mal epilético documentado (duração da crise ≥ 30 min ou crises sem recuperação entre si), em que a autópsia não revela uma causa para a morte*
 - 1a. *SUDEP definitiva Plus^a: morte satisfazendo a definição de SUDEP definitiva, se uma condição concomitante, para além da epilepsia, é identificada antes ou depois da morte, se a morte pode ter sido causada pelo efeito combinado das duas condições, e se a autópsia ou observação direta/registos do evento terminal não provarem que a condição concomitante foi a causa da morte*
2. *SUDEP provável/ SUDEP provável Plus^a: o mesmo que SUDEP definitiva, mas sem autópsia. A vítima deverá ter morrido inesperadamente, enquanto num estado de saúde razoável, durante atividades normais e em circunstâncias benignas, sem uma causa estrutural conhecida para a morte*
3. *SUDEP possível^b: existe uma causa competidora para a morte*
4. *Quase SUDEP/ Quase SUDEP Plus: um doente com epilepsia sobrevive à ressuscitação por mais de 1 h, após uma paragem cardíaca que não tem causa estrutural identificada após investigação*
5. *Não-SUDEP: conhece-se uma causa clara para a morte*
6. *Não classificada: a informação disponível é incompleta; impossível de classificar*

12. Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, et al. Population-based study of the incidence of sudden unexpected death in epilepsy.

13. Whitney R, Donner EJ. Risk Factors for Sudden Unexpected Death in Epilepsy (SUDEP) and Their Mitigation.

14. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden.

15. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: A call for action.

16. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study.

17. Derby LE, Tennis P, Jick H. Sudden unexplained death among subjects with refractory epilepsy.

18. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study.

19. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study.

2. Epidemiologia

A SUDEP é a causa de morte relacionada com epilepsia mais frequente, tanto em crianças como em adultos. Embora seja uma causa rara de morte na população de doentes com epilepsia, excede em quase 24 vezes a taxa esperada de morte súbita da população geral (12).

De entre outras condições neurológicas, surge em segundo lugar, relativamente ao número de potenciais anos de vida perdidos, sendo a primeira o acidente vascular cerebral (AVC) isquémico (13, 14).

É difícil determinar a incidência de SUDEP, que é subestimada, sobretudo devido à pouca consciência que ainda se tem relativamente a este tipo de morte, à dificuldade na identificação de casos e a diferentes metodologias utilizadas nessa identificação (14-16).

Thurman et al., numa revisão crítica de 2014, estimaram a taxa de incidência anual bruta de SUDEP em 0,81 casos por 100 000 pessoas, ou 1,16 casos por 1000 doentes com epilepsia, assumindo uma prevalência global de epilepsia de 7,1 por 100 000 pessoas (14).

Segundo os mesmos autores (14), que analisaram 4 estudos populacionais, são poucos os casos reportados na primeira década de vida. O número mais elevado de casos ocorre nas terceira e quarta décadas (14, 17, 18), diminuindo de modo acentuado na sexta década (14, 19).

^a Se uma morte é testemunhada, estabeleceu-se um limite arbitrário de 1 h, entre o colapso agudo e a morte

Em 2017, a *American Academy of Neurology* (AAN) e a *American Epilepsy Society* (AES) publicaram uma recomendação sobre SUDEP, incluindo informação quanto à incidência, a qual reportaram como sendo 1,2 por 1000 doentes-ano [I.C. 95% = (0,64-2,32)], em adultos, e 0,22 por 1000 doentes-ano [I.C. 95% = (0,16-0,31)], em crianças (20).

Embora o risco tenha sido estimado como baixo na população pediátrica, existem estudos mais recentes que reportaram valores mais elevados. Em Ontário, no Canadá, Keller et al., em 2018, reportaram valores de incidência global de SUDEP pediátrica de 1,17 [I.C. 95% = (0,68-1,88)] por 1000 doentes-ano, e de SUDEP definitiva/ provável, também pediátrica, como sendo 1,11 [I.C. 95% = (0,63-1,79)] por 1000 doentes-ano, valores semelhantes aos dos adultos (21). Na Suécia, Sveinsson et al., em 2017, obtiveram incidências similares: 1,11 [I.C. 95% = (0,45-2,29)] por 1000 doentes-ano, em crianças de idade <16 anos, 1,13 [I.C. 95% = (0,76-1,62)], entre os 16 e os 50 anos, e 1,29 [I.C. 95% = (0,88-1,82)], acima dos 50 anos (16).

Não existem dados publicados relativos à incidência de SUDEP em Portugal. Os mais próximos talvez sejam os dados de Espanha. Num estudo decorrido em Málaga (22), tendo como população os doentes atendidos numa Unidade de Epilepsia, estimaram a incidência de SUDEP em 0,44 por 1000 doentes-ano. Quando incluíram os casos de SUDEP provável/ possível, a incidência subiu para 0,55 por 1000 doentes-ano. Os autores explicam esta baixa incidência com o facto de, no seu Centro, não limitarem a assistência em função da gravidade, atendendo também muitos doentes com formas mais benignas de epilepsia. Consideraram, portanto, que esta incidência estaria mais próxima da dos estudos que se baseiam na população geral. Num outro estudo, em Barcelona, Sanches-Larsen et al. reviram todos os doentes seguidos no seu Centro de Referência de Epilepsia Refratária e que morreram entre 2010 e 2018, para estudarem as características da SUDEP. Estes autores estimaram a incidência de SUDEP em 1,3 por 1000 doentes-ano, nessa população de epilepsia refratária (23).

O risco de SUDEP é menor em doentes com epilepsias recentemente diagnosticadas, aumentando cerca de 10 vezes em doentes com epilepsias crónicas (14, 24).

Em doentes livres de crises, a SUDEP é rara, embora possível, sendo a sua incidência inversamente relacionada com o estado de remissão da epilepsia (24, 25). Em populações selecionadas, com *epilepsias mais graves*, algumas com necessidade de institucionalização em centros especializados, a incidência de SUDEP pode chegar a 6 por 1000 doentes-ano (25). O valor reportado mais elevado, 9 por 1000 doentes-ano, corresponde ao de *candidatos a cirurgia de epilepsia* (25). No entanto, se a cirurgia for bem-sucedida e os doentes ficarem livres de crises, a incidência de SUDEP baixa (26). Também foi calculada a incidência de SUDEP em Unidades de Monitorização de Epilepsia (UME) de adultos, como sendo 5,1 [I.C. 95% = (2,6-9,2)] por 1000 doentes-ano, com um risco de SUDEP definitiva ou provável de 1,2 [I.C. 95% = (0,6-2,1)] por 10 000 monitorizações por vídeo-EEG (VEEG) (27).

A maioria dos estudos aponta para uma incidência de SUDEP mais elevada no *sexo masculino* (16, 17, 28-33), mas Tomson et al. (25) alertam para um possível viés de seleção, uma vez que nem o estudo populacional de Ficker et al. (12), nem dois estudos caso-controlo, provavelmente com uma população menos enviesada de doentes, confirmam essa predominância (18, 19).

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35. Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention.

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39. Ravindran K, Powell KL, Todaro M, O'Brien TJ. The pathophysiology of cardiac dysfunction in epilepsy.

40. Shorvon S, Tomson T. Sudden unexpected death in epilepsy.

41. Camacho Velásquez JL, Rivero Sanz E, Mauri Llerda JA, Suller Martí A. Epileptic seizure as a trigger of acute coronary syndrome.

Sveinsson et al. reportaram uma incidência superior de SUDEP, em indivíduos com *comorbilidades psiquiátricas* (16).

Recentemente, Tomson et al. (34) descreveram um facto curioso, para o qual ainda não se encontrou explicação: no seu estudo, verificaram que a incidência de SUDEP diminuiu significativamente com a *duração do seguimento*, cerca de 7% por ano, uma diminuição mais acentuada do que a que verificaram para a mortalidade por todas as causas. Verificaram, ainda, que a taxa de SUDEP foi cerca de 25% inferior, nos últimos 4 anos de seguimento, quando comparada com a dos 2 primeiros anos (total de 6 anos de seguimento). Os autores salientam que este facto deve ser tido em conta quando se avaliam intervenções potencialmente terapêuticas, uma vez que a diminuição no risco de SUDEP pode dever-se simplesmente à evolução natural ou a uma combinação de diferentes intervenções a que são submetidos os doentes com epilepsia ao longo do tempo (34). Uma outra possível explicação pode ser a existência de diferentes *suscetibilidades individuais* para SUDEP, sendo possível que doentes com essas suscetibilidades morram mais cedo, durante o seguimento (34).

3. Fisiopatologia

Os mecanismos responsáveis pela SUDEP ainda não são claros (27, 28, 35-39).

É provável que não exista uma só explicação para todas as mortes, estando envolvidos diferentes mecanismos (24, 35, 38, 40).

Há evidência de **alterações autonómicas** profundas após crises epiléticas (37, 41) que sugerem existir ligação causal a alguns casos de SUDEP (36, 38).

A ínsula, o giro cingulado anterior e o córtex pré-frontal ventromedial afetam a frequência cardíaca (FC), o ritmo e o débito cardíacos. O hipotálamo controla respostas autonómicas relacionadas com a função endócrina (sobretudo catecolaminas) e a amígdala é um mediador das respostas autonómicas. Não é de surpreender, portanto, que a epilepsia possa afetar a função cardíaca (40).

Após as crises epiléticas, dá-se uma intensa libertação de catecolaminas que pode provocar **isquemia** devido a **vasoconstrição coronária** (41), a qual, quando repetida, pode causar **fibrose miocárdica** (37, 42) e, quando próximo do sistema condutor, pode dar origem a **arritmias fatais** (43).

Por outro lado, as bradiarritmias e as taquiarritmias secundárias às crises epiléticas podem induzir alterações isquémicas no miocárdio (41). Opeskin et al. não encontraram fibrose perivascular ou intersticial significativa no exame histológico do coração, tanto em doentes que sofreram SUDEP, como nos seus controlos, mas não excluíram a possibilidade de alterações *minor* do sistema condutor serem, em parte, responsáveis por alguns casos de SUDEP (44).

Na sua maioria, a SUDEP ocorre após uma crise tónico-clónica generalizada (TCG) (18, 24, 27, 45-47). Através da análise da FC, da variabilidade da frequência cardíaca (VFC) e da sensibilidade barorreflexa, verificou-se que as crises TCG induzem maiores alterações na função autonómica, quando comparadas com as crises não-TCG (48-51).

Nem todos os doentes com epilepsia sofrem SUDEP, mesmo com epilepsias crônicas, refratárias, ou com disfunção autonômica interictal, devendo, por isso, existir uma predisposição individual para a sua ocorrência. Poderá haver pelo menos mais um fator que possa despertar a cascata de eventos que culminam na morte. Uma crise TCG (ao provocar estimulação simpática extrema) poderia ser um desses fatores. É possível que uma das crises TCG habituais, num doente em particular, se torne fatal por levar o doente a um extremo de deterioração autonômica (52, 53). Lhatoo et al. colocaram a hipótese de que poderia existir uma anomalia funcional e/ou anatômica no tronco cerebral, possivelmente com base genética, que poderia ter um papel importante durante a crise (54). Tomson et al. interrogaram-se se esses fatores seriam extrínsecos e dependentes das circunstâncias em que ocorrem as crises ou se seriam intrínsecos (52). A Figura 1 esquematiza uma proposta de relação entre os diferentes fatores que, quando conjugados, podem levar a SUDEP.

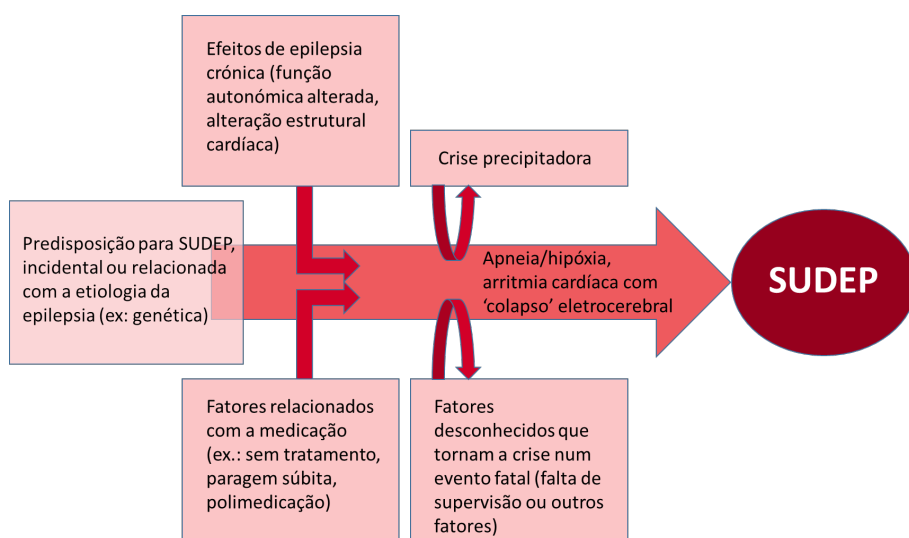


Figura 1. Interação entre fatores predisponentes propostos e fatores precipitantes de SUDEP. Adaptado de Tomson et al., 2008 (52).

Há, porém, alguns (poucos) relatos de SUDEP que não ocorreu em contexto de crises epiléticas (55). Essas mortes não tiveram uma causa primária cardíaca, mas ocorreu um compromisso cardiorrespiratório progressivo, seguido de supressão do eletroencefalograma (EEG).

As alterações autonômicas que os doentes com epilepsia apresentam no período interictal são provavelmente o resultado de lesões crônicas nos centros autonômicos, provocadas por crises repetitivas (56, 57) que, talvez possam, num determinado momento, acionar a insuficiência respiratória.

Os casos de SUDEP testemunhados revelam disfunção cardiorrespiratória (24), mas ainda existe controvérsia relativamente ao que ocorre primeiro: apneia central ou desregulação autonômica central (58).

Apesar de muito raras, as SUDEP ocorridas em unidades de monitorização de epilepsia (UME) constituem uma oportunidade única para estudar a sua fisiopatologia (27, 40, 52).

42. Natelson BH, Suarez RV, Terrence CF, Turizo R. Patients with epilepsy who die suddenly have cardiac disease.

43. Neff JL, Lin PT. An Unexpected Finding in SUDEP Involving a Child: Focal Myocardial Infarct Adjacent to Bundle of His.

44. Opeskin K, Thomas A, Berkovic SF. Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy?

45. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP.

46. Ryvlin P, Rheims S, Lhatoo SD. Risks and predictive biomarkers of sudden unexpected death in epilepsy patient.

47. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study.

48. Hampel KG, Elger CE, Surges R. Impaired Baroreflex Sensitivity after Bilateral Convulsive Seizures in Patients with Focal Epilepsy.

49. Surges R, Scott CA, Walker MC. Enhanced QT shortening and persistent tachycardia after generalized seizures.

50. Toth V, Hejzel L, Fogarasi A, Gyimesi C, Orsi G, Szucs A, et al. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy.

51. Arbune AA, Jeppesen J, Conradsen I, Ryvlin P, Beniczky S. Peri-ictal heart rate variability parameters as surrogate markers of seizure severity.

52. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions.

53. Myers KA, Bello-Espinosa LE, Symonds JD, Zuberi SM, Clegg R, Sadleir LG, et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk.

54. Lhatoo S, Noebels J, Whittemore V. Sudden unexpected death in epilepsy: Identifying risk and preventing mortality.

O estudo MORTEMUS (27), que foi o que despertou em mim a vontade de estudar as possíveis causas de SUDEP, avaliou 29 mortes súbitas ocorridas em diversas UME, incluindo 16 SUDEP e 9 quase SUDEP.

Estavam disponíveis os dados cardiorrespiratórios de 10 dos casos de SUDEP, que mostraram um padrão consistente de respiração rápida (18-50 respirações por minuto) após crises tônico-clônicas com generalização secundária, após o que ocorreu disfunção cardiorrespiratória, nos 3 minutos seguintes, juntamente com supressão pós-ictal do EEG. Para 1/3 dos doentes, este colapso cardiorrespiratório foi terminal. Nos restantes, deu-se um restabelecimento transitório da função cardíaca, com respiração anormal e ineficaz, que agravou progressivamente. A apneia terminal precedeu sempre a assistolia terminal, que ocorreu nos 11 min após a crise. Estes dados sugerem que o mecanismo principal que leva a SUDEP se inicie com uma alteração central grave, tanto das funções respiratória como cardíaca após crises TCG, a que os autores chamaram *colapso neurovegetativo*.

No entanto, alguns estudos experimentais da morte por crises epiléticas em animais apontam para uma causa respiratória primária (59-61). Foi reportada hipoventilação grave em ovelhas que morreram após crises epiléticas, mas não nas que sobreviveram, sendo que as alterações cardíacas encontradas foram benignas.

Os autores concluíram que esse foi o mecanismo principal da morte (59). Um outro estudo, em ovelhas traqueostomizadas, revelou apneia central e hipoventilação em todos os animais. Cerca de 1/3 dos animais morreram. Um dos animais morreu de insuficiência cardíaca, com evidência histológica de isquemia miocárdica. Estas alterações foram verificadas em todos os outros animais, embora de modo menos acentuado (60). Em ratos audiogénicos, preveniu-se a morte (por crises induzidas pelo som), recorrendo a uma atmosfera enriquecida com oxigénio (61), o que também sugere que o mecanismo poderá ser primariamente respiratório.

Num estudo realizado numa UME, o primeiro a investigar os parâmetros respiratórios durante as crises, foi detetada apneia em 10 de 17 doentes (20 de 47 crises, incluindo 3 TCG), que foi central em todos os casos, embora em 3 deles também tivesse um componente obstructivo (62).

A Figura 2 evidencia os diferentes mecanismos possivelmente implicados na SUDEP.

Continuamos, portanto, sem conhecer a causa primária da SUDEP. É provável que seja multifatorial, quer seja no sentido de casos diferentes terem causas distintas, quer no sentido de, em alguns doentes, existir uma conjunção de fatores que, isoladamente, até não seriam fatais, mas que, no seu conjunto e em determinadas circunstâncias, o são.

A hipótese mecanística da apneia central peri-ictal como precipitante de SUDEP é, talvez, a mais bem documentada, tanto em modelos animais como em humanos (64). Cerca de um quinto dos doentes têm apneia central subsequente a uma crise convulsiva generalizada (65) e a presença de Supressão pós-ictal generalizada do EEG (PGES) e de posturas tónicas ictais características (descerebração/descorticação), em crises que cursam com apneias centrais e hipoxemias mais prolongadas no período pós-ictal (66), reforça a hipótese de que alguns doentes possam ter suscetibilidade aumentada a uma falência cardiorrespiratória mediada pelo tronco cerebral, como mecanismo subjacente a SUDEP.

55. Lhatoo SD, Nei M, Raghavan M, Sperling M, Zonjy B, Lacuey N, et al. Nonseizure SUDEP: Sudden unexpected death in epilepsy without preceding epileptic seizures.

56. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy.

57. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus.

58. Behbahani S, Jafarnia Dabanloo N, Motie Nasrabadi A, Dourado A. Gender-Related Differences in Heart Rate Variability of Epileptic Patients.

59. Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death.

60. Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death.

61. Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice.

62. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy.

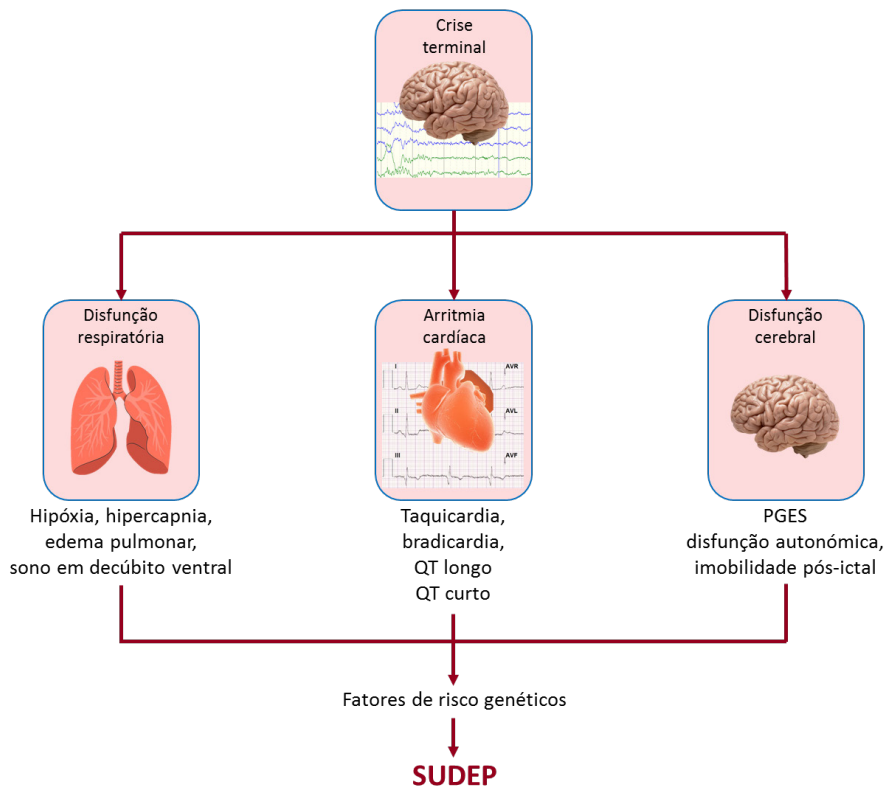


Figura 2. Possíveis mecanismos de SUDEP. PGES: Supressão pós-ictal generalizada do EEG. Adaptado de Bagnall et al., 2017 (63)

4. Fatores de risco

Embora todos os doentes com epilepsia possam sofrer morte súbita e inesperada, o risco não é igual para todos.

A identificação dos indivíduos em maior risco é crucial, na medida em que, para além de permitir intervir para diminuir o risco e/ou prevenir a SUDEP, pode ajudar na compreensão dos seus mecanismos fisiopatológicos (13).

Foram já publicados inúmeros estudos, com o intuito de compreender melhor esses fatores de risco, mas variaram em relação à população estudada, à metodologia, ao desenho do estudo e aos resultados (67).

Não existe nenhum fator de risco isolado que seja comum a todos os casos, o que sugere a existência de múltiplos mecanismos ou fatores desencadeantes (25).

4.1. Tipo de crises

As **crises TCG** (quer sejam primárias ou secundárias) constituem o fator de risco para SUDEP mais consistentemente reportado (18-20, 24, 25, 45-47, 67-69), sendo frequente a SUDEP ocorrer em contexto de uma crise desse tipo (27). Apesar disso, foram descritos casos de SUDEP num doente que apenas teve uma aura (33) e noutros na ausência de crises (55, 70), embora se tratasse de doentes com história de crises TCG.

63. Bagnall RD, Crompton DE, Semsarian C. Genetic Basis of Sudden Unexpected Death in Epilepsy.

64. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention.

65. Vilella L, Lacuey N, Hampson JP, Rani MRS, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP).

66. Vilella L, Lacuey N, Hampson JP, Zhu L, Omid S, Ochoa-Urrea M, et al. Association of Peri-ictal Brainstem Posturing With Seizure Severity and Breathing Compromise in Patients With Generalized Convulsive Seizures.

67. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP.

68. DeGiorgio CM, Markovic D, Mazumder R, Moseley BD. Ranking the Leading Risk Factors for Sudden Unexpected Death in Epilepsy.

69. Timmings PL. Sudden unexpected death in epilepsy: is carbamazepine implicated?

70. Weber P, Bubl R, Blauenstein U, Tillmann BU, Lütschg J. Sudden unexplained death in children with epilepsy: a cohort study with an eighteen-year follow-up.

4.2. Frequência de crises

A **frequência de crises** também é considerada um dos fatores de risco mais significativos para SUDEP, uma vez que o **risco aumenta com o número de crises TCG por ano** (19, 20, 67). Uma a três crises TCG por ano são suficientes para aumentar o risco de SUDEP (19). Quando o número sobe para três ou mais crises TCG por ano, o risco de SUDEP aumenta 15 vezes, o que se traduz num risco absoluto de até 18 mortes por 1000 doentes-ano (20).

Para Nilsson et al., a frequência de crises foi o fator mais fortemente associado ao risco de SUDEP. No seu estudo (um dos maiores estudos caso-controlo), apenas 1,8% dos casos de SUDEP (comparativamente com 31,6% dos controlos) se encontrava livre de crises, no último ano de comparação. O risco aumentou com o aumento da frequência de crises, sendo mais pronunciado em homens do que em mulheres (18). Outros estudos também mostraram que a SUDEP é rara em doentes em remissão (25, 71, 72), tendo sido reportados poucos casos nesse estado. A recomendação da AAN e da AES considerou um fator de risco o doente não estar livre de crises por 1 a 5 anos (20).

71. Lhatoo SD, Langan Y, MacDonald BK, Zeidan S, Sander JW. Sudden unexpected death: a rare event in a large community based prospective cohort with newly diagnosed epilepsy and high remission rates.

72. Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group.

73. Kloster R, Engelskjøn T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors.

74. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials.

75. Tomson T, Kennebäck G. Arrhythmia, heart rate variability, and antiepileptic drugs.

76. Pang TD, Nearing BD, Krishnamurthy KB, Olin B, Schachter SC, Verrier RL. Cardiac electrical instability in newly diagnosed/chronic epilepsy tracked by Holter and ECG patch.

77. Berei TJ, Lillyblad MP, Almquist AK. Lacosamide-Induced Recurrent Ventricular Tachycardia in the Acute Care Setting.

78. DeGiorgio AC, Desso TE, Lee L, DeGiorgio CM. Ventricular tachycardia associated with lacosamide co-medication in drug-resistant epilepsy.

Num estudo conduzido na Noruega, não foram encontradas diferenças estatisticamente significativas na frequência de crises, entre o grupo SUDEP e o grupo controlo, constatação que os autores atribuíram ao facto de os doentes terem sido selecionados com base no mau controlo de crises: doentes com baixa frequência de crises estavam pouco representados nos dois grupos (73).

Relacionado com a frequência de crises está o controlo das mesmas, uma vez que pode ser um fator que reduz o risco de SUDEP (13, 74). No entanto, alguma medicação antiépilética pode, teoricamente, ter o efeito oposto, através de efeitos cardíacos diretos ou indiretos (secção 4.8) (75-78).

4.3. Duração da epilepsia

A duração da epilepsia **não é um fator de risco consistente**. Enquanto alguns estudos a consideram como tal (31, 67), outros não encontraram diferenças significativas entre o grupo SUDEP e os controlos (73).

Hesdorffer et al. encontraram uma associação entre a duração da epilepsia superior a 15 anos e um risco aumentado em 1,95 vezes de ocorrer SUDEP (67), sendo que a maioria dos estudos reporta uma duração média da epilepsia de 15 a 20 anos, nos casos de SUDEP (25).

4.4. Idade de início da epilepsia

A idade de início da epilepsia é outro dos fatores que tem vindo a ser reportado como sendo de risco para SUDEP (18, 73). No estudo de Kloster et al., a idade de início da epilepsia foi significativamente inferior no grupo SUDEP à do grupo controlo (73). A mesma associação entre **início precoce da epilepsia** (infância/início da adolescência) e maior risco de SUDEP foi encontrada por Nilsson et al., mas apenas no sexo masculino (18).

Numa análise combinada de 4 estudos caso-controlo dos Estados Unidos da América, Suécia, Escócia e Inglaterra, os doentes com início da epilepsia antes dos 16 anos de idade tiveram um aumento estatisticamente significativo de 1,72 vezes, no risco de SUDEP, quando comparados com os que iniciaram a epilepsia entre os 16 e os 60 anos (67).

4.5. Crises noturnas

As **crises noturnas** também podem aumentar o risco de SUDEP (79), havendo uma grande percentagem de casos encontrados na cama (33, 80, 81). Embora a evidência seja baixa de que as crises noturnas alterem o risco de SUDEP (20), Lamberts et al. consideraram-nas um fator de risco independente (79). A depressão respiratória pós-ictal é frequente em casos de SUDEP. As crises noturnas não vigiadas que cursarem com depressão respiratória poderão levar a SUDEP, com maior probabilidade (20).

A supervisão noturna de doentes com história de crises noturnas pode ser uma opção, para que a assistência seja prestada atempadamente, para prevenir a paragem respiratória (20, 79). No entanto, providenciar essa supervisão noturna pode ser demasiado pesado para os cuidadores e intrusivo para os doentes (20).

4.6. Má adesão terapêutica

A **má adesão à medicação antiepilética** tem sido outro dos fatores de risco propostos para SUDEP, sobretudo com base em relatórios de concentrações séricas baixas ou indetetáveis de fármacos anti-crisis epiléticas (FACE), *post-mortem*, nos casos de SUDEP (12, 73, 82). Contudo, como as concentrações de alguns fármacos, como a Fenitoína, sofrem alterações *post-mortem*, as baixas concentrações devem ser interpretadas com cuidado (83).

Por outro lado, Opeskin et al. não encontraram diferenças estatisticamente significativas nos níveis dos FACE, entre os casos de SUDEP e doentes com epilepsia que morreram por outras causas (84), e outro estudo caso-controlo avaliou a adesão terapêutica e concluiu que não era diferente nos dois grupos (19).

4.7. Número de fármacos anti-crisis epiléticas

A **politerapia** (três ou mais FACE) também tem sido associada a um maior risco de SUDEP (18, 19, 67), quer isoladamente, quer quando analisada em conjunto com as crises TCG, tendo sido descrito um maior risco em doentes com crises TCG e politerapia, quando comparados com os doentes sem crises TCG e sem politerapia (67). No entanto, num estudo subsequente, desenhado especificamente para esclarecer esse aspeto, concluiu-se que, ajustando para o número de crises TCG, não existia risco aumentado de SUDEP, relacionado com a politerapia (85).

Apesar de dever ser tido em conta o facto de que o número de FACE pode refletir simplesmente uma epilepsia refratária, no estudo de Nilsson et al., o risco de SUDEP aumentou com o número de FACE concomitantemente no último ano, permanecendo quando se controlou para a frequência de crises. Os autores concluem que esse aumento do risco não pode dever-se apenas à associação com a gravidade da doença (18).

Kloster et al. não encontraram qualquer associação entre politerapia e risco de SUDEP. No seu estudo caso controlo, não encontraram diferenças estatisticamente significativas no número de FACE entre o grupo SUDEP e doentes com epilepsia que morreram por outras causas (73).

79. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk.

80. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors.

81. Nashef L, Garner S, Sander JW, Fish DR, Shorvon SD. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives.

82. Bowerman DL, Levisky JA, Ulrich RW, Wittenberg PH. Premature deaths in persons with seizure disorders--subtherapeutic levels of anticonvulsant drugs in postmortem blood specimens.

83. Tomson T, Sköld AC, Holmgren P, Nilsson L, Danielsson B. Postmortem changes in blood concentrations of phenytoin and carbamazepine: an experimental study.

84. Opeskin K, Burke MP, Corderner SM, Berkovic SF. Comparison of antiepileptic drug levels in sudden unexpected deaths in epilepsy with deaths from other causes.

85. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis.

4.8. Fármacos anti-criSES epiléticas específicos

Alguns estudos referem a possibilidade, pelo menos teórica, de que alguns **FACE específicos** possam aumentar o risco de SUDEP (69, 86, 87).

Outros autores, no entanto, não encontraram qualquer risco aumentado de SUDEP relacionado com FACE específicos (18, 19, 67, 84, 85).

As arritmias cardíacas induzidas por FACE são raras e, numa revisão de Tomson et al., ocorreram sobretudo em doentes idosos ou predispostos a arritmias, que os autores consideraram populações diferentes das que têm uma elevada incidência de SUDEP (75). Sob doses terapêuticas (e nos idosos), predominam as bradiarritmias, enquanto a taquicardia sinusal é a principal arritmia na presença de *overdose* (75).

Vários autores referem que a **Carbamazepina** exerce um efeito depressor no sistema condutor cardíaco. O mecanismo deste possível efeito adverso não é claro. A Carbamazepina, assim como outros FACE, partilha propriedades de bloqueio dos canais de sódio com outros fármacos antiarrítmicos que também são proarrítmicos e que têm sido associados a um aumento da mortalidade. Pode relacionar-se com o prolongamento do intervalo QT induzido por este fármaco (88), combinado com um efeito pró-arrítmico moderado das descargas das crises epiléticas, provocando instabilidade cardíaca transitória e levando a morte por arritmia (69).

Há estudos que associaram doses elevadas de Carbamazepina a um maior risco de SUDEP, em doentes em politerapia ou com mudanças frequentes da dose, mas ressalvam que estes fatores podem simplesmente dever-se a uma epilepsia grave e instável (87). Timmings et al. verificaram que a Carbamazepina foi usada em 85% dos casos de SUDEP, comparado com 38% nos controlos (mortes por outras causas). No entanto, não controlaram outros fatores de risco potencialmente confundidores, como a frequência de crises, a politerapia ou a duração da epilepsia (69).

Muitos FACE diminuem a variabilidade da frequência cardíaca (VFC), especialmente os bloqueadores dos canais de sódio, contribuindo para um compromisso da atividade autonómica cardíaca e estando associados a maior risco de morte súbita cardíaca (76, 89).

Aurlien et al., num estudo realizado na Noruega em 2012, de 26 casos SUDEP, verificaram que 10 das 11 mulheres que sofreram SUDEP estavam medicadas com **Lamotrigina** (86). O mesmo grupo, numa revisão em 2016, refere não haver evidência de que a Lamotrigina aumente o risco de SUDEP. No entanto, ressalva o subgrupo de doentes com epilepsia generalizada idiopática (EGI) tratados com Lamotrigina, nos quais parece haver risco acrescido, mas que pode dever-se ao facto de este FACE conferir menor proteção em doentes com EGI, quando comparado com o Valproato (90).

Tomson et al. também avaliaram o risco de SUDEP no grupo tratado com Lamotrigina, comparando com um grupo tratado com placebo, não tendo encontrado diferenças na taxa de SUDEP entre os dois grupos (91).

Num artigo recente (92), a ILAE e a AES contestaram um aviso da FDA no folheto informativo da Lamotrigina, na qual esta última organização (com base num estudo *in vitro*) chama a atenção para as possíveis anomalias arrítmicas

86. Aurlien D, Larsen JP, Gjersetad L, Taubøll E. Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case-control study.

87. Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study.

88. Kennebäck G, Bergfeldt L, Vallin H, Tomson T, Edhag O. Electrophysiologic effects and clinical hazards of carbamazepine treatment for neurologic disorders in patients with abnormalities of the cardiac conduction system.

89. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy.

