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Novel insights regarding haemodynamics in focal seizures

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ABSTRACT

Introduction: We explored the temporal patterns of haemodynamic parameters in four seizures of three patients using the log-ratio method.
Methods: We identified three subjects who experienced a seizure during a tilt table test: one had two focal impaired awareness seizures (FIAS, seizures#1 and#2), one had one FIAS (#3), and one had a focal to bilateral tonic-clonic seizure (fbTCS, seizure#4). Recordings included video, heart rate (HR) and continuous blood pressure (BP). We used the log-ratio method to determine the relative contributions of HR, stroke volume (SV), and total peripheral resistance (TPR) to mean arterial pressure (MAP). A 'phase' was defined as a temporary departure of MAP, HR, SV or TPR from baseline.
Results: BP showed a decrease in all four seizures. We observed one phase with synchronous events for all haemodynamic variables during seizures 1&2; seizure#3 showed one phase for MAP and TPR, three phases for HR, and only one for SV. Seizure#4 showed no autonomic involvement during the first minute of the focal seizure, after which MAP and HR showed an asynchronous triphasic course until the signal was lost when a tonic-clonic seizure occurred.
Conclusion: This chance sample illustrates that haemodynamic variables may change in different directions and asynchronously during focal seizures. We speculate that these complex autonomic patterns represent different ictal propagation pathways and that they may include ictal as well as corrective changes. BP decreased in all four seizures while the literature reports BP increases. As our patients were upright, not supine, we hypothesise that ictal haemodynamic changes impair normal control and are therefore likely to cause hypotension in the upright position.

1. Introduction

Epileptic seizures can be accompanied by autonomic changes that may help diagnosis but can cause complications, including sudden unexpected death (Baumgartner et al., 2019; Thijs et al., 2021). Autonomic manifestations are generally more marked in temporal seizures, suggesting limbic involvement (Thijs et al., 2021). Alternatively, autonomic responses may reflect attempts to correct ictal changes (Thijs et al., 2021). The well-known ictal bradycardia occurs in fewer than 5 % of focal seizures (Sevcencu and Struijk, 2010; Van der Lende et al., 2016), predominantly in temporal lobe epilepsy (Van der Lende et al., 2016; Tinuper et al., 2001).

Focal ictal cardiovascular involvement is rarely fully examined due to lacking heart rate (HR) and blood pressure (BP) recordings. We gathered three cases with focal impaired awareness seizures (FIAS) recorded by chance during tilt table tests (TTT) with continuous HR and BP recording. All three showed ictal bradycardia and hypotension. To explore ictal patterns of parameters governing blood pressure, we applied a novel method (Van Dijk et al., 2020, 2021).

1.1. Cases

1.1.1. Case 1

A 61-year-old man presented to a tertiary neurological syncope outpatient clinic with episodes of light-headedness and dizziness

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Abbreviations

BP	blood pressure
fbTCS	focal to bilateral tonic-clonic seizure
FIAS	focal with impaired awareness seizure
HR	heart rate
LR	log-ratio
MAP	mean arterial pressure
SV	stroke volume
TLOC	transient loss of consciousness
TPR	total peripheral resistance
TTT	tilt table test

without transient loss of consciousness (TLOC). TTT was performed to test for orthostatic hypotension (OH) or reflex presyncope, after ancillary tests did not reveal abnormalities. In this laboratory, video-EEG is an integral part of TTT. Three minutes after head-up tilt, the patient reported a tingling sensation on the left side of the body coinciding with EEG changes meeting criteria for a focal seizure from the left temporal lobe. BP and HR decreased simultaneously at the onset of the seizure but not sufficiently to warrant immediate tilting back. A second similar episode occurred later during the same TTT (seizure#2). The patients denied having had earlier similar episodes. A diagnosis of focal epilepsy was made and the patient started anti-seizure medication. During follow-up, no recurrences of light-headedness, dizziness, or tingling sensation were reported.

