VILMA PLUŠČIAUSKAITĖ

A METHOD FOR IDENTIFYING PERSONAL TRIGGERS OF PAROXYSMAL ATRIAL FIBRILLATION

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CONTENTS

List of Terms and Abbreviations

AF	Atrial fibrillation
ANS	Autonomic nervous system
CI	Confidence interval
ECG	Electrocardiogram
HR	Heart rate
MAD	Mean amplitude deviation
Mcc	Matthews correlation coefficient
MET	Metabolic equivalent of task
non-AF	Other rhythm than atrial fibrillation
PPG	Photoplethysmogram
RR interval	Time interval between two contractions of the ventricles
Se	Sensitivity
SDNN	Standard deviation of normal-to-normal RR intervals
Sp	Specificity
SQI	Signal quality index

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INTRODUCTION

Relevance of the research

Atrial fibrillation (AF) is the most common cardiac arrhythmia, estimated to affect more than 50 million individuals worldwide [1,2]. However, the true prevalence may be much higher due to asymptomatic AF cases, especially at the beginning of arrhythmia development [3,4]. AF poses a significant burden on the healthcare system due to serious complications such as stroke and heart failure [5]. In addition, the global incidence and prevalence of AF continue to rise due to aging, increasing obesity rates, and cardiovascular diseases. In Europe and the US, it is estimated that one out of four individuals aged over 55 years will develop AF in their lifetime [6].

The effectiveness of managing AF complications largely depends on early detection, which is still a challenging task [7]. However, even if detected early, the management is often restricted to oral anticoagulants and antiarrhythmic drugs, both associated with serious side effects [8,9,10]. An increasing number of studies have identified modifiable factors, under the name of AF triggers, that can potentially contribute to AF episode occurrence [11]. AF triggers should not be misunderstood as AF risk factors, like diabetes, hypertension, obesity, sleep apnea, or smoking [12], but rather as an exposure contributing to the occurrence of AF episodes. The most commonly studied AF triggers are alcohol consumption [13,14], physical exertion [15,16], and psychophysiological stress [17,18]. A better understanding of triggers in individual patients would enable clinicians to address the underlying causes of AF episode occurrence and empower patients to actively participate in their AF management through lifestyle modifications. This strategy closely aligns with a key direction in advanced medicine, which is to emphasize personalized disease management [2,5].

Many prior studies investigating AF triggers relied on subjective trigger identification through questionnaires [11,19,20,21]. A considerable number of AF patients were able to identify a few trigger types, suggesting confirmation bias [11]. Conversely, the fact that certain triggers were not reported by some patients may be attributed to recall bias, such as reluctance to acknowledge events that are harmful to health [11]. To mitigate these biases, quantitative approaches are needed to supplement questionnaires and enhance the understanding of triggers.

Technological advancements have led to the development of wearable devices equipped with biosensors capable of acquiring various physiological signals, which can potentially be used for detecting suspected AF triggers and obtaining AF episodes by using a single device. Nevertheless, detecting AF episodes is more challenging than merely identifying the presence of AF [22]. This requires long-term, continuous monitoring because interruptions or poor signal quality often results in missed AF episodes, thereby complicating the assessment of a relation between the suspected trigger and AF occurrence. Currently, the only commercial options for reliable long-term mon-

itoring are implantable devices and ECG (electrocardiogram) patches. Implantable devices, however, are expensive, and they also carry risks associated with the implantation procedure [23], while even modern ECG patches can be inconvenient due to adhesive electrodes [24]. Wrist-worn devices capable of acquiring a photoplethysmogram (PPG) are more convenient but less accurate in detecting AF [25, 26]. Additionally, there has been no research focused on detecting suspected triggers in physiological signals or relating trigger information with the occurrence of AF episodes.

The other important challenge that remains to be solved is understanding the relation between the suspected trigger and the AF episode occurrence on an individual level. Since timestamps of suspected triggers and onsets and offsets of AF episodes are represented by nonstationary binary data, conventional methods for assessing the relation, such as Granger causality or causal forecasting, are not easily applicable, while distance- and correlation-based methods [27, 28] are only useful for finding similarities between two processes. Quasi-experimental approaches, such as regression discontinuity design [29], have limited practical application due to the need for data points in both pre- and post-effect periods. Unfortunately, methods for identifying the relation between the suspected triggers and the AF episode occurrence on an individual patient basis are lacking, thereby highlighting the need for research in this area.

> *An AF trigger — acute exposure (e.g., alcohol consumption, physical exertion, psychophysiological stress) that contributes to the occurrence of an atrial fibrillation episode due to the interplay between the arrhythmogenic substrate in the atria and modulating factors (e.g., the state of the autonomic nervous system).*

> *A suspected AF trigger — an event commonly reported by patients as their trigger for AF, which is detected in physiological signals acquired using wearable devices, recorded by patients using a dedicated smartphone app, or self-reported via a questionnaire.*

> *Control AF triggers — AF triggers randomly placed throughout the observation interval, matching the number of detected suspected triggers, to enable the comparison of relational strengths.*

Scientific-technological problem

Detection of suspected AF triggers in physiological signals and the identification of the relation between the suspected trigger and the occurrence of AF episodes in an individual patient.

Research object

A method for personalized identification of suspected AF triggers from physiological signals obtained by using wearable devices.

Aim of the research

This doctoral thesis aims to develop and investigate a method for personalized identification of AF triggers.

Objectives of the research

1. To propose a methodology for detecting suspected AF triggers in physiological signals.

2. To develop a model for simulating an effect of a trigger on the occurrence of AF episodes.

3. To propose an approach for assessing the relation between the suspected trigger and the occurrence of AF episodes.

4. To investigate the relation between the suspected AF trigger and the occurrence of AF episodes by using physiological signals acquired from patients with paroxysmal AF.

Scientific novelty

Identifying individual triggers and implementing behavioral changes can be an effective strategy to supplement conventional pharmaceutical treatment. In this doctoral thesis, a methodology has been proposed to detect suspected AF triggers in physiological signals. Additionally, the feasibility of using long-term PPG-based AF detection as an alternative to conventional ECG-based detection was investigated.

Due to the absence of databases with annotated triggers and AF episodes, this doctoral thesis also proposes an alternating, bivariate Hawkes model for simulating trigger-affected AF episode occurrence. To illustrate the principle, the effect of alcohol on AF episodes is represented by an alcohol body reactivity function whose properties depend on the amount of consumed alcohol.

Currently, the main approach for the identification of suspected triggers relies on questionnaires. To mitigate the biases related to the subjectivity of trigger identification, a quantitative approach for assessing the relational strength between the suspected trigger and AF occurrence for an individual patient has been proposed. One of the strengths of the proposed approach is that it overcomes the limitations posed by non-stationary and binary data.

Finally, the proposed method for identifying suspected AF triggers has been investigated by using a database of wearable-based physiological signals, collected from patients diagnosed with paroxysmal AF at their homes.

Practical significance

1. The proposed method, model, and methodology for personalized identification of suspected AF triggers can be used in the following applications:

    (a) The algorithms that use ECG and acceleration signals enable the detection of suspected AF triggers due to physical exertion, psychophysiological stress, lying on the left side, and sleep disorders.

    (b) The model for simulating the effect of the trigger allows to model trigger-affected AF episode occurrence. Various triggers, such as alcohol consumption, large meals, cold drinks or cold food, acute stress and anxiety can be simulated, by relying on available scientific evidence. The model addresses the problem of the lack of annotated databases; therefore, it is valuable for testing the approaches for assessing the relation between the suspected triggers and the AF episode occurrence.

    (c) The approach for quantifying the relational strength between the suspected trigger and the occurrence of AF episodes has the potential to facilitate the implementation of longitudinal studies and can serve as a less biased alternative to the conventional questionnaire-based approaches.

2. The methods provided in this thesis have been developed in the framework of the project *Wearable technology for personalized identification and management of paroxysmal atrial fibrillation triggers – TriggersAF* funded by the European Regional Development Fund (01.2.2-LMT-K-718-03-0027) under grant agreement with the Research Council of Lithuania (LMTLT), 2020–2023.

3. Some parts of algorithms presented in the thesis have been described in the European patent application *Method for Establishing a Causality Score Between Atrial Fibrillation Triggers and Atrial Fibrillation Pattern*, Kaunas University of Technology, Vilnius University. EP21179681.8. 16 June 2021.

Approval of the results

The doctoral thesis relies on two main papers published in international scientific journals referred in the *Clarivate Analytics Web of Science* database. The essential results have been presented in two international worldwide recognized conferences: the 49th and the 50th conferences of *Computing in Cardiology*.

The statements presented for defense

1. The suspected AF triggers can be detected in physiological signals acquired in free-living. ECG and acceleration signals can be used to compute time-varying parameters, with distinct thresholds for specific trigger detection.

2. Trigger-affected AF episode occurrence can be simulated by using an alternating, bivariate Hawkes model by accounting to the body reactivity function which represents the trigger effect.

3. A relation between the suspected trigger and the AF episode occurrence can be quantified by relying on the pre- and post-trigger AF burden within the specific analysis time interval, dependent on the duration of the trigger effect.

4. The proposed approach for establishing the relational strength between the suspected AF trigger and the occurrence of an AF episode is a less-biased alternative to questionnaire-based approaches.

Structure of doctoral thesis

The doctoral thesis is organized as follows. Section 1 analyzes the relevant scientific literature with respect to the clinical significance of AF triggers, together with the information on available technologies that provide signals indispensable for detecting AF episodes and suspected AF triggers. Section 2 presents algorithms for detecting suspected triggers in physiological signals, a model for simulating the effect of a trigger on the AF episode occurrence, and an approach for assessing the relational strength between the suspected triggers and the AF occurrence. Section 3 describes the two databases used in the work: a simulated database, with various effects of alcohol and a week-long physiological signals database obtained from paroxysmal AF patients. Section 4 presents results obtained from the detection of suspected triggers in physiological signals, modeling of trigger-affected AF episode occurrence, and investigation of the relational strength between the suspected AF triggers and the AF episode occurrence in simulated and physiological signals. The findings of the doctoral thesis are generalized by providing its conclusions in Section 5.

Parts of the thesis have been quoted verbatim from the previously published articles: [30, 31, 32, 33].

The thesis consists of 112 pages, 28 figures, 7 tables, and 141 references.

Work done in collaboration

The proposed method was developed collaborating with Leif Sörnmo from Lund University (Lund, Sweden). The ECG- and PPG-based detectors for obtaining the occurrence of AF episodes were earlier developed by Andrius Sološenko [25] and Andrius Petrėnas [34], respectively.

1. OVERVIEW

This chapter discusses the limitations and emerging opportunities for AF management and reviews the technologies for AF detection, while focusing on long-term monitoring. The chapter also introduces the concept of AF triggers, reviews potential approaches to identifying the relation between the suspected triggers and the AF episode occurrence, and discusses the suitability of the available technologies for detecting suspected triggers in physiological signals.

1.1. Atrial Fibrillation Background

Atrial fibrillation is characterized by irregular and rapid atrial activity, with atrial cells depolarized at rates of 300–600 times per minute, far exceeding the normal rate of approximately once per second. The atrioventricular node acts as a filter between the electrical systems of the atria and the ventricles, thus allowing only a fraction of these rapid atrial impulses to reach the ventricles.

Clinical diagnosis of AF requires documentation of an episode lasting more than 30 seconds, recorded in a 12-lead ECG [35,36]. Key features of AF visible on an ECG include an irregular rhythm, the absence of P waves, and the presence of fibrillatory waves (Fig. 1.1).
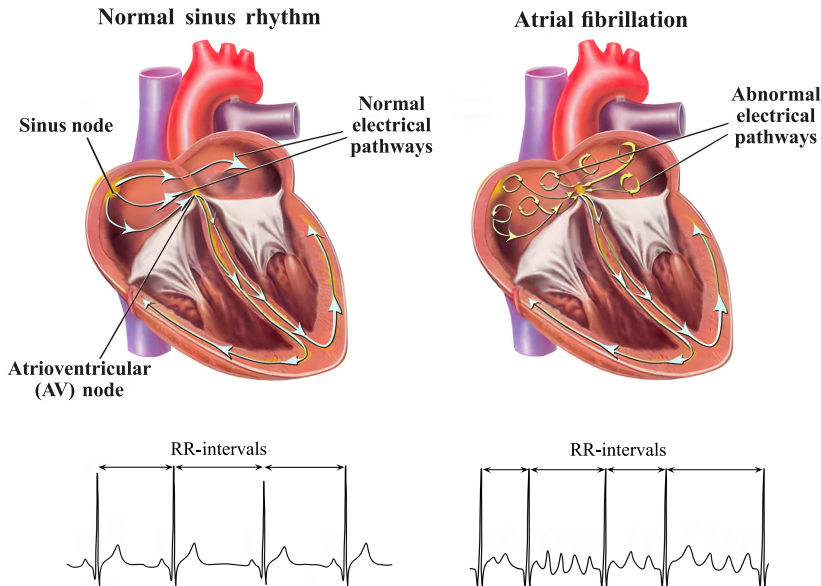
Figure 1.1. Electrophysiological heart activity during non-AF and AF and corresponding ECG signals

When arrhythmia is at an early stage of development, AF episodes are often short and self-terminating. However, AF is often a progressive disease [37], and it may progress to persistent, when episodes last continuously for more than 7 days. Ultimately, it can develop into permanent, when the rhythm does not restore to the sinus rhythm without medical treatment or a surgery [38]. The serious complication of AF is the formation of blood clots in the atria due to impaired atrial contraction and blood stasis. Blood clots can reach the brain, lungs, kidneys, or become lodged in an artery, thereby posing significant health risks [39].

According to the latest understanding of AF initiating mechanisms, AF episodes occur due to the interplay between the arrhythmogenic substrate, modulating factors, and potentially modifiable acute exposures – AF triggers [40,41,42]. Since prolonged AF leads to electrical and structural remodeling of the atria, maintaining sinus rhythm for as long as possible is a crucial challenge [43].

Despite advancements in arrhythmia treatment, managing AF remains a complex challenge [44]. Current management options are largely confined to oral anticoagulants and antiarrhythmic medications, both of which carry the risk of serious or potentially life-threatening side effects, such as bleeding, hypotension, alterations in the hemodynamics and autonomic nervous system (ANS), and even lead to life-threatening arrhythmias [9, 10, 36, 45, 46]. Modern treatment approaches, such as catheter ablation, involve substantial costs and can be unsuccessful, resulting in AF recurrence following the procedure [47]. Thus, an effective strategy may include integrating the lifestyle and modifiable factor interventions alongside the conventional AF management approaches [12] (see Fig.1.2) and, in such a way, lead to a reduced AF burden.

1.2. Commercial Wearable Devices for Monitoring Atrial Fibrillation

AF episode occurrence can only be obtained from continuous long-term cardiac activity-reflecting signals, such as ECG or PPG. Further, an overview of the currently available commercial wearable devices that potentially can be used to obtain the occurrence of AF episodes is provided. Also, the devices are reviewed regarding the possibility of accessing the unprocessed physiological signals that can be used for the detection of suspected AF triggers.

1.2.1. Electrocardiogram-based technologies

Information on AF episode occurrence can be obtained by using physiological signals from implantable devices or external ECG recorders equipped with specialized software for AF detection. However, implantable devices are both costly and risky due to the surgical implantation procedure [23]. For ambulatory monitoring, the Holter monitor remains one of the most commonly used devices offering continuous ECG
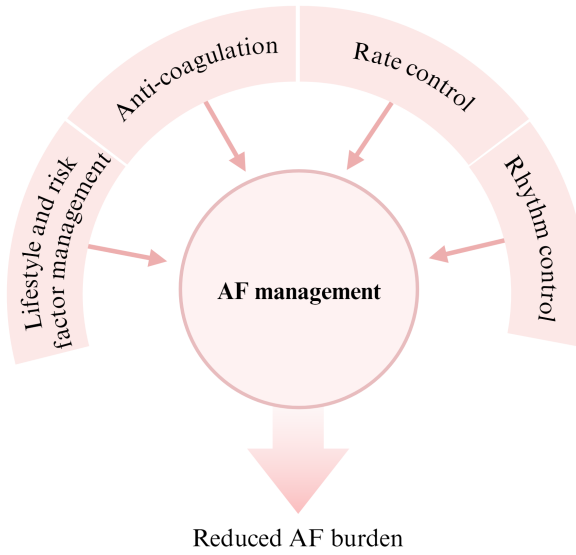
Figure 1.2. Four AF management strategies according to American Heart Association [12]

recording for 1–2 days, or up to two weeks with newer models [48]. While the Holter monitor is suitable for obtaining AF episode occurrence, the adhesive electrodes and connecting wires can cause discomfort during extended use.