90. Aurlien D, Gjersetad L, Taubøll E. The role of antiepileptic drugs in sudden unexpected death in epilepsy.

91. Tomson T, Hirsch LJ, Friedman D, Bester N, Hammer A, Irizarry M, et al. Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials.

e de condução do fármaco, pela sua ação nos canais de sódio. O aviso refere a possibilidade de atrasar a condução ventricular (prolongar o QRS) e induzir proarritmia, incluindo morte súbita, em pessoas com alterações da condução cardíaca (ex.: bloqueios de segundo ou terceiro grau), arritmias ventriculares ou outra anomalia/doença cardíaca (ex.: isquemia miocárdica, insuficiência cardíaca, síndrome de Brugada ou outra canalopatia do íon sódio). Neste artigo, a ILAE e a AES, baseando-se nos estudos em humanos, consideraram não haver risco aparente de arritmia, provocada pela Lamotrigina, em pessoas sem doença cardíaca, visto, nessa população, não haver alterações do QRS ou do intervalo QT, e apenas um ligeiro prolongamento do intervalo PR, mesmo em doses elevadas (93-95). Referem, ainda, que até à data não foi demonstrado um risco aumentado de morte súbita em doentes sob Lamotrigina, quando comparados com outros FACE, embora esse hipotético aumento possa teoricamente não ser notado, se ocorrer a uma frequência muito baixa, quando comparada com a de SUDEP (92).

Os novos fármacos bloqueadores dos canais de sódio, como a **Lacosamida**, também têm sido associados a maior risco de morte súbita cardíaca e paragem cardíaca (77, 78).

A **Fenitoína** endovenosa é outro dos FACE apontado como eventual fator de risco para SUDEP, na medida em que também pode causar arritmias potencialmente fatais (96).

Nas recomendações da AAN/AES, foi considerado que a evidência é muito baixa ou contraditória de que a Carbamazepina, a Fenitoína ou o Valproato (quer em níveis terapêuticos, quer abaixo ou acima desses níveis) estivessem associados a alteração do risco de SUDEP, bem como o uso de Lamotrigina em doentes com epilepsia altamente refratária (20).

4.9. Sexo masculino

Em alguns estudos, foi encontrada uma preponderância de indivíduos do sexo masculino, nos casos de SUDEP, o que levou a que fosse considerado um fator de risco (67, 69, 97).

Pelo contrário, outros artigos referem não terem sido encontradas diferenças estatisticamente significativas, relativamente ao sexo, entre o grupo SUDEP e o não-SUDEP (73). Walkzac et al., para além de não terem encontrado associação entre o sexo masculino e SUDEP, referem que a SUDEP foi mais frequente em mulheres (19), o que também foi descrito por Ficker et al. (12).

A AAN e a AES, na orientação conjunta, consideraram baixa a evidência de que o sexo masculino aumentasse o risco de SUDEP, não fazendo recomendações relativamente a esta possibilidade (20).

4.10. Atraso mental

O atraso mental é outro fator que tem sido reportado como de risco para SUDEP, estando presente em 5-45% dos casos (19, 31, 97). No entanto, tal pode dever-se simplesmente a que é frequente em doentes com epilepsia, sobretudo refratária.

Este fator também não é consistente, uma vez que outros autores não o confirmaram (17, 73).

92. French JA, Perucca E, Sander JW, Bergfeldt L, Baulac M, Auerbach DS, et al. FDA Safety Warning on the Cardiac Effects of Lamotrigine: An Advisory From the Ad Hoc ILAE/AES Task Force.

93. Saetre E, Abdelnoor M, Amlie JP, Tossebro M, Perucca E, Taubøll E, et al. Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine.

94. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, et al. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects.

95. Dixon R, Alexander S, Brickel N. Effect of lamotrigine on the PR interval in healthy subjects.

96. Barron SA. Cardiac arrhythmias after small iv dose of phenytoin.

97. Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada.

98. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty.

99. Terrence CF, Rao GR, Perper JA. Neurogenic pulmonary edema in unexpected, unexplained death of epileptic patients.

100. Bird JM, Dembny KAT, Sandeman D, Butler S. Sudden Unexplained Death in Epilepsy: An Intracranially Monitored Case.

101. Biton V, Gates JR, dePadua Sussman L. Prolonged postictal encephalopathy.

102. DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention.

103. Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy.

104. McGregor A, Wheless J. Pediatric experience with sudden unexplained death in epilepsy at a tertiary epilepsy center.

105. Oguz Akarsu E, Şahin E, Ozel Yıldız S, Bebek N, Gürses C, Baykan B. Peri-ictal Prone Position Is Associated With Independent Risk Factors For Sudden Unexpected Death In Epilepsy: A Controlled Video-EEG Monitoring Unit Study.

106. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy.

107. Surges R, Strzelczyk A, Scott CA, Walker MC, Sander JW. Postictal generalized electroencephalographic suppression is associated with generalized seizures.

Teoricamente, o risco aumentado de SUDEP em doentes com atraso mental poderia ser explicado por um dos possíveis mecanismos fisiopatológicos de SUDEP (19). Os estudos em animais (59, 60), a observação clínica (31, 81, 98, 99), os casos monitorizados por EEG (27, 100) e vídeo sugerem a presença de uma combinação de apneia central pós-ictal, decúbito ventral e edema pulmonar neurogénico que provoca a morte. Um estudo mostrou maior vulnerabilidade de indivíduos com atraso mental (ligeiro a moderado) para sofrerem encefalopatia pós-ictal prolongada (101), o que pode diminuir o *drive* respiratório. As alterações neurológicas que estão frequentemente associadas a atraso mental podem impedir os movimentos e os reflexos em doentes em decúbito ventral, após uma crise TCG. Por tudo o exposto, é possível que os doentes com atraso mental possam ter maior suscetibilidade tanto para apneia central, como para obstrutiva (asfixia posicional), podendo levar a casos de SUDEP (19).

A evidência foi considerada baixa de que o atraso mental constitua um fator de risco para SUDEP, pela AAN e a AES (20).

4.11. Circunstâncias da morte

Trinta a 50% dos casos de SUDEP são encontrados na cama, sendo frequentes os relatos de posição em **decúbito ventral** (27, 28, 32, 73, 102-104). Akarsu et al. encontraram uma associação entre o decúbito ventral e fatores de risco independentes para SUDEP (105).

É possível que uma crise terminal, durante o **sono**, em que o doente fique em decúbito ventral, possa estar associada a maior risco de SUDEP (102). Um estudo de Lamberts et al. considerou haver evidência de que as **crises noturnas** constituem um fator de risco independente para SUDEP, uma vez que os casos de morte súbita tiveram mais frequentemente uma história de crises noturnas do que os controlos (doentes vivos, com epilepsia) (79). Estas circunstâncias, acima descritas, podem estar interligadas.

A AAN e a AES também consideraram que a evidência é baixa de existir associação entre crises noturnas e maior risco de SUDEP (20).

4.12. Supressão pós-ictal generalizada do EEG (PGES)

A PGES é um fenómeno eletrofisiológico que pode ser observado após as crises. Foi originalmente definida por Lhatoo et al. (106) como a ausência generalizada de atividade eletrográfica >10 µV em amplitude, nos 30 s que se seguem ao fim da crise, tendo em conta os artefactos musculares, de movimento, respiratórios e dos eléctrodos. Tipicamente, ocorre após uma crise TCG.

No sentido de compreender o papel da PGES como fator de risco de SUDEP, foram comparados 10 doentes que tinham sido internados numa UME e que mais tarde morreram de SUDEP, com 30 controlos (doentes vivos com epilepsia). A duração da PGES foi significativamente superior no grupo SUDEP do que nos controlos. Uma PGES >50 s pareceu identificar doentes com epilepsia refratária com maior risco de SUDEP. Quando a duração foi >80 s, o risco de SUDEP aumentou 4 vezes (106). No entanto, esses achados não foram confirmados num outro estudo caso-controlo (107).

A PGES está associada a níveis de saturação de oxigênio mais baixos, dessaturações mais prolongadas e níveis mais baixos de CO₂ expirado (108), o que sugere que possa levar a hipoxemia após as crises (um dos possíveis mecanismos fisiopatológicos de SUDEP).

5. Escala de risco SUDEP-7 inventory

Esta escala foi desenvolvida para ajudar a identificar os doentes em risco de SUDEP.

DeGiorgio et al. e Novak et al. desenvolveram a escala SUDEP-7 (109, 110), a partir da ponderação de alguns dos fatores de risco primeiramente identificados por Walczak et al., num grande estudo coorte (19).

As razões de chances (*odds ratio*, OR) para cada um dos 7 fatores de risco principais do estudo original são seguidas da aplicação do logaritmo natural (ln) e arredondamento ao número inteiro mais próximo, para se obter uma ponderação de 0, 1, 2 ou 3, para cada fator de risco (Tabela 1). Os fatores de risco com maior peso são a duração da epilepsia, a frequência de crises de qualquer tipo >50/mês e >3 crises TCG no último ano, bem como a deficiência do desenvolvimento.

Escala de risco SUDEP-7 (versão 2.0)	OR	Ponderação ln(OR)
Mais do que 3 crises TCG no último ano	8,1	0 or 2
Uma ou mais crises TCG no último ano (se estiver presente o fator 1, valorizar 0)	2,4	0 or 1
Uma ou mais crises de qualquer tipo nos últimos 12 meses (se estiver presente o fator 4, valorizar 0)	2,2, 3,8, 4,6*	0 or 1
Mais do que 50 crises de qualquer tipo por mês, no último ano	11,5	0 or 2
Duração da epilepsia > 30 anos	13,9	0 or 3
Uso de 3 ou mais FACE	4,0	0 or 1
Deficiência do desenvolvimento, Q.I.< 70 ou compromisso demasiado grave para testar	5,0	0 or 2

Tabela 1. Escala de risco SUDEP-7, versão 2.0. Adaptado de Novak et al., 2015 (110). OR: razão de *odds*.

*OR múltiplas refletem as seguintes frequências médias de quaisquer crises no último mês, durante um período de 12 meses: ≤1, >1 a ≤15, >15 a ≤50.

Esta escala tem sido utilizada por vários autores, correlacionando-a com biomarcadores de risco de SUDEP. No entanto, ainda carece de validação externa em populações independentes (102).

6. Alterações genéticas e SUDEP

É reconhecido que cerca de 35% de todas as mortes súbitas e 15% de todas as síndromes de morte súbita na infância (<1 ano de idade) têm subjacente uma mutação em um dos genes conhecidos associados às canalopatias, o que poderia explicar a causa de morte em alguns doentes (111). Por outro lado, há

108. Seyal M, Hardin KA, Bate-man LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea.

109. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory.

110. Novak JL, Miller PR, Markovic D, Meymandi SK, DeGiorgio CM. Risk Assessment for Sudden Death in Epilepsy: The SUDEP-7 Inventory.

111. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA).

112. Fialho GL, Wolf P, Walz R, Lin K. SUDEP - more attention to the heart? A narrative review on molecular autopsy in epilepsy.

113. Nashef L, Hindocha N, Makoff A. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms.

114. Kullmann DM. Neurological channelopathies.

115. Hirose S. A new paradigm of channelopathy in epilepsy syndromes: intracellular trafficking abnormality of channel molecules.

116. Heron SE, Scheffer IE, Berkovic SF, Dibbens LM, Mulley JC. Channelopathies in idiopathic epilepsy.

117. Oliva M, Berkovic SF, Petrou S. Sodium channels and the neurobiology of epilepsy.

118. Mei D, Cetica V, Marini C, Guerrini R. Dravet syndrome as part of the clinical and genetic spectrum of sodium channel epilepsies and encephalopathies.

119. Bagnall RD, Crompton DE, Petrovski S, Lam L, Cutmore C, Garry SI, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy.

120. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome.

121. Donner EJ, Camfield P, Brooks L, Buchhalter J, Camfield C, Loddenkemper T, et al. Understanding Death in Children With Epilepsy.

122. Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome.

123. Shmueli S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: A review.

124. Li MCH, O'Brien TJ, Todaro M, Powell KL. Acquired cardiac channelopathies in epilepsy: Evidence, mechanisms, and clinical significance.

125. Hedley PL, Jørgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, et al. The genetic basis of long QT and short QT syndromes: a mutation update.

evidência crescente de que as canalopatias cardíacas e as neuronais se sobrepõem (90). O cérebro e o coração partilham alguns genes relacionados tanto com a epilepsia como com um risco arritmico aumentado (112, 113).

As canalopatias são doenças provocadas por mutações nos genes que codificam os canais iônicos. São geralmente heterogêneas, tanto genotípica como fenotipicamente, sendo que a mesma condição genética pode ser provocada por mutações diferentes e uma dada mutação pode causar fenótipos diferentes, ainda que na mesma família (114, 115).

As epilepsias genéticas têm sido associadas a mutações em genes que codificam os canais de sódio, potássio, cálcio e cloro, assim como aos recetores nicotérgicos da acetilcolina do ácido gama-aminobutírico (GABA). De entre todas, as mais comuns são as mutações dos canais de sódio (116, 117).

Certas síndromes genéticas de epilepsia também estão associadas a um maior risco de SUDEP (13). A **síndrome de Dravet** é a forma de epilepsia genética mais estudada (118). Esta síndrome é uma encefalopatia epilética de início na infância, a maioria das vezes secundária a mutações no gene SCN1A (13, 118, 119). O fenótipo principal é caracterizado por crises epiléticas intratáveis (sobretudo clónicas), precipitadas por aumento da temperatura corporal, com início no primeiro ano de vida, e pelo aparecimento subsequente de múltiplos tipos de crises, também, mas não só, precipitadas por hipertermia. Quando a síndrome completa se manifesta, o compromisso cognitivo também está presente (118, 120). Os indivíduos com síndrome de Dravet têm risco aumentado de SUDEP e mortalidade prematura (120-123). A SUDEP é responsável por até 59% das mortes em doentes com Síndrome de Dravet (122, 123).

Outros exemplos de genes relacionados tanto com epilepsia, como com arritmias cardíacas são os genes KCNQ1 e KCNH2 (síndrome do QT longo 1 e 2, respetivamente), RYR2 (taquicardia ventricular polimórfica catecolaminérgica) e SCN5A (síndrome de Brugada e síndrome do QT longo 3) (63, 119, 124). Cerca de 20% dos indivíduos com síndrome do QT longo tipo 1 e de 39% com tipo 2 também têm um fenótipo de epilepsia (119, 124).

A síndrome congénita do QT longo é causada por genes que codificam canais iônicos cardíacos, sobretudo do potássio e, numa proporção menor, do sódio, estando associada a prolongamento do intervalo QT, no ECG, e a uma propensão para síncope, *torsade de pointes* e fibrilhação ventricular (125).

Bagnall et al. encontraram variantes genéticas patogénicas *de novo* ou previamente descritas, em 28 de 61 casos de SUDEP (119). Numa revisão sistemática recente, foram analisados 8 estudos sobre SUDEP (161 indivíduos) que reportaram variantes patogénicas ou provavelmente patogénicas em 11% dos casos, sobretudo relacionadas com as subunidades dos canais iônicos de sódio e potássio (126).

Indivíduos com mutações no gene SCN8A apresentam uma encefalopatia de início na infância, caracterizada por atraso no desenvolvimento, início de crises epiléticas nos primeiros 18 meses de vida e epilepsia intratável, com múltiplos tipos de crises, e também podem ter risco aumentado de SUDEP (127). No entanto, Johannesen et al. não encontraram aumento desse risco nestes doentes, quando comparados com doentes com outras encefalopatias epiléticas e do desenvolvimento (128).

Em modelos animais, verificou-se que a epilepsia e a disfunção autonómica crónica, com conseqüente toxicidade catecolaminérgica miocárdica crónica, podem potencialmente alterar as expressões epigenética e fenotípica dos canais iónicos miocárdicos, ou seja, uma forma adquirida de canalopatias (112, 129)

O bloqueio de canais iónicos é o mecanismo de ação mais importante da maioria dos FACE. Muitos deles são bloqueadores dos canais de sódio, podendo ser menos eficazes e até agravar as epilepsias genéticas (90).

7. Alterações cardíacas morfofuncionais

7.1. Síndrome de Takotsubo

A síndrome de Takotsubo é caracterizada pelo início súbito de dor torácica e dispnéia, acompanhadas por alterações eletrocardiográficas semelhantes às da síndrome coronária aguda, elevação das enzimas cardíacas e alterações transitórias da contractilidade do miocárdio, sem causa aparente (130-132). Os mecanismos fisiopatológicos também não estão completamente clarificados, sendo possível que ocorra vasospasmo coronário, disfunção da microcirculação e obstrução transitória à ejeção do ventrículo esquerdo. Um aumento excessivo da libertação de catecolaminas parece ter um papel crucial no desenvolvimento da doença, uma vez que o fator precipitante é, muitas vezes, um *stress* súbito e inesperado, que pode ser físico ou emocional (130). Entre esses possíveis fatores precipitantes, estão as crises epiléticas (130), existindo descritos, até recentemente, mais de 100 casos (133-141). A síndrome de Takotsubo induzida por crises epiléticas pode ocorrer imediatamente após uma crise ou horas após (131).

Esta síndrome tem sido considerada como relativamente benigna com rápida recuperação da função do ventrículo esquerdo. No entanto, há evidência crescente de que é uma doença cardíaca mais séria e com variadas complicações em cerca de 52% dos doentes, incluindo insuficiência cardíaca aguda, obstrução à ejeção do ventrículo esquerdo, regurgitação mitral, choque cardiogénico, arritmias, formação de trombos, derrame pericárdico, rotura da parede ventricular e envolvimento do ventrículo direito (130). A mortalidade em doentes internados é de 2-5%, sobretudo causada por choque cardiogénico refratário ou fibrilhação ventricular (130). Uma vez que a morte é uma das complicações possíveis, há casos descritos de SUDEP que podem ser atribuídos a esta síndrome. No entanto, esses casos são raros e Finsterer et al. consideraram que a síndrome de Takotsubo desencadeada por crises epiléticas não parece desempenhar um papel importante na patogénese da SUDEP (133).

7.2. Coração Epilético – *The epileptic heart*

A morte súbita cardíaca ocorre 2,8 vezes mais frequentemente em doentes com epilepsia e 5,8 vezes mais frequentemente em doentes com epilepsia refratária, quando comparamos com a população em geral (142).

Em 1997, quando definiu SUDEP, Lina Nashef excluiu dessa definição as mortes que ocorrem após crises epiléticas habituais, mas cuja autópsia demonstrou doença cardiorrespiratória significativa, embora a crise epilética devesse ser considerada uma causa contribuidora (6).

No entanto, a própria investigadora antecipou que muitos dos mecanismos fisiológicos e moleculares da SUDEP seriam descobertos no futuro, e que esse facto

126. Chahal CAA, Salloum MN, Alahdab F, Gottwald JA, Tester DJ, Anwer LA, et al. Systematic Review of the Genetics of Sudden Unexpected Death in Epilepsy: Potential Overlap With Sudden Cardiac Death and Arrhythmia-Related Genes.

127. Hammer MF, Wagnon JL, Mefford HC, Meisler MH. SCN8A-Related Epilepsy with Encephalopathy.

128. Johannesen KM, Gardella E, Scheffer I, Howell K, Smith DM, Helbig I, et al. Early mortality in SCN8A-related epilepsies.

129. Brewster AL, Marzec K, Hairston A, Ho M, Anderson AE, Lai YC. Early cardiac electrographic and molecular remodeling in a model of status epilepticus and acquired epilepsy.

130. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology.

131. Stöllberger C, Sauerberg M, Finsterer J. Immediate versus delayed detection of Takotsubo syndrome after epileptic seizures.

132. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy.

133. Finsterer J, Bersano A. Seizure-triggered Takotsubo syndrome rarely causes SUDEP.

134. Kyi HH, Aljariri Alhesan N, Upadhaya S, Al Hadidi S. Seizure Associated Takotsubo Syndrome: A Rare Combination.

135. Miller GA, Ahmed YM, Tarant NS. Recurrence of Postoperative Stress-Induced Cardiomyopathy Resulting from Status Epilepticus.

136. Mugnai G, Pasqualin G, Prati D, Menegatti G, Vassanelli C. Recurrent multifocal Takotsubo cardiomyopathy in a patient with epilepsy: Broken heart or brain?

não deveria impedir que essas mortes fossem consideradas SUDEP. Explica que o mais importante é focarmos os nossos esforços de investigação na diminuição da mortalidade, através da correção de mecanismos causais, à medida que cada um for sendo identificado, em vez de 'perseguirmos' um cada vez mais estreito grupo de mortes inexplicadas (4).

Nesse sentido, Verrier et al. propuseram o conceito de Coração epilético (*Epileptic heart*), como sendo um 'coração e uma vasculatura coronária lesionados por epilepsia crónica, como resultado de ondas repetidas de catecolaminas e hipoxemia, levando a disfunção elétrica e mecânica' (143). Uma vez que são encontradas lesões potencialmente fatais em muitos dos casos, estes 'fogem' da definição de SUDEP de Nashef, mas podem corresponder a casos que seriam considerados SUDEP há alguns anos e para os quais já se encontrou a causa. Para os autores, esta nova definição tem importantes implicações em abordagens potencialmente preventivas de morte súbita em doentes com epilepsia.

Com base em:

- dados de autópsia de doentes com epilepsia
- modelos pré-clínicos de patologia cardíaca induzida por crises epiléticas
- evidência clínica de morbimortalidade cardíaca em doentes com epilepsia crónica
- evidência de patologia cardíaca no ECG de doentes com epilepsia,

os autores sugerem que a epilepsia crónica exerça um impacto negativo na integridade estrutural do coração e da sua vasculatura. Essas alterações levariam a instabilidade elétrica cardíaca, vulnerabilidade para arritmias potencialmente fatais e função autonómica alterada. A suscetibilidade para arritmia e a instabilidade elétrica cardíaca podem ainda ser agravadas por FACE que bloqueiam os canais de sódio e por efeitos laterais dos FACE nos perfis lipídicos. Esta proposta de mecanismos fisiopatológicos está ilustrada na Figura 3.

137. Grimaldi S, Doche E, Rey C, Laksiri N, Boussen S, Quilici J, et al. Association of Posterior Reversible Encephalopathy Syndrome and Transient Apical Ballooning Syndrome (Takotsubo): First Case Report of a Man and Review of the Literature.

138. Chieffo R, Bernelli C, Martirelli V, Comi G, Roveri L. Todd's post-epileptic paresis and Takotsubo cardiomyopathy: unusual combination of neurological and cardiac disorder. Trigger or triggered?

139. Harris ZM, Alonso A, Kennedy TP. Adrenergic Inhibition with Dexmedetomidine to Treat Stress Cardiomyopathy during Alcohol Withdrawal: A Case Report and Literature Review.

140. Uemura J, Wada Y, Yagita Y. [Non-convulsive status epilepticus with Takotsubo cardiomyopathy: a case report].

141. Warren J, Baber U, Mohanty B, Sharma SK, Kini A, Mehran R. Seizure-related takotsubo cardiomyopathy in a patient with recurrent malignant meningioma.

142. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MC, Tan HL. Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications.

143. Verrier RL, Pang TD, Nearing BD, Schachter SC. The Epileptic Heart: Concept and clinical evidence.

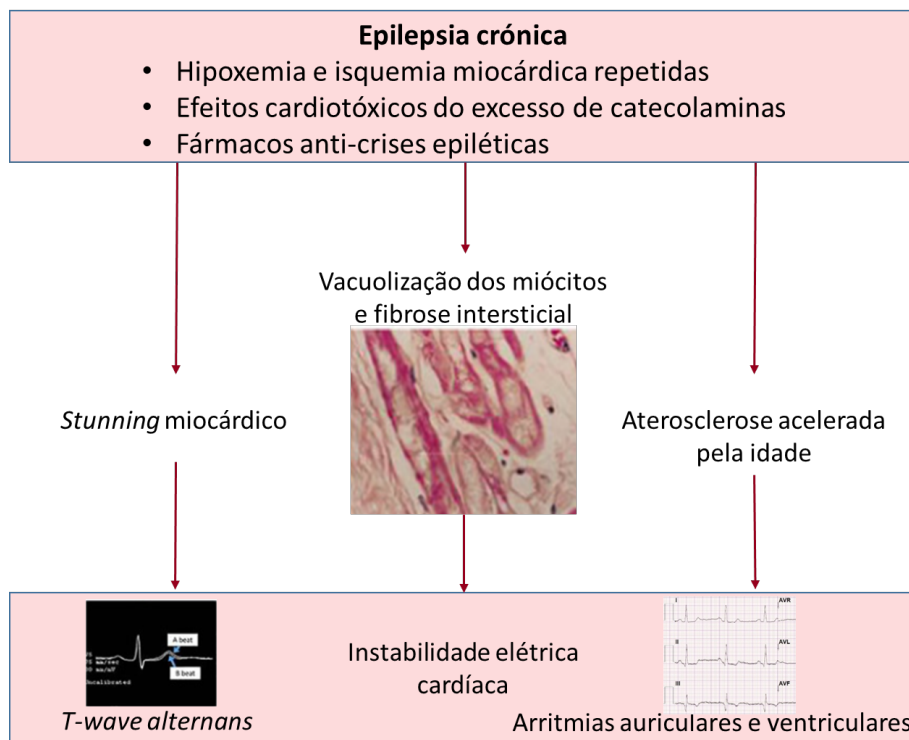


Figura 3. Possível ligação entre epilepsia e progressão aumentada de doença cardiovascular. Adaptado de Verrier et al., 2020 (143)

Os dados que reviram sugerem múltiplos mecanismos fisiopatológicos e modelos de morte prematura em doentes com epilepsia. Consideram, portanto, importante revisitar a definição tradicional de SUDEP, que exclui causas de mortalidade identificadas, incluindo causas cardíacas, para incluir o ‘coração epilético’.

A figura 4 mostra a inter-relação proposta pelos autores, entre SUDEP e morte súbita cardíaca em doentes com epilepsia.

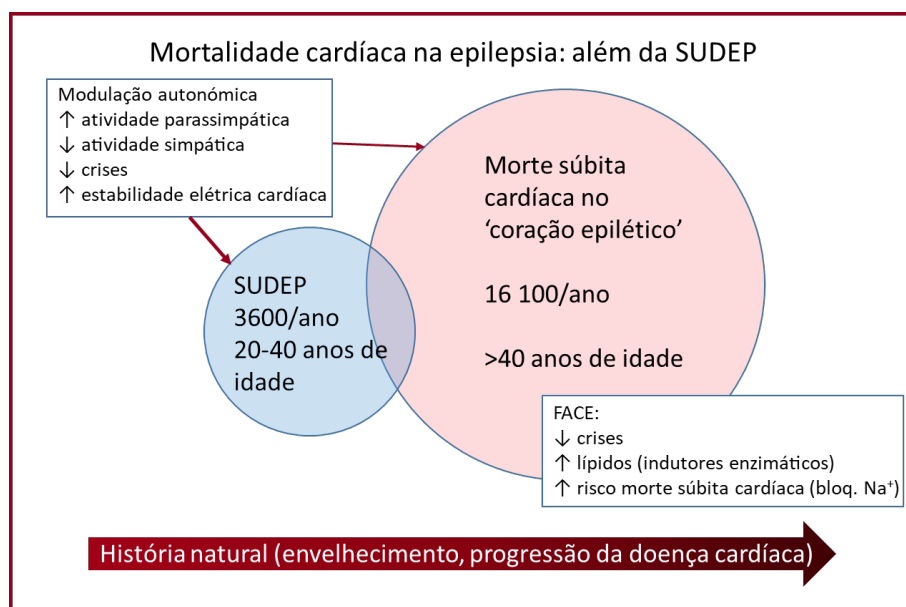


Figura 4. Diagrama de Venn da inter-relação entre SUDEP e morte súbita cardíaca em doentes com epilepsia. Adaptado de Verrier et al., 2020 (143)

Contudo, o seguimento clínico dos doentes com epilepsia crónica ainda não inclui, por rotina, avaliações cardíacas. A incidência elevada de doença cardíaca em doentes com epilepsia, incluindo angina e enfarte do miocárdio, sublinha a necessidade de incorporar a avaliação cardíaca como parte essencial do seguimento de doentes com epilepsias de longa duração.

8. Biomarcadores

Existe uma necessidade premente de identificar biomarcadores, que ajudem a distinguir doentes com maior risco de sofrer SUDEP, para que possam ser sujeitos a uma vigilância mais apertada.

Ao longo do tempo, foram surgindo múltiplos candidatos, mas, infelizmente, nenhum provou ser um biomarcador inequívoco de SUDEP. É fundamental prosseguir com a investigação nesta área, que se tem focado mais nos potenciais marcadores eletrocardiográficos, eletroencefalográficos, séricos e de imagem [Ressonância magnética nuclear (RMN) e RMN funcional] (102).

Cada uma destas áreas tem contribuído para se conhecer melhor o risco individual de SUDEP, podendo ser utilizada para identificar os candidatos apropriados para determinadas intervenções para reduzir o risco (102).

144. Nass RD, Meiling S, Andrié RP, Elger CE, Surges R. Laboratory markers of cardiac and metabolic complications after generalized tonic-clonic seizures.

145. Sieweke N, Allendörfer J, Franzen W, Feustel A, Reichenberger F, Pabst W, et al. Cardiac Troponin I elevation after epileptic seizure.

146. Fawaz A, Nasreddine W, Makke Y, Atweh S, Wazne J, Arabi M, et al. Association of cardiovascular risk factors and troponin elevation after generalized tonic-clonic seizures.

147. Chatzikonstantinou A, Ebert AD, Hennerici MG. Temporal seizure focus and status epilepticus are associated with high-sensitive troponin I elevation after epileptic seizures.

148. Rauchenzauner M, Haberlandt E, Foerster S, Ulmer H, Laimer M, Ebenbichler CF, et al. Brain-type natriuretic peptide secretion following febrile and afebrile seizures - a new marker in childhood epilepsy?

149. Sohn HS, Kim SK, Lee SY. Inflammatory markers associated with seizures.

150. Park KI. Plasma brain-type natriuretic Peptide level following seizure and syncope: pilot study.

151. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018).

152. Jaffe AS. New standard for the diagnosis of acute myocardial infarction.

153. Baker P, Leckie T, Harrington D, Richardson A. Exercise-induced cardiac troponin elevation: An update on the evidence, mechanism and implications.

154. Parekh N, Venkatesh B, Cross D, Leditschke A, Atherton J, Miles W, et al. Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage.

155. Chin PS, Branch KR, Becker KJ. Postictal neurogenic stunned myocardium.

Neste projeto de doutoramento, que se foca nas alterações cardíacas ictais, em doentes com epilepsia refratária, foram investigados possíveis biomarcadores cardíacos de SUDEP, que passo a desenvolver.

8.1 Biomarcadores séricos

Após crises epiléticas, estão descritos aumentos de diferentes marcadores séricos, muitos deles de lesão/disfunção miocárdica, podendo refletir lesões cardíacas, possivelmente associadas a SUDEP.

Até ao momento, a maioria dos estudos nesta área usou metodologias diferentes, de natureza retrospectiva (144-146) e/ou incluía apenas doentes admitidos em salas de emergência (144, 147-150).

8.1.1 Troponina I

As Troponinas I (cTnI) e T (cTnT) são biomarcadores de lesão miocárdica com sensibilidade e especificidade elevadas (151, 152) e as orientações mais recentes recomendam o uso clínico, por rotina, dos *kits* de ensaio de elevada sensibilidade (hs) (151). Baker et al. consideram que, para ser válida, é necessária uma alteração de 50-60%, quando o valor de base se encontra abaixo do percentil 99 do limite superior de referência (153).

Em algumas doenças neurológicas, como a hemorragia subaracnoideia, a cTnI está já estabelecida como um marcador altamente sensível e específico de disfunção cardíaca (154). No entanto, a presença de Troponina elevada, por si só, não identifica os mecanismos fisiopatológicos de lesão miocárdica subjacentes. Pode ser provocada por *stress* fisiológico ou estiramento relacionado com a pré-carga, em corações normais (151). A isquemia miocárdica pode ser causada não só por lesões vasculares, mas também por um desajuste entre o fornecimento e a necessidade de oxigénio no miocárdio (151), o que é mais provável que aconteça após crises epiléticas (146-150).

Está igualmente descrito que as crises epiléticas, sobretudo as crises TCG (155), podem induzir aumentos da cTnI ou da cTnT (41, 144-147, 155, 157, 158).

Em doentes com crises não complicadas, alguns autores não encontraram alterações após as crises (156, 159). Eskandarian et al. encontraram valores normais de cTnI, dias após tanto crises complicadas como não complicadas (embora os valores tivessem sido mais elevados após as crises complicadas) (160).

8.1.2 Peptídeos natriuréticos

As crises epiléticas também podem provocar elevação do peptídeo natriurético do tipo B (BNP) (148, 155, 161, 162).

As lesões cardíacas têm o potencial de causar disfunção miocárdica (163), a qual é passível de ser detetada através de aumento no valor de BNP (148).

O BNP é secretado tanto pelo coração como pelo cérebro e, que saibamos, nenhum estudo demonstrou, até agora, a origem deste fator natriurético após as crises epiléticas.

O *stress* associado às crises epiléticas e a libertação secundária de norepinephrina podem acionar a produção cardíaca de BNP (148, 162). Por outro lado, a atividade epilética cerebral pode ativar a secreção de BNP, tanto no cérebro, como no coração (148).

Até agora, poucos estudos abordam os níveis de BNP após crises epiléticas e, apesar de serem prospectivos, incluem apenas doentes com crises TCG (158), doentes admitidos em salas/centros de emergência (148, 150) ou crianças (148, 164). Dentre estes estudos, Kyung-Il Park não demonstrou qualquer diferença no valor de NT-proBNP, entre os grupos com crises epiléticas e com síncope vasovagal, mas o seu estudo incluiu apenas 12 doentes com síncope e 15 com crises epiléticas, para além de que os doseamentos foram feitos em diferentes pontos temporais até 24 h após cada episódio (150). Rauchenzauner et al. encontraram níveis mais elevados de BNP em crianças com crises TCG e convulsões febris (148), tal como foi descrito num estudo mais recente, relativamente ao NT-proBNP (164).

8.1.3 Proteína C reativa

A proteína C reativa (PCR) também pode sofrer elevação após crises epiléticas (149, 164-166).

A inflamação tem sido reconhecida na epilepsia, mas, contrariamente a outras condições neurológicas não-inflamatórias, ainda faltam estudos da PCR, neste contexto (165).

Os poucos artigos publicados sobre este tema sugerem elevações da PCR, tanto crónicas (165, 167) como agudas (149, 164-166), em doentes com epilepsia.

Nestes doentes, há a considerar, ainda, o facto de que alguns FACE alteram os níveis de PCR, sendo que o Valproato, a Lamotrigina e o Levetiracetam estão associados a níveis mais baixos de PCR, enquanto a Fenitoína e a Carbamazepina estão associadas a níveis mais altos (168).