1.1.2. Case 2

A 70-year-old man underwent a TTT with video-EEG in a centre for epilepsy and sleep disorders due to multiple episodes of TLOC. Several months later, he developed episodes marked by a strange sensation in the abdomen, followed by impaired awareness but without TLOC, lasting between 20 seconds and a few minutes. During head-up tilt, the patient reported these symptoms and recognised them as identical to earlier spells. The EEG showed a focal seizure with onset in the right frontotemporal region, starting 30 seconds before his first symptoms. At the start of his symptoms, BP and HR decreased simultaneously. As the focal seizure continued, the epileptic discharges spread diffusely, and HR accelerated.

1.1.3. Case 3

A 62-year-old man presented to a cardiological syncope outpatient clinic with episodes of unexplained TLOC over a one-year period without clear precipitating factors. After cardiac causes were found unlikely, TTT was performed without video-EEG. Four minutes after being tilted upwards, he started staring, followed by automatisms of hands and lips, which had not been reported earlier. BP and HR decreased simultaneously at the onset of these clinical events. Part of the seizure was captured on smartphone video by the attending cardiologist (FJdL). After returning to a supine position, a bilateral tonic-clonic seizure evolved, and video registration was ceased.

2. Methods

2.1. EEG analysis

The start and end of seizures 1, 2, and 3 were based on EEG inspection; the onset of seizure 4 was determined using clinical video signs.

2.2. Haemodynamic analysis

TTT included at least 10 minutes of supine rest followed by head-up tilt to 70 degrees. BP was measured in a supine position with a validated automated cuff sphygmomanometer, while continuous measurements were obtained by finger volume-clamp analysis using Finometer (Finapres) or Nexfin (BMEye). At least one ECG lead was used.

Continuous beat-to-beat BP recordings allowed Modelflow analysis of mean arterial pressure (MAP), stroke volume (SV), total peripheral resistance (TPR) and HR. Beat-to-beat records were interpolated to obtain regularly placed samples at 1 Hz and were interactively inspected with custom Matlab (The Mathworks, Natick, USA) software to remove artifacts.

We calculated mean values over a baseline period about one minute before the seizure, as well as minima and differences from baseline for SBP, MAP, DBP and HR.

We applied the log-ratio method for a quantitative comparison of relative effects on MAP of SV, HR, and TPR (Van Dijk et al., 2020). We calculated the mean of the baseline for each parameter and expressed all results as ratios of baseline values. We then computed the logarithms of ratios ($_{LR}$), creating an additive relationship: $MAP_{LR}=HR_{LR}+SV_{LR}+TPR_{LR}$. To aid interpretation of the MAP change, we visualized the relative contributions of HR, SV, and TPR for each point in time.

2.3. Haemodynamic patterns

We first noted log-ratio values for MAP, HR, SV, and TPR at the time of the lowest MAP, to investigate how much the three factors contributed to the maximal BP decrease. Second, we explored phases, defined as temporary decreases or increases away from baseline. We qualitatively used these phases to study whether parameters changed synchronously and in the same direction.

3. Results

Table 1 summarises BP and HR data. Lowest HR (42 bpm) and SBP (51 mmHg) were seen in seizure #4, while the largest SBP decrease (69 mmHg) occurred in seizure #1 and the largest HR decrease in seizure #4 (19 bpm).

3.1. Phases

Fig. 1 illustrates haemodynamic phases. Seizures#1 and #2 showed a monophasic decrease of MAP, HR, and TPR, while SV increased. All parameters reached apex values at almost the same time, suggesting one underlying process. Seizure#3, showed one negative phase for MAP and TPR, but three phases for HR (positive-negative-positive) and only one

Table 1
Summary of the haemodynamic data represented for each seizure. SBP – systolic blood pressure, MAP – mean arterial pressure, DBP – diastolic blood pressure, HR – heart rate.

	Seizure #1	Seizure #2	Seizure #3	Seizure #4	Mean (SD)
baseline SBP	249	208	144	115	179 (60)
baseline MAP	142	133	112	84	118 (26)
baseline DBP	110	109	95	65	94 (21)
baseline HR	66	74	70	62	68 (5)
minimum SBP	180	177	75	51	121 (67)
minimum MAP	98	114	59	38	77 (35)
minimum DBP	78	88	52	28	62 (27)
minimum HR	50	65	55	42	53 (10)
difference SBP	69	31	69	65	58 (19)
difference MAP	45	19	53	46	41 (15)
difference DBP	33	21	43	37	33 (9)
difference HR	16	9	16	19	15 (5)

