Towards tonic seizure detection based on multimodal detection methods using the EpiSense sensor

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Towards tonic seizure detection based on multimodal detection methods using the EpiSense sensor

Joyce van Sluis, MSc.

23 January 2018
Towards tonic seizure detection based on multimodal detection methods using the EpiSense sensor

Executed at

Kempenhaeghe Academic Center for Epileptology

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23 January 2018
2018/004

Confidential
The work described in this report is executed in accordance with the TU/e Code of Scientific Conduct
CONFIDENTIAL: YES/NO

One year project presented to Eindhoven University of Technology

...
Summary (publicly available)

Introduction
Tonic seizures in epilepsy are characterized by a severe continuous contraction of multiple muscle groups in the body, including the respiratory muscles. This type of seizure may lead to unconsciousness, cardiorespiratory depression, and in severe cases even to Sudden Unexpected Death in Epilepsy (SUDEP). Current detection methods are based on measurement of heartrate and movement. However, a tonic seizure is not always associated with a rise in heartrate. And little movement (or a lack thereof) makes current detection methods suboptimal for tonic seizure detection. Especially during night-time, when supervision is minimal, a real-time method for detecting tonic seizures is necessary.

Design project
The overall goal of this project is to design an algorithm for the detection of tonic seizures using the EpiSense system in order to apply it in patients’ home environments. Families and friends fear a tonic seizure, with its possible detrimental outcomes, to pass unnoticed during night-time. The use of a sensor for the detection of tonic seizures, could decrease anxiety amongst the patient’s loved ones. Because then, if a seizure does occur, direct medical intervention (which can be of vital importance) can be provided immediately if necessary. The EpiSense is a system developed by Kempenhaeghe in collaboration with Holst centre/Imec, and Eindhoven University of Technology (TU/e). This system consists of a multimodal sensor (measuring electromyography (EMG), electrocardiography (ECG), and accelerometry (ACM)) and a control tablet (with Android application software).

Setup and implementation
The complexity of this design project mainly lies in the designing, setting up, and performing of clinical trials with the newly developed sensor for the design of an adequate tonic seizure detection algorithm. Furthermore, prior to setting up and initiating the trials, the sensory system should first comply to specific requirements for safety and to be able to collect high-quality data. Subsequently, clinical trial protocols must be written (and adjusted) for approval from ethical committees to execute the clinical trials (phase 1: intramural, phase 2: extramural). For setting up and performing the clinical trials a close collaboration between the investigator, neurologists and other healthcare providers is necessary. Ultimately, after sufficient measurement data have been collected, a detection algorithm should be designed (considering all three measurement modalities of the EpiSense sensor) and validated.

Results
During this project, first the EpiSense system has been tested and re-designed. Next it has been used in the first clinical trials, both intramural (in Kempenhaeghe) and extramural (at the long-stay facilities of Kempenhaeghe). Unfortunately, the development of an adequate detection algorithm has been hindered by the relatively small amount of measured tonic seizures captured during these clinical trials. In the trials, only 11 seizures with a tonic component were collected in 11 patients over approximately 800 hours of measurements. For the moment, it can be concluded that solely based on EMG measurements, nocturnal tonic seizures can be detected with a sensitivity (SEN) of 72.7% and a positive predictive value (PPV) of 80%.

Discussion
Based on this first preliminary analysis and limited data it may be concluded that EMG measurements could be valuable in detecting nocturnal tonic seizures.
The loss of the ECG signal in most recordings as well as the loss of the EMG signal in some recordings during these clinical trials were caused by letting loose of the skin electrodes. Furthermore, the conclusions in this design project have been drawn on a very small number of measured tonic seizures.

**Recommendations**

Follow-up studies in which more patients can be measured during longer periods of time should validate this new detection algorithm and prove whether the sensor can effectively be used in the patients’ home environments.  
To be able to include heart rate data in future analysis, skin electrodes should be replaced by photo plethysmography (PPG) based heart rate measurement to avoid loss of the signal through electrodes letting loose (as was the case during this project). A suggestion for expansion of the detection algorithm to be able to include ACM measurements in the detection algorithm as well, is to get rid of the ever-changing offset in the ACM signal.
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I have read the TU/e Code of Scientific Conduct.

I hereby declare that my PDEng thesis has been carried out in accordance with the rules of the TU/e Code of Scientific Conduct.

Date

22 January 2010

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Joyce van Stuijs

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The Netherlands Code of Conduct for Academic Practice of the VSNU can be found here also.
More information about scientific integrity is published on the websites of TU/e and VSNU.

January 15 2016
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<td>ACM</td>
<td>accelerometry</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>EMU</td>
<td>Epilepsy Monitoring Unit</td>
</tr>
<tr>
<td>EPD</td>
<td>Electronic Patient Directory</td>
</tr>
<tr>
<td>FA</td>
<td>False Alarms</td>
</tr>
<tr>
<td>HF</td>
<td>high frequency</td>
</tr>
<tr>
<td>LF</td>
<td>low frequency</td>
</tr>
<tr>
<td>MF</td>
<td>Median frequency</td>
</tr>
<tr>
<td>MUP</td>
<td>motor unit potential</td>
</tr>
<tr>
<td>MVIC</td>
<td>maximal voluntary isometric contraction</td>
</tr>
<tr>
<td>PPG</td>
<td>photo plethysmography</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>PSD</td>
<td>Power spectral density</td>
</tr>
<tr>
<td>QME</td>
<td>Qualified Medical Engineer</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>SEN</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>SUDEP</td>
<td>Sudden Unexpected Death in Epilepsy</td>
</tr>
<tr>
<td>TU/e</td>
<td>Eindhoven University of Technology</td>
</tr>
<tr>
<td>WMO</td>
<td>Wet medisch wetenschappelijk onderzoek met mensen</td>
</tr>
<tr>
<td>ZCR</td>
<td>zero-crossing rate</td>
</tr>
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**Introduction**

1.1 Epilepsy

Epilepsy is a common neurological disease worldwide. Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. In the Netherlands, about 120,000 patients suffer from epilepsy. When seizures are recurrent and untreatable with medication, it is referred to as refractory epilepsy and has a prevalence of approximately 30% [1]. Often, refractory epilepsy is associated with tonic-clonic seizures. Of the group of 120,000 patients, 44% have epileptic seizures including a tonic component; tonic-clonic seizures and generalized tonic seizures [2], [3]. During the tonic seizure or preceding tonic phase in tonic-clonic seizure all muscles suddenly stiffen and contract, whereas in clonic seizures rhythmic twitching and jerking of the muscles is involved [4]. An ongoing project at Kempenhaeghe Center for Epileptology in the Netherlands, the EpiSense project, specifically focuses on the detection of nocturnal tonic seizures using a newly developed sensor: the EpiSense.

1.2 Kempenhaeghe

Kempenhaeghe Academic Center for Epileptology is one of two centres of expertise regarding epilepsy in the Netherlands. At Kempenhaeghe patients are diagnosed with and treated for epilepsy or suspected epilepsy. On yearly basis 1600 new epilepsy patients are referred to Kempenhaeghe and therefore, this centre is always on the lookout for new and/or improved diagnostics and treatment for its patients. Hence, parallel to the regular patient care, Kempenhaeghe is also engaged in scientific research. For further development of Kempenhaeghe’s academic engagement, an official partnership between Eindhoven University of Technology (TU/e) and Holst Centre/Imec was set up in 2010.

1.3 Consortium

During the EpiSense project there was a multidisciplinary collaboration with TU/e and Holst Centre/Imec. Within this project, Holst Centre/Imec has been mainly involved in the technical development and maintenance of the EpiSense system.

The EpiSense project was funded by Fonds NutsOhra.