8.2 Variabilidade da frequência cardíaca

A análise da variabilidade da frequência cardíaca (VFC) permite a avaliação da atividade autonómica cardíaca (169). Uma VFC baixa foi associada a um maior risco de morte súbita em enfartes do miocárdio (170, 171), a um pior prognóstico em muitas condições clínicas diferentes (172), e independentemente associada a maior risco de morte súbita cardíaca, na população geral (173).

As crises epiléticas, sobretudo em doentes com epilepsia refratária, geralmente afetam a FC e a sua variabilidade (174, 175), com uma possível ligação à SUDEP (175). Alguns FACE podem, também, influenciar a função do sistema nervoso autónomo (89).

As conclusões dos diferentes estudos sobre esta matéria variam. Alguns consideram que uma VFC diminuída constitui um fator de risco potencial para SUDEP (56, 176), relacionada com aumento da mortalidade cardíaca e da morte súbita arritmica. Outros não encontraram diferenças significativas na VFC, entre grupos de doentes que morreram de SUDEP e controlos vivos (177, 178).

156. Woodruff BK, Britton JW, Tigarán S, Cascino GD, Burritt MF, McConnell JP, et al. Cardiac troponin levels following monitored epileptic seizures.

157. Hocker S, Prasad A, Rabinstein AA. Cardiac injury in refractory status epilepticus.

158. Nass RD, Motloch LJ, Paar V, Lichtenauer M, Baumann J, Zur B, et al. Blood markers of cardiac stress after generalized convulsive seizures.

159. Hajsadeghi S, Afsharian S, Fereshtehnejad SM, Keramati MR, Mollahoseini R. Serum levels of cardiac troponin I in patients with uncomplicated epileptic seizure.

160. Eskandarian R, Asghari N, Darban M, Ghorbani R. Cardiac troponin levels following complicated and uncomplicated epileptic seizures.

161. Alehan F, Erol I, Cemil T, Bayraktar N, Ogüs E, Tokel K. Elevated CK-MB mass and plasma brain-type natriuretic peptide concentrations following convulsive seizures in children and adolescents: possible evidence of subtle cardiac dysfunction.

162. Rauchenzauner M, Haberlandt E, Högl W, Luef G. Brain-type natriuretic peptide release and seizure activity during vagal nerve stimulation.

163. Stollberger C, Finsterer J. Cardiac troponin levels following monitored epileptic seizures.

164. Mahgoob M, Moussa M. Usefulness of Serum NT-proBNP in Diagnosis of Generalized Seizures in Egyptian Children.

165. Alapirtti T, Waris M, Fallah M, Soilu-Hänninen M, Mäkinen R, Kharazmi E, et al. C-reactive protein and seizures in focal epilepsy: a video-electroencephalographic study.

166. Peltola J, Laaksonen J, Haapala AM, Hurme M, Raine-salo S, Keränen T. Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels.

167. Ishikawa N, Kobayashi Y, Fujii Y, Kobayashi M. Increased interleukin-6 and high-sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures.

168. Yuen AW, Bell GS, Peacock JL, Koeppe MM, Patsalos PN, Sander JW. Effects of AEDs on biomarkers in people with epilepsy: CRP, HbA1c and eGFR.

169. Malik M, Bigger JT, Camm AJ, Kleiger RE, Malliani A, Moss AJ, et al. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use.

170. Kleiger RE, Miller JP, Bigger JT, Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction.

171. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction.

172. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study.

173. Maheshwari A, Norby FL, Soliman EZ, Adabag S, Whitsel EA, Alonso A, et al. Low Heart Rate Variability in a 2-Minute Electrocardiogram Recording Is Associated with an Increased Risk of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities Study.

174. Moridani MK, Farhadi H. Heart rate variability as a biomarker for epilepsy seizure prediction.

175. Myers KA, Sivathamboo S, Perucca P. Heart rate variability measurement in epilepsy: How can we move from research to clinical practice?

176. Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs.

177. Odom N, Bateman LM. Sudden unexpected death in epilepsy, periictal physiology, and the SUDEP-7 Inventory.

Estes resultados confusos, parcialmente relacionados com diferentes metodologias, encorajam a investigação nesta área, para perceber se e como os parâmetros da VFC devem ser incluídos na prática clínica, nomeadamente na avaliação prognóstica do risco de SUDEP, em doentes com epilepsia refratária.

9. Intervenções preventivas

As intervenções preventivas podem passar por medidas que visem o controlo das crises, a deteção de crises ou de apneia, a supervisão noturna, almofadas anti-asfixia, a alteração da posição de sono, a correção da posição corporal, a estimulação após a crise e diferentes intervenções farmacológicas (102, 179-182).

A **cirurgia ressetiva** é globalmente aceite como um fator que reduz o risco de mortalidade relacionada com epilepsia, incluindo a SUDEP, sobretudo se os doentes ficarem sem crises. Múltiplas séries cirúrgicas demonstraram uma redução das mortes por todas as causas, após a cirurgia, sobretudo relacionada com a diminuição do número de crises (183-185). No entanto, Almeida et al. não encontraram diferenças estatisticamente significativas na incidência de SUDEP entre doentes com epilepsia refratária operados e não operados (186).

A **estimulação do nervo vago** (ENV), que consiste na estimulação elétrica do nervo vago esquerdo, é uma terapêutica auxiliar bem aceite para a epilepsia refratária. Um estudo avaliou o impacto da ENV na função autonómica cardíaca em 9 doentes com epilepsia refratária, analisando a VFC antes e após neuroestimulação. Descobriram que, após a estimulação, ocorreu uma melhoria no balanço simpático/parassimpático, colocando a hipótese de um efeito cardioprotetor (187).

Outra medida preventiva pode ser o uso de **aparelhos de deteção de crises** (102, 188, 189) ou de **deteção de apneia/hipoxemia** (28, 102), mas a maioria dos aparelhos de deteção de crises tem sensibilidade e especificidades baixas (102), e até 87-90% das dessaturações detetadas pelos oxímetros de pulso podem ser falsas ou secundárias a movimento do doente (190).

B. Imagem funcional: avaliação da perfusão regional cerebral (e também da cardíaca?)

178. Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy?

179. Tomson T, Surges R, Delamont R, Haywood S, Hesdorffer DC. Who to target in sudden unexpected death in epilepsy prevention and how? Risk factors, biomarkers, and intervention study designs.

180. Devinsky O, Nashef L. SUDEP: The death of nihilism.

181. Rugg-Gunn F, Duncan J, Hjalgrim H, Seyal M, Bateman L. From unwitnessed fatality to witnessed rescue: Nonpharmacologic interventions in sudden unexpected death in epilepsy.

182. Richerson GB, Boison D, Faingold CL, Ryvlin P. From unwitnessed fatality to witnessed rescue: Pharmacologic intervention in sudden unexpected death in epilepsy.

183. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients.

184. Seymour N, Granbichler CA, Polkey CE, Nashef L. Mortality after temporal lobe epilepsy surgery.

185. Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. Mortality after epilepsy surgery.

186. Almeida AG, Nunes ML, Palmieri AL, Costa JC. Incidence of SUDEP in a cohort of patients with refractory epilepsy: the role of surgery and lesion localization.

187. Schomer AC, Nearing BD, Schachter SC, Verrier RL. Vagus nerve stimulation reduces cardiac electrical instability assessed by quantitative T-wave alternans analysis in patients with drug-resistant focal epilepsy.

188. Jeppesen J, Fuglsang-Fredrikson A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, et al. Seizure detection based on heart rate variability using a wearable electrocardiography device.

Um dos possíveis mecanismos de SUDEP é a presença de isquemia cardíaca, estando descritos alguns casos de síndrome coronária aguda relacionada com crises epiléticas (41, 43, 191). No entanto, não há casos documentados por imagem funcional, como por exemplo por cintigrafia **miocárdica** de perfusão com [^{99m}Tc]Tc-Tetrofosmina ictal, ou seja, com a injeção do radiofármaco durante a crise epilética.

O [^{99m}Tc]Tc-hexametilpropilenoaminóxima ([^{99m}Tc]Tc-HMPAO) é um outro radiofármaco, desenvolvido nos anos 80 do século XX, para estudar o fluxo regional **cerebral** (192-195). Desde então, tem sido amplamente utilizado em doentes com epilepsia, para localizar a zona epileptogénica, sendo injetado o mais precocemente após o início da crise epilética. É uma técnica bem estabelecida, na qual tenho vasta experiência. A Figura 5 mostra a localização da zona epileptogénica por tomografia computadorizada de emissão de fóton único (SPECT) cerebral com [^{99m}Tc]Tc-HMPAO, num dos nossos doentes.

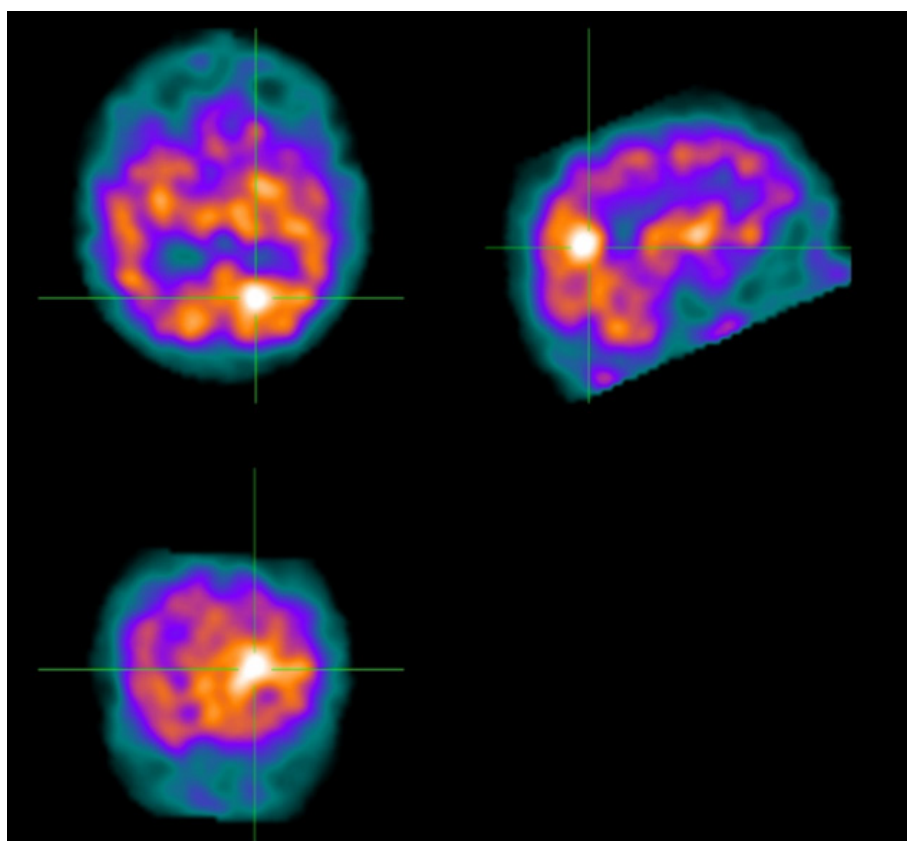


Figura 5. Localização da zona epileptogénica parieto-occipital esquerda, por cintigrafia de perfusão cerebral ictal com [^{99m}Tc]Tc-HMPAO. Cortesia do Serviço de Medicina Nuclear do Centro Hospitalar Universitário de São João, E.P.E..

Embora a biodistribuição deste radiofármaco inclua o coração (195), nunca foi usado para estudá-lo. A razão principal, para além das alternativas excelentes, pode ser a proximidade do coração a órgãos com captação elevada de [^{99m}Tc]Tc-HMPAO, como os pulmões e o fígado (195, 196), potencialmente interferindo com a qualidade da imagem cardíaca. A Figura 6 ilustra a biodistribuição normal deste radiofármaco.



Figura 6. Biodistribuição normal do $[^{99m}\text{Tc}]\text{Tc-HMPAO}$: vista anterior de corpo inteiro, evidenciando elevada captação cerebral e hepática, assim como captação no miocárdio e nos pulmões. In Sharp et al., 1986 (195).

Sendo um radiofármaco para avaliar a perfusão cerebral e exibindo captação cardíaca, parece possível que também possa mapear a perfusão miocárdica, permitindo o uso de apenas um radiofármaco para avaliar os dois órgãos, em doentes com epilepsia (que, como descrito previamente, têm maior suscetibilidade para alterações cardíacas), com menor exposição a radiação. Foi nesta hipótese que se baseou a segunda parte desta investigação.

189. Leal A, Pinto MF, Lopes F, Bianchi AM, Henriques J, Ruano MG, et al. Heart rate variability analysis for the identification of the preictal interval in patients with drug-resistant epilepsy.

190. Wilson S. Conscious sedation and pulse oximetry: false alarms?

191. Akrawinhawong K, Leelasinjaroen P, Ng YS, Dean MN, Piyaskulkaew C, Al-najafi S, et al. Seizure-induced acute coronary syndrome: the value of postictal screening.

192. Ell PJ, Hocknell JM, Jarritt PH, Cullum I, Lui D, Campos-Costa D, et al. A $^{99\text{Tcm}}$ -labelled radiotracer for the investigation of cerebral vascular disease. .

193. Ell PJ, Jarritt PH, Cullum I, Hocknell JM, Costa DC, Lui D, et al. Regular cerebral blood flow mapping with $^{99\text{mTc}}$ -labelled compound.

194. Holmes RA, Chaplin SB, Ro1ston KG, Hoffman TJ, Volkert WA, Nowotnik DP, et al. Cerebral uptake and retention of $^{99\text{Tcm}}$ -hexamethylpropyleneamine oxime ($^{99\text{Tcm}}$ -HM-PAO).

195. Sharp PF, Smith FW, Gemmell HG, Lyall D, Evans NT, Gvozdanovic D, et al. Technetium- $^{99\text{m}}$ HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies.

196. Neirinckx RD, Canning LR, Piper IM, Nowotnik DP, Pickett RD, Holmes RA, et al. Technetium- $^{99\text{m}}$ d,l-HM-PAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion.

2. OBJETIVOS E QUESTÕES DE PESQUISA

Tendo em conta:

- a importância das alterações cardíacas em doentes com epilepsia,
- o desconhecimento que ainda existe, relativamente aos mecanismos fisiopatológicos de SUDEP,
- a possibilidade de avaliar os doentes em condições controladas, estando internados numa UME, numa instituição com recurso a diferentes metodologias diagnósticas,

pretendemos avaliar possíveis biomarcadores séricos, eletrocardiográficos e imagiológicos, que possam acrescentar informação, às inúmeras dúvidas e incongruências que ainda persistem, relativamente a uma possível implicação primária do coração na SUDEP.

Assim, o **objetivo principal** desta tese foi documentar as alterações cardíacas durante as crises epiléticas, em doentes com epilepsia refratária, candidatos a cirurgia ressetiva da zona epileptogénica, internados na UME do Centro Hospitalar Universitário de São João, E.P.E. (CHUSJ).

Questões 1 e 2:

Podemos documentar isquemia e/ou disfunção miocárdicas, provocadas por crises epiléticas, em doentes com epilepsia refratária, através do doseamento de biomarcadores de lesão e disfunção miocárdicas, bem como de inflamação? Qual a relação dessas alterações com a escala de risco SUDEP-7? (**Artigo 1**)

Questão 3:

Qual o impacto das crises TCG na função autonómica cardíaca (avaliada através da VFC), em doentes com epilepsia refratária? (**Artigo 2**)

Questão 4:

A disfunção autonómica (avaliada através da VFC) relacionada com as crises epiléticas depende do tipo de crise? (**Artigo 3**)

Como **objetivo secundário**, pretendeu-se validar o [^{99m}Tc]Tc-HMPAO como agente de perfusão do miocárdio, no sentido de, com um só agente e uma só dose de radiação, ser possível localizar a zona epileptogénica e avaliar a perfusão e função do ventrículo esquerdo.

Questão 5:

Qual o melhor intervalo de tempo, entre a injeção do radiofármaco e a aquisição das imagens cardíacas com [^{99m}Tc]Tc-HMPAO? (**^{99m}Tc-HMPAO and the heart - a new way for an old molecule?** - trabalho apresentado na International Conference on Nuclear Cardiology and Cardiac CT, em maio de 2017, em Viena).

Questão 6:

É possível avaliar a perfusão regional do ventrículo esquerdo e a sua função com [^{99m}Tc]Tc-HMPAO? (**Artigo 4**)

Questão 7:

Como é a distribuição do [^{99m}Tc]Tc-HMPAO no ventrículo esquerdo de doentes com epilepsia refratária? (**[^{99m}Tc]Tc-HMPAO cardiac SPECT: a method to detect ischemia in patients with refractory epilepsy?** - trabalho apresentado na International Conference on Nuclear Cardiology and Cardiac CT, em maio de 2019, em Lisboa).

3. MATERIAL E MÉTODOS

Participantes

Artigos 1, 2 e 3

Foram avaliados, de modo prospetivo, 121 doentes com epilepsia refratária, internados consecutivamente, na UME do CHUSJ, entre janeiro de 2015 e julho de 2018, como parte da sua avaliação pré-cirúrgica. Todos os doentes foram avaliados clinicamente por epileptologistas experientes. O diagnóstico foi feito com base nos critérios da ILAE (197) e confirmado por vídeo-eletroencefalograma (VEEG) e imagem (todos realizaram RMN cerebral com um protocolo específico para epilepsia e alguns doentes selecionados realizaram imagem funcional com SPECT cerebral com [^{99m}Tc]Tc-HMPAO e/ou tomografia por emissão de positrões - PET - com [^{18}F]Fluorodesoxiglicose - FDG).

Por questões logísticas, os doseamentos analíticos só foram iniciados em maio de 2016. A Figura 7 ilustra a integração das amostras dos artigos 1, 2 e 3, na população total avaliada.

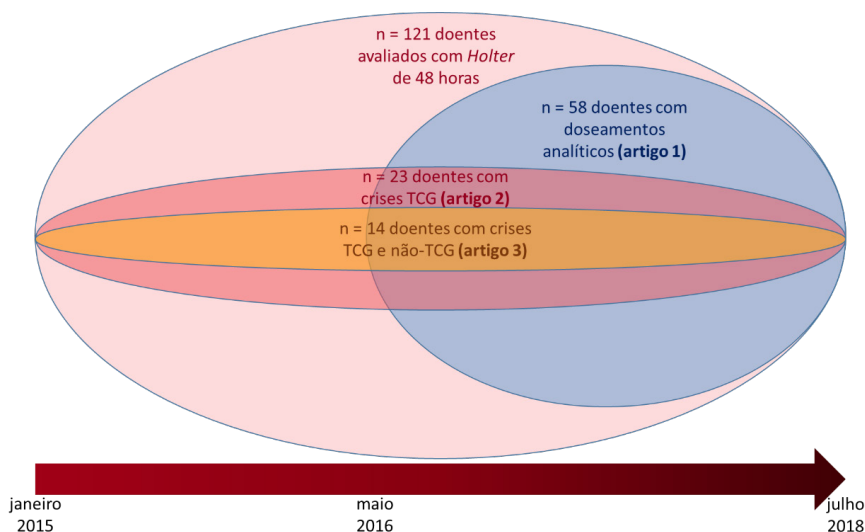


Figura 7. Diagrama representando a interligação das amostras estudadas nos artigos 1, 2 e 3. Crises TCG: crises tónico-clónicas generalizadas.

197. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology.

198. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines.

Foram recolhidos dados demográficos e clínicos, incluindo idade, sexo, duração da epilepsia, etiologia provável, frequência e semiologia das crises (duração, classificação, localização da zona de início ictal, ocorrência de PGES), medicação em curso (particularmente FACE), presença de fatores de risco cardiovasculares [hábitos tabágicos, hipertensão arterial (tensão arterial sistólica ≥ 140 mmHg e/ou diastólica ≥ 90 mm Hg (198)), dislipidemia (definida como colesterol total ≥ 190 mg/dL e/ou triglicéridos ≥ 150 mg/dL), ou sob terapêutica específica para controlar estes fatores de risco, e obesidade [definida como um índice de massa corporal ≥ 30 - Organização Mundial de Saúde (OMS)].

Nenhum doente tinha diagnóstico prévio de doença cardiovascular ou evidência clínica de doença inflamatória ou infecciosa.

Estudo preparatório, realizado previamente ao Artigo 4 (^{99m}Tc-HMPAO and the heart - a new way for an old molecule?)

Foram avaliados 10 voluntários saudáveis, 5 mulheres e 5 homens, pertencentes à ou relacionados com a equipa de investigação deste projeto de doutoramento.

Recolheram-se dados demográficos, incluindo idade e hábitos tabágicos.

Artigo 4

Foram selecionados 3 doentes internados no Serviço de Angiologia e Cirurgia Vascular do CHUSJ, que necessitavam ou tinham já realizado uma cintigrafia de perfusão do miocárdio com [^{99m}Tc]Tc-Tetrofosmina, como parte da avaliação clínica da sua própria doença.

Foram, também, recolhidos dados demográficos e clínicos, incluindo idade, sexo e hábitos tabágicos.

Estudo de avaliação da distribuição do [^{99m}Tc]Tc-HMPAO no ventrículo esquerdo de doentes com epilepsia ('HMPAO-Tc-99m cardiac SPECT - a method to detect ischemia in patients with refractory epilepsy?')

Foram avaliados prospetivamente 88 doentes com epilepsia refratária, internados na UME do CHUSJ, entre junho de 2014 e agosto de 2018, que realizaram tomografia de perfusão cerebral com [^{99m}Tc]Tc-HMPAO ictal e/ou interictal. A Figura 8. ilustra o número de doentes avaliados no período ictal e no período interictal.

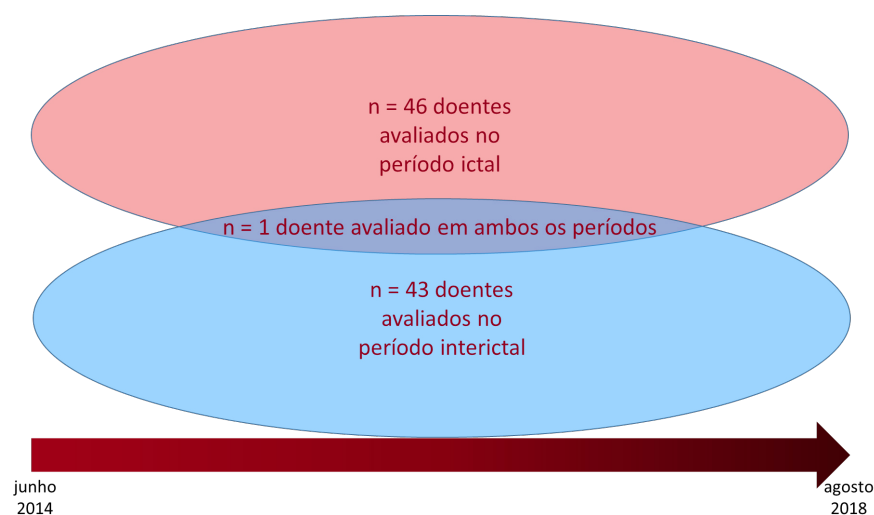


Figura 8. Representação do número de doentes com avaliação da distribuição do [^{99m}Tc]Tc-HMPAO no ventrículo esquerdo nos períodos ictal e interictal.

Recolheram-se dados demográficos e clínicos.

Metodologia

As metodologias específicas de cada artigo e de cada estudo estão descritas nos mesmos.

Aprovação Ética

A Comissão de Ética para a Saúde do CHUSJ aprovou este projeto.

Financiamento/ subsídio

Este projeto de investigação recebeu um subsídio da Fundação Calouste Gulbenkian.

4. RESULTADOS/ INVESTIGAÇÃO CLÍNICA

Biomarcadores séricos

cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy

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cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy



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ABSTRACT

Purpose: To profile serum levels of high sensitivity Troponin I (hs-cTnI), B-Type Natriuretic Peptide (BNP), and high sensitivity C Reactive Protein (hs-CRP), after epileptic seizures in patients with focal drug-resistant epilepsy, relating the results to the revised SUDEP-7 inventory.

Methods: We prospectively evaluated patients admitted to our Epilepsy Monitoring Unit. hs-cTnI, BNP, and hs-CRP were measured at admission and after the first seizure. The revised SUDEP-7 Risk Inventory was calculated. The statistical significance level was set at 0.05.

Results: Fifty-eight patients were included (53.4 % female). The index seizure was a focal to bilateral tonic-clonic seizure (FBTCS) in 25.9 % of the patients, and 17.5 % had post-ictal generalized EEG suppression (PGES). After the seizure, 25.9 % had a significant (above 50 %) increase in hs-cTnI, 23.3 % in BNP, and 4.3 % in hs-CRP. About 40 % had cardiovascular risk factors (CRF), without known cardiac disease. The elevation of one biomarker did not compel the elevation of another. hs-cTnI increase was associated with FBTCS, PGES, longer seizures, maximal ictal heart rate, and HR change. Increases in BNP were associated with CRF. hs-CRP increase was associated with PGES. We found no significant association between SUDEP-7 and any biomarker increase.

Significance: Several patients had increases in biomarkers of myocardial necrosis/dysfunction after seizures, without significant association with the SUDEP-7 inventory. Different patterns of biomarkers' elevations point to multifactorial pathophysiologies hypothetically associated with incipient myocardial lesions. A larger cohort with follow-up data could help to clarify the clinical relevance of these findings.

Abbreviations: hs-cTnI, high sensitivity troponin I; BNP, B-type Natriuretic Peptide; hs-CRP, high sensitivity C reactive protein; FBTCS, focal to bilateral tonic-clonic seizure; FS, focal seizure without evolution to bilateral tonic-clonic seizure; GTCS, Generalized Tonic-clonic Seizure; PGES, post-ictal generalized EEG suppression; CRF, cardiovascular risk factors; maxHR, maximal ictal heart rate; Δ HR, heart rate change; SUDEP, Sudden Unexpected Death in Epilepsy; EMU, Epilepsy Monitoring Unit; CMIA, Chemoluminescent Microparticle Immuno Assay; VC, Variation Coefficient; AED, antiepileptic drugs; EKG, electrocardiogram; TLE, temporal lobe epilepsy

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1. Introduction

Epileptic seizures may induce elevations of serum cardiac Troponin I (cTnI) or T (cTnT) [1–8], B-Type Natriuretic Peptide (BNP) [1,9–11], and C reactive protein (CRP) [12–14], which could reflect cardiac injuries, possibly associated with Sudden Unexpected Death in Epilepsy (SUDEP).

Until now, most studies in this field have used different methodologies, were mainly retrospective [4,5,7], and/or included only patients admitted to emergency rooms [4,6,7,10,14,15].

In patients with uncomplicated seizures, some authors found no changes in troponin after seizures [16,17]. Eskandarian et al. [18] found normal cTnI values days after both complicated and uncomplicated seizures (although values were higher after complicated seizures).

In patients admitted to the emergency room, Rauchenzauner et al. [10] reported elevated plasma NT-proBNP levels after seizures in children with tonic-clonic seizures or febrile convulsions, but not in those with partial motor seizures or syncope, while Park et al. [15] reported similar levels of pro-BNP in patients with syncope and patients with seizures.

Both significant [12] and not significant [13,14] increases in CRP have been found after seizures. Ishikawa et al. [19] reported higher baseline levels of high sensitivity (hs) CRP in children with daily generalized motor seizures compared to those with intermittent seizures or to control subjects.

In this study, we aimed to profile serum hs-cTnI, BNP and hs-CRP after epileptic seizures in patients with focal refractory epilepsy, during video-electroencephalography monitoring, and to correlate the results with clinical variables and the revised SUDEP-7 risk inventory.

2. Methods

2.1. Study population

We prospectively evaluated consecutive patients admitted to our Institution's Epilepsy Monitoring Unit (EMU) with focal drug-resistant epilepsy, from May 2016 to July 2018. Patients with only psychogenic nonepileptic seizures and those without seizures during monitoring were excluded.

Demographic and clinical data were collected, including index seizure's semiology and duration, the occurrence of post-ictal generalized EEG suppression (PGES), and cardiovascular risk factors. No patient had previously known cardiovascular disease or clinical evidence of infectious or inflammatory diseases.

2.2. EEG

Scalp recordings were obtained placing gold cup electrodes (with conductive paste and collodium), according to the 10–20 system, with additional 10–10 locations, namely to cover the anteroinferior temporal regions, for a total of 35–44 electrodes. Polygraphic derivations included an EKG channel (as standard on EEG recordings) and an optional EMG one. The signal was sampled at 512 Hz and recordings were visually analyzed using standard bipolar and referential montages. Anti-epileptic drugs were maintained, reduced, or discontinued, following the EMU protocol (which depends mainly on baseline seizure types and frequency), under the supervision of an epileptologist.

2.3. Seizure characteristics

The index seizure was considered the first unequivocally observed and was classified according to the semiological seizure classification [20] and the International League Against Epilepsy (ILAE) classification [21]. The index seizure ought to have clear motor features and/or loss of consciousness; auras were included, only if accompanied by

unequivocal electrographic seizure patterns; subclinical seizures, subjective symptoms without EEG correlation, and very brief clinical seizures (< 5 s) were excluded. Experienced clinical neurophysiologists determined temporal clinical and EEG ictal onsets and offsets, the lobar regions of ictal onset (first unequivocal location of the ictal pattern), as well as the presence and duration of PGES (determined by visual analyses of the EEG trace, using the original definition by Lhatoo et al. [22], as the generalized absence of electrographic activity > 10 μ V in amplitude, within the 30 s following seizure termination, allowing for muscle, movement, breathing and electrode artifacts).

All seizures had focal EEG onset with variable initial ictal phenomenology; those that evolved to prominent tonic and/or clonic manifestations of both arms, both legs, the trunk and head (i.e., 'generalized' motor involvement), were classified as 'focal to bilateral tonic-clonic seizures' (FBTCS), according to ILAE's position paper [21]. In SUDEP-related literature, these seizures are often designated as 'generalized convulsive', 'generalized tonic-clonic', or 'secondarily generalized tonic-clonic'. We subclassified FBTCS according to Alexandre V. et al. [23] into: type 1 – tonic-clonic generalized convulsive seizure with bilateral symmetric tonic arm extension; type 2 – clonic generalized convulsive seizure without tonic arm extension or flexion; type 3 – generalized convulsive seizure with unilateral or asymmetric tonic arm extension or flexion.

2.4. Serum biomarkers

All patients were evaluated as follows: at admission (basal) – hs-cTnI, BNP, and hs-CRP; 6 h after the index seizure – hs-cTnI and hs-CRP; 12–18 h after the index seizure – hs-cTnI, BNP and hs-CRP. This timeline was established to detect acute changes in the levels of the biomarkers. Given the analytical and biological variabilities, only increases above 50 % of each basal level were considered significant [24–27], even if still below the reference values (BNP and hs-CRP) or below the 99th percentile upper reference limit which defines myocardial lesion (hs-cTnI) [28].

All serum samples were collected to 3 mL lithium heparinized plastic tubes (BD Vacutainer™ LH PST™ II), kept at 2–8 °C, and analyzed in 12 h.

2.4.1. hs-cTnI

We used the autoanalyzer Architect i2000 SR System® from Abbott Laboratories Diagnostic Division Abbott Park with the last version of the High Sensitive Troponin I immunoassay (Abbott Laboratories, IL), which uses the Chemoluminescent Microparticle Immuno Assay (CMIA) method for quantitative determination. This assay has a 26 ng/L concentration at the 99th percentile of the reference population with < 5 % Variation Coefficient (VC), a detection limit of 1.9 ng/L, a limit of blank of 1.3 ng/L, and a quantification limit of 4.7 ng/L at 10 % VC. The assay measurement interval is between 1.9 and 50 000 ng/L.

2.4.2. BNP

Analysed using the CMIA method in the Architect i2000 SR System® from Abbott Laboratories. The Architect BNP assay has an imprecision \leq 12 % of the VC at the 95 % upper limit of the confidence interval, an analytic sensitivity of 10 pg/mL, and a measurement interval between 10 and 5000 pg/mL.

2.4.3. hs-CRP

Analysed using Immunonephelometry with the BN™ II/BN ProSpec® Systems (Siemens). The analytical sensitivity is 0.175 mg/L. The assay has a concentration of 2.87 mg/L at the 99th percentile of the reference population with a VC < 3.1 %. The reference value is considered \leq 3 mg/L.

Table 1

The SUDEP Risk Inventory (SUDEP-7, version 2.0).

Adapted, with permission, from Novak et al. 2015. *Frontiers in Neurology* [27].

SUDEP Risk Inventory (version 2.0)	Odds ratio	Weighting Log _e x odds ratio
1. More than three tonic-clonic seizures in last year	8.1	0 or 2
2. One or more tonic-clonic seizures in last year (if factor 1 is present, score as 0)	2.4	0 or 1
3. One or more seizures of any type over the last 12 months (if factor 4 is present, score as 0)	2.2, 3.8, 4.6	0 or 1
4. More than 50 seizures of any type per month over the last 12 months	11.5	0 or 2
5. Duration of epilepsy > 30 years	13.9	0 or 3
6. Use of three or more AEDs	4.0	0 or 1
7. Developmental disability, I.Q. < 70 or too impaired to test	5.0	0 or 2

2.5. The SUDEP-7 inventory

For each patient, we calculated the revised SUDEP-7 Risk Inventory [29,30], according to what is stated in Table 1, which includes the weighing of some of the original SUDEP risk factors by Walczak et al. [31]

2.6. Statistical analysis

Quantitative variables were described as median (range) in the tables and median (inter-quartile range) in the graphical representations. Categorical variables were described through absolute and relative frequencies. The statistical association between categorical variables was evaluated through Chi-square or Fisher's exact tests, whereas the association between quantitative and categorical variables was assessed using the Mann-Whitney statistical test. The significance level was set at 0.05. Statistical analysis of the results was performed using the commercially available software SPSS version 25 (IBM Corp., Armonk, NY, USA).

2.7. Standard protocol approvals, registrations, and patient consents

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Also, the study was approved by our Institution's Ethics Committee and all patients gave their written informed consent.

2.8. Data availability statement

The data generated and/or analyzed during this study are available from the corresponding author on reasonable request.

3. Results

Fifty-eight patients (53.4 % female) were enrolled (Table 2), with a median age of 40 years. The median duration of epilepsy was 12 years (min;max, 1;67). Most patients had a low frequency of seizures (till 8 seizures per month) and needed 2 or 3 antiepileptic drugs (AED), with a mean of 2.75 (± 0.939). More than 75 % of the patients were on anti-epileptic drugs (AED) known to be associated with lower CRP values [32], at the time of the admission to the EMU.

Hippocampal Sclerosis was the most commonly identified etiology for our patients' epilepsy (19 %), but we could not determine the cause in 25 (43 %) of them.

Cardiovascular risk factors (CRF) were present in 40 % of the patients, mainly smoking and dyslipidemia. None of the patients had known cardiac disease.