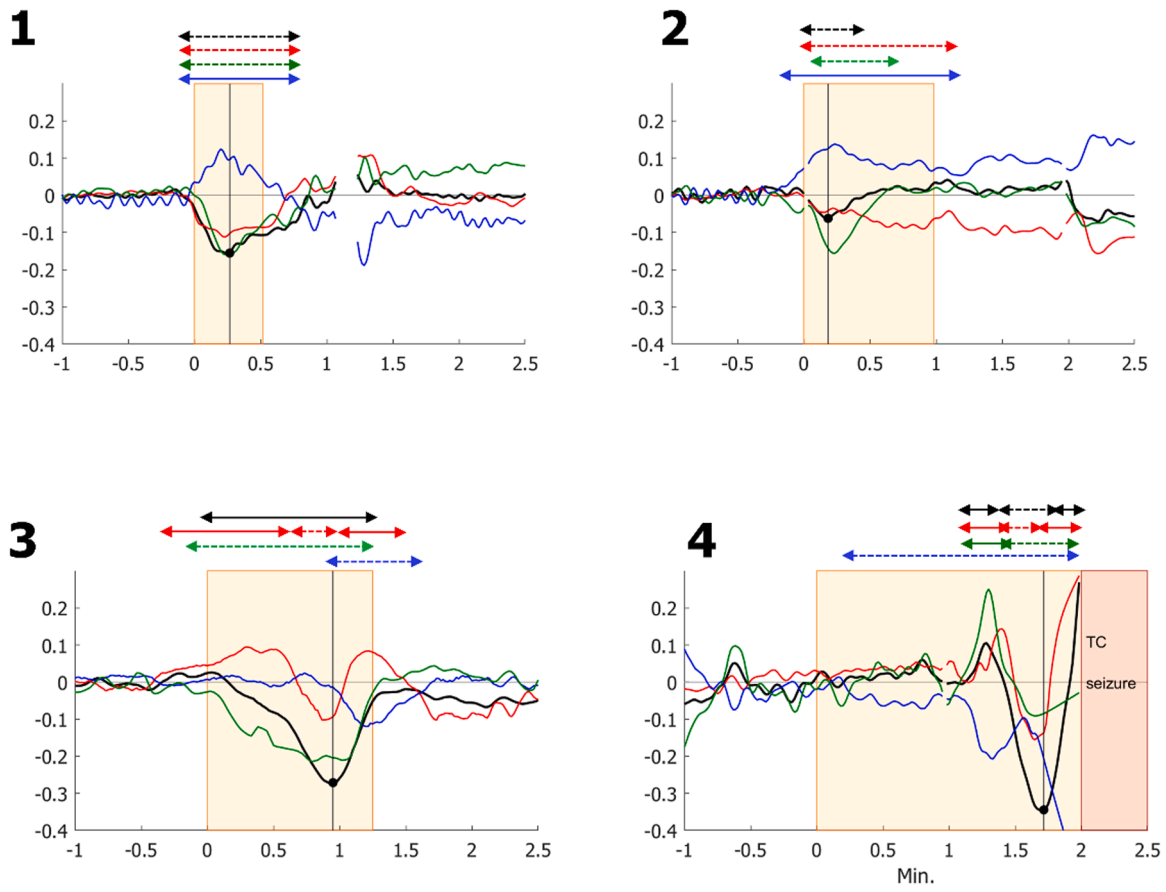

Fig. 1. Log-ratio results of the four focal seizures:seizure#1 and #2 (case 1) and #3 (case 2): focal impaired awareness seizure; seizure #4 (case 3): focal to bilateral tonic-clonic seizure. Colours for lines and arrows indicate parameters: black is mean arterial pressure; red: heart rate; blue: stroke volume; green: total peripheral resistance. Rectangles represent the duration of the seizure. The black dot represents the lowest MAP. Each horizontal arrow indicates a phase: dotted lines indicate BP-decreasing effects (negative log-ratios), and uninterrupted lines indicate BP-increasing effects.

late negative phase for SV. Hence, HR changed out of phase with TPR and MAP. In the first part of seizure#4, there was no apparent autonomic activity during the first minute of the focal seizure, after which parameters followed different courses: MAP and HR showed a triphasic course (positive-negative-positive) in which HR and MAP did not change simultaneously. TPR showed a biphasic course (positive-negative), while SV showed one protracted negative phase, split into two parts.