2 Rationale

2.1 Introduction

In the long stay facilities of Kempenhaeghe (Kloostervelden), patients with refractory epilepsy who require special care are monitored day and night. Monitoring is important especially during nighttime since direct supervision by nurses is minimal. Mainly tonic and tonic-clonic seizures are of importance to detect because these seizures pose a high risk to cause harm to the patients. Each year, more than 1 out of 1,000 people with epilepsy die from Sudden Unexpected Death in Epilepsy (SUDEP) and this occurs mainly during night-time when supervision is at its minimum.

2.2 Tonic seizure detection

Epileptic nocturnal seizure detection to date, has mainly been focused on developing detection methods based on heartrate (electrocardiography (ECG)/photoplethysmography (PPG)), and accelerometry (ACM) measurement [1]. These detection methods are successful in detecting clonic seizures, where ictal activity is characterized by rhythmic muscle contraction and an increase in heartrate. However, current detection methods often fail to detect tonic epileptic seizures and the preceding tonic phase in tonic-clonic seizures. This, because tonic seizures are characterized by a severe continuous contraction of multiple muscle groups in the body, including the respiratory muscles [5]. Air being forced past the vocal cords sometimes results in a cry or groan and the person loses consciousness. Tonic seizures may lead to unconsciousness, post-ictal cardiorespiratory depression, and are associated with an increased risk of SUDEP [6]–[8]. During tonic seizures an increase in heartrate does not always occur and ACM based detection does not comply due to no (or little) movement.
2.3 **Rationale**

Tonic seizures are most hazardous during nighttime, when supervision is minimal. Due to the possible detrimental outcomes, patients’ caretakers and/or close relatives are anxious to go to sleep because of the fear of losing their loved ones without notice. To reduce the risk of SUDEP and to be able to provide immediate medical care when necessary, a tonic seizure detection method with a high sensitivity (SEN) and a high positive predictive value (PPV) that can be used in patients’ home environments is needed. The detection method needs to be able to generate a real-time alarm so that the environment can intervene when necessary as soon as possible.

2.4 **The EpiSense project**

The EpiSense project specifically focuses on the detection of nocturnal tonic seizures. The addition of electromyography (EMG) measurement to existing detection methods based on ECG and ACM measurement is expected to enable tonic seizure detection at night.

2.5 **Requirements with respect to the detection method**

The primary endpoint of this design project was to assess whether the addition of EMG measurement to ECG and ACM based seizure detection methods will have an adequate level of performance regarding the detection of tonic seizures at night.

The extent to which detection methods are capable of detecting seizures in epilepsy is indicated with two parameters: SEN and PPV. The more sensitive the detection method, the better it is capable of registering seizures.

A SEN of 100% means that all seizures that occurred were registered by the detection system. A specificity of 100% means that all registrations by the detection system are in fact only seizures (i.e., no false-positive registrations). Specificity can also be expressed in PPV. This is the chance that an alarm was truly caused by a seizure in epilepsy.

The ultimate endpoint for the new detection method, to be designed, is set to a SEN of 80% and a PPV of 80%.

2.6 **Background**

Existing portable seizure monitoring is based on extracerebral signals (i.e., EMG, ECG or PPG, movement, electrodermal activity, ACM, and so on). Systems for continuous seizure detection throughout the day and night are available and some systems only focus on nocturnal seizure detection. Although their popularity increases, in practice, their infrequent use is due to detection failures and frequent false alarms [1], [9].

An overview of current detection methods based on EMG and ACM for detecting tonic seizures and/or tonic-clonic seizures in epilepsy described in literature is given in Table 1.

Table 1: current tonic or tonic-clonic seizure detection methods based on ACM and EMG measurement described in literature (FA = False alarms).

<table>
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<th>Outcome Method</th>
<th>Test subjects</th>
<th>Remark</th>
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<tr>
<td><strong>Nijsen et al. (2008)</strong> [5]</td>
<td>SEN 80%; PPV 16% ACM with 1 sensor on wrist</td>
<td>15 patients for training and 21 for testing, 29 seizures for training and 35 for testing</td>
</tr>
<tr>
<td><strong>Kramer et al. (2011)</strong> [10]</td>
<td>SEN 91%; FA: 0.1/24h ACM with 1 sensor in bracelet on limb</td>
<td>31 patients (15 with seizures), 22 seizures</td>
</tr>
<tr>
<td><strong>Lockman et al. (2011)</strong> [11]</td>
<td>SEN 88% ACM with 1 sensor on wrist or ankle</td>
<td>40 patients (6 with seizures), 8 seizures</td>
</tr>
<tr>
<td><strong>Beniczky et al. (2013)</strong> [12]</td>
<td>SEN 87.7%; FA: 0.2/24h ACM with 1 sensor on wrist</td>
<td>73 patients (20 with seizures), 39 seizures</td>
</tr>
<tr>
<td><strong>Poh et al. (2012)</strong> [13]</td>
<td>SEN 94%; FA: 1.05/24h ACM with 1 sensor on wrist</td>
<td>80 patients (7 with seizures), 16 seizures</td>
</tr>
<tr>
<td><strong>Adriaans (2012)</strong> [14]</td>
<td>SEN 100%; PPV 94% Detection based on EMG + ACM</td>
<td>3 healthy volunteers, 14 simulations each</td>
</tr>
<tr>
<td><strong>Conradsen et al. (2012)</strong> [15]</td>
<td>SEN 80%; PPV 96%; FA: 1/24h Detection based on EMG</td>
<td>5 patients (2 with seizures), 7 seizures</td>
</tr>
</tbody>
</table>
In general, not all systems are suitable for online detection of tonic seizures. In addition, in most studies using ACM based detection (described in Table 1), the alarm of the detection method did only occur during the clonic phase [11]–[13]. One of the promising systems is ACM combined with EMG as described by Adriaans in 2012 [14] using wavelength of the EMG signal as key feature for the detection. However this method has not been verified on patient data (the seizures were simulated). The most promising method was EMG based detection as described by Conradsen et al. in 2012 [15] using zero-crossing rate of the EMG signal as key feature for tonic seizure detection. However, this detection method is based on seizures acquired from only two patients. To have a clinically usable detection method, it needs to be validated on a higher number of patients.

By adding EMG measurement to existing detection methods based on ACM and heartrate detection, this could be the key to success for real-time non-invasive tonic seizure detection. In the EpiSense project a sensory system has been developed with these three measurement modalities, therefore being a multimodal sensor.

2.7 Objectives

The main objective of this design project was to design a detection algorithm for the EpiSense sensor to be able to detect tonic seizures. Therefore, the following sub-goals have been defined:

- Testing and re-design of the EpiSense system;
- Design and set-up of the clinical trials;
- Collecting and analysing the measurement data;
- Designing and validation of a real-time detection algorithm.

Hence, during this design project, it has been investigated whether the multimodal approach is promising for nocturnal tonic seizure detection. After first data collection distinctive features of tonic seizures in all three modalities were isolated from the data and based on these distinctive features, a real-time detection algorithm has been developed. The final objective is that the algorithmic aspects developed in this project are designed in such a way that – in the future – they can be implemented in an ultra low-power miniaturized system.

Performance of the sensor in terms of SEN and PPV were evaluated to determine the extent to which the tonic seizure or the preceding tonic phase in tonic-clonic seizures can be detected during night-time using the EpiSense sensor.

3 Testing and set-up for re-design of the EpiSense system

3.1 Introduction

At the start of this design project, at Kempenhaeghe there were no data sets available containing tonic seizures for algorithm development and verification. Hence, setting up and performing measurements in patients was necessary for collecting EMG, ECG, and ACM data representative for tonic seizures.