Regarding the index seizure (Table 3), 25.9 % were Focal to bilateral Tonic-clonic Seizures (FBTCS), the majority of which belonged to Type 3 (60.0 %). The median duration exceeded 1 min and 17.5 % had PGES (all patients with Type 1 FBTCS, half of the patients with type 3 FBTCS, and 1 patient with focal seizure without evolution to bilateral

Table 2

Demographic and clinical data.

Characteristics of Patients	
Total number of patients	58
Age (years), median (range)	40 (16;73)
Gender, n (%)	
Female	31 (53.4)
Male	27 (46.6)
Duration of epilepsy (years), median (range)	12 (1;67)
Etiology of epilepsy, n (%) ^a	
Hippocampal Sclerosis	11 (19.0)
Malformations of Cortical Development	6 (10.3)
Tumor	5 (8.6)
Vascular Malformations	2 (3.4)
Other ^b	8 (13.7)
Indeterminate	25 (43.1)
Frequency of seizures per month, n (%)	
≤ 8	39 (67.2)
9–25	5 (8.6)
≥ 26	14 (24.1)
Cardiovascular Risk Factors, n (%)	23 (39.7)
Smoking	10 (17.2)
Arterial Hypertension	2 (3.4)
Dyslipidemia ^c	7 (12.1)
Obesity ^d	3 (5.2)
Dyslipidemia ^e , Arterial Hypertension, and Obesity ^d	1 (1.7)
None	35 (60.3)
Number of Antiepileptic Drugs, mean (SD)	2.75 (0.939)
Use of Sodium Channel Blockers, n (%)	48 (82.8)
Use of antiepileptic drugs associated with lower CRP, n (%) ^f	45 (77.6)
Use of antiepileptic drugs associated with higher CRP, n (%) ^f	9 (15.5)

^a 1 missing.

^b Other: Meningitis, Hypoxic-ischemic lesions, Hydrocephalia.

^c Defined as total cholesterol ≥ 190 mg/dL and/or triglycerides ≥ 150 mg/dL.

^d Defined as body mass index ≥ 30 (WHO).

^e Valproate, lamotrigine, levetiracetam.

^f Phenytoin, carbamazepine.

tonic-clonic - FS). The majority of seizures was Temporal (80.4 %) and occurred during wakefulness (67.2 %). The ictal onset site was mainly right-sided (50 %). The mean maximal (max) ictal heart rate (HR) was 106.6 bpm (± 27.3) and the median HR change [difference between maxHR and mean basal HR (ΔHR)] was 60.8 (min;max, -3;106).

Table 4 shows the number of patients presenting with each SUDEP-7 score, which ranged from 1 to 9, out of a possible maximum of 10.

In 25.9 % of the patients (n = 15, 12 with FBTCS and 3 with FS), we found significant increases of hs-cTnI, 6 h after the index seizure, or 12–18 h after, or on both moments. hs-cTnI increase was associated with the presence of FBTCS (p < 0.001), PGES (p = 0.001), longer seizure duration (p = 0.002), higher maxHR (p = 0.001), and higher ΔHR (p = 0.003). From the 12 patients with FBTCS and hs-cTnI increase, 8 belonged to type 3, and 4 belonged to type 1.

Three of the patients (5.2 %) presented elevations above the 99th percentile upper reference limit, compatible with myocardial lesion, but none had chest pain or EKG abnormalities suggesting an acute coronary syndrome [28]. All three performed a Myocardial Perfusion

Table 3
Index Seizure Characteristics.

Index Seizure Characteristics	
Semiology, n (%)	
Focal to bilateral tonic-clonic seizure	15 (25.9)
Type 1	5 (33.3)
Type 2	1 (6.7)
Type 3	9 (60.0)
Focal seizure without evolution to bilateral tonic-clonic	43 (74.1)
Duration (seconds), median (range) ^a	69.0 (5;171)
Postictal Generalized EEG suppression, n (%) ^b	10 (17.5)
While awake, n (%)	39 (67.2)
Ictal onset side, n (%) ^c	
Right	28 (50.0)
Left	16 (28.6)
Bilateral	6 (10.7)
Central	1 (1.8)
Indeterminate	5 (8.9)
Ictal onset localization, n (%) ^c	
Temporal	45 (80.4)
Extra-temporal	10 (17.9)
Indeterminate	1 (1.8)
Maximal ictal Heart Rate (bpm), mean (SD) ^b	106.6 (27.3)
Δ Heart Rate (bpm), median (range) ^b	60.8 (-3;216)
Δ Heart Rate, n (%) ^b	
< 50 %	25 (43.9)
50 – 99%	11 (19.3)
100 – 149%	18 (31.6)
≥ 150 %	3 (5.3)

^a 6 missing.
^b 1 missing.
^c 2 missing.

Table 4
Distribution of patients according to the SUDEP-7 score.

SUDEP-7 score	n	%
1	11	19.0
2	19	32.8
3	6	10.3
4	7	12.1
5	5	8.6
6	3	5.2
7	5	8.6
8	1	1.7
9	1	1.7

Scintigraphy afterward, which showed no perfusion defects in two of them. The third had a small septal perfusion defect, without significant reversibility, and with normal function. That patient does not have cardiovascular risk factors.

Their clinical data are summarized in Table 5.

All of the above-mentioned patients are part of the ones having FBTCS, accounting for 20 % raises above the 99th percentile upper reference limit in that group.

3 patients with FS also had hs-cTnI elevation. Table 6 summarizes their clinical data.

Significant increases in BNP occurred in 23.3 % of the patients, from baseline to 12–18 h after the index seizure, and those patients had more CRF (p = 0.019). We did not find any significant association between BNP increases and seizure type, PGES, seizure duration, maxHR or ΔHR (p = 1.000, p = 0.558, p = 0.973, 0.570, and p = 0.236 respectively).

hs-CRP increased from baseline to 6 h or 12–18 h after the index seizure only in 4.3 % of the patients. hs-CRP increases were associated with the presence of PGES (p = 0.028), and there is a trend favouring an association with FBTCS (p = 0.088). We did not find any association between hs-CRP elevations and seizure duration, maxHR, or ΔHR (p = 0.498, p = 0.139, and p = 0.591). We also found no significant

Table 5
Clinical data from the patients with hs-cTnI above the 99th percentile upper reference limit.

Age (years)	Sex	Cardiovascular risk factors	Duration of epilepsy (years)	Frequency of seizures/month	Seizure semiology	Type of FBTCS	Seizure onset localization	Duration of seizure (seconds)	PGES (seconds)	Max HR (bpm)	Seizure onset side	SUDEP-7
16	F	No	4	≤ 8	FBTCS	3	Temporal	90	0	115	Left	2
50	M	Yes	6	≤ 8	FBTCS	1	Temporal	101	126	144	Left	1
44	F	No	35	≤ 8	FBTCS	3	Temporal	152	30	156	Right	7

FBTCS: Focal to bilateral tonic-clonic seizure; PGES: Postictal Generalized EEG Suppression; MaxHR: maximal ictal heart rate.

Table 6
Clinical data from the patients with elevation in hs-cTnI following a Focal seizure without evolution to bilateral tonic-clonic.

Age (years)	Sex	Cardiovascular risk factors	Duration of epilepsy (years)	Frequency of seizures/month	Seizure semiology	Type of seizure	Seizure onset localization	Duration of seizure (seconds)	PGES (seconds)	max HR (bpm)	Seizure onset side	SUDEP-7
45	M	Yes	26	≤ 8	FS	Vegetative aura	Temporal	Ind.	0	90	Right	2
24	M	No	8	≤ 8	FS	Automotor	Temporal	88	0	100	Right	2
73	F	No	67	≤ 8	FS	Extra-Temporal	Ind.	Ind.	0	107	Ind.	5

FS: Focal seizure without evolution to bilateral tonic-clonic; Ind.: indeterminate; PGES: Postictal Generalized EEG Suppression; maxHR: maximal ictal Heart Rate.

association between hs-CRP elevations and the use of AED reported to lower (valproate, lamotrigine, levetiracetam) or probably raise (phenytoin, carbamazepine) CRP [12,19,32] ($p = 0.357$ and $p = 1.000$, respectively).

One patient had increases in both hs-cTnI and BNP, and 2 patients in hs-cTnI and hs-CRP.

No significant association could be found between CRF and elevations of hs-cTnI ($p = 0.519$) or hs-CRP ($p = 0.524$).

Age, sex, seizure frequency, ictal onset localization (temporal/extratemporal), onset side (right or left hemisphere), or seizure during sleep/wakefulness did not show any association with biomarkers increases.

We also found no significant differences in SUDEP-7 inventory scores between patients with and without either biomarker increase – p values of 0.326, 0.173, and 0.464, for hs-cTnI, BNP, and hs-CRP, respectively.

Fig. 1 shows the evolution of each biomarker after index seizure, related to the different clinical variables (CRF, FBTCS, PGES, seizure duration, and seizure onset – TLE vs extra-TLE).

Maximal ictal HR was significantly higher both in patients with FBTCS and in patients with PGES ($p < 0.001$ for both), the same occurring for Δ HR ($p < 0.001$ and $p = 0.01$, respectively).

4. Discussion

Our main finding was a significant increase in hs-cTnI or BNP after seizures in a considerable percentage of patients (25.9 % and 23.3 %, respectively), with no significant associations with the SUDEP-7 inventory scores.

4.1. Biomarkers and seizures' characteristics

4.1.1. Troponins

cTnI and cTnT are high sensitivity and specificity biomarkers of myocardial injury [28,33], and the newest guidelines recommend the routine clinical use of high-sensitivity (hs) assays [28]. Baker et al. [34] consider that a change of 50–60 % is needed for clinical situations when the baseline value is below the 99th percentile upper reference limit, and our study followed that rule.

In some neurologic diseases, such as in subarachnoid hemorrhage, troponin I is already established as a highly sensitive and specific marker of cardiac dysfunction [35]. However, the presence of elevated troponins by itself does not identify the underlying pathophysiological mechanisms of myocardial injury. It may be caused by physiological stresses or preload-related stretch in normal hearts [28]. Myocardial ischemia may be caused not only by vascular lesions but also by a mismatch of oxygen supply and demand in the myocardium [28], which, following seizures, is more likely to happen [1,7,16].

Troponin I elevation occurs more frequently after GTCS [1], one of the most consistent risk factors for SUDEP [36–39]. Stollberger and Finsterer [40] postulated that myocardial injury might occur only in severe and prolonged seizures, a finding that was also suggested by our results: hs-cTnI increases were associated with FBTCS, the presence of PGES, longer seizure duration, maxHR, and Δ HR. These elevations could be related to the physical exertion due to this type of crisis, as some studies report troponin elevations after physical activity [34,41]. Shave et al. [41] report cTnI elevations in healthy humans after a 30-minute high-intensity run, but the type and duration of exercise are much different from muscle contractions in FBTCS. A meta-analysis also indicated that hs-cTnI raises 32–72 % in non-ischemic individuals, after exercise stress testing, with considerable overlap with the values seen in patients with myocardial ischemia [42].

Although there is controversy about the mechanisms implicated in cTnI elevations after exercise, some kind of alteration at the cardiomyocyte level probably occurs [34]. Some of the proposed mechanisms, like the formation of blebs at the cardiomyocyte membrane, may lead to cell necrosis if the ischemia is sustained [43].

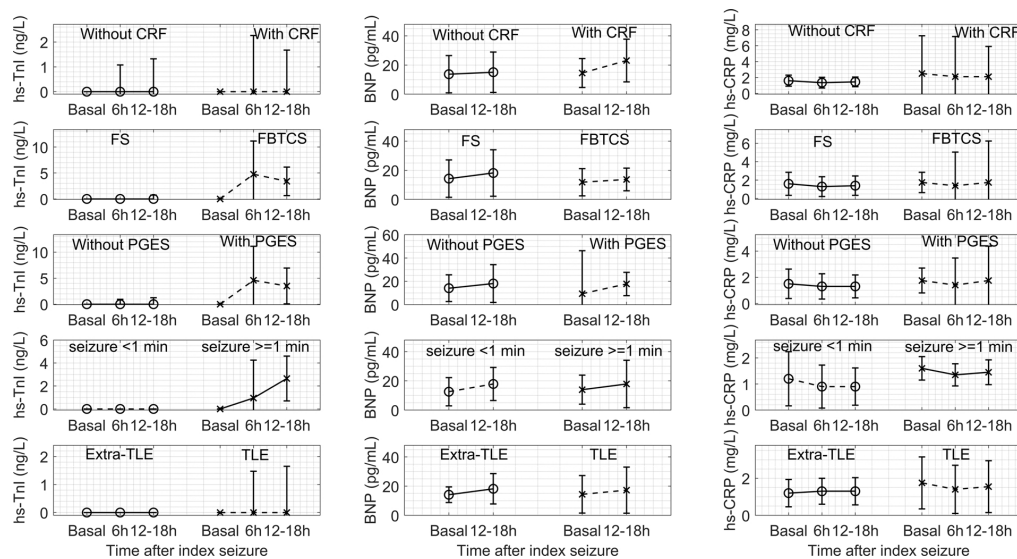


Fig. 1. Evolution of hs-cTnI (first column), BNP (second column) and hs-CRP (third column): basal, 6 h and 12-18 h after index seizure, related to CRF (first row), FBTCS (second row), PGES (third row), seizure duration (< 1 min or \geq 1 min, fourth row) and seizure onset (TLE or extra-TLE, fifth row). Data are presented in the form of median \pm (inter-quartile range/2). CRF: cardiovascular risk factors; FBTCS: Focal to bilateral tonic-clonic seizure; FS: focal seizure without evolution to bilateral tonic-clonic; PGES: postictal generalized EEG suppression; TLE: Temporal Lobe Epilepsy.

Contrarily to cTnT, there are no reports of rises in cTnI with origin in non-cardiac tissues [28].

Minor, repetitive changes, that might not cause death by themselves, could affect the conduction system and cause fatal arrhythmias [7,44]. Despite there is no evidence of short-term increased risk of cardiac events in individuals with troponin elevation after exercise [34], some cases of true acute coronary syndrome following seizures were reported [3,4,44,45].

In our study, 3 patients (5.2 %) had hs-cTnI elevations above the 99th percentile upper reference limit, a value similar to the one reported by Sieweke et al. [5], but that percentage rose to 20 in the group with FBTCS, which parallels the recently published paper by Nass et al. [8], who found 26 % of patients with GTCS having an elevation of hs-cTnI above the normal upper limit. None of our patients had signs or symptoms of an acute coronary syndrome, as also reported by other authors [5,7,8]. Nevertheless, in a subsequent myocardial perfusion scintigraphy, the patient with longer duration of epilepsy had a small fixed septal perfusion defect, which could be due to repetitive seizures, as pointed out by Akrawinathawong et al. [45].

The number of patients with FBTCS and hs-cTnI increase ($n = 12$) is not enough to perform a formal statistics regarding the types of FBTCS, nor to perform a multivariable analysis regarding the presence of PGES. Eight patients corresponded to type 3, half of which with PGES. Four patients belonged to type 1, all of which with PGES (Alexandre et al. [23] found a strong association between PGES and type 1). None of them corresponded to type 2, the only type without arm tonic extension or flexion.

Sieweke et al. [5] found an association between troponin elevation and CRF, and other authors [7,8,40] add that myocardial damage is more probable to occur in elderly patients, as cardiovascular disease increases with age.

However, in our work, we found no difference in age, between the groups with or without each biomarker increase, and hs-cTnI increases were not related to CRF. Particularly, one of the three patients that had hs-cTnI elevation above the 99th percentile upper reference limit was only 16 years old and had no CRF. In this setting, attention to younger

patients and those without CRF seems also advised. Contrarily to other reports [16,17], our study showed an hs-cTnI increase after focal seizures without evolution to bilateral tonic-clonic (FS) in some patients ($n = 3$; about 5 % of all patients, 7 % of FS), but previous works included smaller samples and their measurement timelines were different from ours. This particular issue should be explored in future investigations. Interestingly, none of those 3 patients had PGES, and one of the seizures associated with hs-cTnI elevation was a vegetative aura.

HR is an easy non-invasive way to detect autonomic activity [46]. Ictal tachycardia is common especially after generalized convulsive seizures, which are associated with ictal tachycardia and or significant increases in HR in 48 %–100 % of seizures [46]. The fact that it is also documented in otherwise subclinical epileptic seizures supports that it is not merely a physical or psychological stress response [47].

In our study, patients with hs-cTnI elevation had higher maxHR, and higher Δ HR compared to those without, indicating changes in the autonomic nervous system. We did not find any association between the other biomarkers (BNP and hsCRP) and maxHR or Δ HR. It would have been interesting to perform a multivariable analysis, once maxHR or Δ HR were also associated with FBTCS and PGES, but we did not have a sufficient number of patients. Nass et al. [8] found a correlation between troponin elevations and postictal dopamine levels, reflecting catecholaminergic overdrive, which is in line with our findings of stronger autonomic activation in seizures that elicit hs-cTnI elevation.

4.1.2. Natriuretic peptides

Heart lesions can equally cause cardiac dysfunction [40], which can be detected by BNP elevations [10].

BNP might be secreted both by the heart or the brain and, to our knowledge, no study previously demonstrated the origin of this natriuretic factor after seizures.

The stress associated with seizures and the secondary noradrenaline release might trigger BNP cardiac production [10,11]. On the other hand, the epileptic activity in the brain can activate BNP secretion in both the heart and the brain [10].

Until now, few studies addressed BNP levels after epileptic seizures,

and, although being prospective, they included only patients with GTCS [8], patients admitted to the emergency room/center [10,15], or only children [10]. In these studies, Kyung-Il Park [15] failed to show any differences in NT-proBNP between the seizure and the vasovagal syncope groups, but his study comprised merely 12 patients with syncope and 15 with seizures, and measurements were made up to 24 h after each episode. Rauchenzauner et al. [10] found higher levels of BNP in children with GTCS and febrile convulsions.

In our patients, BNP elevations after seizures were only significantly associated with the presence of CRF, corroborating the hypothesis that cardiac dysfunction and/or BNP cardiac secretion may occur acutely in patients with higher cardiovascular risk. No significant changes in BNP were found after FBTCS, a similar result to that obtained by Nass et al. [8]

4.1.3. CRP

Inflammation is being recognized in epilepsy, but contrarily to other noninflammatory neurologic conditions, a study of CRP in this context is still lacking [12].

The few published studies on this subject suggest both chronic [12,19] and acute [12–14] CRP elevations in patients with refractory epilepsy.

In our study, only 2 patients (4.3 %) had an elevation of hs-CRP after the seizure. We thought the fact that more than 75 % of our patients were taking AED that lower CRP could account for this result, but could not find any significant association between being on that medication and having or not an elevation of hs-CRP. Nevertheless, that medication could have prevented hs-CRP rises in patients in whom they would otherwise happen.

Also, more than 15 % were on medication that could raise CRP, and we could not find any association either. Within the patients who were on AED reported to lower CRP, 15.6 % were also taking AED that could raise CRP. That could explain the fact that the differences did not reach statistical significance.

The 2 patients that had an hs-CRP elevation were not taking AED that could raise CRP levels, and so, those should correspond to true elevations.

Alapirtti et al. [12] found a significant association between GTCS and hs-CRP elevations, – patients being monitored in the EMU –, but it could not be proved by Sohn et al. [14] – patients admitted to the emergency room, in whom they found CRP elevations regardless of seizure type. In our study, the number with FBTCS and hs-CRP elevations were not enough to reach statistical significance, though there is a trend favouring that association. The first authors measured CRP for 24 h after the index seizure and found that CRP values follow a ‘U’ shaped curve, decreasing for the first 3 h and increasing afterward.

According to this, if we had measured hs-CRP past 12–18 h after the seizure, we could have found more patients with hs-CRP increases.

Assadpour Piranfar [48] found a significant relation between hs-CRP levels and coronary atherosclerosis severity. Our patients with hs-CRP elevations also had hs-cTnI elevations, suggesting a cardiovascular origin for those increases. The elevation of hs-CRP was significantly associated with PGES, pointing to a possible association with postictal autonomic dysregulation [49].

4.2. Cardiac biomarkers and SUDEP

SUDEP's pathophysiology is still unknown [37,39,49–52]. In many cases, no structural lesion can be perceived [37,53], and different cases probably have different causes/mechanisms [37,51]. Patients with an elevation of one biomarker did not necessarily have the elevation of another, which could reflect different mechanisms for the cardiac alterations secondary to epileptic seizures.

There is evidence of profound changes in the autonomic nervous system following seizures [50] hinting to its role in some SUDEP cases [49,51]. Massive catecholamine release elicited by epileptic seizures

can cause myocardial ischemia due to coronary artery vasoconstriction [3], which when repeated may provoke myocardial fibrosis [50,54], and if near to the conductive system can cause potentially fatal arrhythmias [44]. Bradycardias and prolonged tachycardias secondary to epileptic seizures may, in turn, prompt myocardial ischemic changes [3]. Opekin et al. [53] did not find significant perivascular or interstitial fibrosis on histological examination of both SUDEP and control groups, but they do not rule out the possibility of minor abnormalities of the conduction system being partly responsible for some SUDEP cases.

GTCS are a consistent risk factor for SUDEP [37,38], and, in the MORTEMUS study [39], preceded every monitored SUDEP case.

DeGiorgio et al. [30] created a 7-item inventory (the SUDEP-7 inventory) intending to estimate the SUDEP risk from risk factors originally identified and validated by Walczak et al. [31] (Table 1).

The fact that many patients with risk factors for SUDEP do not die raises the suspicion that other important mechanism should be the ultimate cause [37].

To our knowledge, the possible association between the SUDEP-7 inventory and serum biomarkers was not previously explored by others.

Our results do not show an association between hs-cTnI, BNP, or hs-CRP elevations with the SUDEP-7 inventory, but the majority of our patients (75 %) have a risk score ≤ 4 and more than 50 % scored one or 2 in the inventory. From this inventory point of view, our patients, though having refractory epilepsy, do not present a severe risk for SUDEP, which may explain the lack of a significant association. Nevertheless, one of the patients with an hs-cTnI elevation above the 99th percentile upper reference limit, and the only one with a perfusion defect in the myocardial scintigraphy had a SUDEP-7 score of 7. That patient had a more prolonged seizure and PGES, conditions associated with hs-cTnI elevation, but whose contribution to SUDEP is controversial and are not included in the SUDEP-7 inventory.

4.3. Limitations

Our major limitation is the relatively small number of patients with FBTCS in our cohort.

Concerning hs-CRP, we could have measured it at 24 h after index seizure as well, given a study found that CRP values initially decrease (till 3 h after the seizure), increasing afterward (till 24 h after the seizure) [12]. Maybe, if we did so, we could find more patients with hs-CRP elevations, and reach a significant association with FBTCS.

Although patients with FBTCS had oxygen saturation evaluated during the postictal phase, this was made on separate cardiopulmonary monitors and not systematically recorded. We did not measure continuous oxygen saturation throughout the video-EEG monitoring process. Mosely et al. [55] found that ictal hypoxemia was significantly associated with generalized tonic-clonic seizures (either primary or secondary) and prolonged seizure duration, variables we found to be associated with rises in hs-cTnI. According to some authors [23,56,57], oxygen saturation might be related to PGES. It would have been interesting to explore any relationship between oxygen saturation and cardiac biomarkers.

Tonic-clonic seizures induce acute metabolic effects that can interfere with cardiac function and excitability, as reported by Nass [58]. In this setting, we could have measured biomarkers like lactate and ammonia, as well as glucose, creatinine, and electrolytes.

We did not measure catecholamines as well, and it would add complementary information, knowing that the catecholamine release after seizures can cause coronary artery vasoconstriction [3] and is related to elevated levels of cardiac injury markers [8].

5. Conclusions

Mechanistically, it is known that SUDEP likely involves a combination of postictal respiratory dysfunction, arousal failure, and cardiac

dysfunction [59]. Our data expand the characterization of the last component of this triad: we documented that a significant number of patients have increases in well-established biomarkers of myocardial necrosis/dysfunction after seizures (hs-cTnI, BNP), without any sign or symptom of cardiac disease. Patients with an elevation of one biomarker do not necessarily have the elevation of another, which could reflect different mechanisms involved in cardiovascular response to seizures and point to multifactorial pathways of myocardial damage potentially related to SUDEP.

We did not find any association between the biomarkers increases and the SUDEP-7 inventory. Nevertheless, taking into account the associations between biomarkers and seizures characteristics, we consider that seizure duration, PGES, and measurements of hs-cTnI after seizures, particularly after FBTCS, should be weighted in future studies exploring clinical predictors of SUDEP, in order to assess if it is worthy to include them in revisions of the SUDEP-7 inventory.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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Variabilidade da frequência cardíaca

**Heart rate variability in patients with refractory epilepsy:
The influence of generalized convulsive seizures**

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Heart rate variability in patients with refractory epilepsy: The influence of generalized convulsive seizures

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ABSTRACT

Objective: Patients with epilepsy, mainly drug-resistant, have reduced heart rate variability (HRV), linked to an increased risk of sudden death in various other diseases. In this context, it could play a role in SUDEP. Generalized convulsive seizures (GCS) are one of the most consensual risk factors for SUDEP. Our objective was to assess the influence of GCS in HRV parameters in patients with drug-resistant epilepsy.

Methods: We prospectively evaluated 121 patients with refractory epilepsy admitted to our Epilepsy Monitoring Unit. All patients underwent a 48-hour Holter recording. Only patients with GCS were included ($n = 23$), and we selected the first as the index seizure. We evaluated HRV (AVNN, SDNN, RMSSD, pNN50, LF, HF, and LF/HF) in 5-min epochs (diurnal and nocturnal baselines; preictal – 5 min before the seizure; ictal; postictal – 5 min after the seizure; and late postictal – >5 h after the seizure). These data were also compared with normative values from a healthy population (controlling for age and gender).

Results: We included 23 patients, with a median age of 36 (min-max, 16–55) years and 65% were female. Thirty percent had cardiovascular risk factors, but no previously known cardiac disease. HRV parameters AVNN, RMSSD, pNN50, and HF were significantly lower in the diurnal than in the nocturnal baseline, whereas the opposite occurred with LF/HF and HR. Diurnal baseline parameters were inferior to the normative population values (which includes only diurnal values). We found significant differences in HRV parameters between the analyzed periods, especially during the postictal period. All parameters but LF/HF suffered a reduction in that period. LF/HF increased in that period but did not reach statistical significance. Visually, there was a tendency for a global reduction in our patients' HRV parameters, namely AVNN, RMSSD, and pNN50, in each period, comparing with those from a normative healthy population. No significant differences were found in HRV between diurnal and nocturnal seizures, between temporal lobe and extra-temporal-lobe seizures, between seizures

Abbreviations: GCS, generalized convulsive seizure; HRV, heart rate variability; SUDEP, sudden unexpected death in epilepsy; EMU, epilepsy monitoring unit; ASMs, anti-seizure medications; FBTCs, focal to bilateral tonic-clonic seizure; TL, temporal lobe; ETL, extra-temporal lobe; PGES, Postictal generalized EEG suppression; PNES, psychogenic nonepileptic seizures; CPS, complex partial seizures; GTCS, generalized tonic-clonic seizures; VNS, vagus nerve stimulation; WHO, World Health Organization; SCB, sodium channel blockers; MRI, magnetic resonance imaging; [^{99m}Tc]Tc-HMPAO SPECT, single photon emission computed tomography with [^{99m}Tc]Tc-HMPAO; [¹⁸F]FDG PET, positron emission tomography with [¹⁸F]FDG.

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with and without postictal generalized EEG suppression, or between seizures of patients with and without cardiovascular risk factors.

Significance/conclusion: Our work reinforces the evidence of autonomic cardiac dysfunction in patients with refractory epilepsy, at baseline and mainly in the postictal phase of a GCS. Those changes may have a role in some SUDEP cases. By identifying patients with worse autonomic cardiac function, HRV could fill the gap of a lacking SUDEP risk biomarker.

1. Introduction

Heart rate variability (HRV) measurements allow the assessment of cardiac autonomic activity (Malik et al., 1996). A low HRV has been associated with an increased risk of sudden death in myocardial infarction (Kleiger et al., 1987; La Rovere et al., 1998), with a worse prognosis in many different clinical conditions (Dekker et al., 2000), and independently associated with increased risk of sudden cardiac death in the general population (Maheshwari et al., 2016).

Seizures, mainly in drug-resistant epilepsy, commonly affect the heart rate (HR) and its variability (Moridani and Farhadi, 2017; Myers et al., 2018b), with a possible connection to sudden unexpected death in epilepsy (SUDEP) (Myers et al., 2018a). Also, some anti-seizure medications (ASMs) may influence the autonomic nervous system function (Persson et al., 2003).

SUDEP is one of the major causes of death directly related to epilepsy (DeGiorgio et al., 2019), particularly in refractory patients (Tomson et al., 2008), which account for 25–30% of all patients with epilepsy (EUCARE, 2003). Generalized convulsive seizures (GCS) are reported as the most consistent risk factor for SUDEP (DeGiorgio et al., 2017; Langan et al., 2005; Nilsson et al., 1999; Ryvlin et al., 2019).

Different studies' conclusions vary from considering decreased HRV a potential risk factor for SUDEP (Lotufo et al., 2012; Sevcencu and Struijk, 2010), related to increased cardiac mortality and sudden arrhythmic death, to devalue HRV parameters as no significant differences were found between groups of patients who died from SUDEP

and living controls (Odom and Bateman, 2018; Surges et al., 2009).

These mixed results, partially related to methodologic issues, encourage the research in this field to understand if and how HRV parameters should be included in clinical practice, namely in the prognostic assessment of SUDEP risk in patients with refractory epilepsy.

This study aims to evaluate the impact of GCS in the HRV of patients with refractory epilepsy, in the preictal, ictal, postictal, late postictal, and baseline periods.

2. Material and methods

Our research method was based on the Guidelines for Reporting Articles in Psychiatry and Heart Rate Variability (GRAPH) (Quintana et al., 2016). It fits the four domains proposed by those guidelines: participant selection, interbeat interval collection, data preparation, and HRV calculation. Fig. 1 illustrates it in general.

2.1. Participants

From January 2015 to July 2018, we prospectively evaluated 121 patients with refractory epilepsy, admitted to our institution's Epilepsy Monitoring Unit (EMU) as part of their pre-surgical evaluation. All patients were clinically evaluated by experienced epileptologists and underwent MRI with a dedicated epilepsy protocol. Selected patients performed functional imaging ($[^{99m}\text{Tc}]\text{Tc-HMPAO}$ SPECT and/or $[^{18}\text{F}]$ FDG PET).

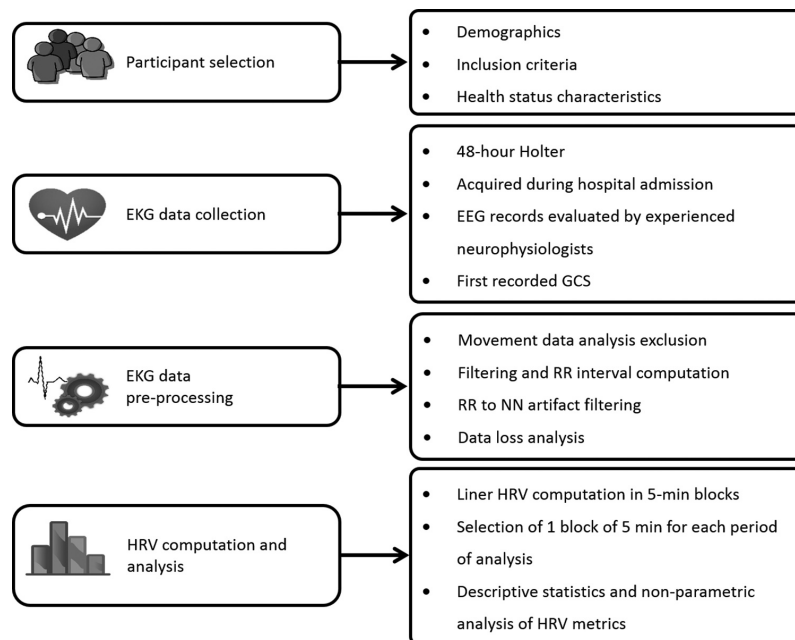


Fig. 1. Study method illustration based on Guidelines for Reporting Articles in Psychiatry and Heart Rate Variability (Quintana et al., 2016). Detailed descriptions of each domain are provided below in the following sections.

We collected demographic and clinical data, including age, duration of epilepsy, probable etiology, seizure frequency and semiology (duration, type of GCS, localization of the ictal onset zone), medication at the time of HRV evaluation (particularly ASMs), cardiovascular risk factors, such as smoking habits, arterial hypertension [systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (Unger et al., 2020)], dyslipidemia (defined as total cholesterol ≥ 190 mg/dL and/or triglycerides ≥ 150 mg/dL), or under targeted therapy to control these risk factors, and obesity (defined as body mass index ≥ 30 – WHO). None of the patients had previously known cardiovascular disease.

We selected patients who had GCS and chose the first recorded GCS as the index seizure (23 patients).

2.2. Data collection procedure

2.2.1. Seizures characterization using EEG

We obtained scalp recordings by placing gold cup electrodes (with conductive paste and collodium), according to the 10–20 system. Additional 10–10 locations were recorded, to include the specific regions of interest (total of 35–44 electrodes). Polygraphic derivations included an EKG channel (as standard on EEG recordings) and an optional EMG one. The signal was sampled at 512 Hz and recordings were visually analyzed using standard bipolar and referential montages. We maintained, reduced, or discontinued ASMs, following the EMU protocol (depending mainly on baseline seizure types and frequency), under the supervision of an epileptologist.

Based on the EEG and video examination and imaging, the seizures were classified according to the semiological seizure classification (Luders et al., 1998) and the International League Against Epilepsy (ILAE) classification (Fisher et al., 2017). Experienced clinical neurophysiologists determined temporal clinical and EEG ictal onsets and offsets, as well as the lobar regions of ictal onset and the presence and duration of postictal generalized EEG suppression, according to the definition by Lhatoo et al. (general absence of electrographic activity > 10 μ V in amplitude, within the 30 s following seizure termination, allowing for muscle, movement, breathing and electrode artifacts (Lhatoo et al., 2010)). GCS were further subclassified according to Alexandre V. et al.: type 1 – tonic-clonic GCS with bilateral symmetric tonic arm extension; type 2 – clonic GCS without tonic arm extension or flexion; type 3 – GCS with unilateral or asymmetric tonic arm extension or flexion (Alexandre et al., 2015).

2.2.2. EKG recording and HRV analysis

All patients underwent a 48-hour Holter recording in the EMU, using the Philips Zymed DigiTrak-Plus 48 recorder, model 3100A, and the Philips Zymed Holter 1810 series software. This software was used to extract the RR intervals based on its proprietary algorithm which detects the ‘R’ points of the EKG waveform.