More convenient alternatives of Holter monitors are ECG patches. These patches enable continuous monitoring without the need of wires, thanks to sticky electrodes. The *Zio-Patch* (*iRhythm Technologies*, USA), for example, acquires single-lead ECG for up to 14 days without needing a battery replacement. The patch has shown a high diagnostic yield for AF detection which is similar and even better to the Holter monitor, since the patch can we worn for longer periods of time [49, 50]. *Bittium Faros* (*Bittium*, Finland) offers another patch-based solution which can acquire single-lead or three-lead ECG for up to 7 days without needing a charge. Unlike most other patches, the *Bittium Faros* is reusable. In addition to ECG, the device acquires several other signals, such as acceleration and temperature. The advantage of *Bittium Faros* is that the device provides access to unprocessed signals. Other ECG patches approved by the US Food and Drug Administration include *BardyDx CAM* (*Bardy Dx*, USA), *BodyGuardian* (*Preventice Solutions*, USA), *BioTel Heart* (*BioTelemetry*, USA), *MediBioSense MBS HealthStream* (*MediBioSence*, UK), *Nuvant MCT* (*Conventis Inc.*, USA), *SmartCardia* (*SmartCardia SA*, Switzerland) [51]. Some of these patches support real-time data transmission for continuous AF monitoring, although the duration of monitoring varies depending on the device. Most patches use a single lead, but some incorporate multiple electrodes to capture a multi-lead ECG. The low-profile design and water-resistant properties of patches allow patients to perform their

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daily activities with minimal disruption [50]. The downside is that adhesive electrodes, which are required to attach the patch to the skin, may cause irritation after prolonged use.

ECG chest straps is another technology without adhesive electrodes. For instance, *Polar H7* and *Polar H10* (*Polar Electro*, Finland) have been found to be resistant to signal loss [52, 53]. Nevertheless, most chest straps are limited to tracking the heart rate (HR) rather than providing ECG signals, thus limiting their utility for the detection of suspected triggers.

KardiaMobile (*AliveCor*, USA) is a credit-card-sized, non-wearable device for AF detection that can acquire a single-lead ECG and provides real-time ECG analysis for AF, bradycardia, and tachycardia.

1.2.2. Photoplethysmogram-based technologies

The use of PPG signals for long-term AF monitoring is gaining popularity, especially as a tool for AF screening [54, 55]. When using the PPG signal, AF detection is based on the irregularity of pulse-to-pulse intervals or signal morphology [56]. Despite the convenience for AF monitoring, PPG poses challenges due to artifacts caused by movement or a poor sensor contact. Moreover, there are currently no established guidelines for diagnosing AF solely based on the PPG signal, and a diagnosis still requires an ECG for confirmation.

Many commercially available wearable smart devices incorporate PPG sensors, appearing in various forms such as wristbands, smartwatches, smartphone cases, or apps for smartphones. For instance, *Apple Watch Series 6* along with its later versions has integrated modalities for acquiring both PPG and ECG. Therefore, when the device detects a rhythm irregularity in PPG, the ECG is acquired for the confirmation.

It is expected that smartwatches could eventually serve as a non-invasive alternative to implantable loop recorders for AF monitoring [57]. In a recent study, five commercial smartwatches with capability to detect AF were compared. In terms of sensitivity, *Apple Watch 6* (*Apple*, USA) and *Samsung Galaxy Watch 3* (*Samsung*, South Korea) were the best, both reaching 85% (72%-91%); while *Fitbit Sense* (*Fitbit*, USA) demonstrated the highest specificity at 79% (70%-86%) [57].

TeltoHeart (*Teltonika*, Lithuania) is a multifunctional smart wristband with an integrated PPG-based AF detector and capability to acquire a six-lead ECG for rhythm confirmation [58]. The device has shown promising results, with a sensitivity of 94.2% and a specificity of 96.9% for AF detection.

Similarly to smartwatches, wrist or arm bands can also acquire PPG signals. A recent study showed that the *Polar Verity Sense* (*Polar*, Finland) armband may be an alternative to chest straps since the detected rhythm corresponded to that obtained by chest strap devices during high intensity workouts [59]. *Corsano 287* (*MMT SA*, Switzerland) is one of wristbands that provide access to unprocessed PPG signals.

These bands are usually more affordable than smartwatches due to their less expensive hardware. In addition, armbands typically offer a longer battery life.

Other PPG-based wearables include rings, such as *Oura Ring* (*Oura*, Finland) and *Motiv Ring* (*Motiv*, USA), which monitor HR, the physical activity, and sleep patterns. Additionally, smart earrings and earbuds, like *Joule Earrings* (*BioSensive*, India) and *Jabra Sport Pulse* (*Jabra Corporation*, China), are available on the market. These devices may be less prone to movement artifacts, while providing more reliable HR during specific types of exercise, such as power-lifting [60]. However, none of these devices have been validated for AF detection yet.

The aforementioned ECG- and PPG-based wearable devices and their modifications are shown in Fig. 1.3, while Table 1.1 emphasizes their potential for detecting AF episodes and suspected AF triggers.

Figure 1.3. Types of wearable devices capable of obtaining cardiac information

1.3. Atrial Fibrillation Triggers

AF triggers are gaining research interest due to their potential role in contributing to AF initiation in certain patients. Therefore, patient-specific detection of triggers can become an important aspect of personalized AF management. Several studies have demonstrated that AF patients can describe exposures that potentially lead them to AF [11]. In the study which investigated patient-reported suspected triggers [11], the majority of AF patients reported at least one suspected trigger possibly related

Table 1.1. Suitability of commercial wearable devices for accessing physiological signals for the purpose of detecting suspected triggers and AF episodes

	Device	Access to physiological signals	Detection of AF episodes
ECG-based	Patch [49, 50, 51]	Some devices provide unprocessed ECG and acceleration signals	1–2 weeks
	Chest strap [52, 53]	Only research-grade devices provide unprocessed ECG and acceleration signals; typically, only HR is provided to the user	Continuous long-term AF monitoring
	Handheld [51]	Short-term user-initiated ECGs are accessible	Not possible; only short-term ECGs
PPG-based	Band [59]	Some devices provide PPG to users; most devices provide only processed HR and blood oxygen saturation	Continuous long-term AF monitoring
	Smartwatch [58, 61]	Most consumer-grade devices do not provide unprocessed PPG to the user; some research-focused devices or developer platforms offer application programming interfaces or tools to access physiological signals	Continuous long-term AF monitoring
	Ear buds [60]	Do not provide unprocessed PPG, only HR and acceleration signals for fitness and wellness metrics	Not investigated
	Ring [60]	Access to unprocessed signals is limited; provides continuous HR, HR variability, sleep tracking for the user	Not investigated

to their AF episode occurrence, with alcohol consumption being the most frequently reported; see Fig. 1.4 for commonly reported suspected triggers.

In another study, based on self-identified suspected triggers [13], caffeine was the most commonly reported. However, caffeine did not show any relation with AF in the dedicated study [62]. With nearly 1400 older adults involved, no evidence was found that habitual coffee, tea, or chocolate consumption could be associated with AF.

Among many suspected AF triggers [11, 19], alcohol is the most extensively studied, and also consistently found to be associated with AF episode occurrence [20].
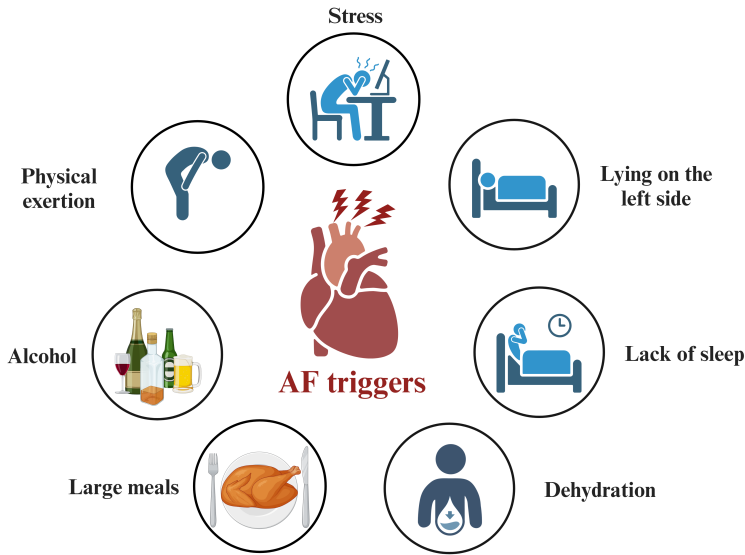
Figure 1.4. Suspected AF triggers commonly reported in questionnaire-based studies

Abstaining from alcohol for several months reduces arrhythmia recurrence twofold in habitual drinkers [21], while the consumption of two or more standard alcoholic beverages is associated with a threefold increase in the prevalence of AF within the next four hours [63]. Although the precise mechanism is not fully understood, alcohol may contribute to AF by affecting atrial electrical properties through direct cardiac toxicity or by effect on the autonomic tone [14, 64].

Evidence suggests a J-shaped relation between physical activity and the risk of AF, indicating that light and moderate physical activity can reduce the risk of AF, while both inactivity and vigorous physical activity can elevate the risk of AF [16]. However, the precise mechanisms through which vigorous physical activity may trigger AF are not elucidated. One plausible explanation involves the interplay between the ANS and atrial remodeling, leading to AF episodes [65]. Regarding vagally induced AF, patients who engage in regular physical activity tend to experience AF episodes more frequently than their sedentary counterparts [66]. Furthermore, increased vagal activity is associated with a shortened atrial refractory period, facilitating re-entry and potentially triggering AF [67].

Psychophysiological stress has an adverse impact on the cardiac system, potentially elevating the risk of developing AF [68]. Their potential role as triggers for AF is indicated by findings from laboratory-induced stress tests and several observational studies [42, 68, 69]. While experiencing stress and negative emotions, the body releases stress hormones, including adrenaline, noradrenaline, and cortisol. These hormones impact the blood flow by triggering mechanisms such as elevated HR and increased blood pressure. Moreover, stress exerts direct effects on the heart, inducing

alterations in the cardiac electrical activity, which in turn may contribute to the initiation and perpetuation of AF. The interplay between stress, physiological responses, and cardiac electrophysiology underscores the multifaceted nature of the relation between psychophysiological stress and AF, warranting further investigation to elucidate the underlying mechanisms and targeted interventions.

Patients frequently report that a left lateral body position triggers AF episodes [11]. Twenty-two percent of the patients noted a particular body posture that induced their AF symptoms. Among those, the left lateral position has been identified as the triggering posture in 57% of all cases [70]. The AF triggering mechanism of a left lateral body position can be explained by a heightened stretch of the pulmonary veins, which are known to be proarrhythmic for AF. Changing from a supine to the left lateral position causes the heart to shift in an anterior-left lateral direction within the thorax. This alteration leads to an increase in the left atrial volume and an elevation in the local wall stress in the pulmonary vein regions [71].

Sleep disorders, including poor sleep quality, insufficient sleep duration, snoring, or obstructive sleep apnea, may contribute to the development of AF and the onset of AF episodes. Individuals with sleep-disordered breathing have AF episodes during sleep five times more frequently than those without breathing issues [72], whereas sleep apnea is the most established risk factor for AF [73, 74]. One potential mechanism by which sleep apnea induces AF is through the increase in blood pressure caused by bursts of sympathetic activity triggered by reduced oxygen levels and chemoreflex near the end of a sleep apnea episode. This can lead to an increased pressure and stretching on the left atria ant trigger an AF episode to occur [75, 76].

Table 1.2 summarizes the studies that investigated triggers in AF patients.

Parts of this subsection have been quoted verbatim from the previously published article: [33].

1.4.   Physiological Mechanisms Contributing to Initiation of Atrial Fibrillation

Due to the complexity of arrhythmia, the pathophysiological mechanisms that trigger AF still remain poorly understood. Some studies have shown that ectopic beats originating from the muscle sleeves of the pulmonary veins precede AF episodes about 90% of the time [77, 78]. However, the factors driving this increased ectopic activity are still unclear, and the mechanisms leading to AF episodes are difficult to distinguish. Additionally, numerous well-established AF risk factors, such as diabetes, hypertension, smoking, obesity, and underlying heart disease should be considered, as they may interact with triggers [79].

Triggers may alter the physiological systems, for example, the ANS, and, in this way, contribute to AF [2, 80, 81]. The autonomic activation affects the intracellular calcium dynamics, leading to a reduction in action potential duration and refractoriness, which in turn may result in ectopic firing in atrial muscles surrounding the pulmonary

Table 1.2. Studies on self-reported AF triggers with the corresponding percentage to study sample size

Trigger	Study	Sample size	Reported as trigger
Alcohol	Groh et al. 2019 [11]	1 295	35%
	Hansson et al. 2004 [19]	100	34%
	Marcus et al. 2021 [63]	100	—
	Marcus et al. 2022 [20]	446	10%
	Voskoboinik et al. 2020 [21]	140	—
Physical exertion	Groh et al. 2019 [11]	1 295	23%
	Hansson et al. 2004 [19]	100	42%
	Marcus et al. 2021 [63]	100	30%
Stress	Groh et al. 2019 [11]	1 295	20%
	Hansson et al. 2004 [19]	100	54%
	Lampert et al. 2014 [69]	95	—
Lying on the left side	Groh et al. 2019 [11]	1 295	16%
	Hansson et al. 2004 [19]	100	17%
	Gottlieb et al. 2021 [71]	20	—
	Gottlieb et al. 2021 [70]	94	22%
Lack of sleep	Groh et al. 2019 [11]	1 295	22%
	Marcus et al. 2021 [63]	100	31%
Dehydration	Groh et al. 2019 [11]	1 295	21%
	Marcus et al. 2021 [63]	100	20%
Large meals	Groh et al. 2019 [11]	1 295	20%

'—' indicates that study focused on a single suspected trigger

veins [82]. A noteworthy observation is that AF patients without structural heart disease tend to exhibit an increase in the vagal tone before AF onset. Conversely, patients with structural heart disease have an increased sympathetic tone before AF onset [83]. Sympathetic activation increases calcium entry and the spontaneous release of calcium, leading to atrial ectopies – forming a trigger loop. Increased parasympathetic activation, combined with AF-induced atrial electrical remodeling, shortens the action potential duration, facilitating re-entry and thereby promoting AF, i.e., creating an electrical loop. Also, there is the third – structural loop, where the atrial stretch during conditions including congestive heart failure, hypertension, or obstructive sleep apnea activates numerous profibrotic pathways resulting in atrial structural alterations and conduction disturbances, also facilitating re-entrant mechanisms (see Fig 1.5) [84]. The alterations in the ANS can be studied by using HR variability indices, potentially enhancing the understanding of the processes that contribute to the initiation of AF.

The long-term experience of cardiologists points to hypothesis that changes in arterial blood pressure constitute another important element in the AF occurrence. This reasoning is further supported by a notable correlation between an elevated blood

pressure and an increased risk of developing AF [85]. Even a slight increase of 1 mmHg in blood pressure is linked to approximately a 2% rise in the relative risk of AF [86]. The relation between a high blood pressure and AF is bidirectional and complex, involving both the left atrial and ventricular myocardium. Central to this process is atrial cardiomyopathy, which is a combination of changes in the left atrium, affecting its contractility and electrophysiology. These changes in the atrial tissue are likely to trigger ectopic focal firing, create re-entry, and disrupt atrial conduction due to the heterogeneity of impulse conduction. The pathophysiology of AF in hypertensive patients involves a range of coexisting processes, including structural, hemodynamic, and neuroendocrine changes [87].

Parts of this subsection have been quoted verbatim from the previously published article: [33].
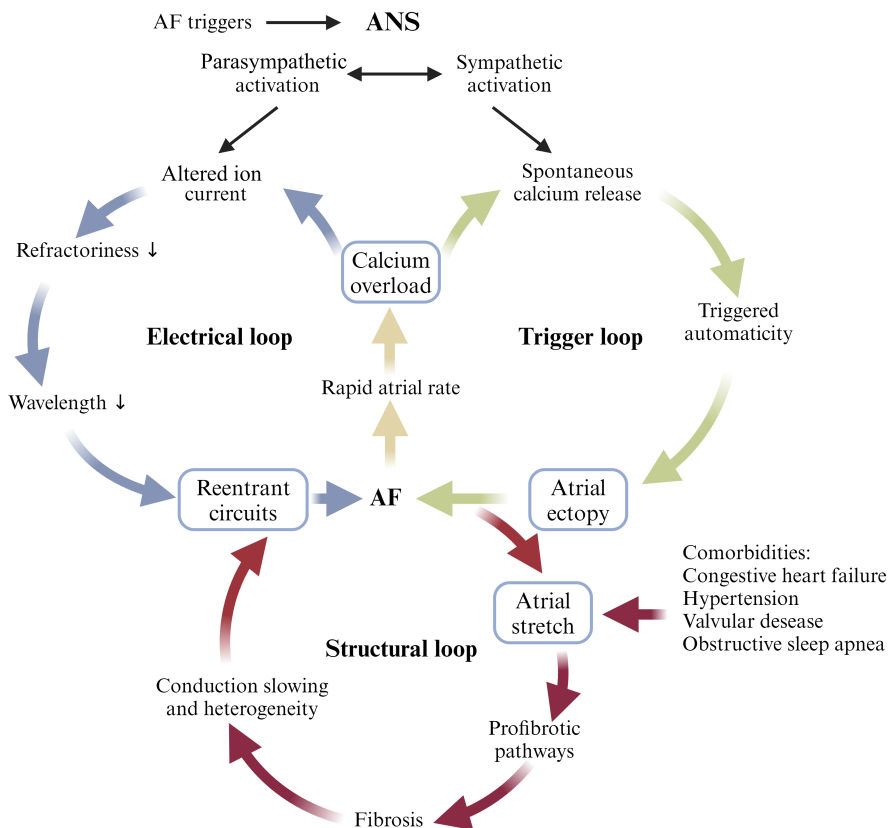
Figure 1.5. Potential interaction of the ANS with different mechanisms of AF [84]. '↓' indicates shortening

1.5. Current Approaches to Identifying Atrial Fibrillation Triggers

1.5.1. Questionnaire-based collection of suspected atrial fibrillation triggers

The identification of suspected triggers remains a research gap because, so far, there are no established quantitative methods. In majority of previous studies, AF triggers were identified subjectively, as they were self-reported through questionnaires [11, 13, 19, 21]. This approach presents a major limitation, as many patients in questionnaire-based studies are able to identify several types of suspected triggers, although their responses can be influenced by confirmation bias [11]. Conversely, recall bias —such as the hesitation to disclose behaviors harmful to health, like alcohol consumption—might explain why some patients failed to report any suspected trigger [11].