The proposed combination of sensor modalities (EMG, ECG, and ACM) has only once been used before at Kempenhaeghe, in a study by Steven van der Vlugt in 2013 on patients with tonic epileptic seizures. However, insufficient and poor quality of data hindered drawing any conclusions regarding the performance of the measurement system. A similar approach will be used in this project, but a redesigned enhanced measurement system will be used and a detection algorithm will be developed.

3.2 The EpiSense system

The EpiSense system exists of a sensory system and a control tablet. In the new design, only a single sensor is used to measure all three modalities (instead of separate sensors as was the case in Van der Vlugt’s trial). Therefore, all data are automatically synchronized, and herewith a major technical drawback of the sensor used in the previous study (of Van der Vlugt) has been overcome. Furthermore, the measurement data are directly stored on an SD card in the new sensor whereas Van der Vlugt’s sensor used radio transmission prior to storage which resulted in loss of data.

In addition, the possibility of a real-time data measurement check via the tablet’s application software (Nyx) available for Android provides assurance that measurements are performed accurately e.g., under the condition of correct lead connection to - and placement of electrodes.
3.3 **Functional requirements**

From earlier research by Steven van der Vlugt in 2013 it became clear that:

- all three modalities should be synchronized automatically;
- data transfer via radio transmission should be avoided;
- the gain and bandwidth of the EMG signal should be sufficiently large to avoid clipping of the EMG signal during tonic seizures;
- disturbance of the ECG signal by EMG should be avoided;
- the battery life should be sufficiently large (preferably for measurements over a week);
- noise caused by wire movement should be avoided.

In addition, because the EpiSense system would be used in patient trials, safety was of high priority aspect. A risk analysis has been performed to gain insight regarding safe use of the EpiSense system. For further explanation regarding the risk analysis, please refer to section 3.5 ‘Risk Analysis’.

3.4 **Technical requirements**

At the start of this design project, there was a prototype of the EpiSense system that has first been tested. The results and points of improvement were reported back to the manufacturer (Holst centre/Imec). For detailed feedback - as reported to Holst centre/imec - regarding the technical specifications and the desired adjustments, please refer to Appendix 1: EpiSense tests.

3.5 **Risk analysis**

In order to comply to the ‘Convenant Veilige toepassing van medische technologie in het ziekenhuis’ [16] introduced in hospitals throughout the Netherlands in 2011, it was of importance to extensively test the EpiSense system prior to its use in clinical trials. In addition to testing, possible hazards were collected and risks were scored according to severity. The most important aspects to take into account are:

- Users of the EpiSense system should be instructed carefully to never charge the device while it is in use, because there exists a risk on severe burn, injuries and an electrical shock.
- Users of the EpiSense system should be instructed to keep Bluetooth devices out of the near vicinity of the EpiSense sensor and the control tablet whilst connected to prevent malfunction and corrupt data of the EpiSense measurements.
- Users of the EpiSense system should make sure the leads of the sensor are in place and taped to the body to prevent possible restriction by the leads (or at worst, suffocation).

For a complete overview of the risk analysis, please refer to Appendix 8: risk analysis.

4 **Design and set-up of the clinical trials**

4.1 **Introduction**

Originally, the clinical study in this design project was divided into two subsequent phases:

1. Phase 1: the intramural phase (measurements at the Epilepsy Monitoring Unit (EMU) at Kempenhaeghe)
   - to collect the first measurement data;
   - to see whether the study would be feasible;
   - to develop a first detection algorithm based on the collected tonic seizures.

2. Phase 2: the extramural phase (measurements at the patients’ home environment at Kloostervelden, which are the long stay facilities of Kempenhaeghe)
   - to validate and further improve the designed detection algorithm

4.2 **Phase 1: intramural clinical study**

The design of phase 1 was set-up in such a way that the trial would be a non-WMO study. Therefore, only a local approval of the ethics committee of Kempenhaeghe was required to start the intramural measurement study.
Because during this part of the study it would be the first time the EpiSense system would officially be used in patients, safety and effectiveness were of high importance. To reduce the level of discomfort for the patients and for practical reasons the first measurement data should be collected from patients already subjected to pre-surgical or clinical test procedures. These patients were admitted to the EMU for up to a week and would undergo electroencephalography (EEG) testing and video monitoring. The addition of measurements using the EpiSense sensor were considered to be of no extra burden to the patient - in comparison to the EEG/video tests they would already be coming in for.

Expert review of the nocturnal video and EEG recordings would serve as the gold standard for comparison of the collected data. At least two experienced observers (nurses, technicians, and/or physicians) would review all recorded video/EEG material at times of listed events. To avoid false negatives, 10% of the video recordings would again be screened for (possibly missed) seizures.

The first phase was an exploratory study to investigate whether measurements with the EpiSense system could be performed, how patients would react to these measurements, how the data would look like, and if there would be any tonic seizures present in the data.

It was expected that there would be a high variability of seizures in patients; in the amount of seizures as well as in seizure characteristics. Therefore, for the design of a proper detection algorithm, measurement data were desired from multiple patients each having multiple tonic seizures.

Originally, it was decided that phase 1 should include 20 patients selected via inclusion criteria from the pre-surgical and clinical admissions list. These admission lists would be screened on a history of tonic- or tonic-clonic seizures about 2 weeks prior to the patients’ scheduled admission. Subsequently, information and informed consent letters were sent out so that the patients could decide whether to participate in the trial beforehand.

A more elaborate description of the setup of phase 1 can be found in the full study protocol, see Appendix 18: clinical trial protocol phase 1.

### 4.3 Phase 2: extramural clinical study

After phase 1, the clinical trials would be continued in patients’ home environments at the long stay facilities of Kempenhaeghe, Kloostervelden. During this phase, as originally defined, the designed detection algorithm would be validated. Since the EpiSense system would be introduced here with additional video monitoring (not present in every patient’s bedroom at Kloostervelden), and the patients are mentally impaired, before starting with this part of the project, first an approval of the ethical committee was required.

In order to obtain sufficient measurement data with tonic seizures for validation and further development of both the EpiSense system and the designed detection algorithm, in this phase 30 patients would be monitored for maximal three months. In case of high seizure frequencies, the three-month period could be shortened.

Expert review of the nocturnal video recordings would serve as a gold standard in this phase as well.

Through an EPD search, possible candidates for this phase of the trial would be selected according to the inclusion criteria. Then, the general practitioner would be inquired whether he or she regards the specific patient suitable for partaking in the trial. Thereafter, the regularly attending nurse would be asked for her opinion regarding the suitability of the patient to participate in the trial. Next, the patients’ legal representatives would receive a phone call to get to know their possible interest in the trial and to find out whether they would like to receive additional information via mail (information and informed consent letters). If so, then information informed consent letters were sent to the patients’ legal representatives.

The patients’ legal representatives are capable to make a well-informed decision and their consent would be required for participation of the patients in this study.

### 4.4 Schematic representation of the design

A concise schematic representation of the initial design of the clinical trials is shown in Figure 1.
5 Final set-up and realization of the clinical trials

5.1 Phase 1

As mentioned before in section 4.2 the first phase of the clinical trials was an exploratory study to see whether measurements could be performed, how patients would react to the measurements, how the data would look like, and whether there would be any tonic seizures present in the data. Furthermore, it was also meant to develop a first detection algorithm based on the collected tonic seizures.

5.1.1 Exploratory study

Overall, patients reacted very positively. In comparison to the measurements they were already subjected to, the additional burden of wearing the EpiSense sensor at night was negligible. However, because of a recent renovation of the EMU resulting in more beds, the usual waiting list for admissions to the EMU was no longer there. On top of that, the number of patients that were admitted with a history of tonic seizures was disappointingly low. This resulted in a total number of 1 tonic seizure in 11 patients over the course of 7 months.