We used the extracted RR interval and used the INESC TEC proprietary and validated HRV analysis system, named VJ Assembly, already used in previous studies (Pimentel et al., 2019). Before computing the HRV parameters a simple verification according to the literature was made to verify if all the RR intervals detected by the Philips software were physiologically valid (Clifford et al., 2006) – this procedure eliminates any possible mistakes made by the RR interval detection algorithm that can occur in the case of a noisy EKG signal. The RR intervals physiologically valid are called normal-to-normal (NN) intervals.

For the HRV analysis, we followed the guidelines presented by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik et al., 1996), having considered the parameters AVNN, SDNN, RMSSD, pNN50, LF, HF, and LF/HF. Table 1 summarizes the HRV parameters analyzed and their purpose.

We evaluated HRV parameters by analyzing 5-min-EKG epochs during interictal, preictal, ictal, and postictal periods: baseline (diurnal

Table 1
Description of the HRV parameters analyzed in this study.

Domain	Measure	Description
Time-domain	AVNN	Average of NN intervals (ms)
	SDNN	Standard Deviation of all NN intervals (ms)
	RMSSD	Root Mean Square of the Successive Differences between NN intervals (ms)
Frequency-domain	pNN50	NN variations above 50 ms (%)
	LF	Power in the Low-Frequency range 0.04–0.15 Hz (ms^2)
	HF	Power in the High-Frequency range 0.15–0.40 Hz (ms^2)
	LF/HF	Describes the ratio between the LF and HF frequency power bands

and nocturnal), preictal (5 min before the GCS), ictal, postictal (5 min after the seizure), and late postictal (> 5 h after the seizure).

The diurnal baseline period corresponded to the first 5 min of EKG data following wake-up, without noise or artifacts. The nocturnal baseline was selected during stage 2 of sleep for all patients, in a period without seizures nor movement, therefore without the influence of noise or artifacts.

Additional 1-min epoch analyses were performed in the preictal period, to clarify eventual changes in shorter periods. These periods were annotated by the clinicians involved in this study during patients’ stay at the EMU.

Ictal data were influenced by muscle artifacts, varying in extent and severity in each patient. That situation made the R-peak detection unreliable at least in some part of the analyzed period. We opted to include those results in the Results section, but we do not discuss them further.

We also compared HRV data from these patients with normative values from a healthy population (Voss et al., 2015), controlling for age and gender (Fig. 4).

2.3. Statistical analysis

Quantitative variables were described using median (inter-quartile range or min-max) or mean (standard deviation) depending on the symmetry of the variable distribution, while categorical variables were described through absolute and relative frequencies. The statistical association between quantitative and categorical variables was assessed using the Wilcoxon or Mann-Whitney statistical tests for the comparison of two paired or independent samples, respectively. In the comparison of three or more paired groups, the Friedman test (for non-parametric data) was used and the Wilcoxon test for the post hoc pairwise comparisons. The significance level was set at 0.05, and the Bonferroni correction was applied to each analyzed parameter in the comparison of three or more periods, to account for multiple testing (i.e., the significance level of 0.05 was divided by the number of hypotheses tested). Statistical analysis was performed using the commercially available software IBM SPSS Statistics for Windows software, Version 27.0 (Armonk, NY: IBM Corp).

2.4. Protocol approval and patient consents

The study was approved by our Institution’s Ethics Committee and all patients gave written informed consent.

3. Results

3.1. Characterization of the patients and index seizures

Twenty-three patients were included, with a median age of 36 (min-max, 16–55) years, and 65% were female (Table 2). Thirty percent presented cardiovascular risk factors without known cardiac disease. The median duration of epilepsy was 13 (min-max, 2–49) years. Eighty-

Table 2
Demographic and clinical data.

Characteristics of patients (n = 23)	
Age (years), median (range)	36 (16–55)
Gender, n (%)	
Female	15 (65.2)
Male	8 (34.8)
Duration of epilepsy (years), median (range)	13 (2–49)
Etiology of epilepsy (presumed), n (%)	
Hippocampal Sclerosis	6 (26.1)
Malformations of Cortical Development	4 (17.4)
Hypoxic-ischemic lesion	1 (4.3)
Idiopathic generalized epilepsy	1 (4.3)
Indeterminate	11 (47.8)
Frequency of seizures per month, n (%)	
≤ 8	18 (78.3)
9–25	2 (8.7)
≥ 26	3 (13.0)
Cardiovascular risk factors, n (%)	
Smoking (isolated)	1 (4.3)
Dyslipidemia (isolated)	3 (13.0)
Obesity (isolated)	2 (8.7)
Arterial Hypertension (isolated)	0 (0.0)
Dyslipidemia, Arterial Hypertension and Obesity	1 (4.3)
None	16 (69.6)
Number of Anti-Seizure Medication, mean (SD)	2.4 (0.8)
Use of Sodium Channel Blockers, n (%)	20 (87.0)

seven percent were under sodium channel blockers (SCB) to control their epilepsy. At admission, 16 patients (69.6%) suspended all ASMs, 6 patients (26%) reduced ASMs, with the suspension of SCB, whereas only one patient (4.3%) could not suspend any medication (including SCB), but reduced all of them.

Concerning the index seizure characteristics, only one seizure had a generalized onset, while the remaining 22 were focal to bilateral tonic-clonic seizures (FBTCS). The majority corresponded to a type 3 (61%), including the one with generalized onset. Ten patients (43.5%) had temporal lobe (TL) seizures, 61% had Postictal Generalized EEG Suppression (PGES) and 65% of the seizures occurred during sleep (Table 3).

3.2. Individual HRV parameters evolution and baseline analysis

The evolution of the considered HRV parameters for each patient throughout the six studied periods is presented in Fig. 2. Overall, the individual profile is similar within each HRV parameter. Diurnal and nocturnal values are connected through a distinct line (dashed) to highlight that the sequence of these two recorded periods was not the same for all patients.

Diurnal baseline values of AVNN, RMSSD, pNN50, and HF were significantly lower than nocturnal baseline values, which reflects a

Table 3
Index seizure characteristics.

Index seizure characteristics of the 23 patients	
Type of GCS, n (%)	
Type 1	8 (34.8)
Type 2	1 (4.3)
Type 3	14 (60.9)
Duration (seconds), median (range)	97 (55–171)
Postictal generalized EEG suppression, n (%)	14 (60.9)
Awake, n (%)	8 (34.8)
Ictal onset side, n (%)	
Right	8 (34.8)
Left	9 (39.1)
Bilateral	5 (21.7)
Generalized	1 (4.3)
Ictal onset localization, n (%)	
Temporal	10 (43.5)
Extra-temporal	12 (52.2)
Generalized	1 (4.3)

global lower HRV during the day (Table 4), whereas LF/HF and basal HR were significantly higher during this period.

3.3. HRV from baseline to peri-ictal periods and comparison with a normative population

Fig. 3 is an overall representation of each parameter in each time point. Figs. 4 and 5 show significant differences between the analyzed periods for all HRV parameters and HR (Friedman test, $p < 0.003$, two-tailed). Specifically, during the postictal period, we found a significant reduction of AVNN, SDNN, RMSSD, LF, and HF, comparing with the diurnal baseline (Wilcoxon test, $p < 0.003$; two-tailed). LF/HF was increased during this period, but the changes were not statistically significant.

We did not find any significant difference between the preictal period and the diurnal baseline. In a more detailed analysis performed in the preictal period (1-min epochs), there were no changes either. Considering the variations from preictal to postictal periods, we found statistically significant reductions in AVNN, RMSSD, pNN50, and HF, as well as a rise in LF/HF (Wilcoxon test, $p < 0.003$; two-tailed).

There is an overall tendency for a reduction in HRV in our patients when compared with normative healthy population values (Voss et al., 2015) (Fig. 4). In particular, controlling for age and gender (Fig. 4), and excluding nocturnal values, AVNN, RMSSD, and pNN50 were lower, in each time point, whereas LF/HF was always higher.

3.4. Additional analyses

We did not find significant differences in HR or any of the HRV evaluated parameters within the non-baseline period, between seizures in awake and sleep periods, between seizures with and without PGES, between seizures with temporal and extra-temporal onset, or between seizures of patients with and without cardiovascular risk factors.

4. Discussion

In our work, we found significant changes in autonomic function parameters in patients with refractory epilepsy and GCS, particularly during the postictal period. This is of particular relevance since witnessed SUDEP cases occur during the early postictal period (Kloster and Engelskjøn, 1999; Nashef et al., 1998; Ryvlin et al., 2013).

4.1. Diurnal and nocturnal baselines

HRV baseline values of AVNN, RMSSD, pNN50, and HF were significantly lower during the day. LF/HF and basal HR were significantly higher in the same period, denoting a higher sympatho-vagal balance during the day.

In normal populations, HRV circadian variation has long been known, globally with higher values during the night (Malpas and Purdie, 1990), but with LF/HF and HR increased during daytime (Nakagawa et al., 1998), indicating a shift toward sympathetic dominance. In patients with epilepsy, both diurnal and nocturnal HRV values are lower than healthy controls, but the amplitude of the variation is shorter, mainly due to even lower nocturnal values (Persson et al., 2007; Ronkainen et al., 2005; Yang et al., 2018). This might contribute to the lack of significance we found in SDNN and LF when comparing diurnal and nocturnal HRV parameters.

The reasons underlying altered HRV in patients with epilepsy are unknown. One hypothesis is that the mechanisms of epileptogenesis may also induce disrupted functioning of autonomic centers. Alternatively, repetitive seizures may cause structural brain damage (Dingledine et al., 2014), and if that damage occurs in autonomic centers, it might be responsible for interictal HRV changes (Lotufo et al., 2012; Wasterlain et al., 1993), as observed in our patients' baseline HRV.

We could only visually compare our data to HRV normative values

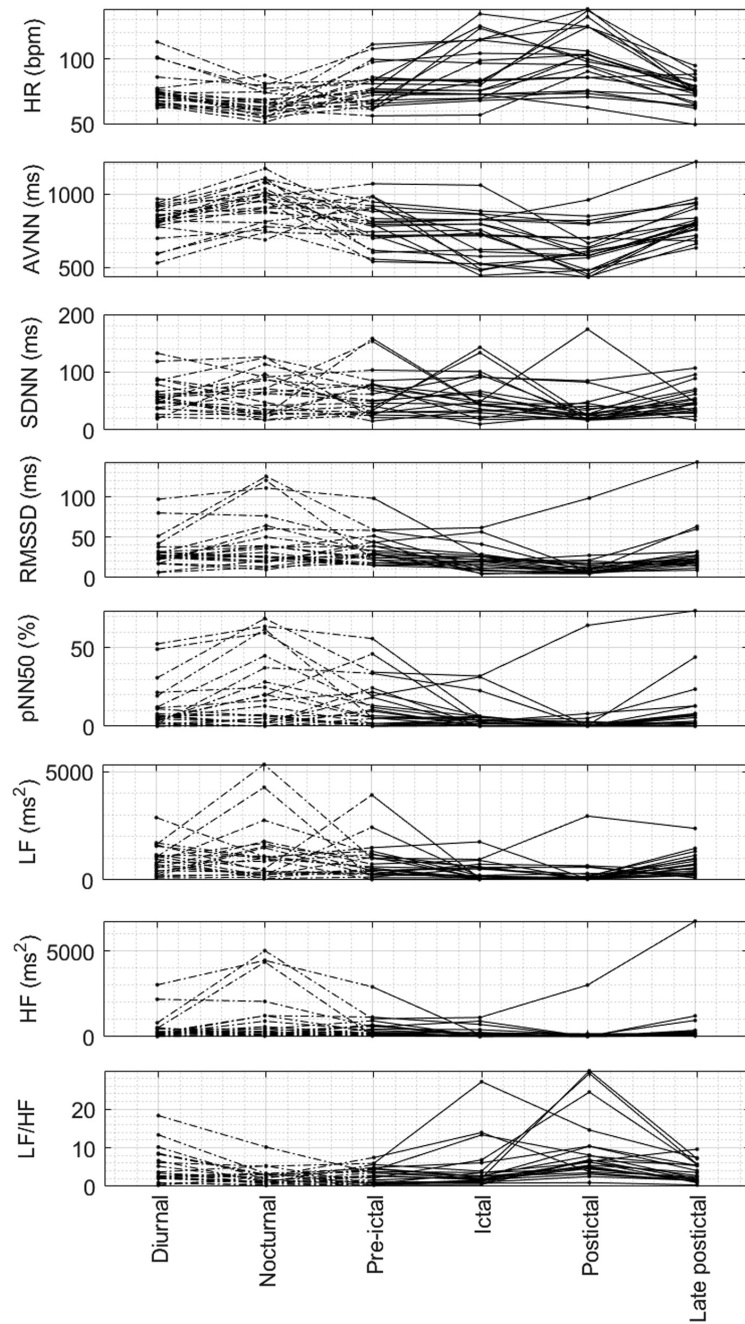


Fig. 2. Individual evolution of HR (bpm), AVNN (ms), SDNN (ms), RMSSD (ms), pNN50 (%), LF (ms^2), HF (ms^2), and LF/HF throughout the six studied periods: diurnal (baseline), nocturnal (baseline), preictal, ictal, postictal, and late postictal. The baseline periods are connected through dashed lines because the recording sequence diurnal-nocturnal was not the same for all individuals.

Table 4

HR (bpm), AVNN (ms), SDNN (ms), RMSSD (ms), pNN50 (%), LF (ms²), HF (ms²), and LF/HF in the diurnal and nocturnal periods. Data are presented as median (inter-quartile range).

HRV parameter	Diurnal baseline	Nocturnal baseline	p-value
HR	72.3 (8.8)	62.9 (15.9)	< 0.001
AVNN	829.6 (102.3)	954.1 (222.7)	< 0.001
SDNN	56.7 (40.2)	62.4 (60.0)	0.784
RMSSD	25.8 (9.7)	31.4 (39.4)	0.036
pNN50	6.2 (9.7)	12.9 (34.8)	0.008
LF	803.6 (762.7)	976.9 (1303.2)	0.627
HF	215.1 (306.6)	293.5 (1078.6)	0.045
LF/HF	2.7 (4.6)	2.3 (2.3)	0.021

from a healthy population that does not have specific nocturnal data (Voss et al., 2015). Our patients' diurnal baseline values of AVNN, RMSSD, and pNN50 were lower, and baseline LF/HF was higher, which is in line with published literature (Baysal-Kirac et al., 2017; Lotufo et al., 2012). In addition, higher LF (sympathetic tone) and lower HF (vagal tone) are predictors of cardiovascular morbidity and mortality (Lotufo et al., 2012), and so, there might be a connection to SUDEP risk.

That would be in line with some studies that showed an inversely and significant association between HRV (RMSSD) and a SUDEP risk score (the SUDEP-7 inventory), with subjects with the highest SUDEP-7 score having changes in the autonomic function similar to those seen in patients with high risk for heart failure (DeGiorgio et al., 2010; Novak et al., 2015). A more recent study failed to show any significant association in time domain HRV parameters and the SUDEP-7 score (Baysal-Kirac et al., 2017), but the mean seizure frequency of their cohort was inferior to that of the previously reported study.

Regarding the possible interference of ASMs, a high percentage (87%) of our patients were medicated with sodium channel blockers, and all but one discontinued them at admission. Nonetheless, Stefani et al. did not find any change in HRV in patients with refractory epilepsy undergoing video-EEG monitoring, after reduction/cessation of ASMs (HRV was assessed at admission and on the day of minimal, or nil, medication), even in the subgroup of patients treated with sodium channel blockers (Stefani et al., 2013).

Another study assessed the effects of ASMs on night versus daytime HRV in patients with newly diagnosed and refractory epilepsy (Persson et al., 2007), and found no significant differences from controls in the night/day HRV ratios, whether before or after initiation of treatment with carbamazepine. Nevertheless, when patients served as their own controls, night/day HRV ratios were significantly lower after initiating carbamazepine.

In the systematic review and meta-analysis by Lotufo et al., they

found no significant differences in HF and LF, between treated and untreated groups of patients. There was only a trend for a lower LF in the treated group, which they interpreted as a possible suppressed sympathetic activity during pharmacotherapy, but they could not conclude there were detrimental effects from ASMs on HRV. They did not consider the type of ASMs, the dosage, or the period of use (Lotufo et al., 2012).

In a study by Ponnusamy et al. which compared HRV (SDNN, RMSSD, LF, HF, and other parameters that we did not evaluate) in patients with epilepsy, patients with psychogenic nonepileptic seizures (PNES), and healthy volunteers, the only resting HRV parameter that was affected by ASMs (including sodium channel blockers) was the SDNN (Ponnusamy et al., 2011).

In light of the above-reported evidence, we cannot exclude the possibility of a contribution of ASMs to further lower HRV diurnal baseline parameters in our patients, comparing to the normal population, but this pharmacological interference seems to not critically affect the obtained results.

4.2. Impact of index seizures on HRV parameters

In our study, no HRV parameters in the preictal period were significantly different from their respective diurnal baselines, as found by other authors (Toth et al., 2010). Contrarily, another study found diminished parasympathetic activity starting before the seizure (Novak et al., 1999), which we could not find even in 1-min epochs. That study comprised only 12 patients, and the methodology was different from ours, including the timings and parameters evaluated. There is also evidence of altered preictal HRV parameters in a study comprising only 14 patients exclusively with temporal lobe epilepsy, newly diagnosed and untreated (Romigi et al., 2016). Methodological issues may be responsible for the differences observed.

Our major finding was a global significant decrease in HRV in the postictal period, following a GCS. Other authors found similar results, in different types of seizures, including GCS (Pernice et al., 2019; Toth et al., 2010). Furthermore, those authors also found rises in LF/HF in the postictal period, as we did.

All our HRV parameters returned to basal values at the late postictal period, which is contrary to the study by Toth et al. (2010), in which HRV changes persisted 5–6 h after the seizure. They hypothesized that there is a long-lasting risk of death, after a seizure, which we could not corroborate.

HR increases from preictal to postictal periods in our patients, as we can see in other studies (Nass et al., 2019; Toth et al., 2010). In our patients, late postictal HR returned to baseline, which could also be seen in the study by Toth et al. This physiologic response to stress indicates an

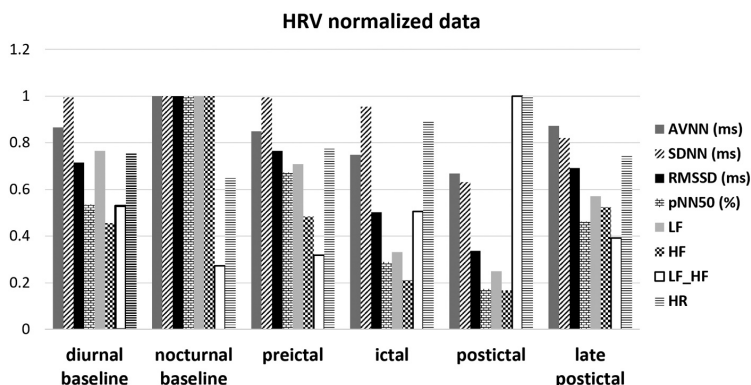


Fig. 3. Normalized analysis of HRV parameters in different time points (diurnal and nocturnal baselines, preictal, ictal, postictal, and late postictal); normalization to the highest value of each parameter.

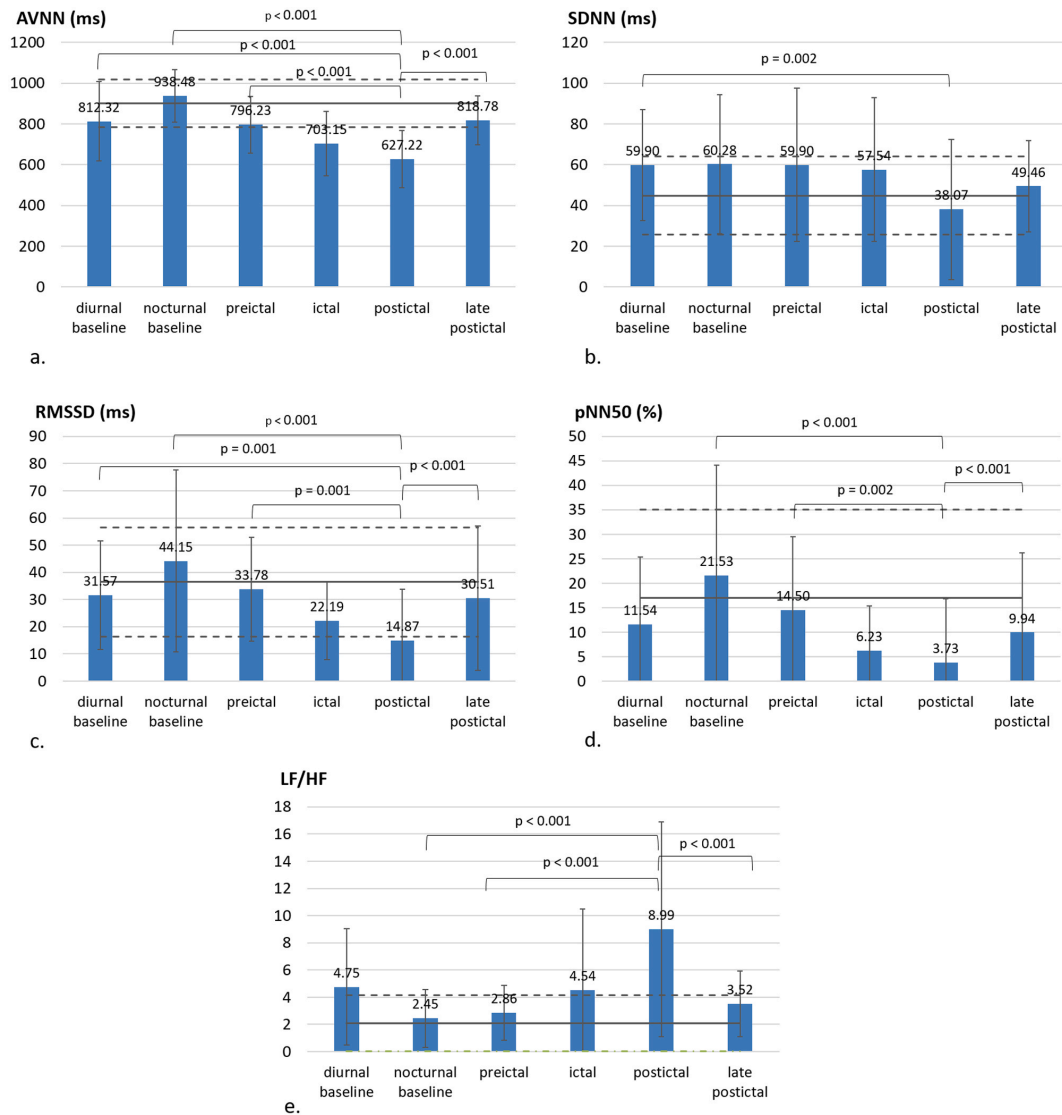


Fig. 4. Comparison of the HRV parameters AVNN, SDNN, RMSSD, pNN50, and LF/HF in the diurnal (baseline), nocturnal (baseline), preictal, ictal, postictal, and late postictal periods (bars represent the average, and the error bars the standard deviation) with the normative values for a healthy population [solid horizontal line – mean; dashed horizontal lines – standard deviation; (Voss et al., 2015; n = 1906, controlling for age and gender)]. The p-values next to the brackets correspond to the comparison between the postictal period and the other periods for which their difference was statistically significant.

increased sympathetic activity immediately after the seizure, which is not persistent. Novak et al. (1999) found a marked ictal tachycardia, the HR returning to baseline 1 min after the seizure, but they excluded GCS and evaluated only 12 patients with TL epilepsy.

It is known that patients with epilepsy have interictal autonomic dysfunction, as we could also verify and discuss in Section 4.1, since our patients' diurnal baseline HRV was globally lower than the values of a healthy population. As a result of GCS, HRV parameters were further altered in our patients, compared with the same healthy population. Some authors link interictal autonomic dysfunction with an increase in SUDEP (Myers et al., 2018a), or with risk factors for SUDEP (DeGiorgio et al., 2010), but the exact mechanism by which these patients die

suddenly remains unknown. Other authors did not find significant differences in HRV parameters between patients who died from SUDEP and living patients with epilepsy (Odom and Bateman, 2018; Surges et al., 2009). Their cohorts were relatively small (16 SUDEP and 48 controls, 7 SUDEP and 7 controls, respectively), and the fact that they used living patients as controls is another limitation since those controls might die from SUDEP. Szurhaj et al., also using matched living controls, had similar results to the above-mentioned studies, regarding resting HRV parameters. But they went further and evaluated the cardiac autonomic response to hyperventilation (using HR and HRV parameters) in a larger group of SUDEP cases (n = 20) and controls. They found differences in HR between the end of hyperventilation and 4 min later, which were

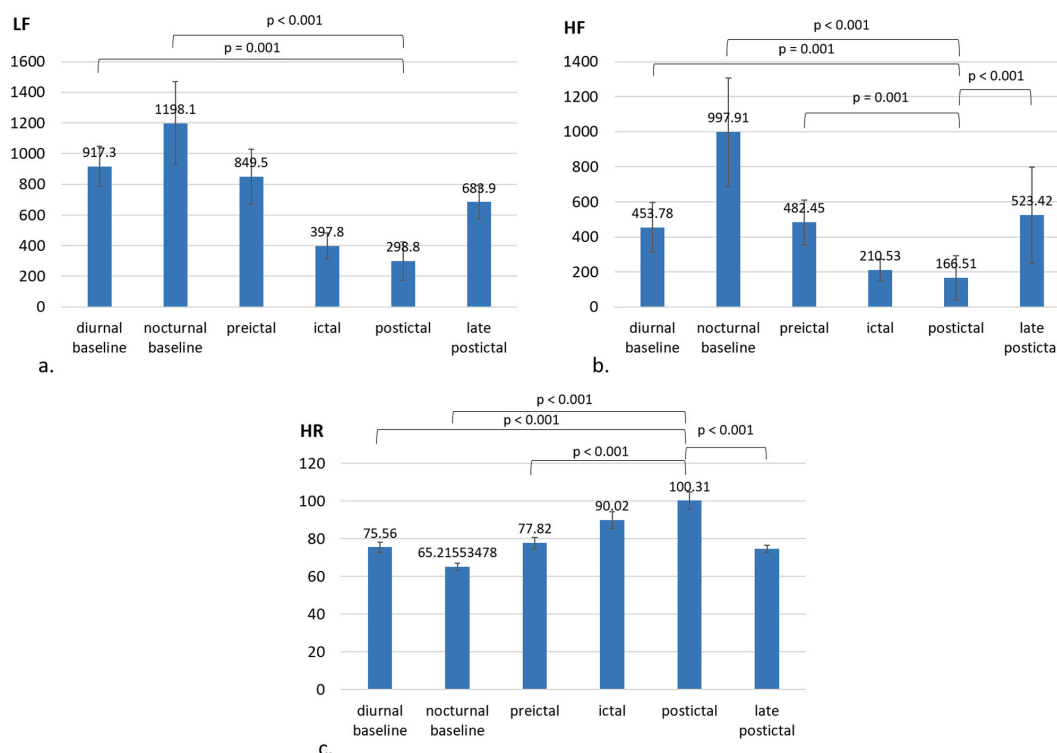


Fig. 5. a.–c. Significant differences for LF, HF, and HR, respectively, in different time points ($p < 0.05$; Friedman); Wilcoxon, post hoc pairwise comparison, $p < 0.003$. The p-values next to the brackets correspond to the comparison between the postictal period and the other periods for which their difference was statistically significant. Comparison with normative values was not performed for these parameters, due to different methods to calculate them (Lomb periodogram versus Fast Fourier transformation).

able to distinguish both groups. RMSSD decreased more significantly in the control group (Szurhaj et al., 2021). Their findings express an abnormal autonomic response only evident after sympathetic stimulation by hyperventilation.

Not all patients with interictal autonomic dysfunction suffer SUDEP. There might be a second factor or even more that can ignite the cascade of events terminating in death. As we can see from our work, a GCS (which may prompt extreme sympathetic stimulation) could be one of those factors. Maybe one of the usual GCS of a particular patient becomes fatal because it pushes the patient toward an extreme autonomic deterioration, which could develop terminal (Myers et al., 2018a). Lhatoo et al. hypothesized that there might be anatomical and/or functional abnormalities in the brainstem, possibly with a genetic basis, which altogether could have an important role during the seizure (Lhatoo et al., 2015).

Although that could be a possible explanation, there are a few reports of SUDEP not following seizures (Lhatoo et al., 2016). Those deaths did not have a primary cardiac cause, instead, there was a progressive cardiorespiratory compromise, followed by EEG suppression.

The autonomic changes during the interictal period are probably the result of chronic insults in autonomic centers by repetitive seizures (Sevcencu and Struijk, 2010; Wasterlain et al., 1993), and maybe, at some point, those lesions trigger a cardiorespiratory failure.

4.3. Additional analyses

We found no statistically significant differences in all parameters within the non-baseline period between seizures occurring during

wakefulness and sleep, including HR. There is a study that found that patients who later died from SUDEP had a more pronounced HR increase when seizures occurred during sleep than when awake (Nei et al., 2004), including complex partial seizures (CPS), generalized tonic-clonic seizures (GTCS), and absence seizures. They hypothesized that when seizures occur during sleep, there is an abrupt shift from a predominant vagal to an utmost sympathetic tone, possibly precipitating fatal cardiac arrhythmias. Apart from HR, they did not analyze other HRV parameters as we did, and although we have seen some authors pointing that they should have considered the circadian rhythm when analyzing HRV in seizures while in sleep and awake periods (Behbahani et al., 2018), we could not find any significant difference in HRV between seizures in both periods.

PGES is one of the features proposed as a potential biomarker of SUDEP, being significantly more prolonged in patients suffering SUDEP, when compared with living refractory patients with epilepsy (Lhatoo et al., 2010). A study demonstrated that after GTCS there is a correlation between the degree of sympathetic activation and parasympathetic suppression, with the duration of PGES. They concluded that there is a particularly critical postictal period of autonomic dysregulation which might be pertinent to SUDEP (Poh et al., 2012). Some other studies tried to identify clinical and physiological conditions that might distinguish patients with epilepsy susceptible to PGES. Although there are reports of changes in HRV parameters prior to and after GCS with and without PGES, at greater extent when followed by PGES, in children (Oknari et al., 2020) as well as in adults (Sivathamboo et al., 2020), that finding could not be reproduced in our patients, as we did not find any significant differences between GCS with and without PGES, in any of the

evaluated parameters and in each time point (preictal, postictal, and late postictal).

In general, as we discussed above, there is evidence of sympathetic dominance during seizures (irrespective of type or onset site). There are studies analyzing HRV parameters exclusively in the temporal lobe (TL) epilepsies (Ansakorpi et al., 2004; Novak et al., 1999; Romigi et al., 2016; Ronkainen et al., 2005), because they are relatively common, but also with the assumption that temporal lobe structures have plenty autonomic connections. In the HRV context, few studies compare TL seizures with extra-TL (ETL) seizures, and they only compare HR. A study found that in TL seizures, the HR variation was greater and lengthened than in frontal lobe seizures (Son et al., 2016). Another one, comparing HR increase in otherwise subclinical seizures, found significant tachycardia in 8 out of 13 TL seizures, yet in only 1 out of 9 ETL seizures (Weil et al., 2005). Both refer to a potential role of the amygdala and the insular cortex, given their autonomic regulation function in epilepsy. In our study, we went further and analyzed other HRV parameters beyond HR, and we could not find any significant difference between seizures with TL onset and ETL onset, in each period (preictal, ictal, postictal, and late postictal).

There are reports that cardiovascular risk factors may influence HRV (Kubota et al., 2017; Pope et al., 2001), but in our cohort, we did not find any significant differences between seizures in patients with and without cardiovascular risk factors.

We must state, however, that the lack of significant differences might be related to the size of our cohort. Since we did not find any association with other specific conditions, it seems advised in future studies with larger cohorts, to analyze HRV parameters in every patient with epilepsy (at least with GCS), to be able to get more robust data.

4.4. Clinical implications

In our study, we found changes in baseline HRV parameters compared with a normal population and particularly in the postictal period.

These autonomic dysfunctions, shifting the autonomic balance toward parasympathetic withdrawal and sympathetic dominance, may have clinical relevance, not only because they can lower the thresholds for life-threatening arrhythmias (Pernice et al., 2019), but because they might have influence when deciding which therapy best suits a patient with refractory epilepsy, and maybe in predicting the response to certain therapies.

Vagus nerve stimulation (VNS) consisting of electrical stimulation of the left vagus nerve is a well-accepted ancillary therapy for refractory epilepsy. A study evaluated the impact of VNS on cardiovascular autonomic function in nine patients with refractory epilepsy, by performing HRV analysis before and after neurostimulation. They found decreases in LF and LF/HF, after stimulation, reflecting a better sympathetic/parasympathetic balance, which they hypothesize having a cardioprotective effect (Schomer et al., 2014).

Prognostic biomarkers are lacking to predict responders to this therapy (Hödl et al., 2021; Liu et al., 2018). Liu et al. reported that patients that experienced a reduction of at least 50% of seizures with VNS had less impaired preoperative interictal HRV linear parameters than those who did not respond (Liu et al., 2018). Hödl et al. studied HRV parameters preictally and found that non-responders had a significant decline in preictal HRV. They attributed the abrupt autonomic imbalance to defective central autonomic function, which makes them unlikely to respond to this therapy (Hödl et al., 2021). This might be of importance to avoid needless VNS surgeries.

Although it is likely that successful epilepsy surgery reduces the risk of SUDEP, published data are conflicting, and SUDEP has occurred in patients not known to have postoperative seizures (Almeida et al., 2010; Seymour et al., 2012).

Epilepsy surgery seems not to affect HRV (Dericioglu et al., 2013; Persson et al., 2006). Another study evaluated the impact of epilepsy

surgery on the night/day ratios, and they did not find significant changes from the ratios before surgery (Persson et al., 2007).

Many ASMs decrease HRV, especially sodium channel blockers, contributing to impaired autonomic cardiac activity and being associated with a higher risk for sudden cardiac death (Pang et al., 2019; Persson et al., 2007). Treatment with carbamazepine was associated with lowering night/day ratios (Persson et al., 2007). Close monitoring with HRV evaluation in these patients might be of importance whether to consider another treatment option.

Another clinical possible application of HRV analysis is the development of seizure detection devices. There are already studies exploring this possibility. A study found no significant differences in the detection sensitivity between convulsive and nonconvulsive seizures, or between temporal and frontal lobe seizures, or even between left and right onset seizures. Although none of those characteristics were associated with better seizure detection, they found that patients with pronounced autonomic changes during seizures were the ones who had their seizures more frequently detected (Jeppesen et al., 2019). Another recent study found HRV changes in more than 53% of seizures preictally (40–0 min) and encourage new investigation to find out which kind(s) of seizures exhibit those changes (Leal et al., 2021).

The absence of standardized protocols to evaluate and report HRV in patients with epilepsy is a limitation to its use in clinical practice (Myers et al., 2018b).