1.5.2. Application of sensors for collecting signals related to suspected triggers

The first attempt to mitigate the effect of questionnaire-related bias was to employ a wearable ECG monitor and a transdermal alcohol sensor [63]. In such a way, self-reported drinking events were complemented with sensor-based data.

Accelerometers and gyroscopes integrated into wearable devices can detect changes in the body position, including lying down, standing, and sitting. With a single accelerometer, the best posture detection performance is obtained when the sensor is positioned on the chest or thighs [88].

1.5.3. Limitations of computational methods for quantifying the relation between the suspected triggers and atrial fibrillation occurrence

Understanding the relation between the suspected triggers and AF episode occurrence on the individual level is challenging because the trigger information includes only timestamps when the suspected trigger occurs. Also, the onset and end of AF episodes represents non-stationary binary data. Therefore, methods for causality assessment, e.g., Granger causality or causal forecasting, are not easily applicable. On the other hand, methods such as distance- and correlation-based ones [27, 28], are only useful for finding similarities between two processes. The practical application of quasi-experimental approaches, such as regression discontinuity design [29], is limited because data points are required in both the pre- and the post-effect periods to estimate the regression and compute the difference between them.

Joint modeling-based approaches are commonly utilized in analyzing time-to-event data in groups of patients, with various applications ranging from AF risk assessment to the prediction of new-onset AF in the distant future [89]. In one application, a univariate Cox proportional-hazards model was employed to analyze the time to AF recurrence among groups characterized by alcohol abstinence and regular alcohol consumption [21]. Although these models offer the advantage of adjusting for patient

characteristics and other risk factors, they are less suitable for analyzing individual-level data. Additionally, to obtain reliable estimates, joint modeling-based approaches typically require a minimum number of the event/trigger of interest, generally exceeding 20 [90]. Given that AF episodes can manifest without the effect of a specific trigger, relying on the time to the onset of AF may prove unreliable for identifying suspected AF triggers.

This subsection has been quoted verbatim from the previously published article: [32].

1.6. Conclusions of the Chapter

1. Patient-specific detection of suspected triggers may be an important aspect of personalized AF management, enabling clinicians to focus on the underlying causes of AF episodes in individual patients. In addition, patients would be encouraged to actively participate in managing their AF by making lifestyle changes.

2. Limited knowledge exists on the effects of triggers that contribute to AF episode occurrence. Most commonly investigated suspected triggers include alcohol, psychophysiological stress, physical exertion, and sleep disturbances. This gap in knowledge is also due to the lack of algorithms capable of detecting short-term physiological changes associated with suspected AF triggers.

3. Existing studies on the identification of suspected triggers rely on questionnaires. However, this approach suffers from confirmation bias when patients believe that certain events lead to AF episode occurrence. Additionally, patients may be hesitant to provide information about harmful events, such as alcohol consumption. Solutions beyond questionnaires to detect a broader range of suspected triggers are still lacking.

2. METHODS

This chapter describes the algorithms for detecting suspected AF triggers in physiological signals, the proposed approach for assessing the relation between trigger and AF episode occurrence, and a model for simulating trigger-effected AF episode occurrence.

2.1. Detection of Suspected Atrial Fibrillation Triggers in Physiological Signals

The AF triggers investigated in this thesis were chosen based on the findings in questionnaire-based studies [11, 19]. The principles of the detection of suspected triggers are described in the following text. Each type of trigger is based on a detection parameter computed in successive intervals throughout the ECG and/or acceleration signals, resulting in a time series which is subject to threshold-based detection. For simplicity, physical exertion, psychophysiological stress, lying on the left side, and sleep disturbances are in the following referred to as suspected triggers irrespective of whether AF occurs or not.

2.1.1. Physical exertion

Participating in higher-intensity exercise is considered a contributing factor to AF occurrence, both in athletes and the general population [91]. The metabolic equivalent of task (MET), serving as a physiological measure of the energy expenditure associated with various physical activities relative to the resting metabolic rate, is used for detecting physical exertion.

MET is estimated by using acceleration and HR to account for patient-specific variability, as patients may exhibit different HR responses to the same physical activity due to variation in the fitness level and health condition. The following regression equation is used to estimate MET [92]:

$$y_{\mathrm{MET}} = 0.0043 x_{\mathrm{ACC}} + 0.047 x_{\mathrm{HRR}} + 1.4238, \tag{2.1}$$

where x_{ACC} denotes the vector magnitude of the tri-axial acceleration signals and x_{HRR} denotes HR reserve, which depends on the heart's ability to increase HR during physical activity.

To eliminate the gravitational acceleration component, the tri-axial acceleration signals were high-pass filtered with a cut-off frequency of 0.7 Hz [93]. Then, the vector magnitude was computed and averaged within 1-min intervals to yield x_{ACC}.

The HR reserve x_{HRR} is defined as follows [94]:

$$x_{\mathrm{HRR}} = \frac{x_{\mathrm{HR},a} - x_{\mathrm{HR},r}}{x_{\mathrm{HR},m} - x_{\mathrm{HR},r}} \cdot 100, \tag{2.2}$$

where $x_{\mathrm{HR},a}$ is the mean HR in 1-min intervals, and $x_{\mathrm{HR},r}$ is the mean of the 5-min HR during daytime sedentary activities, determined as the mean amplitude deviation

(MAD) of the tri-axial, unfiltered acceleration signals within the range of 3 to 15 milligravity. The measure $x_{\text{HR},m}$ is the maximum HR determined using the standard formula 220 minus age.

A suspected trigger is detected if the mean y_{MET}, computed for 1-min intervals with non-AF rhythm, exceeds 5 units. Considering that most patients were elderly, the threshold for detecting physical exertion was adjusted to 5 instead of 6 units typically used to characterize vigorous activity in a younger population [95]. This adjustment accommodates activities such as stair climbing, brisk walking, and table tennis [96].

2.1.2. Psychophysiological stress

When experiencing psychophysiological stress, the body releases stress hormones, thereby contributing to elevated HR and intensified cardiac contractions, potentially leading to the occurrence of AF episodes [68]. Detection of psychophysiological stress relies on the assumption that a sudden elevation in HR, not attributable to notable physical activity or arrhythmia, is indicative of a stress-inducing event.

A suspected trigger is detected when the elevation in HR exceeds 15 beats per minute within a 1-min interval [97], provided that no physical activity is present and no suspected trigger has been detected during the preceding 4 hours. Physical activity is considered absent when both the average MAD of the 5-min interval before and the analyzed 1-min interval remain below 22.5 miligravity, which is a level indicating sedentary behavior such as sitting and standing still [98]. To reduce the impact of outliers, the elevation is not determined directly from the HR series, i.e., the inverse of the RR intervals, but by computing the difference between the end and the onset of a first-degree polynomial fitted to the HR series in the 1-min interval.

2.1.3. Lying on the left side

A left lateral lying position has been self-reported as a suspected trigger of AF episodes [11, 70]. This finding can be explained by the left lateral position exerting heightened pressure on the walls of the atrial and pulmonary vein, thereby functioning as a proarrhythmic factor [71, 99, 100].

A suspected trigger is detected when the acceleration signal of the mediolateral axis (ACC_y), i.e., the signal best reflecting the left lateral lying position, remains below -600 miligravity for at least 1 hour, and no suspected trigger has been detected during the preceding 4 hours. Given that changes in the lying position occur multiple times during the night, only the first detected suspected trigger is considered for the preceding 4 hours.

2.1.4. Sleep disorders

Sleep disorders, particularly obstructive sleep apnea, have been identified as

suspected triggers for AF [74, 101]. Given that episodes of obstructive sleep apnea are often accompanied with cyclic variations in HR, certain HR variability indices are well-suited for detecting such episodes [102]. In this work, nocturnal alterations in HR are explored by using the standard deviation of normal-to-normal RR intervals (SDNN), serving as an indicator of the dominant component of sympathetic and vagal activity [103].

Before SDNN is computed, the RR interval series is corrected with respect to missed beats, false detections, and ectopic beats, using the algorithm described in [104]. False detections are eliminated, and, for a missed beat, a new beat is inserted to divide the prolonged RR interval into two RR intervals of the same length. Ectopic beats are handled by interpolation of the adjacent RR intervals.

To detect sleep disorders, the nighttime interval from midnight to 7:00 was analyzed, computing SDNN within 1-h increments. A threshold of 116 ms is employed to determine the large variations in HR based on the SDNN [102]. When the SDNN exceeds the threshold in a 1-h interval, the onset of the interval is taken as the occurrence time of the suspected trigger.

Parts of Section 2.1 have been quoted verbatim from the previously published article: [33].

2.2. Modeling of Trigger-Affected Atrial Fibrillation Episode Occurrence

Identification of individual triggers related to AF episode occurrence is a difficult task since the available quantitative approaches to relation assessment either involve large groups of patients (e.g., randomized control trials) or are suitable at an individual level but have serious restrictions (e.g., Granger causality). One solution to understanding the suitability of relation assessment is to employ simulated databases that allow to control the properties of generated AF episode occurrence.

The alternating, bivariate Hawkes model [105] is used to simulate AF episode occurrence. The counting processes $N_1(t)$, describing transitions from non-AF to AF, and $N_2(t)$, describing transitions from AF to non-AF, are associated with the conditional intensity functions $\lambda_1(t)$ and $\lambda_2(t)$, respectively, defined by:

$$\lambda_m(t) = \mu_m + \sum_{n=1}^{2} \sum_{\{k:t>t_{n,k}\}} \alpha_{m,n} e^{-\beta_{m,n}(t-t_{n,k})}, \tag{2.3}$$

where $\mu_m > 0$, $\alpha_{m,n} \geqslant 0$, $\beta_{m,n} \geqslant 0$ for $m, n = 1, 2$, and $t_{n,k}$ are transition times. The main characteristic of the Hawkes model is that $\lambda_1(t)$ increases by $\alpha_{1,1}$ immediately after a transition ('self-excitation') and then decreases exponentially, defined by the decay parameter $\beta_{1,1}$, to the base intensity μ_1; the same characteristic applies to $\lambda_2(t)$ but then defined by $\alpha_{2,2}$, $\beta_{2,2}$, and μ_2. In addition to self-excitation, 'cross-excitation' exists when $N_2(t)$ affects $N_1(t)$ and vice versa: it is defined by the parameters $\alpha_{1,2}$, $\beta_{1,2}$ and $\alpha_{2,1}$, $\beta_{2,1}$, respectively.

Assuming, for simplicity that $\beta_{1,1} = \beta_{1,2} = \beta_1$ and $\beta_{2,1} = \beta_{2,2} = \beta_2$ [105], the Hawkes model is defined by a total of eight parameters: μ_1, $\alpha_{1,1}$, $\alpha_{1,2}$, and β_1 describing $\lambda_1(t)$ and μ_2, $\alpha_{2,1}$, $\alpha_{2,2}$, and β_2 describing $\lambda_2(t)$. Thus, the model parameters can be compactly represented by the vector:

$$\boldsymbol{\theta} = [\mu_1, \mu_2, \alpha_{1,1}, \beta_1, \alpha_{1,2}, \alpha_{2,1}, \beta_2, \alpha_{2,2}]. \tag{2.4}$$

When using statistical goodness-of-fit analysis, the Hawkes model was found to fit the AF episode occurrence in the vast majority of recordings in three databases of long-term ECGs [105].

2.2.1. Trigger transformation to body reactivity function

Alcohol pharmacokinetics is characterized by a body reactivity function which depends on several factors: the number of consumed units, the consumption time, the time needed for ethanol to be eliminated from the blood, as well as the absorption and elimination rates.

Alcohol consumption is typically quantified by standard alcohol units, providing a measure of the amount of ethanol in a beverage. For example, a shot (40 ml) of 40% alcohol (e.g., vodka) contains about one alcohol unit, a glass (200 ml) of 10% wine contains about two alcohol units, and a bottle (500 ml) of 5% beer contains about three alcohol units [106]. Absorption starts immediately after the alcohol has reached the stomach, lasting from as short as 10 min, when gastric emptying is fast, to as much as one hour. Alcohol metabolism follows zero-order kinetics, meaning that one alcohol unit is typically metabolized per hour [107]. In the present work, it is assumed that one standard alcoholic drink consists of 10 ml of pure ethanol [108].

In practice, a patient can provide the type and amount of the consumed alcohol and the exact time of a drinking event, which are quantities that can be included in the body reactivity function. Based on [109], a number of assumptions are made to reduce the number of degrees of freedom: absorption and elimination rates for a standard male weighing 70 kg, 30 min to absorb one standard alcohol unit, and one hour to eliminate one alcohol unit under non-fasting conditions. Alcohol absorption is modeled by a bounded exponential growth function defined as

$$y(t; u) = u(1 - e^{-at}), \quad a > 0, \tag{2.5}$$

where u is the number of alcohol units, and a is the growth parameter, here set to $10.6/u$ units/h [109]. Alcohol elimination from the body is modeled by a linear function whose downslope b is set to 1 unit/h [107]. Assuming that the alcohol is consumed

at time $t = 0$, the body reactivity function is defined as

$$r(t; u) = \begin{cases} y(t_s; u), & 0 \leqslant t < t_s; \\ y(t_s; u) - b(t - t_s), & t_s \leqslant t < t_s + y(t_s; u)/b; \\ 0, & \text{otherwise}, \end{cases} \quad (2.6)$$

where t_s is the onset of alcohol elimination. Then, the 'multi-trigger' body reactivity function is defined as

$$R(t; \boldsymbol{\tau}) = \sum_{i=1}^{N_t} r(t - \tau_i; u_i), \quad (2.7)$$

where the vector $\boldsymbol{\tau}$ contains the timestamps $\tau_1, \ldots, \tau_{N_t}$, u_i is the number of alcohol units of the i:th drinking event, and N_t is the number of drinking events. In the following, $u_i = 1$ for $i = 1, \ldots, N_t$.

The body reactivity function for three drinking events is illustrated in Fig. 2.1. It should be noted that the third drinking event at 21:30 occurs before the second alcohol elimination has been completed. Because of this, the body reactivity function starts at 0.5 and reaches 1.5 alcohol units.
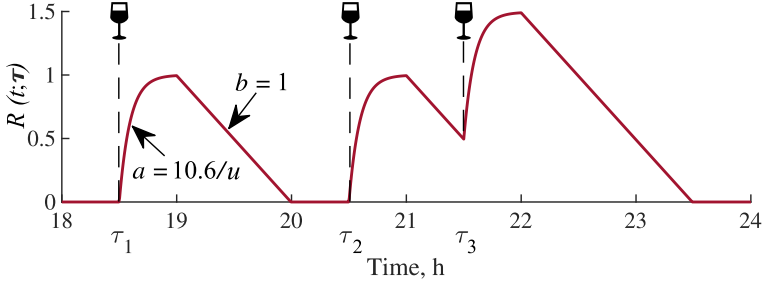
Figure 2.1. Body reactivity function with drinking events occurring at 18:30, 20:30, and 21:30, when one alcohol unit is consumed at each event

Other triggers, e.g., physical load, large meals, cold beverages [11], can also be represented as time series signals and used to affect AF episode occurrence in the Hawkes model.

Large meal intake may be expressed in terms of energy production and the digestion time. Following ingestion of a large meal, energy production increases up to a maximum level, which depends on the meal type and size. The maximum level can be defined based on the food energy (kJ) and digestion time (h). A large meal (e.g., a serving of beef, pork, fried fish) provides about 1000 kJ and takes about 5 h to digest, resulting in the maximum level of 200 kJ/h. An increase in energy production can be characterized by a bounded exponential growth function, where b is the maximum level set to 200 kJ/h, while a_0 is the growth parameter set to -3.8 kJ/h. Digestion

starts after 2 h and may be characterized by a linear function with a decay parameter a set to -40 kJ/h [110].

Cold beverages and foods may stimulate the parasympathetic system due to a decreased intragastric temperature and thus contribute to the initiation of an AF episode or a cluster of episodes. Intragastric temperature, which is about 37 °C, drops to about 22 °C after 10 ingestions of 400 ml of cold drink (of about 4 °C) and returns to body temperature within 30 minutes. A decrease in temperature may be characterized by a linear function with the decay parameter set to -15 °C/min. The return to body temperature may be characterized by a bounded exponential growth, where b is intragastric temperature, i.e., 37 °C, with the growth parameter set to -0.2 °C/min [111].

Psychological stress, in particular, anger or hostility, is known to produce perturbations in autonomic activity. Here, a surge in sympathetic activity and rise in catecholamines together with a decrease in vagal activity [112]. During an episode of acute emotional stress or anxiety, the sympathetic system is activated to the 'fight or flight' response which results in an increase in skin conductance due to sweat production and an increase in HR. Body's response, to the acute emotional stress may be characterized by a bounded exponential growth function, where 20 b is stress units, with the growth parameter a_0 set to -1.1 stress units/min. Meanwhile, the body recovery from stress may be characterized by an exponential decay function with a decay parameter a set to -0.3 stress units/min [113].

Table 2.1 summarizes parameters to transform triggers to time-series signals.