5.1.2 Design of a first detection algorithm

During the design of this phase 1, it was expected that there would be a high variability of tonic seizures in multiple patients; in amount as well as in seizure characteristics. For a proper detection algorithm design, data was desired from multiple patients each having multiple seizures. However, with the actual low number of collected tonic seizures and the relatively low number of patients that came in over the course of 7 months, it was not possible to develop a first detection algorithm. Hence, the original setup of the clinical trials, in which it was planned to subsequently perform phases 1 and 2, was doubted.

5.2 Final set-up of the clinical trials

Because of the lack of tonic seizures measured in phase 1 (intramural), it was decided to bring phase 2 (extramural) forward. However, the approval request for this extramural clinical study was intended to be based on the first results of phase 1. Therefore, the ethical committee was hard to convince for the clinical trials in phase 2, which had to be conducted in a protected patient population of Kempenhaeghe.

5.3 Phase 2

The entire set-up of phase 2 of the trial took longer than expected due to extended delivery times and delayed ethical approval.

Due to time constraints it was then decided to include 10 patients in the remaining time frame of this design project and to monitor them for two weeks during nighttime at Kloostervelden. This longer amount of measurement time (in comparison to measurements in phase 1 at the EMU for only a maximum of one week) brought about some extra issues with the skin electrodes:

- Not all patients were content with wearing the skin electrodes that long
In some cases, the electrodes would not stay in place because of much perspiration. In addition, even though the cameras were placed as unobtrusive as possible, some patients did mind the presence of a camera in their bedroom.

Measurements were conducted for ten nights per patient and ideally an introduction was given once at the start of the measurements and data were collected twice. However, the regularly attending nurses encountered many difficulties when operating the EpiSense system. Therefore, measurements took approximately a week longer than intended and visitations to the nursing homes for additional instruction were in abundance. Moreover, since the timing of relocation of the camera from one patient’s bedroom to another all depended on the schedule of one very busy employee, patient measurements did not immediately follow up one another.

5.4 Schematic representation of the design

A concise and schematic representation of the final design of the clinical trials is shown in Figure 2.

![Figure 2: schematic representation of the final design of the clinical trials, phase 1 and 2.](image)

5.5 Final realization of the clinical trials

Finally, phase 2 resulted in ten recorded nocturnal tonic seizures in two patients. This could have been more, but unfortunately - due to a crash of the main computer at Kempenhaeghe - one seizure has been lost and another was lost due to detachment of the electrodes. Hence, ten nocturnal tonic seizures in two patients remained for further analysis amongst the one recorded earlier in phase 1 at the EMU.

A more elaborate description of the setup of phase 2 can be found in the full study protocol, see Appendix 19: clinical trial protocol phase 2.

6 Technical characteristics

6.1 The sensory system

The EpiSense sensor is a miniaturized ultra low-power wearable device that – as stated earlier in this report - could be a promising detection tool specifically for this type of seizure. This system only uses a single sensor to measure three modalities: EMG, ECG, and ACM.

In collaboration with Holst centre/Imec, the sensor system for synchronous measurement of EMG, ECG, and ACM has been designed. The sensor consists of a single upper armband and is synchronized with the local network time which provides a time stamp for the measurements. The local network time synchronization enables simultaneous video monitoring (gold standard) for comparison of the data and validation of epileptic
seizures. The data can be logged for at least 5 nights and can be stored on a micro SD card in the sensor. The recorded data can be retrieved from the SD card after a full week of measurements.

Considering the possible hazard of trauma to the patient when measuring and charging simultaneously (see section 3.5 ‘Risk Analysis’), the sensor has a built-in safety-procedure. When charging, the EpiSense sensor’s measurements are automatically paused.

6.1.1 Five electrodes

During trial measurements, the upper arm sensor band measures synchronous EMG, ECG, and ACM using a total of five electrodes (silver/silver chloride 9-mm surface electrodes). Two electrodes are used for EMG measurement, two electrodes are used for ECG measurement, and the remaining electrode is used as a ground electrode. The accelerometer is built in in the sensor body.

6.1.2 EMG

The bipolar EMG signal is derived from the left deltoid muscle where EMG signal measurement is most pronounced [14]. The two skin electrodes are placed approximately 2 cm apart from each other on the coronal plane on the medial deltoid muscle belly (as shown in Figure 1).

6.1.3 ECG

ECG measurement has been considered to be able to detect an increase in heart rate that may occur during nocturnal tonic seizures. An increase in heart rate of at least 10 beats/minute has been observed in 73% of all seizures, mostly around seizure onset [17], [18].

- one ECG lead runs from the sensor located on the upper arm across the chest slightly right from the sternum to measure heart rate whilst minimizing artefacts through muscle activity;
- The other ECG lead runs from the sensor to the lower ribs on the left chest.

By positioning the ECG leads as described above, the heart rate is measured in lead-II position. The final electrode (ground; i.e., reference electrode) is placed on the lateral side of the elbow joint. Figure 3 shows the EpiSense sensor with the five measurement leads and their placement as described above.

6.1.4 ACM

As mentioned, the ACM sensor is embedded in the sensor body. ACM measurement could be a valuable addition for the detection of nocturnal tonic seizures. In addition, ACM measurement could be used to identify the patient’s body posture to minimize false-positive alarms. I.e., when the patient for example needs to use the bathroom during night-time, ACM measurement could ensure movement artefacts registered by the sensor will not evoke an alarm.
6.1.5 Installing the EpiSense system

To check whether the leads are properly connected to the correctly placed electrodes, visual assessment of the real-time signal can be done through an Android software application available on the control tablet, Nyx. The sensor connects with the control tablet via Bluetooth connection via a double tap on the sensor body. The sensor is applied around the patient’s upper arm each night before bed and the recording is initiated via a series of double taps.

After a week of recording has completed, the data need to be retrieved from the sensor’s SD card. The measurement data are stored on the SD card in an encoded form.

For an elaborate manual on how to configure the sensor for the first time, how to use the sensor for measurements, how to convert the data to.h5 extended files in Nyx, and how to convert .h5 extended files to .mat extended files in Matlab please refer to the following appendices: Appendix 2: EpiSense tablet 1st connection, Appendix 3: manual Nyx, Appendix 4: EpiSense protocol (new sensor).

The specifications regarding the sensor’s measurement capabilities is summarized in Table 2.

Table 2: the EpiSense’s EMG, ECG and ACM measurement specifications

<table>
<thead>
<tr>
<th>Technical specifications</th>
<th>EMG</th>
<th>ECG</th>
<th>ACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling frequency</td>
<td>4096 Hz</td>
<td>4086 Hz</td>
<td>32 Hz</td>
</tr>
<tr>
<td>Built in filtering</td>
<td>High-pass with cut-off 20 Hz</td>
<td>High-pass with cut-off 5 Hz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-pass with cut-off 1024 Hz</td>
<td>Low-pass with cut-off 1024 Hz</td>
<td></td>
</tr>
<tr>
<td>Dynamic range bits</td>
<td>-7.5 mV to +7.5 mV</td>
<td>-3.75 mV to +3.75 mV</td>
<td>-/+8 g</td>
</tr>
<tr>
<td></td>
<td>12 bits</td>
<td>12 bits</td>
<td>8 bits</td>
</tr>
</tbody>
</table>

6.1.6 Redesign

Unfortunately, after only two weeks of intramural measurement at the EMU (phase 1), the upper arm sensor’s housing showed signs of wear and tear. Repairing the sensor was logistically (and regarding the materials in...
stock) not feasible. Hence, it was agreed to redesign the sensors’ housings. For the steps that have been completed in the redesign process, please refer to Appendix 17: redesign of the sensor.