4.5. Limitations

A major limitation of the present work may be considered the small number of patients in our cohort, which might explain the lack of statistical significance in some of the studied situations.

We did not analyze possible HRV differences between seizures with right and left onset, although there are reports of decreased interictal vagal tone in patients with left-sided newly diagnosed TL epilepsy (Romigi et al., 2016). Nonetheless, Nei et al. did not find any association between a specific epileptic zone (laterality or lobe) with SUDEP, including various types of seizures: CPS, GTCS, and absence seizures (Nei et al., 2004). In a systematic review and meta-analysis, Lotufo et al. also did not support the hypothesis of lateralization (Lotufo et al., 2012).

We did not analyze the possible influence of gender, which is reported in various studies (Behbahani et al., 2018; Koenig and Thayer, 2016; Voss et al., 2015), but there are also reports that gender differences are relatively subtle (Lotufo et al., 2012). Kuo et al. found that the largest differences occurred between 40 and 59 years, but there were no differences between genders when the age was equal to or over 60 years (Kuo et al., 1999). Our small sample did not allow us to stratify age to make a formal analysis.

Another limitation is that we did not compare seizures occurring during the night with nocturnal data from a healthy population, because we could not find those values to compare. The normative values that we used included only diurnal data.

Oxygen saturation was not measured continuously. We measured it postictally, but on separate cardiopulmonary monitors. Controversy still exists concerning which comes first: central apnea or central autonomic deregulation (Behbahani et al., 2018). It would be interesting to investigate any possible relation between the HRV patterns in our patients and oxygen saturation.

5. Conclusion

The evaluation of HRV parameters has not yet become integrated into the clinical practice by epileptologists, in part due to the lack of standardized protocols, which may justify some contradictory results in published literature (Myers et al., 2018b).

Of course, after the initial exploratory studies to identify the most significant changes in epileptic patients, as our work is an example, future methodological standardization of protocols should take into

account not only the relative importance of each parameter but also the development of the simplest methods (using portable or wearable devices) that could be integrated in daily clinical practice. In an attempt to make our results comparable to others, we used the Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication (Quintana et al., 2016). Although we have adopted an HRV group analysis in specific moments, HRV time series analysis might be considered in future studies to analyze eventual patterns not visible in HRV group analysis.

Our work supports other studies' findings demonstrating autonomic cardiac dysfunction in patients with refractory epilepsy, both in the interictal period and after GCS.

This autonomic imbalance, associated with cardiovascular risk, might be responsible for some of the SUDEP cases. The fatal risk might be related to structural abnormalities produced by repetitive seizures (justifying the interictal changes in HRV), which might per se trigger a cardiovascular failure, or might be worsened by another GCS. In that context, HRV measurements could eventually be clinical biomarkers of SUDEP risk.

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Declarations of interest

None.

Data statement

The data generated and/or analyzed during this study are available from the corresponding author on reasonable request.

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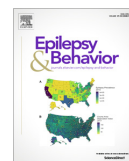
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Brief Communication

Does the type of seizure influence heart rate variability changes?



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ABSTRACT

Objective: Heart rate variability (HRV), an index of the autonomic cardiac activity, is decreased in patients with epilepsy, and a low HRV is associated with a higher risk of sudden death. Generalized tonic-clonic seizures are one of the most consistent risk factors for SUDEP, but the influence (and relative risk) of each type of seizure on cardiac function is still unknown. Our objective was to assess the impact of the type of seizure (focal to bilateral tonic-clonic seizure – FBTCs – versus non-FBTCs) on periictal HRV, in a group of patients with refractory epilepsy and both types of seizures.

Methods: We performed a 48-hour Holter recording on 121 patients consecutively admitted to our Epilepsy Monitoring Unit. We only included patients with both FBTCs and non-FBTCs on the Holter recording and selected the first seizure of each type to analyze. To evaluate HRV parameters (AVNN, SDNN, RMSSD, pNN20, LF, HF, and LF/HF), we chose 5-min epochs pre- and postictally.

Results: We included 14 patients, with a median age of 36 (min–max, 16–55) years and 64% were female. Thirty-six percent had cardiovascular risk factors, but no previously known cardiac disease.

In the preictal period, there were no statistically significant differences in HRV parameters, between FBTCs and non-FBTCs. In the postictal period, AVNN, RMSSD, pNN20, LF, and HF were significantly lower, and LF/HF and HR were significantly higher in FBTCs.

From preictal to postictal periods, FBTCs elicited a statistically significant rise in HR and LF/HF, and a statistically significant fall in AVNN, RMSSD, pNN20, and HF. Non-FBTCs only caused statistically significant changes in HR (decrease) and AVNN (increase).

Significance/conclusion: This work emphasizes the greater effect of FBTCs in autonomic cardiac function in patients with refractory epilepsy, compared to other types of seizures, with a significant reduction in vagal tonus, which may be associated with an increased risk of SUDEP.

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Abbreviations: HRV, heart rate variability; SUDEP, sudden unexpected death in epilepsy; EMU, epilepsy monitoring unit; FBTCs, focal to bilateral tonic-clonic seizure; TL, temporal lobe; PGES, Postictal generalized EEG suppression; GTCS, generalized tonic-clonic seizures.

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1. Introduction

Heart rate variability (HRV) is an indicator of the autonomic activity of the heart [1] and it has been long known to be decreased in patients with epilepsy, even when newly diagnosed [2,3].

Sudden unexpected death in epilepsy (SUDEP) is a major concern in patients with epilepsy, mainly drug-resistant. Some studies suggested an association with lower HRV [4,5], which is already

known to be related to cardiovascular mortality in many other diseases [6,7].

It is consistent across different studies that generalized tonic-clonic seizures (GTCS) are one of the risk factors for SUDEP [8–11]. Some researchers found that focal to bilateral tonic-clonic seizures (FBTCS) induce greater changes in the autonomic function (HR, HRV, baroreflex sensitivity) [12–15], compared to non-FBTCS, but the magnitude of the changes (and the SUDEP relative risk) induced by each type of seizure on cardiac function is still uncertain [16,17]. As a specific biomarker for SUDEP risk is still lacking, HRV could be a candidate. Some authors compared peri-ictal HRV parameters in different types of seizures, with diverse results [13–15,18]. Most of the comparative studies evaluated two groups of patients with different seizure types, not considering the inter-individual variation in the autonomic response.

This study aimed to evaluate the influence of seizure type (FBTCS vs non-FBTCS) on peri-ictal HRV in a group of patients with focal refractory epilepsy and both types of seizures.

2. Material and methods

2.1. Participants

We prospectively evaluated 121 consecutive patients with focal refractory epilepsy, admitted to our institution's Epilepsy Monitoring Unit (EMU), diagnosed using the criteria of the International League Against Epilepsy (ILAE) [19], and confirmed by video electroencephalogram examination and imaging.

Demographic and clinical data were collected and we selected patients who had both FBTCS and non-FBTCS (focal seizures of different types/classifications, but without secondary generalization) during the recording period, to avoid possible bias due to different individual autonomic responses. We chose the first seizure of each type to analyze. We excluded patients with previously known cardiovascular disease, as well as subclinical paroxysms and auras without electroencephalogram (EEG) correlation, resulting in the inclusion of 14 patients.

2.2. Data collection procedure

2.2.1. Electroencephalogram

Scalp recordings were collected by placing gold cup electrodes (with conductive paste and collodium), according to the 10–20 system. We recorded additional 10–10 locations, to cover the specific regions of interest (35 to 44 electrodes). Polygraphic derivations included EKG and EMG channels. The signal was sampled at 512 Hz and recordings were visually analyzed using standard bipolar and referential montages. Antiepileptic drugs were maintained, reduced, or discontinued, following the EMU protocol, under the supervision of an Epileptologist.

We classified seizures according to the semiological seizure classification [20] and the ILAE classification [19]. Clinical and EEG ictal onsets and offsets, as well as the lobar regions of ictal onset, and the presence and duration of postictal generalized EEG suppression (PGES) were determined by experienced neurophysiologists. They applied the definition by Lhatoo et al. to confirm PGES (general absence of electrographic activity $>10 \mu\text{V}$ in amplitude, within the 30 s following seizure termination, allowing for muscle, movement, breathing, and electrode artifacts) [21]. FBTCS were further subclassified into: type 1 – tonic-clonic generalized convulsive seizure with bilateral symmetric tonic arm extension; type 2 – clonic generalized convulsive seizure without tonic arm extension or flexion; type 3 – generalized convulsive seizure with unilateral or asymmetric tonic arm extension or flexion [22].

2.2.2. EKG recording and HRV analysis

A 48-hour Holter recording was acquired for all patients in the EMU. We used the Zymed DigiTrak – Plus 48 recorder, model 3100A, and the Philips Zymed Holter 1810 series software to extract the RR intervals (its algorithm detects the 'R' points of the EKG waveform).

Those extracted RR intervals were analyzed by the INESC TEC proprietary validated HRV analysis system, already used in published studies [23].

A simple verification was done to verify if all the RR intervals detected by the Philips software were physiologically valid [24], to eliminate any mistakes by the RR interval detection algorithm that might occur in case of a noisy EKG signal. The physiologically valid RR intervals are called normal-to-normal (NN) intervals.

We analyzed the HRV parameters AVNN, SDNN, RMSSD, pNN20, LF, HF, and LF/HF, following the guidelines by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [1].

To have a balanced number of blocks, we analyzed a 5-min-EKG epoch for each period, starting 5 min before (preictal period) and 20 min after the identification of the seizures.

2.3. Statistical analysis

Quantitative variables were described using median (interquartile range or min–max). Categorical variables were described through absolute and relative frequencies. We assessed the statistical association between quantitative and categorical variables with the Wilcoxon statistical test, for the comparison of two paired samples. The statistical significance of the association between categorical variables and the type of seizure was evaluated through the McNemar test. The significance level was set at 0.05. The statistical analysis was performed using the IBM SPSS Statistics for Windows software version 27.0 (Armonk, NY: IBM Corp).

2.4. Protocol approval and patient consents

The study was approved by our Institution's Ethics Committee and all patients gave written informed consent.

3. Results

The 14 patients included had a median age of 36 (min–max, 16–55) years, and 64% were female. The median duration of epilepsy was 9 (min–max, 2–49) years. Five patients (36%) had cardiovascular risk factors, but without manifest cardiac disease (Table 1).

As Table 2 shows, half of the FBTCS were type 3. FBTCS were significantly longer than non-FBTCS ($p = 0.010$). Half of the FBTCS had PGES, but none of the non-FBTCS did. The majority of FBTCS occurred during sleep (57.1%), but only 35.7% of non-FBTCS did so. Even so, there was no significant change between the time of occurrence of seizures (sleep or awake) between FBTCS and non-FBTCS ($p = 0.453$, McNemar test). Regarding the hemisphere of seizure onset (right, left, bilateral), there were no statistically significant differences between both types of seizures either ($p = 0.392$, McNemar-Bowker test). Six seizures of each type were temporal; lateralization was possible but the lobe of seizure onset could not be determined on one of the non-FBTCS. There was no statistically significant difference in the lobe of seizure onset between both types of seizures ($p = 1.000$, McNemar test).

No statistically significant difference was found in HRV parameters, in the preictal period, between FBTCS and non-FBTCS. Most of the HRV parameters (AVNN, RMSSD, pNN20, LF, HF) were significantly inferior in the postictal period of FBTCS when compared to non-FBTCS (Table 3). LF/HF and HR were significantly higher in that

Table 1
Demographic and clinical data.

Characteristics of patients (n = 14)	
Age (years), median (range)	36 (16–55)
Gender, n (%)	
Female	9 (64.3)
Male	5 (35.7)
Duration of epilepsy (years), median (range)	9 (2–49)
Etiology of epilepsy (presumed), n (%)	
Hippocampal Sclerosis	3 (21.4)
Malformations of Cortical Development	3 (21.4)
Hypoxic-ischemic lesion	1 (7.1)
Indeterminate	7 (50.0)
Frequency of seizures per month, n (%)	
≤8	10 (71.4)
9–25	2 (14.3)
>25	2 (14.3)
Cardiovascular Risk Factors, n (%)	5 (35.7)
Smoking (isolated)	1 (7.1)
Dyslipidemia (isolated)	2 (14.3)
Obesity (isolated)	1 (7.1)
Arterial Hypertension (isolated)	0 (0.0)
Dyslipidemia, Arterial Hypertension and Obesity	1 (7.1)
Number of Antiepileptic Drugs, median (range)	2.5 (1–4)
Use of Sodium Channel Blockers, n (%)	12 (85.7)

Table 2
Seizures' characteristics.

Seizure Semiology	FBTCS	Non-FBTCS
Type of FBTCS, n (%)		
Type 1	6 (42.9)	–
Type 2	1 (7.1)	–
Type 3	7 (50.0)	–
Duration (seconds), median (range)	99.50 (59–164)	42 (3–209) ^a
PGES, n (%)	7 (50.0)	0 (0.0)
Awake, n (%)	6 (42.9)	9 (64.3)
Ictal onset side, n (%)		
Right	5 (35.7)	6 (42.9)
Left	7 (50.0)	4 (28.6)
Bilateral	2 (14.3)	3 (21.4)
Indeterminate	0 (0.0)	1 (7.1)
Ictal onset localization, n (%)		
Temporal	6 (42.9)	6 (42.9)
Extra-temporal	8 (57.1)	7 (50.0)
Indeterminate	0 (0.0)	1 (7.1)

FBTCS – focal to bilateral tonic-clonic seizure; PGES – postictal generalized EEG suppression.

^a 1 missing (imprecise).

period, and there were no statistically significant differences in SDNN (Table 3).

When analyzing the differences between the preictal and the postictal HRV parameters in each type of seizure (Table 4), we found that in FBTCS there was a statistically significant increase

in HR and LF/HF, and statistically significant decreases in AVNN, RMSSD, pNN20, and HF. In non-FBTCS, we found a statistically significant decrease in HR and an expected increase in AVNN, since these two variables are inversely related. No other statistically significant differences were found in non-FBTCS.

4. Discussion

Our results highlight the impact of FBTCS in HRV parameters compared to non-FBTCS in patients with refractory epilepsy, stressing the importance of avoiding/being aware of that type of seizure.

In our patients, there was a significant increase in postictal HR after FBTCS, and a significant decrease after non-FBTCS, which denotes a higher sympathetic activation after FBTCS. Other authors also report that convulsive seizures have higher postictal HR elevation compared with nonconvulsive seizures [14,15,18].

Concerning HRV parameters, we did not find significant differences in HRV parameters between FBTCS and non-FBTCS in the preictal period, which was also reported by Sivathamboo et al., who compared convulsive with non-convulsive seizures [18]. Another study, however, reported that parasympathetic activity was higher in the preictal period of GTCS compared to other seizure types [25], evaluating the index of cardiac parasympathetic activity (CIPA). From the measures we evaluated, HF is the one that best reflects parasympathetic activity. Although it is higher before FBTCS than before non-FBTCS, the difference is not statistically significant, as seen in Table 3. Toth et al. had a result similar to ours [14].

Postictally, we found that, after FBTCS, AVNN, RMSSD, pNN20, LF, and HF were significantly lower, and LF/HF was significantly higher than after non-FBTCS, indicating a higher sympatho-vagal balance after FBTCS. Also, from the preictal to the postictal periods, we found significant variations in almost all parameters (except SDNN and LF) induced by FBTCS, which show a shift toward sympathetic dominance. Those changes were not seen after non-FBTCS. A higher sympathetic tone and a lower vagal tone predict cardiovascular morbidity and mortality [16], with a possible link to SUDEP risk.

Other studies, with fewer evaluated parameters, also showed a more prominent postictal lowering of RMSSD and HF in GTCS than non-GTCS [14,15]. Most of them did not perform an intraindividual comparison. We did it, in an attempt to take into consideration the individual autonomic responses. Surges et al. had an approach identical to ours, in that they evaluated a GTCS and a non-GTCS in each patient, but their cohort comprised only refractory temporal lobe epilepsies and they evaluated 30-sec epochs. They included one Complex Partial Seizure (CPS) and one secondary GTCS per patient [13]. In their study, HR was also higher during secondary GTCS and SDNN (the only HRV parameter evaluated) was decreased after secondary GTCS [13]. In our work, although

Table 3
Differences in perictal HRV parameters between FBTCS and non-FBTCS. Data are presented in the form of median (interquartile range). p-values in bold correspond to statistically significant differences.

	Preictal			Postictal		
	FBTCS	Non-FBTCS	p-value	FBTCS	Non-FBTCS	p-value
HR (bpm)	76 (18)	77 (20)	0.470	100 (26)	76 (17)	0.002
AVNN (ms)	787 (196)	779 (190)	0.510	598 (173)	793 (179)	0.002
SDNN (ms)	43 (36)	67 (44)	0.074	25 (37)	42 (40)	0.158
RMSSD (ms)	26 (19)	22 (10)	0.245	10 (12)	22 (15)	0.011
pNN20 (%)	44 (34)	34 (23)	0.177	8 (27)	39 (31)	0.004
LF (ms ²)	458 (788)	462 (394)	0.826	113 (545)	469 (828)	0.030
HF (ms ²)	236 (392)	140 (136)	0.397	12 (125)	185 (282)	0.019
LF/HF	2.7 (3.6)	4.7 (4.6)	0.109	6 (6)	3.2 (5.0)	0.019

FBTCS: focal to bilateral tonic-clonic seizure.

Table 4
Comparison of preictal and postictal HRV parameters in both types of seizures (FBTCS and non-FBTCS).

	Preictal → Postictal			
	FBTCS		Non-FBTCS	
	Variation	p-value	Variation	p-value
HR (bpm)	↑	0.002	↓	0.004
AVNN (ms)	↓	0.004	↑	0.005
SDNN (ms)	–	0.245	–	0.272
RMSSD (ms)	↓	0.048	–	0.198
pNN20 (%)	↓	0.005	–	0.109
LF (ms ²)	–	0.158	–	0.594
HF (ms ²)	↓	0.041	–	0.056
LF/HF	↑	0.006	–	0.221

FBTCS: focal to bilateral tonic-clonic seizure.

↑ – increase; ↓ – decrease.

we did not find any statistically significant difference regarding SDNN between both types of seizures (preictally, postictally, or in the variation preictally to postictally), we found a trend to higher SDNN in non-FBTCS in the preictal period ($p = 0.074$). Sivathamboo et al. only found differences in HRV parameters (between convulsive and non-convulsive seizures) in the ictal period (higher SDNN and RMSSD in convulsive seizures), but no differences in the postictal period [18].

Our results show a higher sympatho-vagal balance after FBTCS independently of temporal or extra-temporal seizure onset.

4.1. Limitations

The major limitation of this work is the small number of patients in our cohort, which did not allow a multivariate analysis (necessary to evaluate the impact of PGES and the duration of seizures, for example, in HRV parameters).

We only measured oxygen saturation postictally after seizures, on separate cardiopulmonary monitors. It is not yet clear if apnea precedes central autonomic deregulation [26]. Ictal hypoxemia was significantly associated with GTCS and with lengthened seizures [27], and it would be worthy to evaluate any differences in oxygen saturation between FBTCS and non-FBTCS.

As we assessed HRV parameters 20 min after the seizures, there might have been changes in the immediate postictal period that we overlooked, both after FBTCS and after non-FBTCS. Nevertheless, we can say that changes persisted at least 20 min after FBTCS, which did not happen after non-FBTCS.

Other limitations were minimized, since we controlled for different patients' characteristics, by comparing both types of seizures intraindividually.

5. Conclusion

FBTCS have a greater impact on HRV than other types of seizures in patients with focal refractory epilepsy, with a significant reduction in the vagal tonus, indicating greater autonomic cardiac dysfunction. These changes could be associated with a higher risk of SUDEP.

Epileptologists have not incorporated HRV in decision-making processes, as it is not yet a biomarker of SUDEP risk. Studies in larger cohorts are still lacking, but our work is a step forward in that direction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data statement

The data generated and/or analyzed during this study are available from the corresponding author on reasonable request.

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Imagem funcional (^{99m}Tc]Tc-HMPAO)

^{99m}Tc]Tc-HMPAO and the heart - a new way for an old molecule?

Apresentado na International Conference on Nuclear Cardiology and Cardiac CT (ICNC)
Viena, maio de 2017

**Imaging myocardial perfusion with ^{99m}Tc]Tc-HMPAO: fiction or reality?
- preliminary results**

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**^{99m}Tc]Tc-HMPAO cardiac SPECT - a method to detect ischemia in patients
with refractory epilepsy?**

Apresentado na International Conference on Nuclear Cardiology and Cardiac CT
Lisboa, maio de 2019

[^{99m}Tc]Tc-HMPAO and the heart - a new way for an old molecule?

Apresentado na International Conference on Nuclear Cardiology and Cardiac CT (ICNC)

Viena, maio de 2017

Introdução

O [^{99m}Tc]Tc-HMPAO nunca foi usado para estudar o coração. A principal razão, para além da existência de excelentes alternativas, pode ser o facto de este órgão ser vizinho de outros com captação do radiofármaco, como os pulmões e o fígado (195, 196), o que pode interferir com a qualidade da imagem cardíaca.

Sendo um radiofármaco utilizado para avaliar a perfusão cerebral, pareceu-nos possível que pudesse mapear a perfusão miocárdica, o que permitiria o uso de um só radiofármaco e uma só dose de radiação (menor exposição a radiação), em doentes com epilepsia, sabendo-se que são mais suscetíveis de sofrerem alterações cardíacas.

Objetivos

Com este trabalho, o nosso objetivo foi o de estabelecer o intervalo de tempo ótimo, entre a administração do radiofármaco e a aquisição das imagens cardíacas, bem como avaliar a reprodutibilidade das imagens ao longo do tempo.

Acreditamos que este seja o primeiro estudo a avaliar a possibilidade de analisar a perfusão do miocárdio com [^{99m}Tc]Tc-HMPAO.

Material e Métodos

Adquirimos tomografias computadorizadas de emissão de fóton único (SPECT) cardíacas, em modo *gated* (sincronizadas com o eletrocardiograma – ECG), após a administração de [^{99m}Tc]Tc-HMPAO, em 10 voluntários sãos. As imagens foram adquiridas 30 min, 1 h, 1h30 e 2 h após a administração endovenosa (e.v.) de 555 MBq (15 mCi) do radiofármaco.

A partir das imagens coronais da reconstrução das SPECT, somámos todas as que tinham representação do coração. Posteriormente, desenhámos regiões de interesse (*regions of interest* – ROI) sobre a parede anterior do ventrículo esquerdo (VE), o pulmão esquerdo e o fígado (com representação de ambos os lobos na ROI), como evidenciado na Figura 9, e calculámos as razões coração/ pulmão (C/P) e coração/ fígado (C/F). As razões foram calculadas usando as contagens médias por pixel das ROI acima descritas.

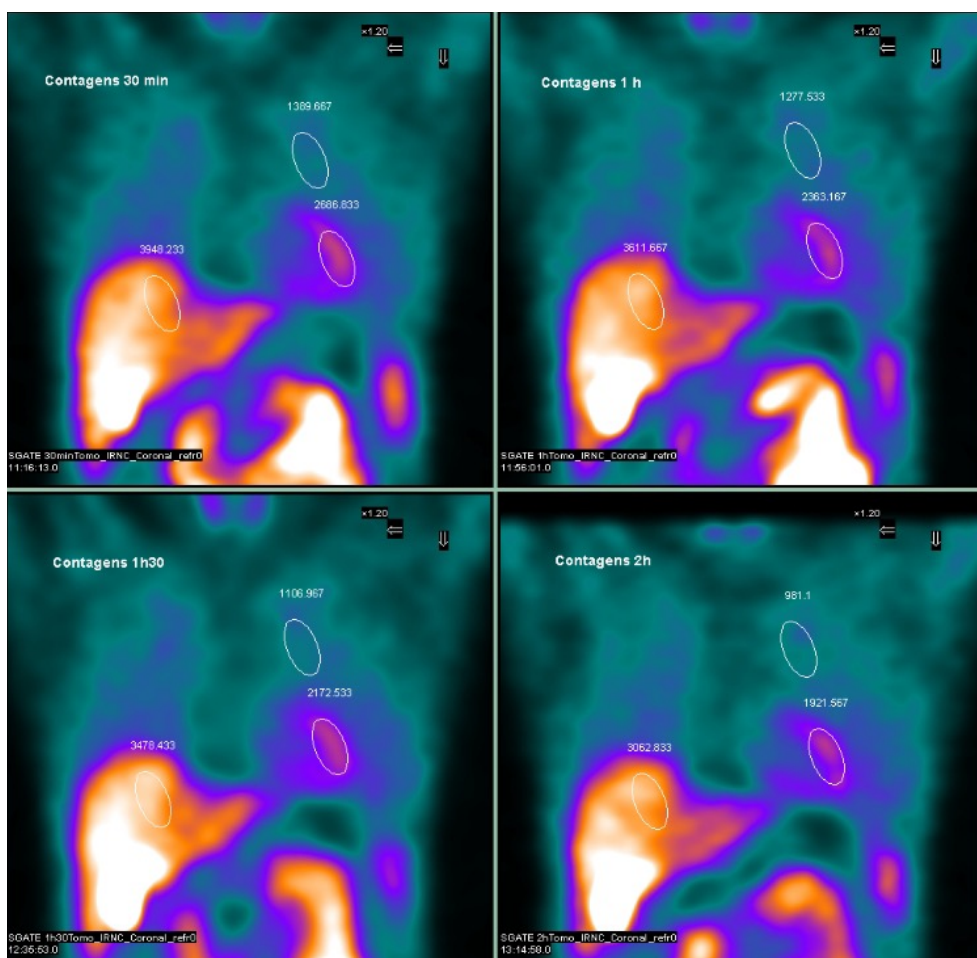


Figura 9. Localização das ROI no somatório dos cortes coronais com representação do coração, aos 30 min, 1 h, 1h30 e 2 h após a administração e.v. de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$, para calcular as razões coração/ pulmão e coração/ fígado.

Todas as imagens foram também analisadas com *software* cardíaco dedicado (QGS/ QPS), obtendo-se a quantificação das contagens no VE, expressas como percentagem das contagens por parede, relativas ao pixel com as contagens máximas (Figura 10).

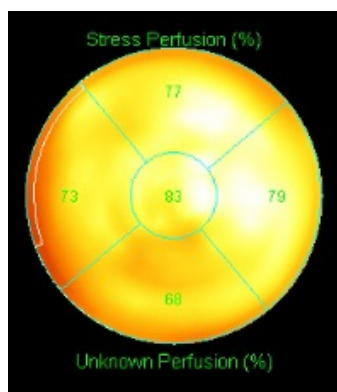


Figura 10. Bullseye com a segmentação por paredes e exemplo de quantificação das contagens do ventrículo esquerdo (percentagem das contagens por parede relativas ao pixel com maiores contagens).

Foi usado o Coeficiente de Variação de Pearson (199) para analisar a variabilidade das razões C/P e C/F ao longo do tempo.

Atribuímos uma ordem a cada parede do VE, baseada na percentagem relativa de contagens, e testámos se essa ordem se mantinha ao longo do tempo para cada indivíduo, usando o teste de Kruskal-Wallis (200).

O nível de significância foi estabelecido em 0,05.

Resultados

Dos 10 voluntários saudáveis, 5 eram homens. A idade média foi de 47 anos (min-máx, 32-64). O Coeficiente de Variação de Pearson foi 0,04, tanto para a razão C/P, como para a C/F, significando que apenas encontramos uma variabilidade de 4% entre os resultados nos diferentes momentos de aquisição.

Não obtivemos evidência estatística de que as 'ordens' variassem ($p > 0,05$) e calculámos, então, o valor preditivo de uma 'ordem se manter ao longo do tempo, que foi de 72,5%. A Figura 11 mostra a comparação intraindividual das contagens por parede ao longo do tempo e a posição relativa de cada 'ordem'.

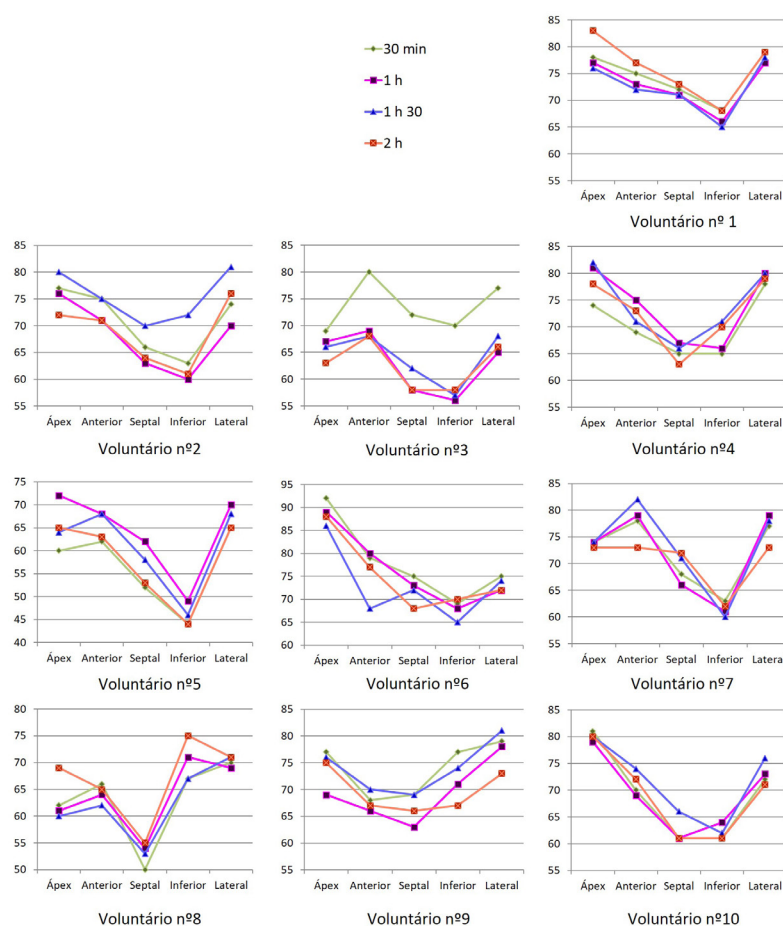
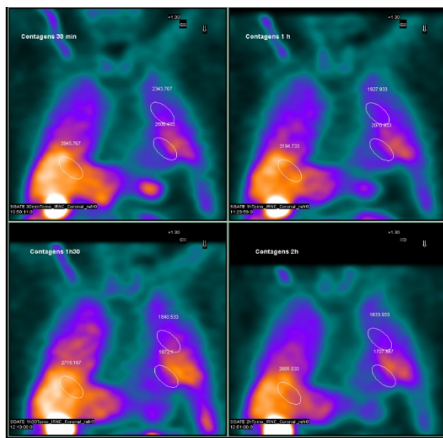
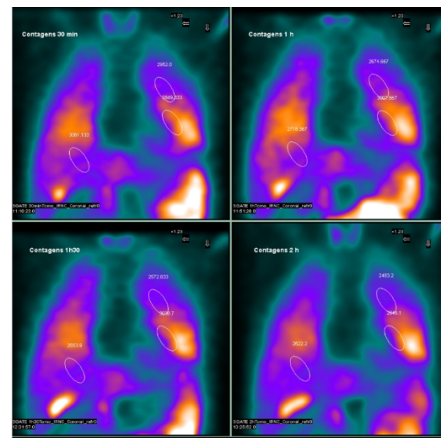


Figura 11. Representação gráfica da comparação intraindividual das contagens por parede (percentagem relativa ao pixel com as contagens máximas), ao longo do tempo.

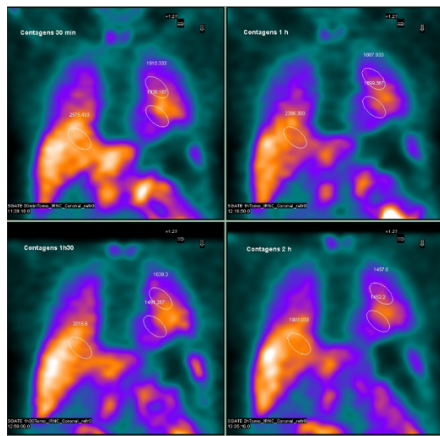
Os três voluntários fumadores tiveram captação pulmonar significativa de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$, o que interferiu com o processamento das imagens (Figura 12).



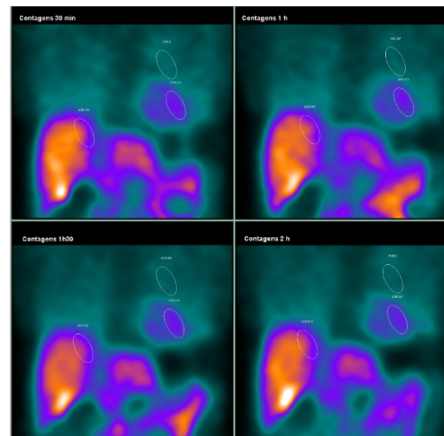
Voluntário nº5 – **Fumador** – elevada captação pulmonar de $[^{99m}\text{Tc}]\text{TcHMPAO}$



Voluntário nº8 – **Fumador** – elevada captação pulmonar de $[^{99m}\text{Tc}]\text{TcHMPAO}$



Voluntário nº2 – **Fumador** – elevada captação pulmonar de $[^{99m}\text{Tc}]\text{TcHMPAO}$



Voluntário nº1 – **Não-fumador** – sem captação pulmonar significativa de $[^{99m}\text{Tc}]\text{TcHMPAO}$

Figura 12. Captação pulmonar de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ em fumadores, comparativamente com um voluntário não fumador.

Discussão e Conclusão

O mecanismo de localização do $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ no cérebro é relacionado com a sua natureza lipofílica, que permite a passagem através da barreira hemato-encefálica intacta. Uma vez dentro da célula, é crucial a conversão para a forma hidrofílica, para que ocorra retenção intracelular (201-205).

Não existe consenso relativamente ao papel do conteúdo intracelular de glutatona (206), apontado por alguns autores como um fator importante na conversão de [^{99m}Tc]Tc-HMPAO para a forma hidrofílica (207, 208). Jacquier-Sarlin et al., no seu estudo *in vitro*, reportaram que a retenção de [^{99m}Tc]Tc-HMPAO dentro da célula é muito mais dependente da atividade de redução do que do conteúdo de glutatona na célula (204). El-Shirbiny et al. também chegaram à conclusão de que a retenção de [^{99m}Tc]Tc-HMPAO não estava relacionada com o conteúdo intracelular de glutatona (209).

Estudos em humanos também mostraram que a captação regional de [^{99m}Tc]Tc-HMPAO, pelo cérebro, refletia a perfusão regional cerebral (195, 202, 210, 211). A perfusão cerebral pode, pois, ser efetivamente avaliada por este radiofármaco.

No coração, ainda não sabemos quais os mecanismos de captação e de retenção do [^{99m}Tc]Tc-HMPAO nos miócitos, no entanto, neste trabalho, mostramos que a captação pode refletir a perfusão regional do miocárdio.