Table 2.1. Functions and parameters to transform triggers to time-series signals

No	Trigger	Growth function, growth parameter a	Decay function, decay parameter b
1.	Alcohol	Bounded exponential, $10.6/u$ units/h, where u is a number of alcohol units	Linear, 1 unit/h
2.	Large meals	Bounded exponential, -3.8kJ/h where b is the maximum energy production level	Linear, -40 kJ/h
3.	Cold beverages and foods	Linear, -15 °C/min	Bounded exponential, -0.2 °C/min where b is intragastric temperature
4.	Physiological stress	Bounded exponential, -1.1 stress units/min, where b is stress units	Exponential, -0.3 stress units/min

2.2.2. Modeling of atrial fibrillation episode occurrence affected by alcohol consumption

While information on the relation between alcohol consumption and AF episode occurrence is quite limited, a recent study reports a fairly linear relation [63]. Another study found that alcohol consumption increases the AF burden and the risk of AF recurrence [21]. Based on these findings, in this work, it is assumed that the likelihood of AF occurrence is linearly proportional to consumed alcohol units.

Given that the transition from non-AF to AF is determined by the conditional intensity function $\lambda_1(t)$, a higher base intensity μ_1 leads to a higher transition probability. The effect of alcohol on the AF episode occurrence is modeled by a time-varying base intensity $\mu_1(t)$, defined by the sum of a base intensity η and $R(t; \boldsymbol{\tau})$,

$$\mu_1(t) = \eta + R(t; \boldsymbol{\tau}). \tag{2.8}$$

Depending on the number of consumed alcohol units, $\mu_1(t)$ increases during the alcohol absorption phase and then slowly returns to η during the elimination phase. Simulated AF episode occurrence is illustrated in Fig. 2.2, where the top panel in (a) and (b) shows $\mu_1(t)$, which is constant as long as there is no alcohol drinking event, the impact of the alcohol body reactivity function on $\mu_1(t)$ is visible in (b) where three alcohol units at 10:00 were consumed. The second panel in (a) and (b) shows $\lambda_1(t)$, which is responsible for transitions from the sinus rhythm to AF. The resulting AF episode occurrence is shown in the third panel, where the high level corresponds to AF and the low level is applicable to the sinus rhythm. Prior to the alcohol drinking event, the AF episode occurrence stays the same, but after the transitions are counted separately, it will differ.

Parts of Section 2.2 have been quoted verbatim from the previously published articles: [30, 32].

2.3. Assessment and Interpretation of the Relational Strength between the Suspected Trigger and Occurrence of Atrial Fibrillation Episodes

2.3.1. Assessment of the relational strength

The identification of suspected AF triggers is based on the assumption that the post-trigger AF burden $B_{1,n}$ of the n:th trigger is larger than the pre-trigger AF burden $B_{0,n}$. The analysis time interval T, used for computing $B_{1,n}$, is chosen based on the expected duration of the trigger effect; for simplicity, the same interval length is used for computing $B_{0,n}$. For instance, the effect of alcohol consumption on AF occurrence may last up to 12 hours [13]. The relational strength γ between pre- and post-AF burden is defined by

$$\gamma = \sum_{n=1}^{N_t} \frac{B_{1,n}}{1 + B_{0,n}} H(B_{1,n} - B_{0,n}), \tag{2.9}$$
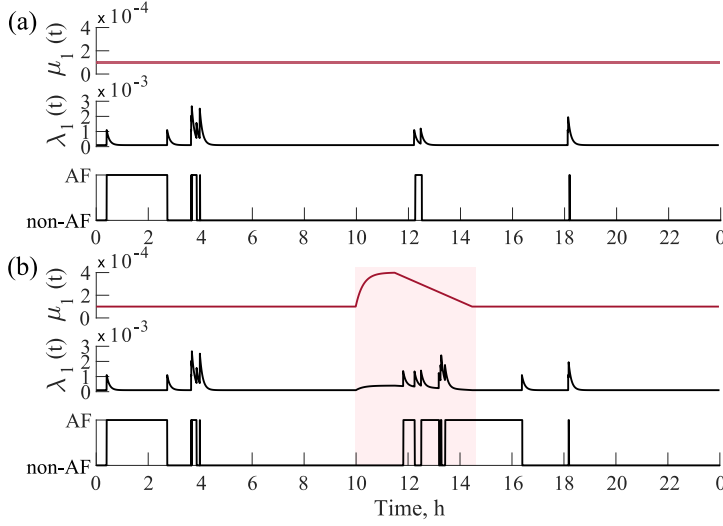
Figure 2.2. Modeled AF episode occurrence (a) without and (b) with the effect of alcohol. Note that the base intensity $\mu_1(t)$, whose shape is determined by alcohol consumption, influences the conditional intensity function $\lambda_1(t)$, and, consequently, the AF episode occurrence. The red area shows the interval of alcohol effect. The following model parameter values were used for simulation: $\boldsymbol{\theta} = [0.1, 0.5, 2, 2.5, 2, 1, 5, 2] \cdot 10^{-3}$ where the first element defines η in (2.8)

where N_t is the number of triggers during the observation interval which represents the overall monitoring duration. The Heaviside step function $H(\cdot)$ is included in (2.9) to exclude cases when the pre-trigger AF burden is higher than the post-trigger burden ($B_{0,n} > B_{1,n}$), as no causal relation can be inferred in such cases.

A cumulative principle governs Equation 2.9 since there is no basis to assume that the trigger will always affect the AF burden. Most likely the following is true: the trigger will occasionally induce AF depending on the manifestation of other factors that increase the propensity for AF [40,42]. The parameter γ is illustrated for different AF episode occurrence in Fig. 2.3.

Figure 2.4 shows γ as a function of $B_{1,n}$ for different $B_{0,n}$. For a single trigger, γ reaches 1 when there is no AF before the trigger ($B_{0,1} = 0$) and the trigger immediately initiates AF, which then lasts the entire analysis time interval T ($B_{1,1} = 1$), see Fig. 2.4(a). On the other hand, γ can take much larger values for multiple triggers, see Fig. 2.4 (b). The amount of the AF burden plays a larger role on γ than does the ratio between $B_{1,n}$ and $B_{0,n}$: γ is only 0.18 for $B_{1,1} = 0.2$ and $B_{0,1} = 0.1$, but 0.67 for $B_{1,2} = 1$ and $B_{0,2} = 0.5$ (the ratio is 2 for both cases). A greater influence of a larger AF burden is introduced to increase the insensitivity of γ against falsely detected AF episodes which are common in ambulatory monitoring [45,46].
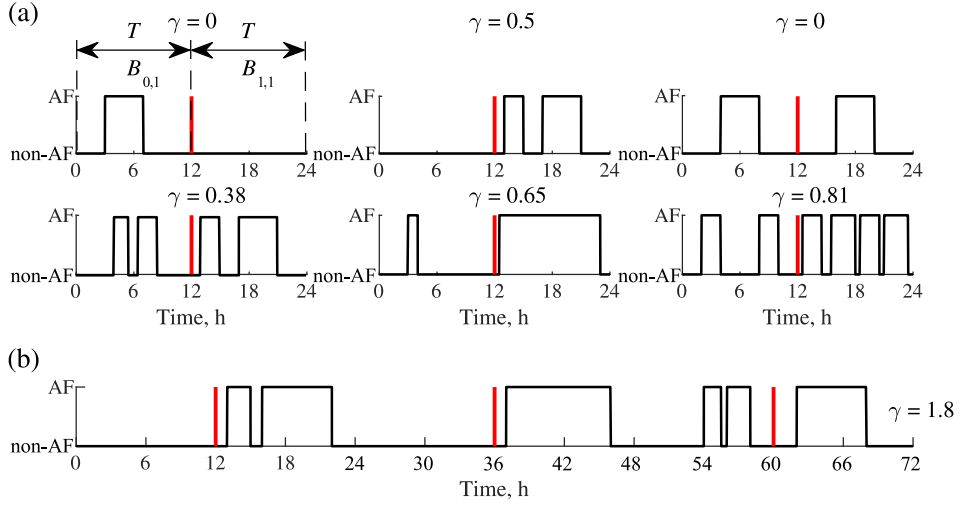
Figure 2.3. Illustration of the relational strength γ for different AF episode occurrence assuming (a) a single trigger in six different AF episode occurrences spanning one day, and (b) three triggers occurring at the same time of the day during three consecutive days. The onset time of a trigger is displayed in red. The analysis time interval T for pre-trigger AF burden $B_{0,1}$ and post-trigger AF burden $B_{1,1}$, based on the expected duration of the trigger effect, is set to 12 h for the entire AF episode occurrence in (a) and (b)
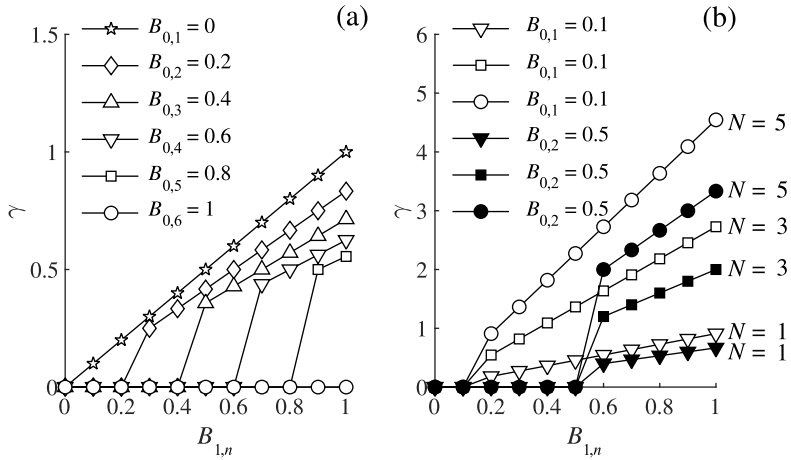
Figure 2.4. The relational strength γ as a function of $B_{1,n}$ for different $B_{0,n}$ assuming (a) a single trigger and (b) multiple triggers

2.3.2. Interpretation of the relational strength

Table 2.2 presents the interpretation of γ, derived from the properties of (2.9). For a single trigger, $\gamma = 1$ indicates moderate strength and is obtained when AF starts immediately after a trigger and persists throughout the analysis time interval ($B_{1,n} = 1$), with no pre-trigger AF burden ($B_{0,n} = 0$). When $B_{1,n} = 1$ and $B_{0,n} > 0$, then $0.5 \leqslant \gamma < 1$, suggesting a weak relational strength. When $B_{1,n}$ and $B_{0,n}$ are close to 0, then, $\gamma < 0.5$, suggesting a very weak relational strength. On the other hand, when $B_{1,n} > B_{0,n}$, a strong relational strength is established when at least two triggers occur.

Table 2.2. Interpretation of γ as a measure of relational strength between pre- and post-trigger AF burden.

Relational strength	γ
Very weak	$\gamma < 0.5$
Weak	$0.5 \leqslant \gamma < 1$
Moderate	$1 \leqslant \gamma < 1.5$
Strong	$1.5 \leqslant \gamma$

2.4. Detection of Atrial Fibrillation in Physiological Signals

Automatic ECG- and PPG-based AF detectors were employed to gather AF episodes to gain insight into the utility of wearable devices for assessing the relation between suspected AF triggers and the occurrence of AF episodes.

2.4.1. Electrocardiogram-based atrial fibrillation detection

The ECG-based detector relies on the fact that the RR intervals during AF are irregular and often associated with an elevated HR [34]. The detector, designed to find short AF episodes, incorporates filtering to remove ectopic beats, suppression of bigeminy, quantification of RR interval irregularity, and signal fusion.

Poor-quality ECG segments were excluded from further analysis. The assessment of the signal quality relies on the *bsqi* index which explores the difference in performance of two different QRS detectors [114]. The first detector (*jqrs*) is from the PhysioNet Cardiovascular Toolbox [115], whereas the second detector is from the R-DECO toolbox [92]. The index is defined by the percentage of beats aligning between the two detectors, here set to 90% if a segment is to be considered for further analysis. Moreover, only segments without premature atrial contractions, atrial flutter, and atrial tachycardia were analyzed.

2.4.2. Photoplethysmogram-based atrial fibrillation detection

The PPG-based detector relies on the analysis of peak-to-peak intervals, while using an adaptive threshold for peak detection [25]. To increase robustness against false alarms, the detector involves blocks of signal quality assessment, suppression of ectopic beats, bigeminy, and respiratory sinus arrhythmia. Irregularity of peak-to-peak intervals q_k is characterized by

$$T_k = \frac{2}{N(N-1)} \sum_{i=0}^{N-2} \sum_{j=i+1}^{N-1} H(|q_{k-i} - q_{k-j}| - \gamma), \tag{2.10}$$

where N is the number of peak-to-peak intervals, $H(\cdot)$ is the Heaviside step function, and γ is the difference of peak-to-peak intervals in seconds.

The parameter T_k is then adjusted by HR:

$$I_k = \frac{\bar{T}_k}{\bar{q}_k}, \tag{2.11}$$

where $\bar{T}_k$ and $\bar{q}_k$ are smoothed versions of T_k and q_k, processed by using second-order exponential averaging. The degree of smoothing is determined by the smoothing factor which is set to 0.02 as done in [25, 34].

The PPG quality is evaluated by comparing it to a template pulse at different time shifts. The first template pulse is a predefined pulse with a dicrotic notch. The subsequent template pulse is derived from the previous pulse, but only if its quality is deemed acceptable. If the quality is unacceptable, the template pulse is reinitialized to the initial pulse. The correlation coefficient between the PPG pulse and the template pulse is computed, and, whenever the correlation coefficient exceeds 0.7, the PPG pulse quality is considered acceptable.

Both AF detectors offer flexibility in determining the minimum duration of a detected episode, controlled by the smoothing coefficient of exponential averaging filters; for details, see [34]. In this work, the smoothing coefficient was set to 0.02, resulting in the detection of AF episodes as brief as 60 beats. Given that HR often increases during AF, this duration is in agreement with the clinical definition of the minimum duration of an AF episode [116].

The annotated and detector-based AF episode occurrence is exemplified in Fig. 2.5. It should be noted that the ECG-based AF detector emphasizes sensitivity, while the PPG-based detector emphasizes specificity, thus, at times, resulting in rather different AF episode occurrence. As a result, ECG-derived episode occurrence may contain more falsely detected episodes, while PPG-derived episode occurrence may miss some episodes due to preferred specificity.

Parts of Section 2.4 have been quoted verbatim from the previously published articles: [31, 32].
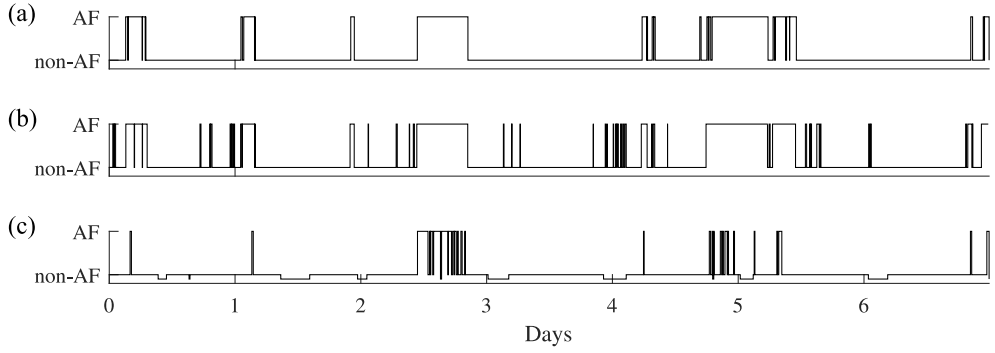
Figure 2.5. An example of AF episode occurrence obtained by (a) annotation, (b) ECG-based detection, and (c) PPG-based detection. (c) Dropouts, indicated by a lowered non-AF baseline, represent non-wear time of the PPG device

2.5.   Practical Implementation

A potential practical implementation of the method for identifying personal AF triggers in a patient diagnosed with paroxysmal AF is illustrated in Fig. 2.6. Physiological signals acquired by using a wearable device are analyzed to detect suspected triggers and obtain AF episode occurrence. Subsequently, the relational strength between each detected suspected trigger and the AF occurrence is assessed. If a strong relation is identified, the suspected trigger is recommended for avoidance.
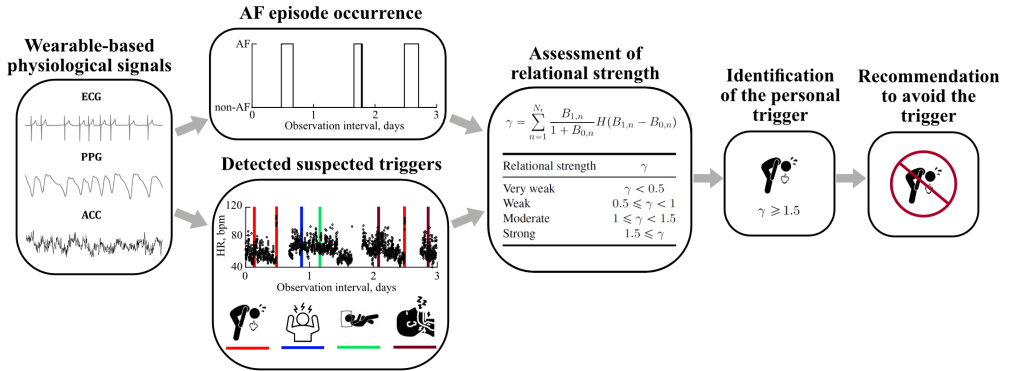
Figure 2.6. A practical implementation of the method for identifying personal AF triggers

Two approaches to establishing the relational strength in practice can be considered. The first approach involves computing the relational strength during screening and confirmation periods, while the second approach compares the relational strength computed for suspected and control triggers, which implies triggers that do not affect the AF episode occurrence.