6.2 The video recording system

For the recording of epilepsy events in phase 2 when monitoring in patients’ home environment, two cameras were purchased for this project. For some of the mentally impaired patients, a change in their environment for instance the over-abundant presence of a camera can really bother them, which had to be considered in placing the camera’s. Small dome camera’s (Bosch FLEXIDOME IP indoor 5000, Bosch Security Systems B.V., Eindhoven, The Netherlands) were purchased and screwed on a wooden plank. This wooden plank could be replaced by the ceiling plates at the patients’ bedrooms. In addition, infrastructure to connect the cameras to the secured network of Kempenhaeghe could be accessed via the space above the ceiling. Configuration and control of the cameras had to be done via a single main computer running iSpy software (iSpy open source video surveillance software, 2017) at the department of Clinical Physics at the main building of Kempenhaeghe. For an elaborate manual on how to configure and use the iSpy software, please refer to Appendix 6: manual iSpy.

7 Data analysis

7.1 Introduction

The primary goal of the data analysis was to find specific aspects in the acquired measurement data based on which a distinction between regular movement and a tonic seizure can be made. The multimodal approach of EpiSense provides three modalities from which a combination of distinctive features could provide the base for a tonic seizure detection algorithm. To find specific signal features for the identification of tonic seizures, different signal processing steps were performed. Please refer to Appendix 16: overview data analysis for an overview of all processing steps.

7.2 Hypothesis

Especially the EMG measurement data have been extensively analysed, due to the expectations that they show distinctive features during tonic seizures in comparison with regular movement [6], [7], [15], [19]. It is hypothesized that during tonic seizures, high EMG activity is observed accompanied by low ACM activity [5]. This, in contrast to the signals seen during regular movement, namely high EMG activity accompanied by high(er) ACM activity.

7.3 Activity of tonic seizures vs. regular movement

The above posed hypothesis with respect to the relative difference of ‘activity’ in EMG and ACM could probably be verified by means of AUC calculations of the measured signals. Pre-processing of the EMG signal consisted of an 8th order notch filter with stop band 49.8 Hz to 50.2 Hz to attenuate 50 Hz interference.

To quantify the amount of activity in the signals, it was chosen to calculate the area under the curve (AUC) for the tonic part of all seizures. Calculation of the AUC was done according to equation 1.

$$AUC_{EMG} = \left( \sum_{n=a}^{b} |EMG(n)| \right) / fs * t$$  \hspace{1cm} (equation 1)

To calculate the AUC of the ACM signal during the tonic seizure, a similar approach was chosen. The AUC was also calculated for the tonic part of the ACM signal of all seizures. Calculation of the AUC of the ACM signal was done according to equation 2.

$$AUC_{ECG} = \left( \sum_{n=a}^{b} |\Delta ACM(n)| \right) / fs * t$$  \hspace{1cm} (equation 2)

These calculations were performed for all periods of regular movement as well. Descriptive statistics can be found in section 8 ‘Results’.
To quantify the difference between tonic seizures and regular movement, a first step was to calculate the ratio between AUC of tonic EMG and the AUC of tonic ACM. This ratio was calculated according to equation 3.

$$ \text{Ratio}_{\text{tonic}} = \frac{\text{AUC}_{\text{EMG}}}{\text{AUC}_{\text{ACM}}} $$ \hspace{1cm} (equation 3)

The next step was to calculate this ratio between AUC of regular EMG and regular ACM as well. This was done according to equation 4.

$$ \text{Ratio}_{\text{reg}} = \frac{\text{AUC}_{\text{reg}}}{\text{AUC}_{\text{reg}}} $$ \hspace{1cm} (equation 4)

Comparing these two ratios gives insight in whether tonic seizures contain high-activity EMG accompanied by low-activity ACM in relation to regular movement. A table containing ratio values and additional boxplots can be found in section 8 ‘Results’.

7.4 Frequency analysis

A study by Conradsen et al. (2011) showed the median frequency (MF) in tonic seizure EMG to be significantly higher relative to simulated seizure EMG. The MF during tonic seizures is stated to shift towards higher frequencies since frequency bands above 100 Hz contain the highest amount of power [6]. Similar calculations have been performed for the obtained dataset of the EpiSense project as well.

The frequency content of the notch filtered EMG was calculated using Pwelch’s estimate for the periodogram. Herewith, the power spectral density (PSD) estimate of all tonic seizure EMG and regular movement EMG was obtained. In addition the 10th, 50th (MF), and 90th percentiles were calculated to provide insight regarding the power distribution.

8 Results

Data was acquired in 11 patients over the course of approximately 100 nights of measurements, i.e., ~800 hours of measurement. In ~800 hours of measurement, ten seizures containing a tonic component were collected versus five periods of regular movement.

The data of synchronously measured EMG, ECG and ACM signal during a tonic-clonic seizure using the EpiSense sensor is shown in Figure 4.
In the figure above, the phenomenon of relatively high EMG activity accompanied by relatively low ACM activity during the tonic seizure or (in this specific case) the tonic phase of a tonic-clonic seizure is illustrated. Please note, the obtained ECG signal is obscured to such an extent that heart rate peaks cannot be distinguished from the interfering EMG signal. Yet, this ECG signal is one of the few ECG measurements that has not been lost at the time of a tonic seizure. Hence, only EMG and ACM could be taken into account in further analysis in this project.

8.1 Activity of tonic seizures vs. regular movement

A summary of the calculated AUC variables of tonic seizure EMG and ACM as well as regular movement EMG and ACM is given in Table 3. Already from this table, the higher activity of the EMG at the time of tonic seizures can be noted.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EMG seizures</th>
<th>EMG regular movement</th>
<th>ACM seizures</th>
<th>ACM regular movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th percentile AUC</td>
<td>0.11 mV·s</td>
<td>0.03 mV·s</td>
<td>0.03 mV·s</td>
<td>0.02 mV·s</td>
</tr>
<tr>
<td>median AUC</td>
<td>0.17 mV·s</td>
<td>0.05 mV·s</td>
<td>0.03 mV·s</td>
<td>0.02 mV·s</td>
</tr>
<tr>
<td>75th percentile AUC</td>
<td>0.19 mV·s</td>
<td>0.05 mV·s</td>
<td>0.03 mV·s</td>
<td>0.04 mV·s</td>
</tr>
</tbody>
</table>

The AUC values per tonic seizure for the EMG signal as well as the ACM signal were calculated. The calculations were also done for the signals during regular movement. The differences between AUC of tonic seizure EMG, regular movement EMG, tonic seizure ACM, and regular movement ACM are presented in the boxplots in Figure 5. This figure illustrates the relatively high EMG activity versus the relatively low ACM activity during tonic seizures. Please note, the ACM during tonic seizures does not differentiate much from the ACM during regular movement.

![Figure 5: overview of the differences in AUC of the measured EMG and ACM during tonic seizures and of the measured EMG and ACM during periods of regular movement.](image)

With respect to the hypothesis as stated in section 7.2 ‘Hypothesis’: a comparison between the ratio EMG activity/ACM activity of tonic seizures and regular movement is illustrated in boxplots in Figure 6. From this
It can be seen that during nearly every tonic seizure, the ratio between EMG activity and ACM activity is larger than the ratio calculated at time of regular movement. Results show that the level of intensity of the ACM during seizures is approximately equal to the level of intensity of the ACM signal during regular movement. The largest difference between tonic seizures and regular movement can be seen in the EMG. The hypothesized additional value of the ACM is therefore questioned. Hence, a detection algorithm can maybe be based solely on EMG measurement, instead of on a combination of ACM and EMG measurements as stated earlier. This will be further investigated later on in this report.