Que saibamos, este é o primeiro estudo a avaliar a possibilidade de avaliar a perfusão do miocárdio por imagem funcional com [^{99m}Tc]Tc-HMPAO.

O nosso achado principal é o de que a captação de [^{99m}Tc]Tc-HMPAO pelo coração é estável nas 2 horas que se seguem à administração e.v. do radiofármaco, assim como o é a sua distribuição cardíaca; assim, uma imagem pode ser adquirida de modo satisfatório a qualquer hora, dentro desse intervalo de tempo.

Três dos voluntários eram fumadores e exibiram captação pulmonar significativa de [^{99m}Tc]Tc-HMPAO. Essa captação foi tão intensa que interferiu com o processamento das imagens. Shih et al. já tinham demonstrado que a captação pulmonar de [^{99m}Tc]Tc-HMPAO estava relacionada com os hábitos tabágicos, e colocaram a hipótese de que fosse dependente de permeabilidade vascular aumentada nesses indivíduos (212). O nosso estudo corrobora esse achado.

Estamos confiantes de que estamos perante uma oportunidade para estudar adicionalmente o coração de doentes que tenham de realizar SPECT cerebral com [^{99m}Tc]Tc-HMPAO – tais como os doentes com epilepsia –, desde que não sejam fumadores.

Research Article

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Imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO: Fiction or reality? – Preliminary results

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Keywords: myocardial perfusion scintigraphy; epilepsy; HMPAO; myocardial SPECT.

Abbreviations: MPS: Myocardial perfusion scintigraphy; i.v: Intravenous; SA: Short Axis; VLA: Vertical Long Axis; HLA: Horizontal Long Axis; EF: Ejection Fraction.

Abstract

Introduction and objectives: [^{99m}Tc] Tc-HMPAO, developed for brain imaging, is taken up by the heart, but never used to study it.

We aimed to compare cardiac images with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, using imaging techniques.

Materials and methods: Cardiac gated SPECTs with [^{99m}Tc] Tc-HMPAO were compared with myocardial perfusion scintigraphies (MPS) with [^{99m}Tc] Tc-Tetrofosmin in three inpatients, from the vascular surgery ward.

We developed algorithms in MATLAB R2016 to compare the [^{99m}Tc] Tc-Tetrofosmin/ [^{99m}Tc] Tc-HMPAO images. Pixel-wise correlations for slices, reversibility, and polar maps were obtained.

Results: Correlations of both radiotracers' myocardial images were as high as 0.93. Polar maps correlations were 0.93-0.95 (for both stress and rest) and 0.62-0.90 (reversibility).

One of the patients (smoker) had significant lung [^{99m}Tc] Tc-HMPAO uptake.

Conclusions: Cardiac SPECT with [^{99m}Tc] Tc-HMPAO might be a screening method for myocardial ischemia in non-smoking patients with epilepsy suspected of having heart changes, and who need to perform a brain perfusion SPECT.

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Introduction

[^{99m}Tc] Tc-HMPAO is a radiotracer developed in the 1980s to study regional cerebral blood flow [1-4]. It has been widely used since then, in patients with epilepsy, to localize the epileptogenic zone.

Although this radiotracer's biodistribution includes the heart [4], to the best of our knowledge, it has never been used to study that organ. The main reason, aside from the excellent existent alternatives, maybe the proximity of the heart to organs with high [^{99m}Tc] Tc-HMPAO uptake (lungs and liver) [4,5], potentially interfering with cardiac imaging quality.

Being a brain perfusion radiotracer, mapping of myocardial perfusion seemed also possible, permitting the use of a single radiotracer in patients with epilepsy (known to be prone to cardiac alterations) with less radioactive exposure.

Our aim was to compare myocardial gated SPECT images made with both [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, using imaging techniques.

Several authors have compared different radiotracers for myocardial imaging, using varying methodologies [6-12].

We believe this is the first study not only evaluating the possibility of imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO, but also comparing myocardial images with different radiotracers, quantifying the similarities.

Material and methods

We selected 3 inpatients from the Vascular Surgery ward, who already had to perform a myocardial perfusion scintigraphy (MPS) with [^{99m}Tc] Tc-Tetrofosmin, as part of their clinical evaluation [one-day protocol, stress/rest, 370 MBq (10 mCi)/1110 MBq (30 mCi), i.v., respectively], and additionally acquired myocardial stress/rest SPECT images with stabilized [^{99m}Tc] Tc-HMPAO [two-day protocol, 555 MBq (15 mCi), i. v., each]. The stress agent was adenosine for both studies and images were acquired in gated mode, 40 min after the i.v. injections.

The interval between each radiotracer scintigraphy varied between 4 months and 1 year, and no major cardiac event was registered in that period, except for patient 3, who developed heart failure.

All studies were processed with a cardiac dedicated software (QGS/QPS), providing three reconstructed planes (short axis – SA –, vertical long axis – VLA –, and horizontal long axis – HLA) and exported into DICOM files.

Due to the inexistence of a heart model on which to calculate normally used clinical parameters, a quantitative analysis of [^{99m}Tc] Tc-Tetrofosmin and [^{99m}Tc] Tc-HMPAO image similarity is proposed here.

Processing algorithms were developed in MATLAB R2016 to compare the [^{99m}Tc] Tc-Tetrofosmin and [^{99m}Tc] Tc-HMPAO images of each reconstructed plane (SA, VLA, and HLA).

For image pre-processing, the first and last two slices of the reconstructed images were removed, since no important heart structures were clearly visible. Then, we applied a 2-dimen-

sional median filter, which replaces each pixel by the median value of its 1 by 1 neighbourhood. Due to low image resolution, higher window sizes lead to a significant distortion of the image shape, so we found 1 by 1 value to be optimal for the available dataset.

Afterwards, images were aligned, applying the affine transformation that maximized the mutual information [13] between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin. Figure 1 exemplifies the initial and final results.

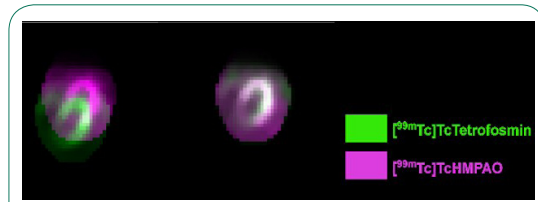


Figure 1: Image alignment algorithm example. On the left, images not aligned; on the right, images aligned after an affine transformation with maximum mutual information.

Then, we thresholded the images by selecting all pixels above an intensity of 0 as the region of interest, and identified the bounding box (minimum rectangle on which all image points are included). The purpose was to calculate image correlation metrics corresponding only to this region. We calculated a pixel-wise correlation for every slice, using Pearson's Correlation Coefficient.

Reversibility of the defects was also evaluated (correlation of the rest-stress subtraction with each radiotracer), as were the polar maps.

We analyzed the LV ejection fraction (EF) and volumes (end diastolic and end systolic) with QGS, in every patient, with both radiotracers.

Ethical approval

This study was approved by our Institution Ethics Committee, as it was in accordance with their ethical standards and with the 1964 Helsinki declaration and its later amendments. All participants gave their informed consent.

Data availability

All datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

We evaluated 3 patients with stress/rest images with both [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin.

All of them had high correlations for perfusion images (Figure 2), better in the VLA: 0.88 to 0.93 (stress), and 0.88 to 0.90 (rest). Reversibility correlations (Table 1, Figure 3) varied between 0.46 and 0.80 (3 axes).

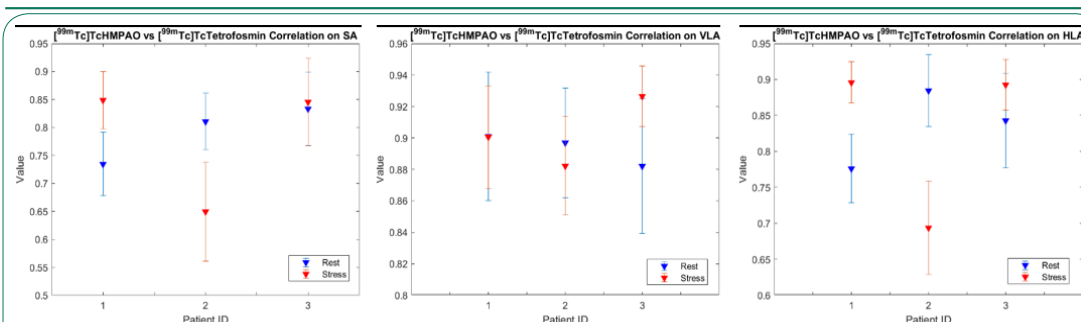


Figure 2: Correlation between $[^{99m}\text{Tc}]$ Tc-HMPAO and $[^{99m}\text{Tc}]$ Tc-Tetrofosmin on the 3 axes, for all patients. SA: short axis; VLA: vertical long axis; HLA: horizontal long axis.

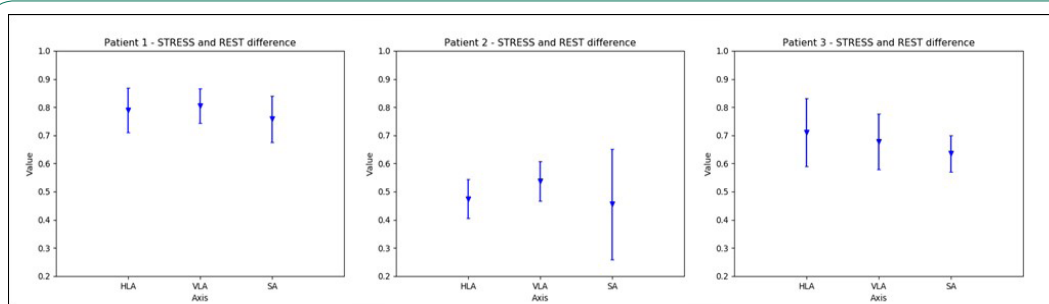


Figure 3: Correlation of reversibility (3 axes) between $[^{99m}\text{Tc}]$ Tc-HMPAO and $[^{99m}\text{Tc}]$ Tc-Tetrofosmin images, for patients 1, 2 (smoker) and 3.

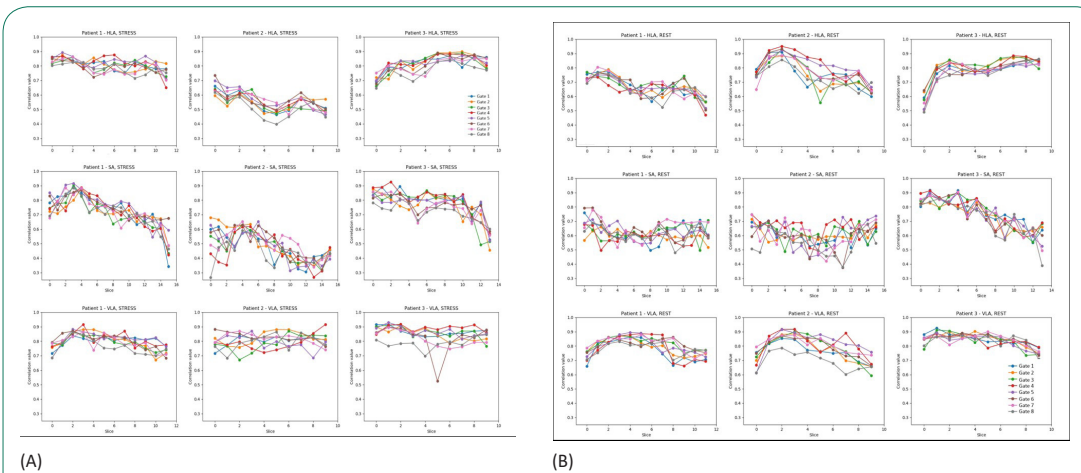


Figure 4: Gated images correlations of each slice, between $[^{99m}\text{Tc}]$ Tc-HMPAO and $[^{99m}\text{Tc}]$ Tc-Tetrofosmin. a. Gated stress images. b. Gated rest images.

Gated images correlations between each slice of each gate were also better in VLA [mean values: 0.78-0.89 (stress), 0.78-0.84 (rest)]. Figure 4 shows the correlations of gated images for all patients.

Table 1: Correlation of reversibility (3 axes) between $[^{99m}\text{Tc}]$ Tc-HMPAO and $[^{99m}\text{Tc}]$ Tc-Tetrofosmin images, for patients 1, 2 (smoker) and 3.

Patient	Correlation Mean (SD)		
	Short Axis	Vertical Long Axis	Horizontal Long Axis
1	0.76 (0.08)	0.80 (0.06)	0.79 (0.08)
2	0.46 (0.20)	0.54 (0.07)	0.47 (0.069)
3	0.63 (0.06)	0.68 (0.10)	0.71 (0.12)

Table 2: Correlation of [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin polar maps: stress, rest, and reversibility, for patients 1-3

Patient	Polar Maps Correlation		
	Stress/Stress	Rest/Rest	Reversibility
1	0.93	0.95	0.82
2	0.95	0.93	0.62
3	0.94	0.94	0.90

The LV ejection fraction (EF) with both radiotracers was equivalent in almost all patients (Table 3). The exception is Patient 3, whose EF calculated with [^{99m}Tc] Tc-Tetrofosmin was significantly lower (severely compromised) when compared to the one calculated with [^{99m}Tc] Tc-HMPAO (normal). Patient 2 had only one value significantly different from the others, which was the rest EF evaluated with [^{99m}Tc] Tc-HMPAO (mildly compromised compared to normal).

LV volumes with [^{99m}Tc] Tc-HMPAO were generally inferior to the ones calculated with [^{99m}Tc] Tc-Tetrofosmin.

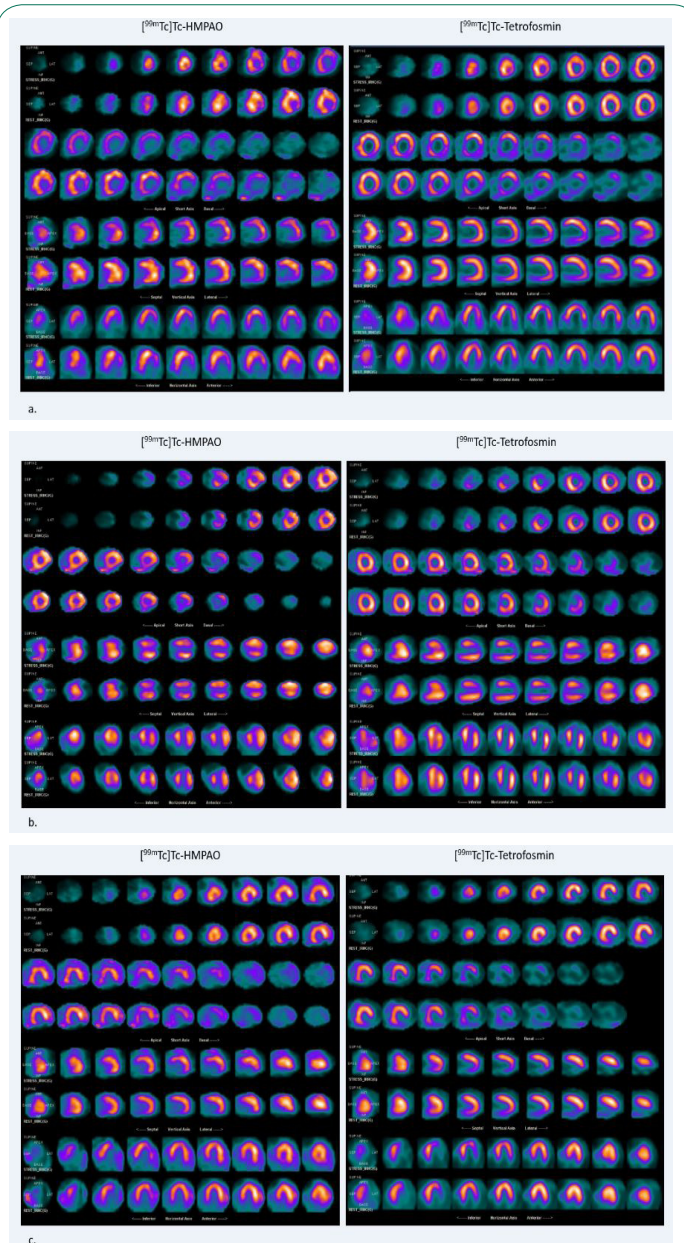


Figure 5: Reconstructed slices in the three axes (SA – short axis; VLA – vertical long axis; HLA – horizontal long axis), with both radiotracers ([^{99m}Tc]Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin), for each patient (a. Patient 1; b. Patient 2; c. Patient 3).

Table 3: Left Ventricle Ejection Fraction and volume values for each patient with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin. EF: Ejection Fraction; ESV: End systolic volume; EDV: End diastolic volume.

Subject (Age in years)	Evaluated Parameter	Stress		Rest	
		[^{99m} Tc]Tc-HMPAO	[^{99m} Tc]Tc-Tetrofosmin	[^{99m} Tc]Tc-HMPAO	[^{99m} Tc]Tc-Tetrofosmin
P1 (63)	EF (%)	23	20	20	23
	ESV (mL)	113	183	124	159
	EDV (mL)	147	230	156	207
P2 (76)	EF (%)	51	51	40	50
	ESV (mL)	32	55	55	56
	EDV (mL)	65	112	91	111
P3 (75)	EF (%)	53	27	55	30
	ESV (mL)	35	62	47	67
	EDV (mL)	74	84	105	96

Discussion

[^{99m}Tc] Tc-HMPAO mechanism of localization in the brain is related to its lipophilic nature, which allows the passage through the intact blood brain barrier. Once into the cell, the conversion to a hydrophilic form is crucial for intracellular retention [14-18]. Debate exists about the role of intracellular glutathione content [19], pointed by some authors as an important factor for the conversion of the [^{99m}Tc] Tc-HMPAO to the hydrophilic form [20,21]. Jacquier-Sarlin et al., in their *in vitro* study, reported that [^{99m}Tc] Tc-HMPAO retention inside the cell is far more dependent on the redox activity than on the glutathione content in the cell [17]. El-Shirbiny et al. also reached the conclusion that [^{99m}Tc] Tc-HMPAO retention was not related to the intracellular glutathione content [22].

Regional [^{99m}Tc] Tc-HMPAO uptake by the brain reflects regional cerebral blood flow [4,15,23,24]. Brain perfusion can thus be effectively evaluated by this radiotracer.

In the heart, the mechanism of [^{99m}Tc] Tc-HMPAO uptake/retention in the myocytes remains unknown. However, we show that this uptake may also reflect regional myocardial blood flow.

To the best of our knowledge, this is the first study evaluating the possibility of imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO.

Overall, we obtained high correlations for cardiac studies with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, especially in VLA. Patient 2 was a smoker and, probably because of that, had poorer correlations due to lung [^{99m}Tc] Tc-HMPAO uptake. Shih et al. had already demonstrated that lung [^{99m}Tc] Tc-HMPAO uptake was related to smoking habits, and they hypothesized that it was dependent on increased vascular permeability [25].

Other methodologies have been previously used for comparing different radiotracers for myocardial imaging. Maddahi et al [6] compared [^{99m}Tc] Tc-Sestamibi and Thallium-201 SPECTs, presenting only the final patient's diagnosis characteristics. Other authors [7,8] compared the same radioisotopes, using different patients and different times. Image quality, final patient's diagnosis, 'normalcy' rate, sensitivity and specificity, were presented for detecting stenosis. Functional parameters were compared by unpaired t-test comparison of several parameters (mean stress EF, mean rest EF, and ΔEF) computed by SPECT software – semi-quantitative analysis 8. In another paper, a comparison between ECG-Gated [^{99m}Tc] Tc-Sestamibi

SPECT with ECG-Gated Rubidium-82 PET was made [9].

Declerck et al [10] and Gilardi et al [11] used methods similar to ours to compare cardiac studies, but none quantified the similarities, which became our major input.

In our study, we used for the first time imaging techniques to compare myocardial images obtained with different radiotracers. We opted to use a simple approach in this preliminary work. We filtered, aligned, selected the regions of interest using a bounding box, and then correlated the images. Our algorithm worked better for the central sections, where the difference between the background noise and the heart was more visible, compared with the initial or final sections, which had a lot more background noise due to the high radiotracer uptake by the surrounding organs. Therefore, we excluded the initial and the final frames.

We obtained high correlations for cardiac studies between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, especially in VLA, in non-smoking patients.

The LV EF was similar with both radiotracers in the majority of patients. Patient 3, showed a normal EF with [^{99m}Tc] Tc-HMPAO but had a severely compromised EF with [^{99m}Tc] Tc-Tetrofosmin (4 months later). Two weeks before the latter, the patient was admitted to the hospital with a severe respiratory infection and decompensated heart failure, which could justify the EF drop. Patient 2 had only one significantly altered value (rest EF evaluated with [^{99m}Tc] Tc-HMPAO). This is the smoker patient, whose lung [^{99m}Tc] Tc-HMPAO uptake was significant.

LV volumes with [^{99m}Tc] Tc-HMPAO were inferior to the ones with [^{99m}Tc] Tc-Tetrofosmin, so this method might not be useful to evaluate them.

Limitations

Our major limitation is the reduced number of cases, not allowing a formal statistical analysis. With these promising preliminary results of myocardial perfusion SPECTs with [^{99m}Tc] Tc-HMPAO, we now intend to increase the sample.

The second limitation is the extended time gap between both radiotracers' scintigraphies. Our Institution Ethics Committee limited our patient recruitment to inpatients that already had performed (or would need) a MPS, posing difficulties in performing both scintigraphies in a lesser time interval.

New knowledge gained

With our work, we describe a potential new application for an old radiotracer, which might allow the simultaneous evaluation of two organs in a selected population, with less radioactive exposure.

Conclusion

Myocardial SPECT with [^{99m}Tc] Tc-HMPAO might be a screening method for myocardial ischemia in non-smoking patients already performing a [^{99m}Tc] Tc-HMPAO brain perfusion SPECT. It might serve as a gateway to MPS, in a subset of patients with epilepsy that are prone to have heart changes (e.g. those with rises in ictal Troponin I).

Although promising, these preliminary results must be confirmed with a larger cohort.

Meanwhile, our group is also trying different approaches to improve the image quality with [^{99m}Tc] Tc-HMPAO.

Declarations

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Declarations of Interest: none.

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[^{99m}Tc]Tc-HMPAO cardiac SPECT - a method to detect ischemia in patients with refractory epilepsy?

Apresentado na International Conference on Nuclear Cardiology and Cardiac CT (ICNC)

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Introdução

O nosso trabalho já desenvolvido mostra uma elevada correlação entre o SPECT cardíaco com [^{99m}Tc]Tc-HMPAO e a cintigrafia de perfusão do miocárdio (CPM) com [^{99m}Tc]Tc-Tetrofosmina.

Assim, parece ser possível avaliar a perfusão miocárdica com [^{99m}Tc]Tc-HMPAO.

Um subgrupo de doentes com epilepsia refratária crónica tem elevações da troponina e alterações ST-T com as crises (41, 144, 145, 147, 155, 157), significando, possivelmente, isquemia miocárdica.

Nenhum estudo prévio avaliou a perfusão do miocárdio durante as crises epiléticas, através de técnicas de Medicina Nuclear.

Objetivo

Avaliar a distribuição do [^{99m}Tc]Tc-HMPAO no miocárdio do VE de doentes com epilepsia refratária.

Métodos

Avaliamos, de modo prospetivo, doentes com epilepsia refratária, admitidos na UME do CHUSJ, entre junho de 2014 e agosto de 2018, referenciados para realização de SPECT cerebral ictal e/ou interictal.

Adquiriram-se imagens cardíacas imediatamente após a aquisição da SPECT cerebral, com 555 MBq de [^{99m}Tc]Tc-HMPAO, e.v.. As imagens obtidas foram processadas com um *software* cardíaco dedicado.

Foram recolhidos dados demográficos e clínicos.

A um subgrupo de doentes, avaliámos os níveis séricos de troponina I de elevada sensibilidade (hs-cTnI), antes da primeira crise reconhecida (nível basal), bem como 6 h e 12h-18 h após a crise. Foram considerados significativos aumentos superiores a 50% do nível basal (153).

A significância estatística foi estabelecida em 0,05.

O estudo foi aprovado pela Comissão de Ética para a Saúde do CHUSJ. Todos os doentes deram o seu consentimento informado.

Resultados

Foram avaliados 89 SPECT cardíacos com $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ (46 ictais e 43 interictais) em 88 doentes. A idade mediana foi de 42 anos (min-máx, 17-63) no grupo ictal e de 36 anos (min-máx, 16-73) no grupo interictal. O número de SPECT interpretáveis foi de 36 ictais e 28 interictais.

Comparando ambos os grupos (ictal e interictal): no grupo ictal, 30,6% dos doentes tinham fatores de risco cardiovasculares (sem doença cardiovascular conhecida), enquanto no grupo interictal, 21,4% dos doentes tinham esses fatores de risco; 34% dos doentes do grupo ictal teve defeitos na captação miocárdica de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$, enquanto no grupo interictal foram 25% os que tiveram defeitos. Estas diferenças não foram estatisticamente significativas ($p=0,469$), assim como não o foram as diferenças no número ($p=0,405$) - (Figura 13) e na extensão dos defeitos ($p=0,915$). A maioria dos defeitos correspondeu a extensões ligeiras, em ambos os grupos.

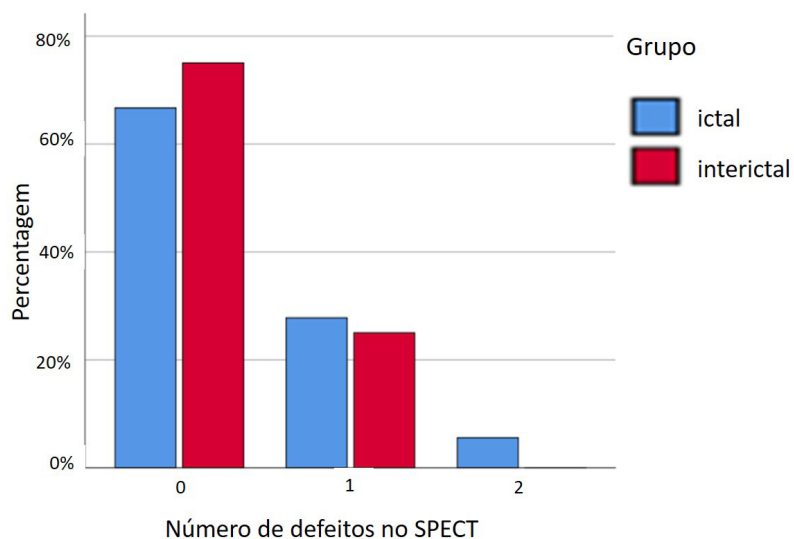


Figura 13. Comparação do número de defeitos entre os grupos ictal e interictal ($p=0,405$).

O número/ extensão dos defeitos não tiveram associação significativa com o sexo, idade, fatores de risco cardiovascular, duração da epilepsia ou frequência de crises em qualquer dos grupos (Figuras 14, 15, 16).

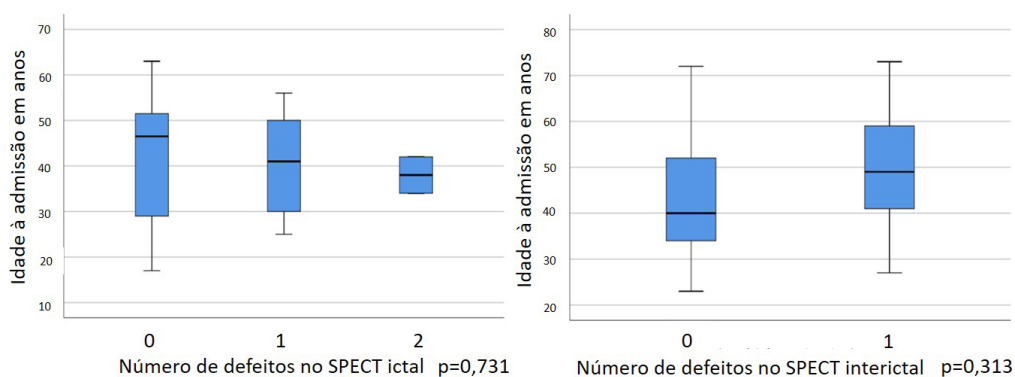


Figura 14. Avaliação da associação entre o número de defeitos e a idade.

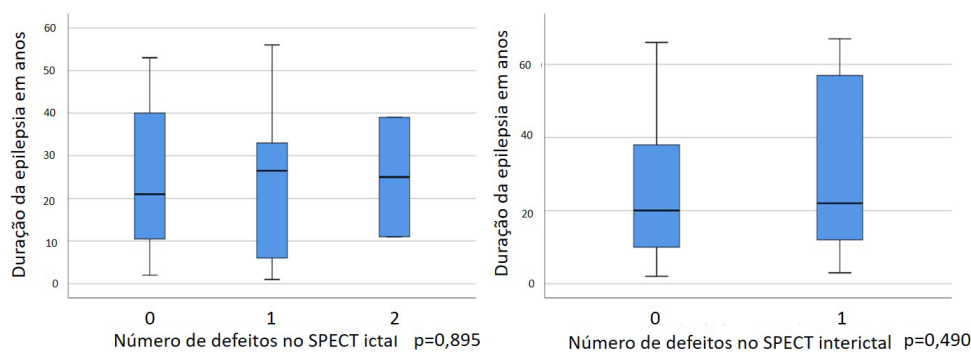


Figura 15. Avaliação da associação entre o número de defeitos e a duração da epilepsia.

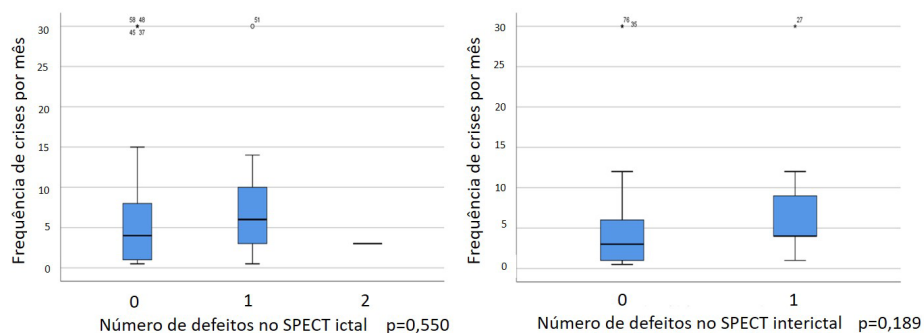


Figura 16. Avaliação da associação entre o número de defeitos e a frequência de crises.

No grupo ictal, não foi encontrada associação estatisticamente significativa entre o número/ extensão dos defeitos e a semiologia da crise, PGES ou duração da crise.

Doentes com início de crise extratemporal, no grupo ictal, tiveram uma associação desse parâmetro com defeitos mais extensos ($p=0,047$) e uma tendência para terem mais defeitos ($p=0,143$).

Não encontramos associação entre os valores de hs-cTnI ($n=22$) e o número/extensão dos defeitos ($p=0,282$ e $p=0,181$, respetivamente).

Conclusão

Tanto os grupos ictal como o interictal exibiram um número significativo de defeitos de captação do $[^{99m}\text{Tc}]\text{Tc-HMPAO}$. Estes resultados apontam para alterações crónicas, uma vez que não encontramos diferenças estatisticamente significativas, nas características dos defeitos, entre os dois grupos. A hipótese de perfusão do miocárdio anormal em doentes com epilepsia refratária, que pode ser mais grave em doentes com início de crise extratemporal, deve ser confirmada com outras metodologias.

5. CONSIDERAÇÕES FINAIS

Cada artigo integrante desta tese apresenta uma discussão aprofundada do respetivo tema tratado, nomeadamente no que diz respeito aos biomarcadores séricos, à variabilidade da frequência cardíaca e à imagem funcional com [^{99m}Tc]Tc-HMPAO, no âmbito das alterações cardíacas provocadas por crises epiléticas.

Neste capítulo, pretende-se apenas englobar os estudos realizados, num resumo único.

Os **achados principais** desta tese podem ser sintetizados como se segue:

Biomarcadores séricos

1. Após as crises, verificou-se um **aumento estatisticamente significativo** da **hs-cTnI** e do **BNP**, numa percentagem considerável de doentes com epilepsia refratária (25,9% e 23,3%, respetivamente), sem associação significativa à escala de risco SUDEP-7.
2. O aumento da **hs-cTnI** esteve associado à presença de **crises TCG** ($p < 0,001$), **PGES** ($p=0,001$), **crises mais prolongadas** ($p=0,002$), **FC máxima mais elevada** ($p=0,001$) e **maior intervalo entre a FC máxima e a basal** ($p=0,003$).
3. **Não** se verificou associação entre os aumentos da **hs-cTnI** e a presença de **fatores de risco cardiovascular** ($p=0,519$).
4. **5,2%** dos doentes apresentaram elevações da **hs-cTnI** acima do percentil 99 do limite superior de referência, **compatível com lesão miocárdica** (sem evidência de síndrome coronária aguda); esse valor subiu para **20%**, se considerarmos apenas os doentes com **crises TCG**.
5. Três doentes com crises **não-TCG** também tiveram **elevação da hs-cTnI** após a crise.
6. Os doentes com aumento do **BNP** tinham mais **fatores de risco cardiovascular** ($p=0,019$) do que os que não tiveram aumento desse biomarcador.
7. A **hs-PCR** aumentou apenas em 4,3% dos doentes, após crises epiléticas.
8. A alteração de um biomarcador **não** implicou a alteração de outro. Apenas um doente sofreu aumento tanto na **hs-cTnI** como no **BNP**, e dois na **hs-cTnI** e na **hs-PCR**.

Variabilidade da frequência cardíaca (VFC)

Encontrámos **alterações significativas** em parâmetros da **função autonómica** em doentes com epilepsia refratária e **crises TCG**, particularmente no período **pós-ictal**.

1. Verificou-se um **maior balanço simpátovagal basal diurno**, comparativamente com o período basal noturno, expresso em valores basais diurnos de AVNN, RMSSD, pNN50 e HF significativamente mais baixos e de LF/HF e FC basal mais elevados.
2. Foi evidente uma **diminuição significativa da VFC**, no período **pós-ictal** de crises **TCG**, comparativamente com os valores basais, os do período pré-ictal e os da população normal de referência.
3. A **FC aumentou**, do período pré-ictal para o pós-ictal.
4. Não encontramos diferenças significativas nos parâmetros de VFC analisados (em qualquer dos tempos – pré-ictal, pós-ictal e pós-ictal tardio), entre: – crises TCG com e sem PGES; – crises temporais e extratemporais; – crises em doentes com e sem fatores de risco cardiovascular.

As **crises TCG** tiveram um **impacto maior na VFC** (maior balanço simpátovagal) do que as crises não-TCG, em doentes com epilepsia refratária.