When using the first approach, to establish a strong relation between the trigger and the altered AF burden, the patient should be monitored during the screening period until γ reaches 1.5, see Table 2.2. Then, the patient should be advised to avoid the trigger for a confirmation period of the same duration as the screening period, see Fig. 2.7. Finally, trigger timestamps during the screening period should be transferred to compute γ during the confirmation period. If the difference between γ of the screening period and γ of the confirmation period exceeds a threshold σ, the trigger is likely causal. Figure 2.8 illustrates the second approach where the relational strength
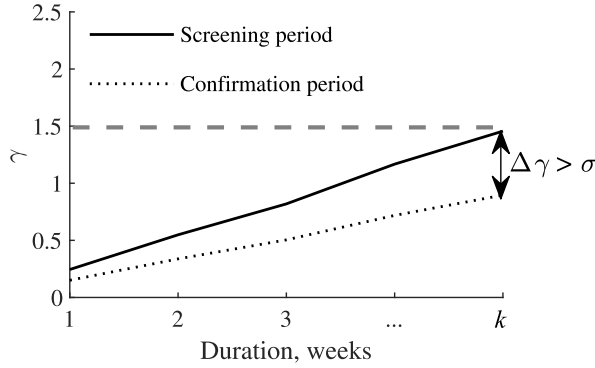
Figure 2.7. Illustration of the approach to identifying a causal relation between a trigger and an altered AF burden when screening and confirmation periods are involved

is computed by using control triggers γ_c and detector-based triggers γ_d for one patient. If the computed relational strengths, γ_c and γ_d, differ significantly, it can be assumed that the detected trigger has an effect on the AF episode occurrence.

Parts of Section 2.5 have been quoted verbatim from the previously published article: [32].
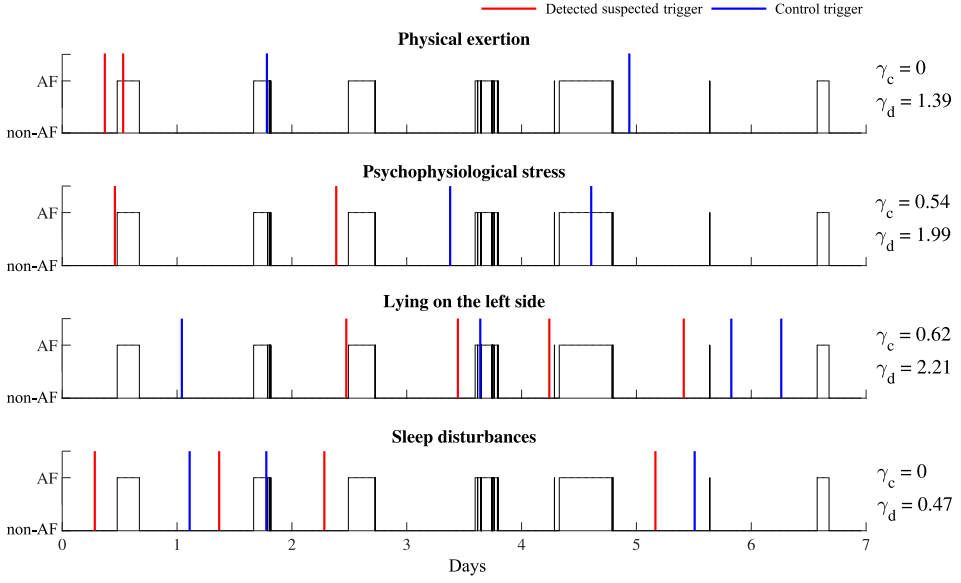
Figure 2.8. Illustration of triggers detected from physiological signals and computed relational strength γ_d and γ_c between the occurrence of AF episodes and triggers

2.6. Conclusions of the Chapter

1. A methodology has been proposed to detect suspected triggers related to physical exertion, psychophysiological stress, lying on the left side, and sleep disturbances in physiological signals. For each trigger type, a detection parameter is computed at successive intervals from ECG and/or acceleration signals, resulting in a time series which is subject to threshold-based detection.

2. A model has been proposed to simulate the occurrence of AF episodes influenced by triggers, aimed at evaluating methods for assessing their relation. The episode patterns are modeled by using an alternating bivariate Hawkes process, where the conditional intensity function defines transitions between non-AF and AF states. The impact of a trigger is incorporated through a body reactivity function, and exemplified by alcohol consumption.

3. Due to the lack of quantitative approaches for assessing the relational strength between the suspected triggers and the occurrence of AF episodes, a measure of relational strength between pre- and post-trigger burden was proposed, accounting for the cumulative effect of the suspected triggers contained in the observation interval.

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3. DATABASES

Both simulated and clinical signals have been used in this thesis. Since there is lack of databases with annotated triggers and related AF episode occurrence, simulated signals with various effects of a trigger were used to explore the proposed approach to assessing the relation strength. Clinical signals were used to individually detect suspected AF triggers and investigate the relational strength between the detected suspected triggers and the AF occurrence when using the proposed approach.

3.1. Simulated Signals

The database containing long-term ECG signals with annotated AF episodes serves as the starting point for designing a simulated AF episode occurrence database [105]. The database is comprised of 36 three-lead ambulatory ECG recordings, each lasting from 1 to 7 days, summing up to a total of 158 days of monitoring. The database was manually annotated, by showing that AF is present during 19% of the monitoring time [117].

The following three distinct types of AF episode occurrence were identified and used for simulation:

1. many clustered episodes, most of these lasting several minutes,

2. many clustered episodes, with durations ranging from several minutes to several hours, and

3. several episodes, most of these lasting several hours.

The model parameters were estimated for each of these three types, resulting in the following vectors for simulation:

$$\boldsymbol{\theta}_1 = [0.03, 1.7, 0.001, 14, 28, 4.3, 6.5, 0.001] \cdot 10^{-3}$$
$$\boldsymbol{\theta}_2 = [0.04, 0.47, 3.2, 8.9, 13, 5.5, 13, 0.001] \cdot 10^{-3}$$
$$\boldsymbol{\theta}_3 = [0.007, 0.02, 10, 22, 19, 188, 231, 10] \cdot 10^{-3}$$

For each AF episode occurrence type, sets of 100 AF episode occurrence profiles of one-month duration were generated, with each set being with different numbers of triggers (0, 2, 4, 6, 8, and 10) and alcohol units (3, 6, 9, and 12). Thus, the simulated dataset contains a total of $3 \cdot 100 \cdot 6 \cdot 4 = 7200$ AF profiles. To avoid an overlap of consecutive analysis time intervals T, AF episode occurrence was simulated while assuming that the next drinking event occurs at least 12 hours after the preceding trigger. The trigger timestamps were generated according to a uniform distribution.

The three types of AF episode occurrence are illustrated in Fig. 3.1. Only the first week of the one-month AF episode occurrence is shown.
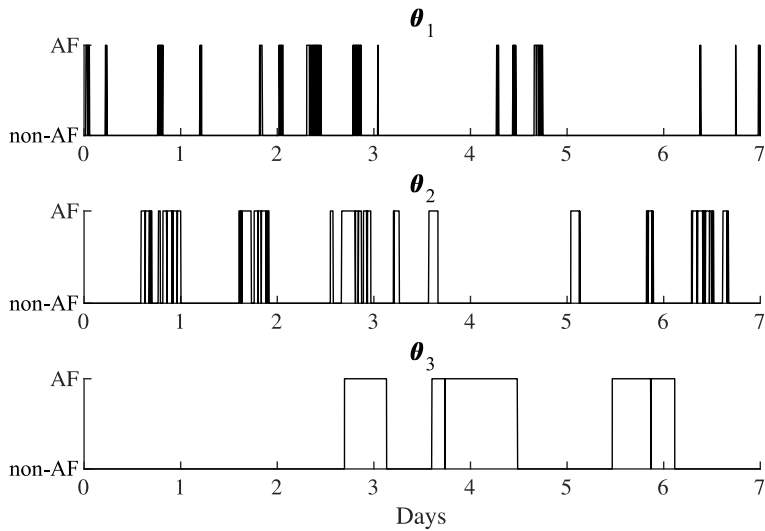
Figure 3.1. Examples of different types of AF episode occurrence used for simulation without the trigger effect added

A smaller database of 50 24-h-long AF episode occurrence profiles for each number of alcohol units, ranging from 0 to 15, were simulated to investigate the model for simulating alcohol-affected AF episode occurrence performance. In total, 300 AF profiles were simulated. The results were determined in terms of the AF burden, defined as the percentage of time spent in AF during the monitored period, the number of AF episodes, and the aggregation of AF episodes. Parameters were computed for all the simulated AF episode occurrence. In this work, it is assumed that all drinking events were entered at once.

3.2. Clinical Signals

3.2.1. Study population

One hundred and eighty-two patients diagnosed with paroxysmal AF were recruited from inpatient and outpatient wards of the Cardiology Department at Vilnius University Hospital Santaros Klinikos. Prior to their involvement, all eligible patients provided a signed, written informed consent in agreement with the ethical principles of the Declaration of Helsinki. Approval of the study was granted by the regional bioethics committee (reference number 158200-18/7-1052-557). Only those patients who had at least one AF episode during the observation interval were included for further analysis, resulting in a database of 35 patients, see Table 3.1.

Table 3.1. Demographic and clinical characteristics of patients with paroxysmal AF. Data is presented as mean $\pm$ standard deviation and absolute frequencies

Variable	Subgroup of patients ($n = 35$)
Women, n	21
Men, n	14
Age, yrs	61 ± 13
Height, cm	175 ± 10
Weight, kg	89 ± 20
Body mass index, kg/m^2	28.4 ± 5.0
Observation interval, days	7.0 ± 0.7
Medication (#patients)	
Beta adrenoblockers	26
Antihypertensive drugs	31
Comorbidities (#patients)	
Hypertension	29
Hyperthyroidism	3
Metabolic syndrome	15

3.2.2. Data acquisition

The database is comprised of physiological signals recorded during unrestrained daily activities, by using a *Bittium OmegaSnap*™ one channel ECG patch (*Bittium*, Finland), and a wrist-worn device developed at the Biomedical Engineering Institute of Kaunas University of Technology [58]. The ECG patch was positioned directly on the sternum to record a continuous ECG sampled at 500 Hz and tri-axial acceleration signals sampled at 25 Hz. The wrist-worn device captured a continuous PPG sampled at 100 Hz. The signal database is available on a multi-disciplinary open repository *Zenodo* [118]. The placement of ECG- and PPG-based devices used to acquire physiological signals can be seen in Fig. 3.2.

3.2.3. Database annotation

For a reference AF episode occurrence, a preliminary annotation of AF episodes was provided by using the ECG-based detector, followed by a manual review to refine the annotations by searching for undetected episodes, excluding falsely detected episodes, and improving the temporal precision of the episode onset and end. Cardiology residents performed the manual review, while consulting an experienced cardiologist in uncertain cases. In addition, the residents annotated premature atrial contractions, atrial tachycardia, and atrial flutter.
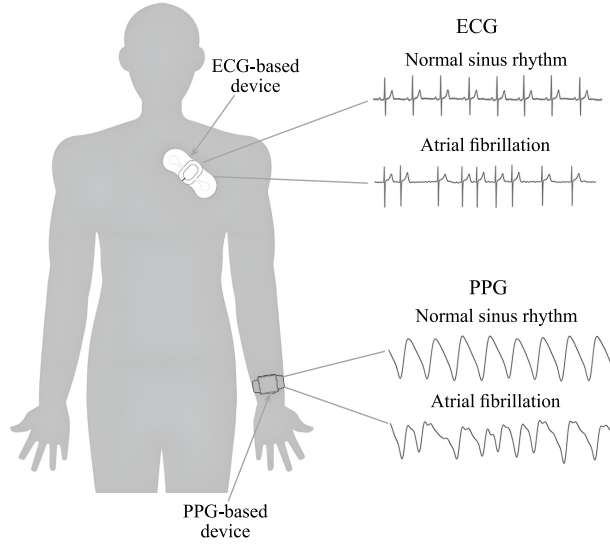
Figure 3.2. Placement of wearable devices for acquiring ECG and PPG signals

3.2.4. Database subset

While the clinical trial was still ongoing, self-reported triggers from 37 patients were used to investigate the pre- and post-trigger burden for different analysis time intervals in annotated and PPG-derived AF episode occurrence. Although, only 15 patients had paroxysmal AF episodes during the observation interval. Figure 3.3 displays the annotated and PPG-derived AF episode occurrence along with the timestamps of the manually entered self-reported suspected triggers.
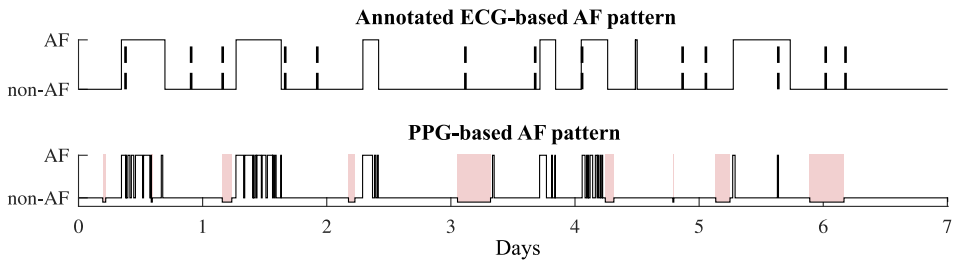
Figure 3.3. Example of annotated ECG-derived and PPG-derived AF episode occurrence. Black dashed lines show suspected triggers logged by the patients. A red area indicates an interval of non-wear time when the wrist-worn device was not being used. In the given example, a low signal quality (signal not displayed) and non-wear time account for 63% and 12.7% of the total observation period, respectively

3.3. Conclusions of the Chapter

1. Due to the lack of databases with annotated triggers and the corresponding AF episode patterns, and the fact that the relation between the suspected triggers and episode patterns has yet to be established, a simulated database using alternating bivariate Hawkes processes was employed. The modeled AF patterns incorporate various real-world characteristics, offering an opportunity to better understand the proposed approach for assessing the relational strength.

2. To explore the utility of the proposed method for identifying AF triggers by using patient data, week-long physiological signals, collected during everyday activities from patients with paroxysmal AF, employing an ECG patch attached to the chest and a PPG-based wrist-worn device, were used.

4. RESULTS

This chapter presents the findings regarding the detection of suspected triggers in physiological signals, the modeling of trigger-affected AF episode occurrence, the development of the approach for assessing the relational strength between the suspected trigger and the AF occurrence, and the investigation of the proposed approach by using physiological signals acquired from patients with paroxysmal AF.

4.1. Suspected Triggers Detected in Physiological Signals

An example of the four series of parameter values used to detect the suspected AF triggers in physiological signals, the detected suspected triggers, and the annotated AF episodes, is shown in Fig. 4.1. The separate graph displays how each suspected trigger was detected and the times when they occurred. For example, the most frequently detected suspected triggers during the 7-day monitoring interval were the left lateral lying position and sleep disturbances, both detected four times.

Figure 4.2 shows the number of each trigger type detected in each patient. At least one suspected trigger of physical exertion, psychophysiological stress, lying on the left side, and sleep disorders was detected in 80%, 74%, 71%, and 89% of the patients, respectively. A median of 2 (IQR 1–3), 2 (1–5), 4 (1–6), and 5 (4–7) suspected triggers was detected for physical exertion, psychophysiological stress, lying on the left side, and sleep disorders, respectively (Figure 4.2b); the related interquartile range is given within the parentheses.

4.2. Investigation of Trigger-Affected Atrial Fibrillation Occurrence in Modeled Data

Trigger-affected AF occurrence in modeled data shows that the AF burden increases almost linearly by increasing alcohol consumption, see Fig. 4.3 (a). Without added alcohol, the AF burden was 17.2%, and it increased twice with 9 alcohol units. A similar tendency can be seen with the number of AF episodes (Fig. 4.3 (b)). Without added alcohol, the mean was 12.9 episodes, whereas it increased by a factor of two with 8 alcohol units. The aggregation tends to decrease after 6 alcohol units (Fig. 4.3 (c)), which means that episodes tend to occupy a large part of the monitoring duration. As expected, alcohol consumption increased the likelihood of AF episodes to occur.

Modeled 24-h long AF episode occurrence shows a fairly high AF burden (17.2%); this was expected because model parameters were obtained from AF databases with more exceptional cases of paroxysmal AF patients with relatively many AF episodes. In this case, the most important thing was to obtain a change in the AF parameters after alcohol consumption.