### 8.2 Frequency analysis

Percentiles derived from the calculated PSDs per tonic seizure and per fragment of regular movement are shown in Table 4. This table provides insight regarding the frequency distribution of the EMG signal during tonic seizures and during periods of regular movement, respectively.

<table>
<thead>
<tr>
<th>Seizure #</th>
<th>p10 (Hz)</th>
<th>MF (p50) (Hz)</th>
<th>p90 (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19,75</td>
<td>49,5</td>
<td>112,875</td>
</tr>
<tr>
<td>2</td>
<td>21,5</td>
<td>48</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>64,25</td>
<td>86,25</td>
</tr>
<tr>
<td>4</td>
<td>23,25</td>
<td>55</td>
<td>85,25</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>54,625</td>
<td>76,875</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>51,5</td>
<td>101,75</td>
</tr>
<tr>
<td>7</td>
<td>19,5</td>
<td>40,5</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>25,5</td>
<td>48</td>
<td>73,5</td>
</tr>
<tr>
<td>9</td>
<td>32,625</td>
<td>64</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>21,25</td>
<td>42,75</td>
<td>70,75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regular movement #</th>
<th>p10 (Hz)</th>
<th>MF (p50) (Hz)</th>
<th>p90 (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8,875</td>
<td>45</td>
<td>88,625</td>
</tr>
<tr>
<td>2</td>
<td>20,25</td>
<td>44,5</td>
<td>76,25</td>
</tr>
<tr>
<td>3</td>
<td>24,875</td>
<td>43,5</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>45</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>20,5</td>
<td>39</td>
<td>67,5</td>
</tr>
</tbody>
</table>

An overview of the difference between tonic seizure MF and regular movement MF can be seen in the boxplots of Figure 7. From this figure it can be seen there are some differences in MF between tonic seizure EMG and regular movement EMG, however these differences are not very pronounced.
8.3 Detection characteristics

Based on the calculation of the differences in ratio between EMG activity and ACM activity of tonic seizures versus regular movement (see Figure 6), a cut-off ratio value (with minimal overlap) of 2 could be set to distinguish between tonic seizures and regular EMG. This has resulted in the outcome that is shown in Table 5:

Table 5: outcome of ratio seizure detection with a detection cut-off ratio value of 2. Red represents an alarm, green represents no alarm.

<table>
<thead>
<tr>
<th>Tonic ratio EMG/ACM</th>
<th>Regular ratio EMG/ACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.405</td>
<td>2.0303</td>
</tr>
<tr>
<td>1.6756</td>
<td>1.7495</td>
</tr>
<tr>
<td>3.9827</td>
<td>0.5545</td>
</tr>
<tr>
<td>5.6613</td>
<td>1.4058</td>
</tr>
<tr>
<td>5.9767</td>
<td>2.4545</td>
</tr>
<tr>
<td>1.6956</td>
<td></td>
</tr>
<tr>
<td>0.8956</td>
<td></td>
</tr>
<tr>
<td>4.006</td>
<td></td>
</tr>
<tr>
<td>2.2763</td>
<td></td>
</tr>
<tr>
<td>1.9131</td>
<td></td>
</tr>
</tbody>
</table>

However, based on the results seen in Figure 5, an even clearer distinction between tonic seizures and regular movement could be made based on EMG activity alone, instead of the EMG/ACM activity ratio. From Figure 5 it can be seen, that a cut-off value (with minimal overlap) between tonic seizure EMG and regular EMG can be set at 0.1 mV-s. This has resulted in the outcome that is shown in Table 6:

Table 6: outcome of tonic seizure detection based on EMG measurement with a detection cut-off value of 0.1 mV-s. Red represents an alarm, green represents no alarm.

<table>
<thead>
<tr>
<th>Tonic seizure EMG</th>
<th>Regular EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1787</td>
<td>0.0167</td>
</tr>
<tr>
<td>0.0439</td>
<td>0.0483</td>
</tr>
<tr>
<td>0.1378</td>
<td>0.011</td>
</tr>
<tr>
<td>0.1755</td>
<td>0.0377</td>
</tr>
<tr>
<td>0.2035</td>
<td>0.022</td>
</tr>
<tr>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>0.0283</td>
<td></td>
</tr>
<tr>
<td>0.1831</td>
<td></td>
</tr>
<tr>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td>0.5546</td>
<td></td>
</tr>
</tbody>
</table>
Regarding the AUC values of the ACM signal alone, no cut-off value could be set, and therefore no detection method can be developed based on this signal on its own.

8.4 Designed detection algorithm

Based on the detection characteristics described in section 8.3 ‘Detection characteristics’, a tonic seizure detection algorithm has been developed solely based on the measured EMG signal.

As was stated above, an AUC threshold in the EMG signal could be set to 0.1 mV·s to distinguish tonic seizures from regular movement. However, this value is based on calculation of the AUC over the course of the entire tonic seizure. Whereas, when a seizure needs to be detected real-time, the AUC over the course of the entire tonic seizure is not available. Therefore, a sliding window has been designed performing the AUC calculation over each window of 4 seconds with 50% overlap.

With respect to the obtained results, the threshold has been adjusted to capture the highest amount of seizures whilst minimizing false positives. A representative result is shown in Figure 8. In Figure 8 it can be seen that at the onset of the tonic seizure, the AUC exceeds the predefined detection threshold and the detection algorithm generates an alarm. Later on, another alarm occurs due to short periods of tonic contractions and interruptions (the clonic phase) resulting in clonic jerking of the extremities. In this specific seizure, the clonic EMG activity was also of sufficient height for exceeding the threshold.

For a complete overview of the calculated results, please refer to Appendix 20: results detection algorithm seizures and Appendix 21: results detection algorithm regular movement.

Subsequently, the designed algorithm was tested over a full night of EMG measurement. The result is shown in Figure 9.

![Diagram](image)

*Figure 8: a representative graph showing the tonic-clonic absolute EMG signal (top), the calculated AUC using the 4 second moving window function (middle), and the generated alarm based on the AUC exceeding the threshold value of 0.9 mV·s (bottom).*
8.5 Results obtained with the designed detection algorithm

In Figure 9, a full night of EMG recording is shown in which - according to the detection algorithm - six tonic seizures have occurred:

1. The first can be disregarded as an application artefact.
2. The second alarm is a clear result of the patient supporting himself using his left arm for a prolonged period of time, thus a true false positive.
3. For reviewing the third alarm, an expert was consulted to give his expert opinion on the video recording. Please note that in this case the expert opinion is biased, since without an alarm the expert would not have been asked for his opinion on this specific period of video recording; i.e., a suspicion of a seizure exists already. In addition, due to obscuring bed sheets, this period of movement is hard to assess in video recordings. According to the expert neurologist, alarm #3 could very well be a tonic seizure.
4. The fourth alarm was a true positive alarm as well as the sixth alarm.
5. However, for reviewing the fifth alarm the expert neurologist was consulted again to provide expert opinion regarding the video recording. The fifth alarm was reviewed as a period of restless movement, possibly containing periods of tonic contraction. As an illustration to this period of movement, Figure 10 was made.

Figure 9: result obtained from running the detection algorithm over a full night of EMG recording. The alarms have been numbered (see the red numbers below the bottom graph).
The different phases of movement in Figure 10 are indicated with numbered arrows below the bottom graph. The subsequent phases can be identified, according to video recording, as:

1. restless movement;
2 and 3. periods of possible tonic extension fully covered underneath bed sheets;
4. restless movement fully covered underneath bed sheets;
5. motionless period;
6. restless movement full covered underneath bed sheets;
7. possible tonic extension fully covered underneath bed sheets;
8. sleep returns.