4. Discussion

This is the first study to quantify haemodynamic contributions to MAP in focal seizures using the log-ratio method.

4.1. Haemodynamic patterns

The first changes of BP and HR appeared together with the first seizure signs. In case 1, haemodynamic and clinical events coincided with the onset of EEG changes, but in case 2, they followed EEG alterations after 30 seconds. The common denominator in all four seizures was low MAP, caused by different mechanisms. The monophasic decrease in BP in FIAS #1 and #2 was the result of low HR and TPR, while the simultaneous high SV was most probably a direct result of low HR, as low HR prolongs cardiac filling time. However, BP did not continue to decrease during the two FIAS (seizure #1 and #2). This may be due to physiological BP corrections or by the cessation of ictal discharges decreasing BP. A monophasic BP decrease does not prove a temporal onset, as the multiphasic seizure #3, also had a temporal onset. In the other two seizures the patterns were neither monophasic nor did the parameters change in unison.

4.2. Autonomic involvement in seizures

The most common ictal haemodynamic pattern consists of tachycardia plus hypertension, which can be explained by increased sympathetic drive (Baumgartner et al., 2019; Sevcencu and Struijk, 2010). A quick decrease in HR may result from increased parasympathetic or decreased sympathetic action. The initial simultaneous decrease of HR and TPR in cases 1 and 2, leading to a monophasic BP decrease, suggests parasympathetic vagal activation and decreased sympathetic vasoconstriction, as in reflex syncope (Mastrangelo et al., 2020). Hampel et al. described more complex patterns of HR and BP changes during focal seizures: both increased, both decreased, or HR increased while BP decreased (Hampel et al., 2016). Remarkably, only two out of their 28 focal seizures (temporal lobe seizures) had a pattern similar to our combined decreases of HR and BP (Hampel et al., 2016). The lowering of TPR cannot be explained by a direct effect on the heart and therefore suggests the existence of ictal 'arterial vasodepression' suggesting two mechanisms behind ictal hypotension: arterial vasodepression and cardioinhibition (Van Dijk et al., 2014).

4.3. One pattern or more?

Our cases, though few in number, highlight variable ictal haemodynamic changes, implying a broad palette of haemodynamic variations during seizures. Hampel et al. also described haemodynamic changes, but in a different population, consisting of long-standing refractory

epilepsy, recorded in supine positions and another setting (Hampel et al., 2016).

It is remarkable that BP decreases occurred in all four seizures, as BP increases are much more likely (Sevcencu and Struijk, 2010). The recorded haemodynamic events are not reflex syncope or orthostatic hypotension, first because the observed haemodynamic patterns did not resemble these causes of hypotension at all, and second because of the clear temporal relation between seizures and haemodynamic changes. Instead, we surmise that focal seizures disrupt normal upright BP control that mostly consists of increases of HR and TPR. Hence, ictal disturbances are more likely to cause upright than supine hypotension. Of note, reports of high BP during focal seizures all regarded supine or sitting patients (Hampel et al., 2016). Note that our BP and HR decreases were considerable but not yet large enough to cause syncope (Van Dijk et al., 2020, 2014). It is important to bear in mind possible decreases of haemodynamic parameters in focal seizures when approaching patients with a mixed presentation of signs of syncope and epilepsy.

These cases emphasize the complexity of ictal haemodynamic changes. Unveiling such patterns in larger cohorts can help understand clinical events in some focal seizures. Upright focal seizures may cause hypotension, which may contribute to falls and ultimately to TLOC, even without severe bradycardia or asystole.

Authorship

We confirm that all authors have contributed equally in the conception, design analysis and interpretation of data for the work, in drafting or revising for intellectual content. All authors have approved the final version to be published and agree to be accountable for all aspects of the work.

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CRediT authorship contribution statement

J Gert Van Dijk: Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Roland Thijs:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Frederik De Lange:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Jorien Van Hoey Smith:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Ineke Van Rossum:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Boriana Gagaouzova:** Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Disclosures

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Author JGvD is scientific advisor to Finapres.

Data availability

Data is available upon reasonable request.

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