Parts of Section 4.2 have been quoted verbatim from the previously published article: [30].
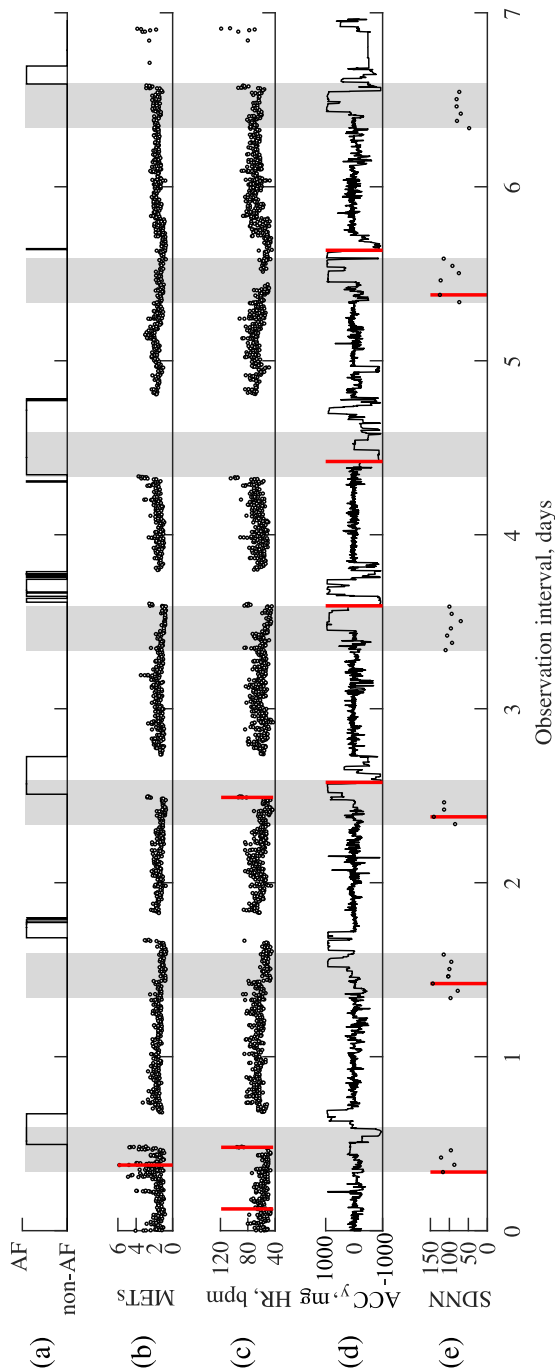
Figure 4.1. An example of (a) annotated AF episodes, and the different time series of parameter values and detected suspected triggers related to (b) physical exertion, (c) psychophysiological stress, (d) left lateral lying position, (e) sleep disturbances. The occurrence times of the suspected triggers are indicated with red vertical lines. The nighttime intervals from midnight to 7:00 are displayed in grey
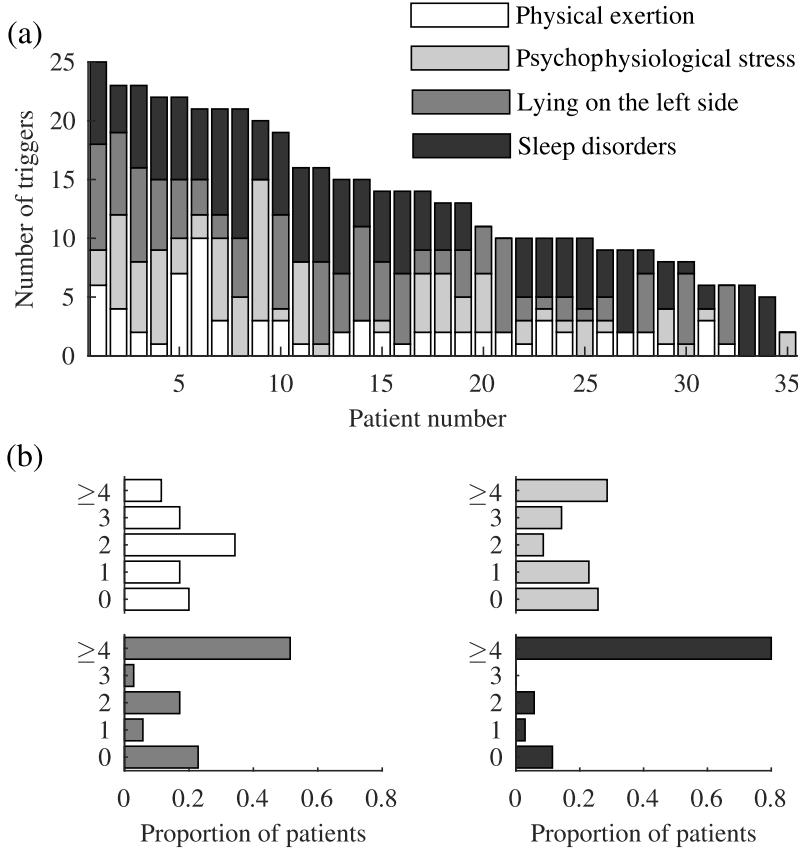
Figure 4.2. (a) Stacked diagrams of the number of suspected triggers detected in each patient, with patients ranked in a descending order based on the total number of detected suspected triggers. (b) The proportion of patients with a particular number of suspected triggers detected over the observation interval

4.3. Investigation of the Relation between the Suspected Trigger and the Occurrence of Atrial Fibrillation Episodes in Modeled Data

Figure 4.4 shows $B_{1,n}$ and γ as functions of the maximum value of $\mu_1(t)$. Notably, γ increases proportionally to $B_{1,n}$ for all AF episode occurrence types, with the AF episode occurrence type $\boldsymbol{\theta}_2$ showing the most substantial increase from 0 to 12 alcohol units. In addition, $B_{0,n}$, which is represented by $B_{1,n}$ at 0 alcohol units, depends to a large extent on the episode occurrence type and is smaller for $\boldsymbol{\theta}_1$ than for $\boldsymbol{\theta}_2$ and $\boldsymbol{\theta}_3$.
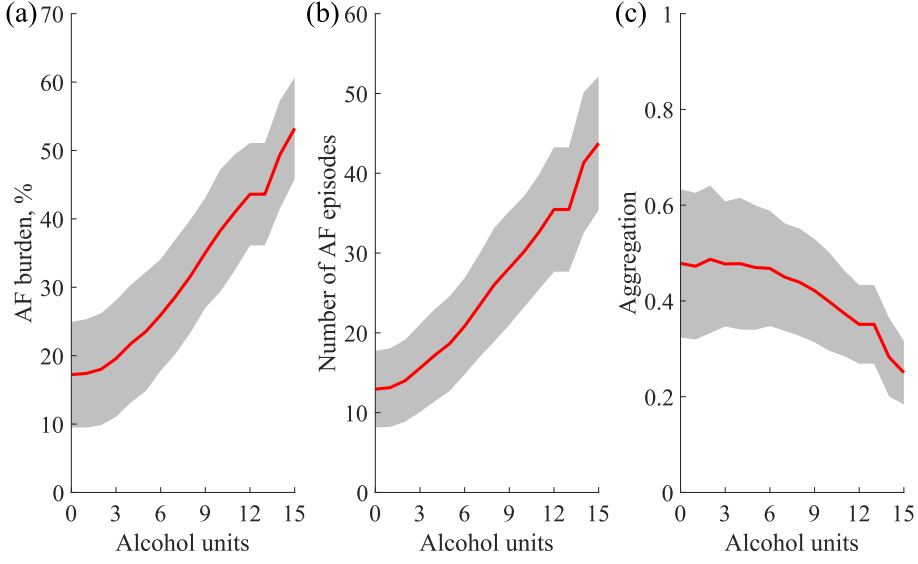
Figure 4.3. Fifty 24-h-long paroxysmal AF episode occurrences for the different number of alcohol units: (a) AF burden, (b) number of AF episodes, and (c) aggregation. Results are given as mean and standard deviation
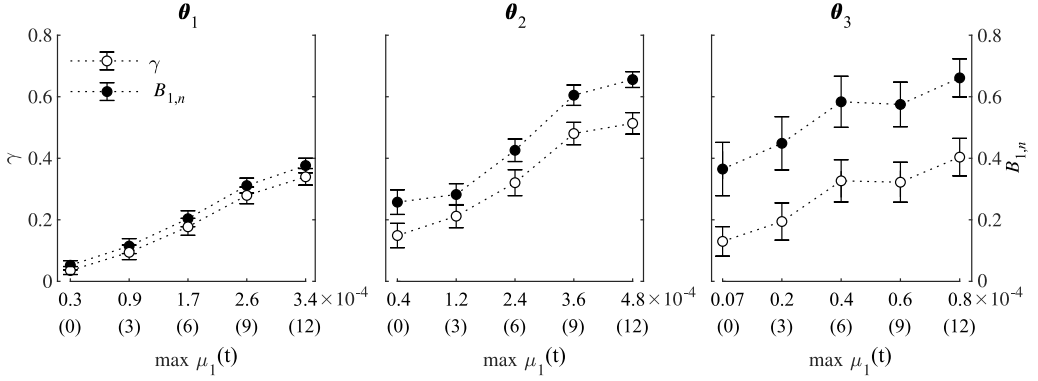
Figure 4.4. Relational strength γ and $B_{1,n}$ as functions of the maximum value of $\mu_1(t)$ when $T = 12$ h. The numbers within parentheses indicate the corresponding number of alcohol units. The results are presented as mean $\pm$ CI (95%). Only the AF episode occurrence adjusted to the first trigger is considered for the computations

Figure 4.5 illustrates the relation between the analysis time interval, the AF episode occurrence type, and the number of consumed alcohol units. The figure highlights that the selection of the analysis time interval to compute γ should consider both the AF episode occurrence profile type and the amount of consumed alcohol. γ for type 1 increases 3–10 times when 12 alcohol units are consumed, to be compared to the same profiles when no alcohol is consumed. On the other hand, γ increases only

1.5–3.5 times for AF episode occurrence types 2 and 3.
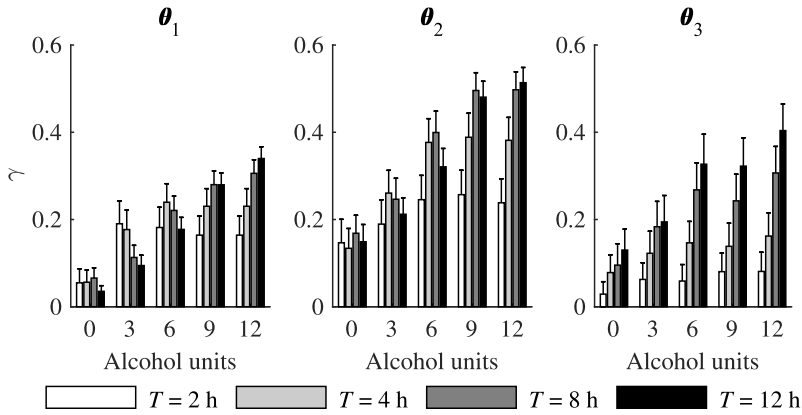
Figure 4.5. Relational strength γ as a function of the number of alcohol units for different values of the analysis time interval T. The results are presented as mean $\pm$ CI (95%). Only the AF episode occurrence adjusted to the first trigger is considered for the computations

Figure 4.6 shows the robustness of the proposed approach against suspected triggers that do not alter the AF episode occurrence, i.e., suspected triggers that are not causal for AF. As expected, non-causal suspected triggers result in 3–6 times lower γ compared to the causal triggers depending on the AF episode occurrence type; this γ ratio was obtained by comparing the episode occurrence with a trigger effect of 12 alcohol units to occurrence with non-causal triggers.

Figure 4.7 illustrates how a causal trigger can be identified. Since the suspected trigger is not causal for AF in Fig. 4.7 (a), γ is similar for both the screening and the confirmation periods. On the other hand, the absence of a trigger during the confirmation period results in a substantially lower γ than that of the screening period (Fig. 4.7(b)).

A set of one-month-duration AF episode occurrence with 10 triggers and a different number of alcohol units was studied. The computation of γ was terminated when $\gamma \geqslant 1.5$. To compute γ for non-causal triggers, AF episode occurrence without the trigger effect was used. Figure 4.8 shows that the number of causal relations decreases when σ increases for all episode occurrence types, especially for type 3. Most causal relations were found for type 1 with 9 and 12 alcohol units. On the other hand, only four out of 100 causal relations were found for type 1 AF episode occurrence with 3 alcohol units.

Parts of Section 4.3 have been quoted verbatim from the previously published article: [32].
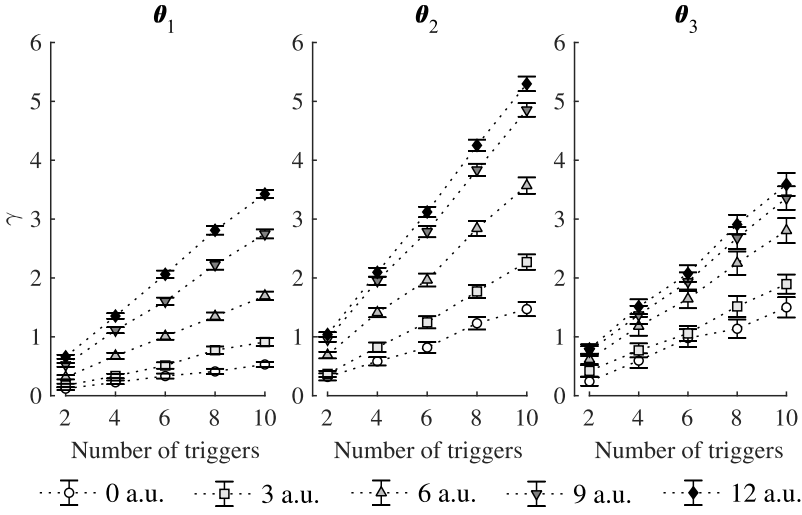
Figure 4.6. Relational strength γ as a function of the number of triggers for different alcohol units (a.u.). The results are presented as mean $\pm$ CI (95%). 0 a.u. means that the AF episode occurrence was modeled without triggers
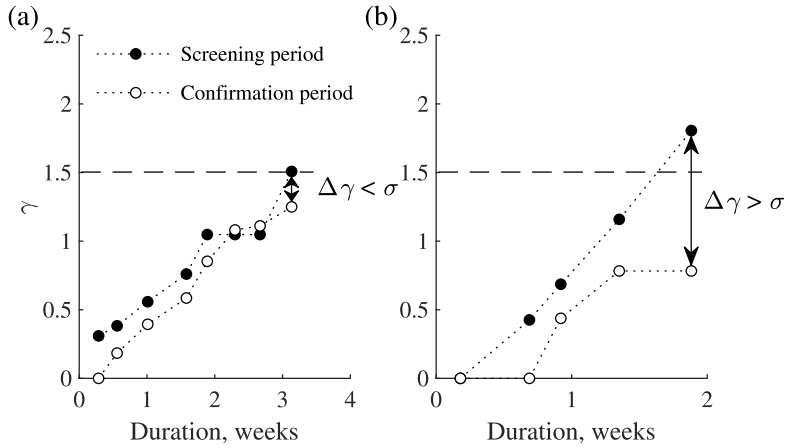
Figure 4.7. An application of the proposed approach to identifying individual AF triggers by using simulated data. The trigger is either (a) not causal for AF, or (b) causal for AF. An arrow shows the change in γ between the screening and the confirmation periods. Note that the screening period was 4 weeks, but only two weeks were required to identify a trigger in (b)
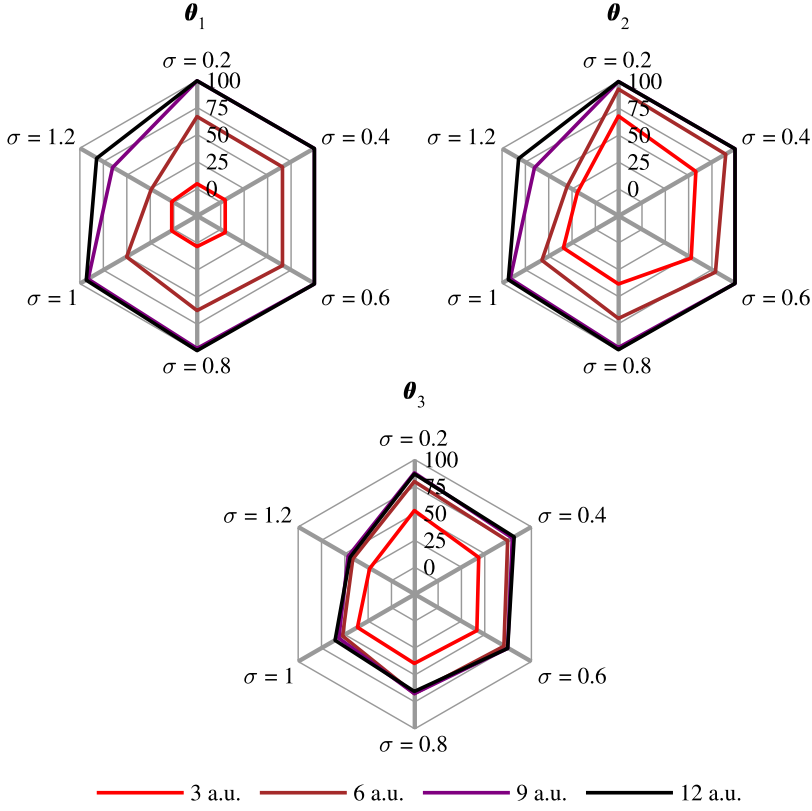
Figure 4.8. Numbers of causal relations for different choices of σ when $T = 12$ h

4.4. Investigation of the Relation between the Suspected Triggers and Atrial Fibrillation Episodes Occurrence in Physiological Signals

4.4.1. Self-identified suspected triggers

In patient data, the average AF burden of the 15 patients with paroxysmal AF determined from annotated AF episode occurrence was 0.15, with a range of less than 0.001 to 0.68. Additionally, the average duration of AF episodes was 54.7 min, ranging from 30.2 sec to 115.3 hours. A total of 288 suspected triggers were recorded by 37 patients, with 237 of them being logged while wearing a wrist-worn device; see Table 4.1.