5. Verificou-se uma **ativação simpática maior** após crises **TCG**, quando comparamos com as crises não-TCG, objetivada por um aumento significativo da FC após as crises TCG ($p=0,002$) e por uma diminuição após crises não-TCG ($p=0,004$).
6. As variações nos parâmetros de VFC que se constataram entre os períodos pré-ictal e pós-ictal de **crises TCG** denotam uma transição em direção a uma **dominância simpática**. Essas alterações não foram observadas após crises não-TCG.

Imagem funcional com [^{99m}Tc]Tc-HMPAO:

1. A captação de [^{99m}Tc]Tc-HMPAO pelo coração é estável nas 2 horas que se seguem à administração e.v. do radiofármaco, assim como o é a sua distribuição cardíaca regional.
2. No geral, obtivemos correlações elevadas entre as SPECT cardíacas com [^{99m}Tc]Tc-HMPAO e [^{99m}Tc]Tc-Tetrofosmina (radiofármaco utilizado para avaliar a perfusão miocárdica), sobretudo nos cortes de eixo longo vertical (VLA).
3. Na maioria dos doentes, a fração de ejeção (FE) do ventrículo esquerdo calculada com os dois radiofármacos foi semelhante.
4. Os fumadores exibiram captação pulmonar significativa de [^{99m}Tc]Tc-HMPAO, que interferiu com o processamento das imagens.
5. Na comparação entre as distribuições cardíacas ictal e interictal do [^{99m}Tc]Tc-HMPAO, não houve diferenças estatisticamente significativas, sendo que tiveram defeitos de captação do radiofármaco 34% dos doentes do grupo ictal e 25% dos do grupo interictal ($p=0,469$).
6. Não se verificaram diferenças significativas no número ($p=0,405$), nem na extensão dos defeitos ($p=0,915$), entre os dois grupos (ictal e interictal).
7. A maioria dos defeitos teve extensões ligeiras, tanto no grupo ictal, como no interictal.
8. Crises extratemporais, no grupo ictal, foram associadas a defeitos mais extensos ($p=0,047$) e observou-se uma tendência para terem mais defeitos ($p=0,143$).

Respostas às questões de pesquisa

Questões 1 e 2: *Podemos documentar isquemia e/ou disfunção miocárdicas, provocadas por crises epiléticas, em doentes com epilepsia refratária, através do doseamento de biomarcadores de lesão e disfunção miocárdicas, bem como de inflamação? Qual a relação dessas alterações com a escala de risco SUDEP-7?*

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Nesta população de doentes com epilepsia refratária, documentamos **elevações da hs-cTnI em 25,9%** dos doentes e do **BNP em 23,3%**, após crises epiléticas.

Relativamente à **hs-cTnI**, embora **não tenhamos encontrado associação à escala de risco SUDEP-7**, esse aumento foi associado às crises TCG, à presença de PGES e a crises mais prolongadas, fatores considerados como de risco para SUDEP.

Não estão descritos aumentos da cTnI com origem em tecidos não cardíacos (ao contrário da cTnT) e é muito provável que este aumento da hs-cTnI corresponda a lesão miocárdica, embora não necessariamente isquémica. Estas elevações da hs-cTnI podem estar relacionadas com o esforço físico provocado por este tipo de crises, uma vez que há estudos que documentam elevações da Troponina após atividade física (153, 213), embora o tipo de exercício descrito seja de um tipo e duração diferentes daqueles evidenciados numa crise TCG. Uma meta-análise encontrou aumentos de 32-72% na hs-cTnI, em indivíduos não isquémicos após provas de esforço, com sobreposição com valores observados em doentes com isquemia miocárdica (214). Existe controvérsia acerca dos mecanismos implicados na elevação da cTnI após exercício, mas deverá ocorrer alguma alteração ao nível do cardiomiócito (153). Apesar de não haver evidência de risco aumentado de eventos cardíacos a curto prazo, em indivíduos com elevação da Troponina após exercício (153), alguns casos de verdadeira síndrome coronária aguda ocorreram após crises epiléticas (41, 43, 144, 191).

Um resultado particular deste estudo, contrário ao que tem sido reportado por outros autores (156, 159), foi o facto de documentarmos elevação da hs-cTnI também após crises não-TCG, incluindo uma aura vegetativa (5% de todos os doentes e 7% dos doentes com crises não-TCG). Nestes casos, a elevação da hs-cTnI não pode atribuir-se ao esforço físico.

Três doentes (5,2%) tiveram elevação da hs-cTnI acima do percentil 99 do limite superior de referência, semelhante ao valor encontrado por Sieweke et al. (145), mas a percentagem subiu para 20%, no grupo com crises TCG, valor da mesma ordem de grandeza do referido por Nass et al. (158), que foi de 26%. Nenhum dos nossos doentes teve sinais ou sintomas de síndrome coronária aguda.

Não encontramos associação entre a elevação da hs-cTnI e FRC, ao contrário de Sieweke et al. (145). Outros autores referiram que é mais provável que as lesões miocárdicas ocorram em doentes mais idosos, dado que a doença cardiovascular aumenta com a idade (146, 158, 163), mas não encontramos qualquer diferença significativa na idade de doentes com e sem elevação da Troponina. Inclusivamente, um dos 3 doentes que tiveram elevação da Troponina acima do percentil 99 do limite superior de referência tinha apenas 16 anos de idade.

Outro facto que nos leva a crer que a elevação da Troponina não está apenas relacionada com o esforço físico é a sua relação com a FC, uma vez que para além de a taquicardia ictal estar associada a crises TCG, também está documentada em crises epiléticas subclínicas (215).

Quanto ao **BNP**, o *stress* associado às crises e a libertação secundária de adrenalina podem provocar a produção de BNP (148, 162). Por outro lado, a atividade epiléptica pode ativar a secreção de BNP, tanto no coração, como no cérebro.

Nos nossos doentes, as elevações no BNP associaram-se significativamente apenas com a presença de FRC, o que corrobora a hipótese de a disfunção cardíaca poder ocorrer de forma aguda em doentes com maior risco cardiovascular.

A **hs-PCR** só sofreu aumento em 2 doentes, neste estudo, o que poderia dever-se ao facto de que 75% dos nossos doentes se encontravam sob FACE que diminuem a PCR. No entanto, não encontramos qualquer associação significativa entre estar sob essa medicação e verificar-se ou não elevação da PCR. Por outro lado, esses FACE podem ter impedido elevações da PCR em doentes que poderiam vir a tê-los.

Doentes com elevação num biomarcador não tiveram necessariamente elevação noutra, o que pode refletir diferentes mecanismos para as alterações cardíacas secundárias às crises epilépticas.

Para além da **hs-cTnI**, também **não encontramos associação estatisticamente significativa entre os aumentos do BNP ou da hs-PCR e a escala de risco SUDEP-7**. No entanto, nessa escala, a maioria dos nossos doentes (75%) tinha um *score* de risco ≤ 4 e mais de 50% tinham um *score* de 2. Deste ponto de vista, embora tivessem epilepsia refratária, os nossos doentes não tinham um risco grave para SUDEP, o que pode explicar a falta de associação significativa. No entanto, um dos doentes com elevação da hs-cTnI acima do percentil 99 do limite superior de referência tinha um *score* de 7. Esse doente teve uma crise mais prolongada e PGES, ambos fatores associados a elevações da hs-cTnI, mas cuja contribuição para a SUDEP é controversa e não estão incluídos nesta escala de risco.

Questão 3: Qual o impacto das crises TCG na função autonómica cardíaca (avaliada através da VFC), em doentes com epilepsia refratária?

Neste estudo, avaliamos o impacto da crise TCG nos períodos pré-ictal, pós-ictal e pós-ictal tardio.

No período pré-ictal, não encontramos diferenças estatisticamente significativas nos parâmetros de VFC analisados, comparativamente com o período basal diurno, tal como foi descrito por outros autores (50). Contrariamente, outro estudo refere atividade parassimpática diminuída, com início antes da crise (216), facto que não conseguimos reproduzir, mesmo em blocos de 1 min. Esse estudo compreendia apenas 12 doentes e a metodologia foi diferente da nossa, incluindo os tempos e os parâmetros avaliados. Um outro estudo com 14 doentes também relata parâmetros de VFC alterados no período pré-ictal, em doentes exclusivamente com epilepsia do lobo temporal, recém-diagnosticados e não tratados (217). As diferenças observadas também podem estar relacionadas com questões metodológicas.

O nosso achado mais significativo foi uma **diminuição** global e significativa da VFC no período **pós-ictal** de uma crise TCG, o que também foi descrito noutros estudos (50, 218). Esses autores, tal como nós, descrevem um aumento no LF/HF no período pós-ictal. Todos os nossos parâmetros retornaram aos

211. Gemmell HG, Evans NT, Besson JA, Roeda D, Davidson J, Dodd MG, et al. Regional cerebral blood flow imaging: a quantitative comparison of technetium-99m-HMPAO SPECT with C15O2 PET.

212. Shih WJ, Gruenewald F, Biersack HJ, Berger R, Brandenburg S, Coupal J, et al. Tc-99m HMPAO diffuse pulmonary uptake demonstrated in cigarette smokers.

213. Shave R, Ross P, Low D, George K, Gaze D. Cardiac troponin I is released following high-intensity short-duration exercise in healthy humans.

214. Samaha E, Avila A, Helwani MA, Ben Abdallah A, Jaffe AS, Scott MG, et al. High-Sensitivity Cardiac Troponin After Cardiac Stress Test: A Systematic Review and Meta-Analysis.

215. Weil S, Arnold S, Eisensehr I, Noachtar S. Heart rate increase in otherwise subclinical seizures is different in temporal versus extra-temporal seizure onset: support for temporal lobe autonomic influence.

216. Novak V, Reeves AL, Novak P, Low PA, Sharbrough FW. Time-frequency mapping of R-R interval during complex partial seizures of temporal lobe origin.

217. Romigi A, Albanese M, Placidi F, Izzi F, Mercuri NB, Marchi A, et al. Heart rate variability in untreated newly diagnosed temporal lobe epilepsy: Evidence for ictal sympathetic dysregulation.

218. Pernice R, Faes L, Kotiuchyi I, Stivala S, Busacca A, Popov A, et al. Time, frequency and information domain analysis of short-term heart rate variability before and after focal and generalized seizures in epileptic children.

valores basais no período pós-ictal tardio, contrariamente ao referido por Toth et al. (50) no seu estudo, no qual as alterações persistiram 5-6 h após a crise. Não podemos, pois, corroborar a hipótese de existir um risco prolongado de morte, após a crise.

A FC aumentou, do período pré-ictal para o pós-ictal, o que também é observado noutros estudos (50, 158). Nos nossos doentes, a FC cardíaca pós-ictal voltou ao valor basal, como no estudo de Toth et al. (50). Esta resposta fisiológica ao *stress* indica uma atividade simpática aumentada, imediatamente após a crise, que não é persistente.

É conhecido que os doentes com epilepsia têm disfunção autonómica interictal, facto que também comprovamos neste estudo, uma vez que a VFC basal diurna dos nossos doentes foi globalmente inferior à de uma população saudável. Após a crise TCG, os parâmetros sofreram uma diminuição ainda mais marcada, quando comparados com os da mesma população saudável. Alguns autores relacionam a disfunção autonómica com um aumento do número de casos de SUDEP (53), ou com fatores de risco para SUDEP (109), mas o mecanismo exato pelo qual estes doentes morrem subitamente permanece desconhecido. Noutros estudos, não foram encontradas diferenças estatisticamente significativas nos parâmetros de VFC entre doentes que morreram por SUDEP e doentes vivos com epilepsia (178, 219). As suas coortes eram relativamente pequenas (16 SUDEP/48 controlos e 7 SUDEP/7 controlos, respetivamente), e o facto de que estudaram doentes vivos como controlos é outra limitação, uma vez que não há garantia de que os controlos não venham a morrer por SUDEP.

Nem todos os doentes com disfunção autonómica interictal sofrem SUDEP. Deverá existir um segundo fator (ou até mais) que provoque o início da cascata de eventos que termina na morte. Do nosso trabalho, consideramos que uma crise TCG (que pode resultar numa estimulação simpática extrema) poderá ser um desses fatores.

No entanto, existem algumas (poucas) descrições de casos de SUDEP não diretamente relacionados com crises epiléticas (33, 55, 70). Essas mortes não tiveram uma causa primária cardíaca, mas um compromisso cardiorrespiratório progressivo, seguido de supressão do EEG. As alterações autonómicas no período interictal são provavelmente o resultado de lesões crónicas nos centros autonómicos, provocadas por crises repetitivas (56, 57) e, talvez, num dado momento, essas lesões possam desencadear uma insuficiência cardiorrespiratória.

219. Lamberts RJ, Laranjo S, Kalitzin SN, Velis DN, Rocha I, Sander JW, et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures.

220. Sivathamboo S, Constantino TN, Chen Z, Sparks PB, Goldin J, Velakoulis D, et al. Cardiorespiratory and autonomic function in epileptic seizures: A video-EEG monitoring study.

Questão 4: *A disfunção autonómica (avaliada através da VFC) relacionada com as crises epiléticas depende do tipo de crise?*

Os nossos resultados mostram que as crises TCG têm um maior impacto na VFC do que as crises não-TCG, em doentes com epilepsia refratária, realçando a importância de evitar/ ter atenção a esse tipo de crises.

Nos nossos doentes, verificou-se um aumento significativo da FC após crises TCG e uma diminuição significativa após crises não-TCG, traduzindo uma maior ativação simpática após as crises TCG. Esse achado também é referido por outros autores (50, 51, 220).

Relativamente ao período pré-ictal, não encontramos diferenças estatisticamente significativas nos parâmetros de VFC, entre crises TCG e não-TCG, de acordo com o trabalho de Sivathamboo et al. (220). No entanto, um outro estudo referiu que a atividade parassimpática foi superior no período pré-ictal de crises TCG, comparativamente com o de outros tipos de crises (221). Das medidas que avaliamos, o HF é o que melhor reflete a atividade parassimpática. Embora tenha sido mais elevado antes de crises TCG do que antes de crises não-TCG, a diferença não foi estatisticamente significativa, estando de acordo com o estudo de Toth et al. (50).

As medidas AVNN, RMSSD, pNN20, LF e HF foram significativamente inferiores e o LF/HF foi significativamente superior, após crises TCG comparativamente com as crises não-TCG, o que expressa um balanço simpátovagal superior após as crises TCG.

Do período pré-ictal para o pós-ictal, encontramos variações significativas, induzidas por crises TCG, em quase todos os parâmetros (exceto o SDNN e o LF), o que mostra uma mudança em direção a uma dominância simpática. Essas alterações não foram observadas após crises não-TCG.

Um tônus simpático mais elevado e um tônus vagal inferior predizem morbimortalidade cardiovascular (176), com uma possível ligação a risco de SUDEP. Outros estudos, com menos parâmetros avaliados, também mostraram uma diminuição pós-ictal mais acentuada do RMSSD e da FC, nas crises TCG, comparativamente com as crises não-TCG (50, 51). A maioria não realizou uma comparação intraindividual, o que foi feito no nosso estudo, no sentido de levar em consideração as respostas autonómicas individuais.

Questão 5: *Qual o melhor intervalo de tempo, entre a injeção do radiofármaco e a aquisição das imagens cardíacas com $[^{99m}\text{Tc}]\text{Tc-HMPAO}$?*

Neste estudo, verificamos que a captação de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ pelo coração é estável nas 2 horas que se seguem à administração e.v. do radiofármaco, assim como o é a sua distribuição cardíaca; deste modo, uma imagem pode ser adquirida de modo satisfatório a qualquer hora, dentro desse intervalo de tempo.

Três dos voluntários eram fumadores e exibiram captação pulmonar significativa de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$. Essa captação foi tão intensa que interferiu com o processamento das imagens. Shih et al. já tinham demonstrado que a captação pulmonar de $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ estava relacionada com os hábitos tabágicos, e colocaram a hipótese de que fosse dependente de permeabilidade vascular aumentada nesses indivíduos (212). O nosso estudo corrobora esse achado.

Questão 6: *É possível avaliar a perfusão regional do ventrículo esquerdo e a sua função com $[^{99m}\text{Tc}]\text{Tc-HMPAO}$?*

O mecanismo de localização do $[^{99m}\text{Tc}]\text{Tc-HMPAO}$ no cérebro está relacionado com a sua natureza lipofílica, que permite a passagem através da barreira hemato-encefálica intacta. Uma vez dentro da célula, é crucial a conversão para a forma hidrofílica, para que ocorra retenção intracelular (201-205).

221. Delamont RS, Julu PO, Jamal GA. Changes in a measure of cardiac vagal activity before and after epileptic seizures.

A captação regional de [^{99m}Tc]Tc-HMPAO pelo cérebro reflete o fluxo sanguíneo (195, 202, 210, 211), mas ainda é desconhecido o mecanismo de captação/retenção nos miócitos.

Na nossa comparação entre as imagens cardíacas obtidas com os dois radiofármacos ([^{99m}Tc]Tc-HMPAO e [^{99m}Tc]Tc-Tetrofosmina), obtivemos correlações elevadas, sobretudo no eixo curto vertical.

O doente fumador teve piores correlações, devido à elevada captação pulmonar de [^{99m}Tc]Tc-HMPAO.

A FE do ventrículo esquerdo foi semelhante com ambos os radiofármacos, na maioria dos doentes. A maior discrepância ocorreu num doente que sofreu uma infecção respiratória grave, com insuficiência cardíaca descompensada, entre os dois estudos, o que pode justificar a queda na FE.

Assim sendo, uma SPECT miocárdica com [^{99m}Tc]Tc-HMPAO poderá ser um método de 'rastreamento' de isquemia em doentes não fumadores que já tenham de realizar uma SPECT de perfusão cerebral com [^{99m}Tc]Tc-HMPAO. Poderá servir como referenciadora para uma cintigrafia de perfusão do miocárdio, num subgrupo de doentes com epilepsia, suscetíveis de sofrerem alterações cardíacas.

Embora promissores, estes resultados preliminares têm de ser confirmados numa coorte maior.

Questão 7: *Como é a distribuição do [^{99m}Tc]Tc-HMPAO no ventrículo esquerdo de doentes com epilepsia refratária?*

Para este estudo, avaliamos a distribuição do [^{99m}Tc]Tc-HMPAO, tanto no período ictal, como no interictal. Ambos os grupos tiveram um número significativo de doentes com defeitos de captação do radiofármaco (34%, no grupo ictal, e 25%, no grupo interictal), mas esta diferença não foi significativa ($p=0,469$). O número de defeitos, bem como a sua extensão também não foram significativamente diferentes nos dois grupos ($p=0,405$ e $p=0,915$, respetivamente). Quanto à extensão dos defeitos, estes foram maioritariamente ligeiros, nos dois grupos.

Não se verificou associação significativa entre o número ou a extensão dos defeitos e o sexo, idade, FRC, duração da epilepsia ou frequência de crises, em qualquer dos grupos.

No grupo ictal, o número/ extensão dos defeitos não se associaram significativamente com a semiologia das crises, a presença de PGES ou a duração das crises. No entanto, foi evidente uma associação entre crise extratemporal e maior extensão dos defeitos ($p=0,047$).

Nos doentes que tiveram doseamento da hs-cTnI, na crise estudada com [^{99m}Tc]Tc-HMPAO ($n=22$), não encontramos associação entre os valores da hs-cTnI e o número ou a extensão dos defeitos ($p=0,282$ e $p=0,181$, respetivamente).

Embora o estudo preliminar de validação do [^{99m}Tc]Tc-HMPAO como agente de perfusão miocárdica só tenha incluído três doentes, os resultados foram muito promissores.

Assim, se partirmos do pressuposto que estamos a mapear a perfusão do miocárdio com este radiofármaco, é provável que estejamos perante alterações associadas a isquemia crónica (ainda que ligeiras), uma vez que não encontramos diferenças estatisticamente significativas, nas características dos defeitos, entre os dois grupos. Deverá ser confirmada por outras metodologias, esta hipótese de perfusão do miocárdio anormal em doentes com epilepsia refratária, que pode ser mais grave em doentes com início de crise extratemporal.

Implicações para a prática clínica

Doseamentos

Nesta tese, ficou documentado que um número significativo de doentes com epilepsia refratária tem aumentos em biomarcadores de necrose/disfunção miocárdica (hs-cTnI, BNP) após crises, sem sinais ou sintomas de doença cardíaca. Doentes com elevação de um biomarcador não tiveram necessariamente elevação de outro, o que pode refletir diferentes mecanismos envolvidos na resposta cardiovascular às crises e apontar para origens multifatoriais para o dano miocárdico, potencialmente relacionado com a SUDEP.

Não foi encontrada associação entre os aumentos dos biomarcadores e a escala de risco SUDEP-7. No entanto, tendo em conta as associações entre os biomarcadores e as características das crises, consideramos que a duração da crise, a presença de PGES e o doseamento da hs-cTnI após as crises, particularmente TCG, devem ser ponderados em estudos futuros que explorem os preditores de SUDEP, para avaliar se é válida a sua inclusão em revisões da escala SUDEP-7 ou noutras escalas de risco.

VFC

A disfunção autonómica corroborada por esta tese, em doentes com epilepsia refratária, pode ter relevância clínica, não só por diminuir o limiar para arritmias que coloquem em risco a vida (218), mas também por poder ter influência na decisão da melhor terapêutica a instituir (talvez até prevenindo a resposta a certas terapêuticas).

A estimulação do nervo vago (ENV), que consiste na estimulação elétrica do nervo vago esquerdo, é uma terapêutica adjuvante da epilepsia refratária. Um estudo avaliou o impacto da ENV na função autonómica cardiovascular em nove doentes, realizando a avaliação da VFC antes e após estimulação. Verificaram uma diminuição no LF e no LF/HF, após estimulação, refletindo um balanço simpático/ parassimpático melhor, colocando a hipótese de existir um efeito cardioprotetor (187). Não existem biomarcadores prognósticos que possam prever os respondedores a esta terapêutica (222, 223). Liu et al. referem que doentes que tiveram uma diminuição de, pelo menos, 50% das crises, com a ENV, tinham uma VFC menos comprometida, no período interictal antes de colocarem os elétrodos, do que aqueles que não responderam (223). Hödl et al. verificaram que os doentes que não responderam à estimulação sofreram uma queda significativa na VFC pré-ictal. A avaliação da HRV pode ter importância para evitar cirurgias de ENV desnecessárias.

Muitos FACE diminuem a VFC, especialmente os bloqueadores dos canais de sódio, contribuindo para uma atividade autonómica cardíaca comprometida

222. Hödl S, Olbert E, Mahringer C, Struhal W, Carrette E, Meurs A, et al. Pre-ictal heart rate variability alterations in focal onset seizures and response to vagus nerve stimulation.

223. Liu H-Y, Yang Z, Meng F-G, Guan Y-G, Ma Y-S, Liang S-L, et al. Preoperative Heart Rate Variability as Predictors of Vagus Nerve Stimulation Outcome in Patients with Drug-resistant Epilepsy.

224. Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart-rate variability in localization-related epilepsy.

e estando associados a maior risco de SUDEP (76, 224). A terapêutica com Carbamazepina foi associada a uma diminuição das razões noite/dia da VFC. Uma monitorização apertada desses doentes, com avaliação da VFC pode ser importante, no sentido de avaliar a necessidade de se alterar para outro FACE ou considerar outra opção terapêutica.

Outra possível aplicação da avaliação da VFC é o desenvolvimento de aparelhos de deteção de crises, havendo já estudos a explorar essa possibilidade (188, 189).

A ausência de protocolos padronizados para avaliar e relatar a VFC em doentes com epilepsia é uma limitação para o seu uso na prática clínica (175).

Imagem cardíaca com [^{99m}Tc]Tc-HMPAO

Nesta tese, descreve-se uma potencial nova aplicação para um radiofármaco antigo, que pode permitir a avaliação simultânea de dois órgãos, com menor exposição radioativa, em doentes com epilepsia.

Em doentes seleccionados, com epilepsia refratária, que tenham de realizar uma SPECT cerebral para localizar a zona epileptogénica, poder-se-ia adquirir, no seguimento, uma SPECT cardíaca, usando o radiofármaco já injetado previamente, para avaliar a distribuição no coração.

A comprovar-se, em estudos futuros, que essa distribuição reflete a perfusão do miocárdio, esse estudo poderia servir de rastreio para a realização de SPECT de perfusão do miocárdio com [^{99m}Tc]Tc-Tetrofosmina.

Ao terminar esta tese, afirmo com agrado que, apesar das limitações presentes, posso apresentar resultados positivos e propor para a prática clínica a avaliação de parâmetros cardíacos específicos nos doentes com epilepsia refratária, com a intenção de lhes diminuir o risco de morte.

Realço, por me ser pessoalmente querido, o ter desenvolvido uma nova aplicação para um radiofármaco da Medicina Nuclear convencional.

No futuro, tenho ainda a perspetiva de explorar a base de dados extensa que mantenho e obter outros resultados igualmente úteis, para a prática clínica e para a vida destes doentes.

6. ■ DISSEMINAÇÃO DO TRABALHO REALIZADO

Publicações em revistas científicas com revisão por pares

- 1. cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy**
Artigo completo publicado na revista *Seizure* [Fator de impacto: 3,184 do *Journal Citation Reports*; 1º Quartil do *Scimago Journal & Country Rank* (Medicina)]
Maria Teresa Faria, Ricardo Rego, Helena Rocha, Francisca Sá, Rui Farinha, Ana Oliveira, Pedro Barata, Dílio Alves, Jorge Pereira, Francisco Rocha-Gonçalves, Hernâni Gonçalves, Elisabete Martins. **cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy.** *Seizure*. 2020 Aug;80:100-108. doi: 10.1016/j.seizure.2020.06.003
- 2. Heart rate variability in patients with refractory epilepsy: The influence of generalized convulsive seizures**
Artigo completo publicado na revista *Epilepsy Research* [Fator de impacto: 3,045 do *Journal Citation Reports*; 2º Quartil do *Scimago Journal & Country Rank* (Neurologia clínica)]
Maria Teresa Faria, Susana Rodrigues, Manuel Campelo, Duarte Dias, Ricardo Rego, Helena Rocha, Francisca Sá, Marta Tavares-Silva, Roberto Pinto, Gonçalo Pestana, Ana Oliveira, Jorge Pereira, João Paulo Silva Cunha, Francisco Rocha-Gonçalves, Hernâni Gonçalves, Elisabete Martins. **Heart rate variability in patients with refractory epilepsy: The influence of generalized convulsive seizures.** *Epilepsy Res*. 2021 Dec;178:106796. doi: 10.1016/j.eplepsyres.2021.106796
- 3. Does the type of seizure influence heart rate variability changes?**
Artigo (comunicação breve) publicado na revista *Epilepsy & behavior* [Fator de impacto: 2,937 do *Journal Citation Reports*; 2º Quartil do *Scimago Journal & Country Rank* (Neurologia)]
Maria Teresa Faria, Susana Rodrigues, Manuel Campelo, Duarte Dias, Ricardo Rego, Helena Rocha, Francisca Sá, Marta Tavares-Silva, Roberto Pinto, Gonçalo Pestana, Ana Oliveira, Jorge Pereira, João Paulo Silva Cunha, Francisco Rocha-Gonçalves, Hernâni Gonçalves, Elisabete Martins. **Does the type of seizure influence heart rate variability changes?** *Epilepsy Behav*. 2021 Dec 1;126:108453. doi: 10.1016/j.yebeh.2021.108453. Epub ahead of print. PMID: 34864377.

4. **Imaging myocardial perfusion with [^{99m}Tc]Tc-HMPAO: fiction or reality? – preliminary results**

Artigo completo publicado na revista *Journal of Clinical Images & Medical Case Reports*.

Maria Teresa Faria, Maria do Carmo Vilas-Boas, Paulo Maia, Pedro Barata, Ana Oliveira, Ricardo Rego, Joel Sousa, Jorge Pereira, Francisco Rocha-Gonçalves, João Paulo Silva Cunha, Elisabete Martins. **Imaging myocardial perfusion with [^{99m}Tc]Tc-HMPAO: fiction or reality? – preliminary results.**

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doi: www.doi.org/10.52768/2766-7820/1586

Apresentações orais/ pósteres

1. **Serão possíveis cintigrafias cardíacas com HMPAO-Tc-99m? – resultados preliminares**

Maria Teresa Faria, Ana Oliveira, Maria Berta Pérez, Tiago Vieira, Víctor Alves, Ricardo Rego, Dílio Alves, Francisco Rocha-Gonçalves, Jorge Pereira, Elisabete Martins

XV Congresso Nacional de Medicina Nuclear, Coimbra, 19 a 21 de novembro de 2015.

2. **Tc-99m-HMPAO and the heart - a new way for an old molecule?**

Maria Teresa Faria, Ana Oliveira, Pedro Barata Coelho, Ricardo Rego, Jorge Gonçalves Pereira, Francisco Rocha-Goncalves, Elisabete Martins

International Conference on Nuclear Cardiology and Cardiac CT (ICNC), Viena, maio de 2017.

3. **Biomarcadores séricos de lesão miocárdica em doentes com epilepsia refractária - possível relação com a perfusão cerebral**

Maria Teresa Faria, Ana Rita Fernandes, Ana Oliveira, Ricardo Rego, Helena Rocha, Dílio Alves, Pedro Barata Coelho, Rui Farinha, Jorge G. Pereira, Francisco Rocha Gonçalves, Elisabete Martins

XVI Congresso Nacional de Medicina Nuclear, Lisboa, novembro de 2017.

4. **Estudo da variabilidade da frequência cardíaca em doentes com epilepsia refractária**

Maria Teresa Faria, Manuel Campelo, Helena Rocha, Ricardo Rego, Pedro Barata, Gonçalo Pestana, Roberto Pinto, Marta Tavares, Delfim Souteiro, Dílio Alves, Jorge Pereira, Francisco Rocha-Gonçalves, Elisabete Martins

Congresso Português de Cardiologia, Albufeira, abril de 2018.

5. **Estudo das alterações cardíacas ictais: possível relação com a morte súbita na epilepsia – projecto de doutoramento em Medicina**

Maria Teresa Faria

Bial Neuro Summlnt, Porto, maio de 2018.

6. **Heart rate variability in patients with refractory epilepsy**

Maria Teresa Faria, Manuel Campelo, Helena Rocha, Ricardo Rego, Pedro Barata, Gonçalo Pestana, Roberto Pinto, Marta Tavares Silva, Delfim Souteiro, Dílio Alves, Jorge Pereira, Francisco Rocha-Gonçalves, Elisabete Martins

Heart Failure Congress, Viena, maio de 2018.

7. **Cardiac damage biomarkers profile after video-EEG documented seizures**
Maria Teresa Faria, Ricardo Rego, Francisca Sá, Helena Rocha, Rui Farinha, Manuel Campelo, Pedro Barata Coelho, Roberto Pinto, Gonçalo Pestana, Marta Silva, Delfim Souteiro, Jorge G. Pereira, Francisco Rocha Goncalves, Elisabete Martins
 European Society of Cardiology Congress, Munique, agosto de 2018.
8. **Avaliação prospectiva da influência do tipo de crise epiléptica em parâmetros de variabilidade da frequência cardíaca ictal e pós-ictal precoce**
Maria Teresa Faria, Susana Rodrigues, Duarte Dias, Ricardo Rego, Helena Rocha, Francisca Sá, Ana Oliveira, Manuel Campelo, Jorge Pereira, Francisco Rocha Gonçalves, João Paulo S. Cunha, Elisabete Martins
 31º Encontro Nacional de Epileptologia, Porto, março de 2019.
9. **Validation of HMPAO-Tc-99m as a radiotracer for myocardial perfusion - preliminary results**
Maria Teresa Faria, Maria do Carmo Vilas-Boas, Paulo Manuel Maia, Ana Oliveira, Ricardo Rego, Joel Sousa, Jorge Pereira, João Paulo S. Cunha, Francisco Rocha Gonçalves, Elisabete Martins
 Congresso Português de Cardiologia, Vilamoura, abril de 2019.
10. **Cardiac damage biomarkers in patients with refractory epilepsy - is there any change after seizures?**
Maria Teresa Faria, Ricardo Rego, Francisca Sá, Helena Rocha, Rui Farinha, Ana Oliveira, Jorge Pereira, Francisco Rocha Gonçalves, Hernâni Gonçalves, Elisabete Martins
 Congresso Português de Cardiologia, Vilamoura, abril de 2019.
11. **Validation of HMPAO-Tc-99m as a myocardial perfusion radiotracer - preliminary results**
Maria Teresa Faria, Ana Oliveira, Maria do Carmo Vilas-Boas, Paulo Manuel Maia, Ricardo Rego, Joel Sousa, Jorge Pereira, João Paulo S. Cunha, Francisco Rocha-Gonçalves, Elisabete Martins
 International Conference on Nuclear Cardiology and Cardiac CT, Lisboa, maio de 2019.
12. **^{99m}Tc-HMPAO cardiac SPECT: a method to detect ischemia in patients with refractory epilepsy?**
Maria Teresa Faria, Ana Oliveira, Ricardo Rego, Helena Rocha, Francisca Sá, Rui Farinha, Jorge Pereira, Francisco Rocha-Gonçalves, Hernâni Gonçalves, Elisabete Martins
 International Conference on Nuclear Cardiology and Cardiac CT, Lisboa, maio de 2019.
13. **The influence of tonic-clonic seizures on heart rate variability in patients with refractory epilepsy**
Maria Teresa Faria, Susana Rodrigues, Duarte Dias, Ricardo Rego, Helena Rocha, Francisca Sá, Ana Oliveira, Manuel Campelo, Jorge Pereira, Francisco Rocha-Gonçalves, João Paulo S. Cunha, Elisabete Martins
 European Society of Cardiology Congress, Paris, agosto/ setembro de 2019.

14. **The effect of seizure type on ictal and early post-ictal HRV in patients with focal resistant epilepsy**

Maria Teresa Faria, Susana Rodrigues, Duarte Dias, Ricardo Rego, Helena Rocha, Francisca Sá, Ana Oliveira, Manuel Campelo, Jorge Pereira, Francisco Rocha-Gonçalves, João Paulo S. Cunha, Elisabete Martins
European Society of Cardiology Congress, Paris, agosto/ setembro de 2019.

15. **Avaliação da variabilidade da frequência cardíaca interictal e factores de risco para SUDEP em doentes com epilepsia refractária**

Maria Teresa Faria, Ricardo Pinto, Miguel Carvalho, Ricardo Rego, Helena Rocha, Francisca Sá, Ana Oliveira, Manuel Campelo, Jorge Pereira, Francisco Rocha Gonçalves, Hernâni Gonçalves, Elisabete Martins
33º Encontro Nacional de Epileptologia, março de 2020.

**'Nobody made a greater mistake than he who did nothing
because he could do only a little.'**

EDMUND BURKE, 1729-97

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