Because there are periods of tonic contraction present in the data given in Figure 10, one could contemplate whether the alarm generated by these periods can be classified as a true false positive. This will be further discussed in section 10 ‘Discussion’. For subsequent calculations, alarm #1 will be disregarded, alarm #3 will be considered a true positive, and alarm #2 and #5 will be considered to be false positives.

8.1 Sensitivity and Positive Predictive Value

Adding alarm #3 to the other detected tonic seizures using the developed detection algorithm gives a total of 8 true positives out of 11 occurred seizures. Running the detection algorithm over a full night of EMG recording gives a total number of 2 false positives. From these results, the SEN and PPV can be calculated using equations 5 and 6, respectively.

\[
SEN = \frac{\text{True positive}}{\text{True positive} + \text{False negative}}
\]  
(equation 5)
The outcome of the designed detection algorithm with respect to this limited number of measurements is a SEN of 72.7% and a PPV of 80%.

9 Conclusion

9.1 EMG/ACM activity ratio between seizures and regular movement

From the results shown in Table 5 it can be concluded that in 60% of the tonic seizures in this (limited) dataset, the ratio between EMG activity and ACM activity is higher relative to periods of regular movement. Even better is the result when differentiating between regular movement and tonic seizures based on EMG signal activity alone. From the results shown in Table 6 it can be concluded that in 70% of the tonic seizures in this dataset, the EMG activity is higher relative to the EMG activity during periods of regular movement. This aspect is possibly an interesting feature for tonic seizure detection.

9.2 Frequency analysis

From the frequency analysis it can be seen that the MF during tonic seizures is slightly higher than the MF of EMG during regular movement. However, much overlap exists as well. In addition, MF calculation for an ultra-low power wearable device requires fast Fourier transformation which is a data processing step that needs a too high computational power. A poor-man’s manner of frequency analysis is to determine the zero-crossing rate (also done by Conradsen et al. in 2012). However, calculations of the ZCR do not allow for distinguishing tonic seizure EMG from regular movement EMG in the EpiSense data set as can be seen in Appendix 9: data analysis EMG tonic clonic seizures, Appendix 10: data analysis EMG tonic part seizures, and Appendix 11: data analysis regular movement.

9.3 Detection algorithm

Regarding the detection algorithm that is designed based on this limited number of measured tonic seizures (due to the time constraints of this design project of effectively one year) for the time being it can be concluded that tonic seizures are detected with a SEN of 72.7% and a PPV of 80%. This means that a total of 72.7% of all tonic seizures are detected and if an alarm occurs, there is an 80% chance the alarm was actually caused by a tonic seizure.

In section 2.5 ‘Requirements for the detection method’, the ultimate endpoint for the new detection method is set to a SEN of 80% and a PPV of 80%.

9.4 Feasibility

Regarding the feasibility it can be concluded that the study is feasible to conduct in the target population. Using unobtrusive camera’s (small dome cameras hanging from the ceiling) and a size-adjustable strap to attach the EpiSense sensor around the upper arm ensure patients are not hampered in their sleeping habits during measurements. The sensor’s measurement leads can be hidden under nightwear and this way, possible entanglement in the wires is prevented.

Unfortunately, the skin electrodes (for sensitive skin) have shown let loose easily. In addition, even when using skin electrodes developed for sensitive skin, using the electrodes for up to two weeks causes skin irritation in some patients over the course of the measurement period.

Letting loose of the ECG skin electrodes caused the loss of ECG signal during most seizures (see Appendix 12: data analysis EMG, ECG, and ACM seizures). Therefore it was chosen not to include the heartrate in the data-analyses of this project. In less frequent cases, EMG electrodes have shown to let loose as well, causing the loss of two seizures of another patient. This will be further discussed in sections 10 ‘Discussion’ and 11 ‘Recommendations for future research’.
10 Discussion

10.1 Design project
During phase 2 it became apparent that using skin electrodes for measurement of ECG and EMG signal is a suboptimal method. Seizure detection based on heartrate variability appeared to be impossible because in most recordings, the ECG electrodes were detached causing full signal loss. Also, two EMG recordings of a third patient containing at least one tonic seizure each, were lost due to letting loose of the skin electrodes. EMG measurement using dry electrodes and heartrate measurement using PPG would eliminate the need for skin electrodes. However, state of the art development of dry electrodes for long term EMG monitoring does not comply with the functional requirements set for measurements with the EpiSense system. Another idea for optimal EMG measurement would be to implant the measurement electrodes just underneath the skin. However, implantation of electrodes is not an option as this involves the risk of inflammation and, moreover, would make this study invasive.

Furthermore, the results obtained during this design project are based on only 11 tonic seizures collected from two patients. Hereof, ten tonic seizures were recorded in one patient and a single one was obtained from the second patient. The detection algorithm is thus mostly based on the seizures of a single patient. As mentioned before, seizures are high in variability between patients, therefore it is unclear whether the designed detection algorithm would perform as well in other patients using equal settings.

10.2 Data analysis
At the start of the data analysis, full attention has been given to the frequency content of the EMG signals, because of the findings from Conradsen et al (2011) suggest that here, key features of tonic seizures different from regular movement. “During tonic seizures there was a significant shift toward higher frequencies, expressed by an increase in the MF and the relative spectral power (100-500 Hz)”, as stated by Conradsen et al. As was seen in the results of the EpiSense data, MF of tonic seizures was perhaps slightly increased in comparison to MF of periods of regular EMG. However, there was a lot of overlap, and in the EpiSense data set tonic seizures did not contain a large proportion of data in the frequency band above 100 Hz in contrast to normal activity EMG [15]. Based on these contradicting results between findings regarding the frequency content of tonic seizures in literature [6], [15], [19] and findings in frequency content in datasets acquired in the EpiSense project, existing detection methods based on EMG measurements could not be reproduced.

The positive results of the High frequency (HF)/Low frequency (LF) calculation for determining the onset of a tonic seizure as described by Conradsen et al. in 2013 was another possible detection method, not fully focused on the so-stated increased MF in tonic seizures. Here, it is stated that the onset of the tonic seizure can be identified through HF/LF calculation in which the HF band contains frequencies from 64-256 Hz and the LF band contains frequencies from 2-8 Hz. It is stated that the tonic phase consists mainly of the HF band and that the LF band ‘plays an important role’ in the clonic phase [7]. In these studies, the HF/LF ratio indeed has a relatively high outcome during the tonic phase which is the key feature for detection. But whether the LF band that Conradsen et al. include in this calculation can be associated with frequencies present in the EMG can be questioned. It is possible that the existing LF components during the tonic phase, resulting in a high HF/LF ratio, are caused by slow movement artefacts (<10 Hz) [20]. In addition, Conradsen et al. state in earlier research, in which the exact same dataset was used, that obscuring of the signal below 10 Hz was caused by movements of the electrodes against the skin [6]. But the study focusing on the HF/LF ratio for detection of tonic seizure onset only added three additional patients with generalized tonic-clonic seizures (GTCS). Thus, since the other ten patients were retrieved from the earlier study, LF calculations were be based on recordings of merely three patients.

With the dataset acquired during the EpiSense project, this HF/LF calculation could not be reproduced due to the built in high pass filter in the sensor itself. The LF band of 2-8 Hz was therefore not available.

A possible reason for the lack of higher frequency content in the EpiSense dataset could be a difference in electrode placement. In their conducted studies, Conradsen et al. used monopolar measurement of EMG (placement of the electrodes over the muscle with a common reference to a distant electrode over non-muscular tissue) [6], [7], [15], [19]. They state it is done to eliminate phase-cancelling, thereby believing to record the monophasic potentials caused by the Motor Unit Potentials’ (MUPs) standing wave by using the
monopolar setting. These standing waves contain relatively high frequencies which can be emphasized by processing techniques such high-pass filtering [20]. This processing step has also been conducted by Conradsen et al.