Table 4.2 displays the performance measures for different post-trigger analysis time intervals. Assuming that the post-trigger effect on AF occurrence varies depending on a trigger type and amount, analysis time intervals of 4, 8, 12, and 16 hours were chosen for investigation. The entire analysis time interval was considered to contain AF if it had at least one AF episode of $\geqslant 30$ s. PPG-based detection performance is assessed by sensitivity (Se), representing the proportion of the correctly identified AF

Table 4.1. Number of suspected triggers logged

Suspected trigger	Total number
Coffee	126
Lack of sleep	43
Physical exertion	38
Emotional stress	36
Alcohol	33
Cold food/drink	6
Overeating	6

cases within the post-trigger interval, and specificity (Sp), representing the proportion of the correctly identified non-AF cases. To account for the substantial imbalance between AF and non-AF cases, the Matthews correlation coefficient (Mcc), normalized to the range $[0, 1]$, is used to reflect the overall performance.

Overall, the AF detection performance, as reflected by Mcc, tends to improve as the analysis time interval becomes increasingly longer. Se of AF detection ranged from 0.43 for the 4-h interval to 0.76 for the 16-h interval, whereas Sp remained consistently high for all intervals under analysis, ranging from 0.95 to 0.98.

Table 4.2. Performance measures for different post-trigger analysis time intervals

	Post-trigger analysis time interval			
	4-h	**8-h**	**12-h**	**16-h**
Se	0.429	0.609	0.678	0.758
Sp	0.981	0.962	0.961	0.949
Mcc	0.748	0.780	0.813	0.833

Figure 4.9 illustrates the AF burden computed for pre- and post-trigger analysis time intervals in both annotated ECG-based and PPG-based AF episode occurrence. The results show a tendency towards a larger average post-trigger AF burden for both annotated ECG-based and PPG-based episode occurrence. Nonetheless, the average AF burden for the PPG-based AF episode occurrence is half of that of the annotated ECG-based episode occurrence. This can be explained by the property of a PPG-based detector to favor specificity over sensitivity.

4.4.2. Suspected triggers detected in physiological signals

The analysis time interval T, used to compute the pre- and post-trigger AF burden, respectively $B_{0,n}$ and $B_{1,n}$, is set to the anticipated duration of the trigger effect, here taken to be 4 hours [63]. Depending on whether γ is based on detector-based or annotated AF episodes, it is denoted γ_d and γ_a, respectively.

To assess γ unrelated to the trigger, a control γ_c was computed by using ran-
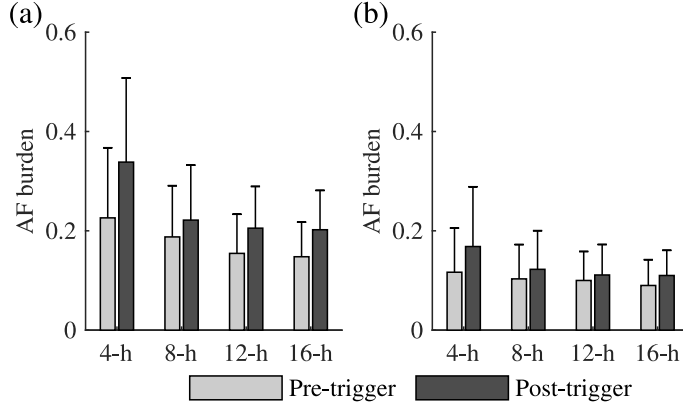
Figure 4.9. Pre- and post-trigger AF burden for different analysis time intervals when computed from (a) annotated ECG-based and (b) PPG-based AF episode occurrence. The results are given as mean $\pm$ CI (95%)

domly placed control triggers throughout the AF episode occurrence. The number of control triggers used for computing γ_c is identical to the number of detected suspected triggers.

Figure 4.10 shows γ_c as a function of the number of suspected triggers for different numbers of random initializations. In the computation of γ_c, N_t uniformly distributed timestamps were generated in the observation interval. To ensure robustness of γ_c, a median of 100 random initializations was used.
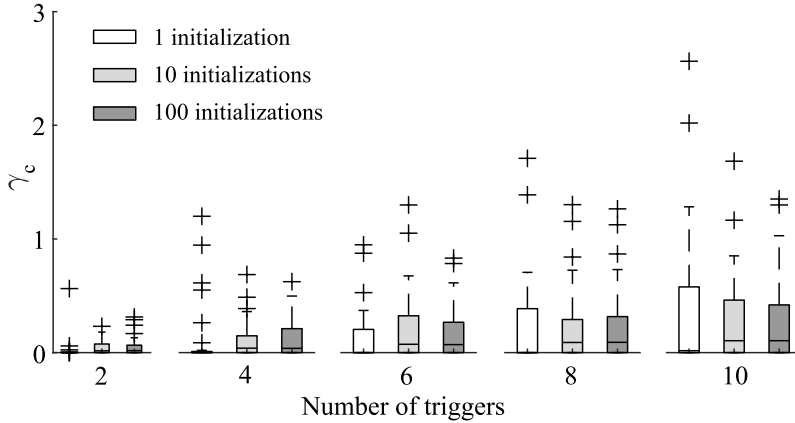
Figure 4.10. Control relational strength γ_c as a function of the number of suspected triggers for different numbers of random initialization

The normality of the relational strength γ computed for detected and random triggers was assessed by using the Shapiro–Wilk test, and, given the non-normal distribution, boxplots are employed to summarize the results. The Wilcoxon signed-rank test is used to compute p-values for the assessment of differences between dependent groups, while the Mann–Whitney U test is used for the assessment of differences between independent groups.

Figure 4.11 shows γ_d for the detected suspected triggers and control triggers γ_c in patients with at least one suspected trigger. The results show that, for some patients, γ_d increases substantially for all the four suspected trigger types relative to γ_c. Overall, physical exertion emerged as the most significant suspected trigger associated with the largest increase in γ_d across the largest number of patients ($p < 0.01$). On the other hand, no significant difference was observed between γ_d and γ_c for psychophysiological stress and sleep disorders. Additionally, no significant difference in γ_d was found between females and males, with p-values of 0.06, 0.34, 0.49, and 0.66 for physical exertion, psychophysiological stress, lying on the left side, and sleep disturbances, respectively. Scatter plots are used to show the degree of association
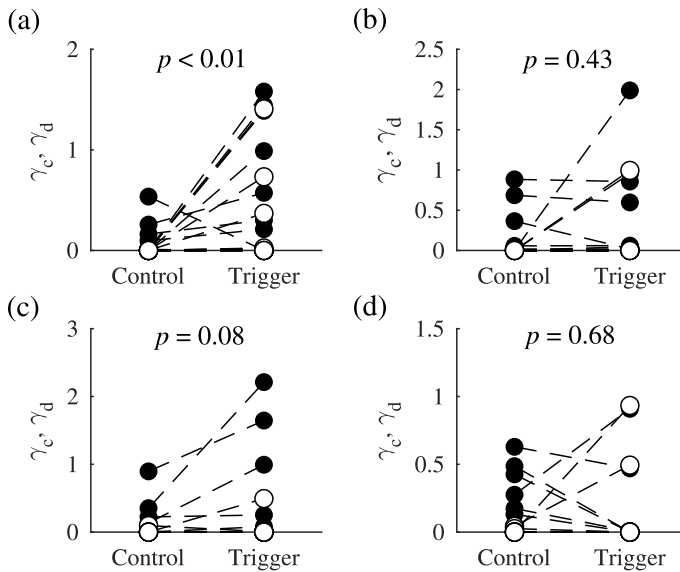
Figure 4.11. (a) γ_c and γ_d computed for each patient. (a) Physical exertion, (b) psychophysiological stress, (c) lying on the left side, and (d) sleep disorders. Females are represented by white circles

between γ, computed for each suspected trigger type, either for annotated or detector-based AF episode occurrence. The association is assessed by using linear regression, and the results are presented by employing the Spearman correlation coefficient. Figure 4.12 shows that γ_a is moderately correlated with γ_d. The correlation coefficients

are $r = 0.66$ and $r = 0.62$ for ECG- and PPG-derived AF episode occurrence, respectively.
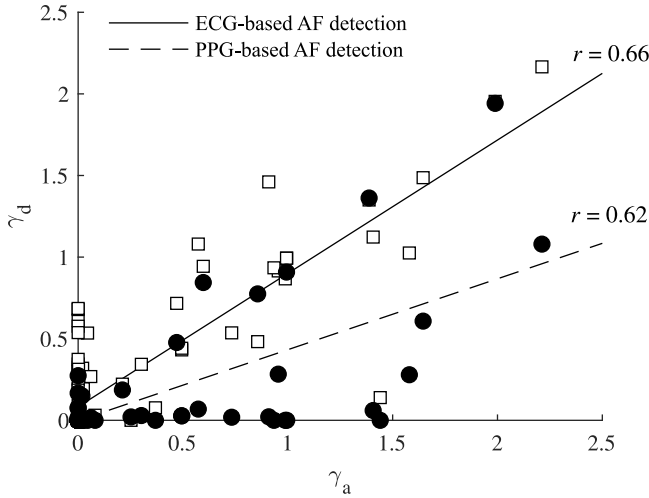
Figure 4.12. Association between γ_a, obtained by using annotated AF episodes, and γ_d, obtained by using detected episodes, for pooled data encompassing all four types of suspected triggers. Bright squares and dark circles represent ECG- and PPG-derived AF episodes, respectively

Parts of Section 4.4 have been quoted verbatim from the previously published articles: [31, 32].

4.5. Conclusions of the Chapter

1. When using the proposed methodology, suspected triggers related to physical exertion, psychophysiological stress, lying on the left side, and sleep disturbances were detected in 80%, 74%, 71%, and 89% of patients, respectively.

2. AF episode patterns were modeled by using a Hawkes process for alcohol consumption ranging from 0 to 15 units. The mean AF burden without alcohol was 17.2%, which doubled with the intake of 10 alcohol units, while the number of AF episodes doubled from 12.9% with the intake of 9 alcohol units.

3. The simulation study shows that the relational strength between AF triggers and the trigger-affected occurrence of AF episodes when using the alcohol effect depends on the type of the AF pattern. For patterns with many short, clustered AF episodes, the relational strength increases 3 to 10 times with the consumption of 12 alcohol units, compared to the same patterns without the alcohol effect. In contrast, for patterns with clustered episodes lasting several minutes and a few

episodes lasting several hours, the relational strength increases only 1.5 to 3.5 times.

4. For some patients, the relational strength increases substantially for all the four types of suspected triggers. Overall, physical exertion emerged as the most significant suspected trigger, associated with the largest increase in relational strength across the highest number of patients ($p < 0.01$). Additionally, no significant difference was found between females and males.

5. DISCUSSION

5.1. Detection of Suspected Triggers

An increasing number of studies are investigating the utility of MET units as a measure for determining thresholds in classifying the intensity of physical activity [94, 119, 120]. However, the majority of these studies have predominantly focused on young or middle-aged adults, while less so on the elderly. Considering the variable effort levels required by patients of different age groups to execute identical activities, discernible differences in energy expenditure become apparent [121]. Relying solely on the estimation of MET from acceleration and HR may inadequately capture the true energy expenditure, potentially resulting in an underestimation of MET [122].

Sleep disorders, such as poor sleep quality, snoring, and obstructive sleep apnea, are frequently associated with AF [17, 18, 74]. Research has shown a 15% higher risk of experiencing an AF episode following a night of poor sleep [101]. Additionally, prolonged instances of poor sleep have been associated with longer AF episodes [101]. Since most adverse health conditions tend to decrease the HR variability [123], SDNN appears to be robust against false detections of sleep disturbances. This can be substantiated by the findings in [102], where a nocturnal SDNN exceeding 116 ms detects sleep apnea with 90% specificity. However, dedicated wearable devices for sleep monitoring may offer a greater accuracy in detecting sleep disturbances. For example, commercial sleep analyzers equipped with pneumatic and acoustic sensors can be used to identify the onset and the end of sleep, as well as detect episodes of snoring and sleep apnea [124].

Alterations in the ANS were also explored by using the widely adopted HR variability index, the low frequency/high frequency ratio, serving as an indicator of the dominant component of sympathetic and vagal activity [103]. However, no difference was observed between post- and pre-trigger intervals in the low frequency/high frequency ratio. This outcome was likely influenced by the collection of physiological signals during unrestricted daily activities, leading to ECG signals of lower quality due to motion artifacts and noise. Additionally, physical activity has an impact on the ANS [125], which makes it challenging to accurately assess its relation to suspected triggers during daily activities.

5.2. Modeling of Trigger Effect on Atrial Fibrillation Occurrence

One approach to understanding the suitability of the causality assessment is to employ simulated signals where the characteristics of the generated AF episode occurrence can be controlled. The modeling of such episode occurrence is here accomplished by the alternating, bivariate Hawkes model [105], accounting for alternating transition times from non-AF to AF, and vice versa, and clustered AF episode occur-

rence. Using three distinct types of AF episode occurrence, the results show that γ is more reliable when the AF burden is rather low and the AF episode occurrence consists of shorter episodes. When the AF burden exceeds 50%, the trigger effect is, as one would expect, less noticeable, and contributes less to γ.

The Hawkes model is used for simulation purposes only; however, the model could also serve as a potential candidate for estimating the impact of alcohol consumption on AF occurrence. For example, the function $R(t; \tau)$ in (2.8) may be scaled by an unknown, multiplicative factor which, together with the other eight model parameters, is subject to maximum likelihood estimation. The impact of alcohol would then be related to the estimated factor, thus serving the same purpose as γ. Since at least 10 AF episodes, i.e., 20 points, are recommended to achieve an acceptable accuracy of the eight parameter estimates [105], the model-based approach is not practical as 10 episodes are not always present during 24-h (12 h before and after the trigger), far less during the shortest interval (2 h before and after the trigger). In two popular, public AF databases (MIT-BIH Atrial Fibrillation Database and Long-Term AF Database), with recording lengths ranging from 10 to 25 h, the number of episodes is less than 10 in as many as 58% of the recordings [126].

The proposed approach was exemplified by using alcohol as a trigger since it is the most commonly recognized acute exposure of AF [13]. However, the approach is not limited to alcohol, but it can be applied to identifying other reported triggers as well. Evidence supports the existence of links between AF occurrence and alcohol [13, 21], physical exertion [15, 16], and sleep disorders [17, 18]. Meanwhile, studies based on questionnaires also revealed that dehydration, stress, large meals, lying on the left side, and cold food may trigger AF [11, 19], although a recent study opposes these findings and shows that only alcohol is clearly associated with more AF episodes [13].

5.3.   Assessment of the Relational Strength

To assess the relational strength of the AF burden, a cumulative principle was proposed which would account for all suspected triggers within the observation interval. Such a principle poses an obvious limitation when many suspected triggers occur that are not causal for AF. For multiple suspected triggers, simply by chance alone, $B_{1,n}$ will be higher than $B_{0,n}$ in some cases, resulting in large γ values. Dividing γ by the total number of suspected triggers would reduce and normalize γ, however, such a principle would not be useful since not all patients are prone to certain triggers, and obviously not in all cases. For example, in [63], almost half of the patients with AF who consumed alcohol did not experience AF during the study period, possibly suggesting that alcohol was not their trigger. Therefore, if alcohol is the trigger, it may not necessarily contribute to AF occurrence every time, but it may as well depend on other factors manifested at the moment. The parameter γ is less sensitive to

short episodes occurring after the trigger. However, in long-term monitoring, there is an inevitable trade-off considering that technologies for the collection of AF episode occurrence are prone to false alarms [45].

The analysis time interval used to compute the pre- and post-trigger burdens is another influential factor on γ. A compromise is needed because an insufficiently long interval may include only a part of the trigger effect, whereas an overly extended interval may involve regions outside the trigger effect. The simulation study showed that the choice of T has a considerable effect on γ, and, therefore, must be selected carefully by accounting for the best available clinical evidence. Based on the findings in [63], the time between alcohol consumption and AF episodes was found to be associated with the prevalence of AF occurrence. The highest prevalence was found to be in the interval of 2–4 hours following the onset of a drinking event, however, an increase in prevalence was observed for up to 10 hours. Thus, a flexible time interval proportional to consumed alcohol may be a better choice. It is equally important to take into account the fact that the time lag between a drinking event and AF occurrence may decrease due to the consumption of food, which would shorten the time of alcohol absorption [127].

The AF burden is chosen for computing γ since evidence shows that the AF burden, on average, is larger among those consuming alcohol [21]. However, the approach is not limited to the AF burden, but AF episode occurrence characterizing parameters reflecting episode aggregation [128], AF density [129], and clustering [105] can be used instead in (2.9). For example, post-trigger AF episode clustering may become more pronounced than pre-trigger clustering, causing γ to grow.

The main finding of the work is a substantial increase in γ_d relative to γ_c found in certain patients. This finding is consistent with those of questionnaire-based studies [11, 19], which indicate the absence of a universal AF trigger. On the contrary, it appears that some triggers occasionally induce AF in certain patients, contingent upon the manifestation of other factors that increase the propensity for AF. To evaluate the temporal relation between a detected suspected trigger and AF occurrence, one might assume that the number of episodes would increase after the trigger. However, the number of episodes in pre- and post-trigger intervals was found to be similar in this work. Therefore, employing a cumulative principle as the one in the definition of γ might prove to be more effective in identifying triggers.