In the EpiSense project all steps were conducted in the same manner as done by the research team from Denmark (see Appendix 9: data analysis EMG tonic clonic seizures, Appendix 10: data analysis EMG tonic part seizures, Appendix 11: data analysis regular movement, and Appendix 16: overview data analysis), except the bipolar setting was used for the measurement of EMG (measuring the difference between two monopolar signals).

Whether the difference in electrode placement could have caused the absence of higher frequencies in collected tonic EMG data has been tested later on in the EpiSense project. Simulated tonic seizures have been measured using the bipolar and monopolar setting to investigate whether electrode placement would have a large influence on frequency content, see Appendix 14: monopolar tests and Appendix 15: bipolar tests. In the simulated EpiSense data set, no differences were observed.

Moreover, for comparing EMG activity between different muscles, in the same muscle on different days, or between different individuals, the EMG must be normalized. The most common and reliable method for EMG normalization is to record the maximal voluntary isometric contraction (MVIC) from the same muscle (as subsequent EMG recordings) to be used as the reference value [21], [22]. Then, for normalization of each period in the EMG signal, equation 7 can be used:

\[
EMG_{\text{norm}}(t) = \left( \frac{EMG_{\text{amplitude}}(t)}{MVIC \cdot EMG_{\text{amplitude}}} \right) \times 100\%
\]  

(equation 7)

Prior to the start of each new measurement night, MVIC should be recorded to be able to normalize the full night of EMG measurement afterwards. However, since the target population of the EpiSense project is patients with cognitive impairment, normalization could not be conducted; most patients could not be instructed to perform a MVIC (or any other task).

A simple task such as ‘clenching your teeth’ could be an option to measure the MVIC in patients with cognitive impairment [23], however, then EMG measurements are normalized for signals derived from the masseter muscle. This issue will be further discussed in section 11.3.

10.3 Detection algorithm

As mentioned earlier in section 10.1, only 11 seizures collected from two patients were used for the design of the detection algorithm. The threshold that was determined, has thus also been based on this low number of collected seizures and has been determined by visual inspection. When in upcoming research, more data will be collected, the optimal threshold should be identified by creating a Receiver Operating Characteristic (ROC) curve. In this curve, the true positive rate (SEN) can be plotted against the false positive rate (100-specificity) for different cut-off points of the AUC of the EMG signal. Using the ROC curve, the optimal threshold to maximize SEN whilst minimizing false positive alarms can be chosen for the EpiSense system.

Regarding the false positives, one could contemplate whether false alarm #5 (see Figure 9) is actually a false alarm or is in fact a true positive. The goal of this project was to detect nocturnal tonic seizures and the alarm went off because a period of tonic contraction occurred (see Figure 10). Even when consulting the expert for his evaluation of the video recording, no firm conclusions could be drawn based on this ‘gold standard’ in the patients’ home environment. A decisive answer could solely have been based on EEG measurement recorded at the time of the alarm, which is not available in this measurement setting. No requirements were set regarding the duration of the tonic seizures as a condition with respect to the alarm.

11 Recommendations for future research

11.1 More data acquisition

The first and most important recommendation for improving the detection algorithm is to collect more measurement data. In future data collection, it is recommended to increase the two-week measurement period to up to three months like the validation study (phase 2) was originally designed. As experienced in this first measurement trial, a high variability in tonic seizure frequency exists among the target patient population.
If a patient truly suffers from at least one tonic seizure per week (according to the inclusion criteria, see Appendix 19: clinical trial protocol phase 2) is difficult to assess, even when looking into the patients’ seizure history in the Electronic Patient Database (EPD).

11.2 Improving the EpiSense system and adjusting the measurement protocol

Other than the loss of data caused by letting loose of the used skin electrodes, they also lead to minor skin irritation when used for a prolonged period of time. Especially in patients in which skin electrodes that needed to be replaced every night (for instance, due circumstances as wearing a medical corset daily because of severe scoliosis). Ideally, the sensor should be re-designed again to replace ECG measurement with PPG measurement. In addition, with regard to EMG measurement, dry electrodes should be used without compromising on quality of measurement (i.e.; a bandwidth and gain should be of sufficient height to avoid clipping of the EMG signal and sampling frequency should be kept at 4 kHz). However, measurements using currently available dry EMG electrodes do not allow for acquisition of these high-quality measurements. If the option of re-designing the sensor is beyond the EpiSense project’s budget, other measures could be tried first. For instance, the length of the ECG measurement leads is limited to minimize the risk of entanglement (and possible suffocation). Large movement of the limbs, a too distal placement of the sensor band on the left upper arm could create too much tension on the leads causing them to let loose (with or without the skin electrode). Placing the EpiSense sensor band as proximal as possible around the upper arm could possibly increase tonic ECG measurements.

Another measure that could be taken right away in upcoming measurements is skin preparation prior to electrode placement, for EMG measurement as well as ECG measurement. Proper preparation should include:

- Clip hair if needed;
- Wash skin with soap and water;
- Dry skin with washcloth.

Proper skin preparation could increase adhesive strength of the skin electrode, furthermore, it could also increase signal measurement quality [24].

In addition, if skin irritation does occur in the measurement period (up to three months, as recommended in the previous section) it is advised to continue measurements every other week.

Also, as described by Staudenmann et al. (2010), EMG electrode placement has a high influence on the acquired amplitude and frequency content. For future measurements regarding the EMG signal, it would be best if electrodes are consistently placed by a single person in exactly the same position. Another option would be to change the measurement setting to monopolar, as this would decrease the influence of electrode placement on the acquired EMG signal with respect to measuring bipolarly.

11.3 Further development of the detection algorithm

Finally, a suggestion for expansion of the detection algorithm to be able to include ACM measurements in the detection algorithm as well. Typically, the ACM signal consists of a part that represents actual movements and a part that represents gravitational acceleration determined by the orientation of the measured spatial direction of the sensor in the gravitational field [5]. When there is no movement, the part of the signal representing the position of the sensor in relation to the gravity field causes an offset in the measured ACM signal between -1 g and 1 g. When a change of posture occurs, the position regarding the gravitational field can change, causing a change in the offset.

Acceleration caused by gravity is much larger with respect to the acceleration caused by movement. Nijsen et al. [5] state that a typical block-like pattern can be seen in the ACM signal during the tonic seizure caused by the slow change in posture. In future analysis on the obtained EpiSense ACM data, this gravity component should be estimated using a low pass filter to investigate whether the typical block-like pattern could be of added value regarding tonic seizure detection using the EpiSense system.

In addition, further analysis on the measured ACM data should also be performed to minimize false-positives. For instance, when the patient is out of bed or even when the patient is upright in bed (as was the case in false alarm #2 in Figure 9), spatial directions derived from the ACM measurements could prohibit the alarm from going off. Due to time constraints of this design project of effectively one year, these developments could not be performed.

Moreover, as described in section 10 ‘Discussion’, the EMG signal needs to be normalized to be able to compare between patients and/or between different days of measurements in one patient. There are other
normalization methods besides determining the MVIC [21], [25], but they all require the patient to perform a certain task. Some patients measured during the EpiSense project were not able to follow any instructions to perform any tasks. It is recommended to adjust inclusion criteria based on this requirement to be able to perform the normalizing processing step prior to future data-analysis. Whether or not a possible inclusion candidate is able to perform the required task for normalization can be discussed with the regular attending nurses.

Implementing the suggested improvements, regarding measurements and the development of the detection algorithm, may improve the performance of the detection algorithm to be able to achieve the ultimate goal of obtaining a SEN of 80% whilst maintaining a PPV of at least 80%.
12 Bibliography


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13 Appendices

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