In this investigation, an ECG patch attached to the chest was employed to acquire physiological signals. While wrist-worn PPG-based devices have attracted increasing attention for continuous monitoring in everyday settings, their suitability for the detection of suspected triggers remains unclear. This is primarily due to two factors: a lack of a stable reference point for accelerations and a lower accuracy in HR estimation. Commonly, the mean absolute percentage error of estimated HR from a PPG is 5-20% [130, 131, 132]. Furthermore, the error increases by up to 30% during

high-intensity physical activity compared to resting states. Such large errors pose a limitation for detecting physical exertion, psychophysiological stress, or sleep disturbances when using HR variability analysis. An additional challenge is the detection of lying on the left side based on wrist-derived acceleration signals since the sleep posture varies considerably between individuals, and behavior is less controlled during sleep. Unsurprisingly, the wrist location was found to be the least reliable for accelerometer-based detection of lying posture [88].

PPG-based AF detection in everyday settings is affected by other factors, such as non-wear time and motion artifacts [133]. In this work, the AF burden, determined from AF episode occurrence acquired by the PPG-based detector, exhibited a reduction of approximately 70% when compared to annotated AF episodes. This reduction was primarily attributed to the exclusion of a substantial portion of the PPG signal due to poor quality and non-wear time. These findings are consistent with those reported in [26], where a coverage rate of 52% was achieved, although the patients were encouraged to wear a device overnight. This reduction in the estimated AF burden is important, particularly in light of the fact that trigger-induced increments in the AF burden are typically on the order of a few percentage points [21].

5.4. Limitations and Future Work

The four suspected triggers were chosen based on their feasibility for detection in physiological signals. However, there may exist several other suspected triggers that are not easily detected in physiological signals, e.g., alcohol consumption, dehydration, large meals, and cold food, which potentially could serve as suspected triggers for AF as suggested by questionnaire-based studies [11, 19].

The simultaneous occurrence of multiple suspected triggers and their overlapping effects were not taken into consideration. Assessing any overlap is a complex task requiring more knowledge about the duration of the effect of each type of the suspected trigger. One solution is to group types of the suspected trigger based on the activated components of the ANS [11]. While physical exertion and psychophysiological stress activate the sympathetic nervous system, the effect of lying on the left side on the ANS is unknown.

Within the initial cohort of patients diagnosed with paroxysmal AF, merely 24% encountered at least one AF episode throughout the one-week observation interval. Consequently, the results may be affected by individual variation. Moreover, a relatively low AF burden among those who had AF episodes influenced the relational strength γ, which is less sensitive to a lower AF burden.

Most patients (74%) were administered with beta-blockers which block the release of the stress hormone adrenaline and thus reduce HR. Since HR is directly involved in detecting physical exertion and psychophysiological stress, this may have led to fewer detected suspected triggers.

This work outlines the principles of the detection of suspected triggers in physiological signals but does not address the issue of missed and falsely detected suspected triggers. This is due to several reasons, primarily the fact that the data were collected in the patients' homes. The occurrence times of the reference suspected triggers can be gathered through mobile apps or questionnaires, but both methods suffer from notable limitations. Triggers are self-reported, leading to bias and a time delay between the actual event and when it is logged. The use of specific sensors, such as ethanol detectors, could shorten such delays for certain suspected triggers. For example, self-reported alcohol consumption closely matched the results obtained from transdermal alcohol sensors [63]. However, not all suspected triggers can be detected by using sensors. Validating physical exertion or psychophysiological stress is even more challenging because these suspected triggers are subjective and therefore may differ from the effects observed on physiological signals. Meanwhile, sleep disturbances can be detected in sleep laboratories or by using a sleeping mat, which offers a cheaper but less reliable alternative.

The flexibility to model AF episode occurrence of various characteristics, which is difficult to achieve in a real-world scenario, is an obvious advantage. On the other hand, the use of simulated signals is a limitation of the work, mainly due to the absence of ECG databases with known effects of AF triggers. Therefore, the assumptions supporting the simulation model may be too simplistic considering the large variety of the effects of alcohol [134, 135, 136]. The interpretation of γ may change following the application of the proposed approach to clinical research, as simulated AF episode occurrence involving the effect of a single trigger is employed. It is important to note that real-world AF episode occurrence can be influenced by multiple triggers, which in turn can affect the interpretation of γ. Therefore, the proposed approach should be investigated on patients to better understand what is the difference in γ between the screening and confirmation periods to pinpoint the effect of alcohol.

Another limitation of the work is the modeling of trigger timestamps generated while assuming a uniform distribution. This distribution was chosen to simplify the simulations and avoid overlap of the analysis time intervals, however, in real life, timestamps may not occur uniformly.

The model for simulating alcohol-affected AF episode occurrence should preferably account for other factors than merely the number of alcohol units. The proposed approach was illustrated assuming that the patient is an average male who consumes all alcohol at once. However, the intake level and the pharmacokinetics of alcohol differ between men and women, largely depending on the body mass index, drinking history, eating habits, and age [135, 137]. Other confounders include high salt intake and decreased sleep duration, which, together with alcohol use, may increase the likelihood of AF occurrence [138].

Alcohol may have the strongest effect on AF occurrence, and, therefore, may

act as a confounder or affect the modifier of other triggers. Although acute alcohol intoxication typically causes temporary ECG changes, such as P-wave prolongation, QT prolongation, T-wave abnormalities, and QRS complex prolongation [139], these changes can also result from other conditions, such as the use of certain medications or electrolyte imbalances. Therefore, information on alcohol consumption is usually obtained through questionnaires or ethanol detectors [63]. In this work, the effect of alcohol on other suspected AF triggers was not explored. However, it constitutes a challenging future research topic, particularly when analyzing the intermediate processes from the initial trigger to the occurrence of an AF episode.

Triggers in females and males is yet another interesting research question to explore, but so far such data are lacking. In a questionnaire-based study [11], females were 2–3 times more likely to report lack of sleep and lying on the left side as a suspected trigger. In the present study, the number of suspected triggers was similar in both sexes, i.e., lying on the left side was detected in 14 females and 12 males, sleep disturbances in 13 females and 14 males, physical exertion in 14 females and 12 males, and only psychophysiological stress was more common among males (14 versus 9). Given that differences may exist between males and females in terms of how triggers are experienced [140, 141], physiological signal-based detection of suspected triggers may provide a more accurate assessment compared to relying solely on self-reported data.

The proposed relational strength approach is expected to have a number of practical applications. Firstly, the identification of suspected AF triggers, and the subsequent recommendation to avoid them, may increase the patient's interest to participate more actively during the course of treatment. The incorporation of behavioral changes next to the conventional AF treatment was part of the American Heart Association scientific statement, suggesting lifestyle and risk factor management next to anticoagulation, HR, and heart rhythm control [5]. Secondly, the approach is intended for individual patients with diagnosed AF; however, it can also be useful in longitudinal studies for groups of patients. Thirdly, the proposed approach can be applied to identify positive effects, such as the efficiency of antiarrhythmic medication. Assuming that the AF burden reduces after taking medication, and swapping $B_{0,n}$ with $B_{1,n}$ in the relational strength computation Equation (2.9), γ will indicate whether a positive effect is achieved.

This investigation represents the first exploration of the relation between suspected triggers detected in long-term physiological signals and AF occurrence. Given the limited understanding of how triggers influence AF occurrence in individual patients, the present work is a step towards resolving this circular problem. The development of a technology capable of collecting long-term AF episode occurrence together with the detection of suspected triggers will contribute to comprehending the mechanisms governing trigger effects on AF occurrence.

Parts of Sections 5.1-5.4 have been quoted verbatim from the previously published articles: [31, 33].

6. CONCLUSIONS

1. A methodology for detecting suspected triggers due to physical exertion, psychophysiological stress, lying on the left side, and sleep disturbances in physiological signals has been proposed and explored. Sleep disturbances emerged as the most frequently detected suspected trigger in physiological signals, occurring with a median of 5 times per week (interquartile range: 4–7).

2. The model for simulating trigger-affected AF episode occurrence has been proposed for the purpose of testing the relation assessment approaches. The alternating bivariate Hawkes model has been modified to account for the effects of trigger and used to simulate alcohol-affected occurrences of AF episodes. Without added alcohol, the AF burden was 17.2%, and it doubled with 9 alcohol units. The model for simulating the trigger effects can be further enhanced by customizing the body reactivity function based on factors such as gender, weight, and age.

3. A quantitative approach has been proposed to assess the relational strength between the suspected AF triggers and the occurrence of AF episodes, relying on the pre- and post-trigger AF burden. The simulation study demonstrates that, depending on the type of the AF pattern, the relational strength increases by 3 to 6 times when the trigger effect is added compared to when it is absent. The proposed approach can facilitate the implementation of longitudinal studies aimed at identifying the suspected AF triggers and complement the questionnaire-based approaches.

4. When using physiological signals acquired from patients with paroxysmal AF and annotated AF episode occurrence, physical exertion emerged as the suspected trigger associated with the largest increase in relational strength among the largest number of patients ($p < 0.01$); no significant differences were observed for psychophysiological stress and sleep disorders. To evaluate the utility of wearable devices in assessing the relational strength, both electrocardiogram- and photoplethysmogram-based AF detectors were used to detect AF episodes. The relational strength of the detected AF episodes showed a moderate correlation with that of annotated AF, $r = 0.66$ for electrocardiogram-based detection, and $r = 0.62$ for photoplethysmogram-based detection.

7. SANTRAUKA

ĮVADAS

Tyrimo aktualumas

Prieširdžių virpėjimas (PV) yra labiausiai pasaulyje paplitusi širdies aritmija, diagnozuota daugiau nei 50 milijonų žmonių [1, 2], tačiau tikrasis paplitimas gali būti daug didesnis dėl besimptomių aritmijos atvejų [3, 4]. PV apkrauna sveikatos priežiūros sistemą, ypač dėl komplikacijų, tokių kaip insultas ir širdies nepakankamumas [5]. Sergamumas PV sparčiai auga visame pasaulyje dėl tokių faktorių, kaip senstanti populiacija, didėjantis nutukusių žmonių skaičius ir gretutinės širdies ir kraujagyslių sistemos ligos [6]. Prognozuojama, kad Europoje ir JAV vienas iš keturių vyresnių nei 55-erių metų asmuo susirgs PV [6].

PV komplikacijų valdymo efektyvumas daugiausia priklauso nuo ankstyvos diagnozės, kuri dėl dažnai besimptomių ligos atvejų yra sudėtinga [7]. Tačiau, net ir anksti diagnozavus PV, įprastai apsiribojama geriamųjų antikoaguliantų ir antiaritminių vaistų, kurie siejami su šalutiniu poveikiu, skyrimu [45, 46]. Vis daugiau tyrimų įvardija potencialiai modifikuojamus paroksizminį PV provokuojančius veiksnius, literatūroje vadinamus trigeriais [11]. Dažniausiai mokslinėje literatūroje tirti potencialūs PV trigeriai yra alkoholio vartojimas [13, 14], fizinė perkrova [15, 16] ir psichofiziologinis stresas [17, 18]. Geresnis asmeninių trigerių supratimas leistų gydytojams valdyti pagrindines PV epizodų pasireiškimo priežastis ir įgalintų pacientus aktyviai dalyvauti aritmijos valdyme keičiant gyvenimo būdą [2, 5].

Daugelis ankstesnių tyrimų, tyrusių PV trigerius, rėmėsi subjektyviu identifikavimu pasitelkiant klausimynus [11, 19, 20, 21]. Tokiuose tyrimuose nemaža dalis pacientų identifikuodavo kelis skirtingus trigerius, kam įtakos galėjo turėti pacientų šališkumas, tikint, kad tam tikri veiksniai jiems sukelia aritmijos epizodus [11]. Atvejai, kai pacientai nenurodė nė vieno trigerio, gali būti siejami su prisiminimo šališkumu, pavyzdžiui, nenoru nurodyti sveikatai žalingų įpročių [11]. Norint išvengti šių šališkumų, reikalingi kiekybiniai metodai, kurie papildytų klausimynais grindžiamą trigerių identifikavimą ir padėtų geriau suprasti veiksnius, prisidedančius prie PV epizodų pasireiškimo.

Technologinė pažanga paskatino nešiojamųjų išmanių įrenginių su įvairiais biojutikliais kūrimą, kurie potencialiai gali būti naudojami PV trigeriams identifikuoti bei rinkti PV epizodų pasireiškimo profilius vienu įrenginiu. Reikia pabrėžti, kad PV epizodų pasireiškimo stebėsena – kur kas sudėtingesnis procesas nei vien tik PV epizodų atpažinimas [22]. Tam reikalinga ilgalaikė, nepertraukiama PV stebėsena, nes dėl signalo trūkių ir nepakankamos signalo kokybės prarandami PV epizodai, kurie padaro ryšio tarp potencialių trigerių ir PV epizodų pasireiškimo vertinimą sunkiai įmanomą. Šiuo metu vienintelės ilgalaikės PV stebėsenos priemonės yra implantuo-

jami ir elektrokardiografiniai (EKG) pleistro tipo įrenginiai. Implantuojami įrenginiai brangūs ir rizikingi gyvybei dėl implantavimo procedūros [23], o EKG pleistro tipo įrenginys ilgainiui gali kelti diskomfortą ar dirginti odą [24]. Ant riešo dėvimi įrenginiai, registruojantys fotopletizmogramos (FPG) signalą, patogesni, tačiau mažiau tikslūs atpažįstant PV [25, 26]. Be to, iki šiol nėra atlikta tyrimų trigeriams identifikuoti fiziologiniuose signaluose ir trūksta duomenų bazių su pažymėtais potencialiais trigeriais ir PV epizodais.

Kitas svarbus iššūkis – suprasti potencialių trigerių ir PV epizodų sąsajas individualiems pacientams. Trigerių laiko žymos bei PV epizodų pradžios ir pabaigos yra nestacionarūs dvejetainiai duomenys, todėl įprasti priežastingumo vertinimo metodai, tokie kaip Grangerio priežastingumas arba priežastinis prognozavimas, nėra lengvai pritaikomi, o atstumo ir koreliacijos metodai [27, 28] tinka tik dviejų procesų panašumui vertinti. Nėra metodų, įgalinančių įvertinti ryšį tarp potencialių trigerių ir PV epizodo pasireiškimo individualiam pacientui, o tai lemia tolesnių šios srities tyrimų poreikį.

Mokslinė ir technologinė problema

Kaip fiziologiniuose signaluose identifikuoti potencialius PV trigerius ir įvertinti ryšį su PV pasireiškimu individualiam pacientui?

Tyrimo objektas

Dėvimiems įrenginiams pritaikytas metodas, skirtas asmeniniams potencialiems PV trigeriams identifikuoti.

Tyrimo tikslas

Šios daktaro disertacijos tikslas yra sukurti ir ištirti metodą, įgalinantį individualiai identifikuoti PV trigerius.

Tyrimo uždaviniai

1. Pasiūlyti metodiką potencialiems PV trigeriams fiziologiniuose signaluose atpažinti.

2. Sukurti modelį skirtą trigerio poveikiui PV epizodų pasireiškimui simuliuoti.

3. Pasiūlyti būdą, skirtą įvertinti ryšiui tarp potencialaus PV trigerio ir PV epizodų pasireiškimo.

4. Ištirti ryšį tarp potencialių PV trigerių ir PV epizodų pasireiškimo naudojant paroksizminiu PV sergantiems pacientams užregistruotus fiziologinius signalus.

Mokslinis naujumas

Individualių trigerių identifikavimas ir elgsenos pokyčių įgyvendinimas gali būti veiksminga strategija papildant tradicinį farmakologinį aritmijos valdymą. Šioje daktaro disertacijoje pasiūlyta metodika skirta potencialiems PV trigeriams fiziologiniuose signaluose identifikuoti. Taip pat ištirta ilgalaikės FPG pagrindu pagrįsto PV atpažinimo galimybė kaip alternatyva tradiciniam EKG pagrįstam atpažinimui.

Dėl duomenų bazių su anotuotais trigeriais ir PV epizodais trūkumo ši daktaro disertacija siūlo Hawkes modelį, leidžiantį simuliuoti trigerio poveikį PV epizodų pasireiškimui. Modeliavimo principui iliustruoti naudojamas alkoholio poveikis, kuris PV epizodams paveikti modeliuojamas kaip alkoholio organizmo reaktyvumo funkcija, kurios savybės priklauso nuo suvartoto alkoholio kiekio, išreikšto standartiniais etanolio vienetais.

Šiuo metu potencialių trigerių identifikavimo tyrimai remiasi klausimynais. Siekiant sumažinti šališkumą dėl subjektyvaus principo, siūlomas kiekybinis metodas, leidžiantis įvertinti ryšį tarp potencialaus trigerio ir PV epizodų pasireiškimo individualiam pacientui. Metodas išsprendžia nestacionarių ir dvejetainių duomenų problemą.

Pasiūlytas potencialių PV trigerių identifikavimo metodas ištirtas naudojant dėvimais įrenginiais užregistruotus fiziologinius signalus, užregistruotus pacientams, kuriems diagnozuotas paroksizminis PV.

Praktinė reikšmė

1. Siūlomas metodas potencialiems PV trigeriams identifikuoti svarbus dėl žemiau išvardintų priežasčių:

   (a) Metodika, kuri naudoja EKG ir akcelerometro signalus, įgalina atpažinti potencialius PV trigerius dėl fizinės perkrovos, psichofiziologinio streso, gulėjimo ant kairiojo šono ir miego sutrikimų ilgalaikiuose fiziologiniuose signaluose, užregistruotuose paciento kasdienės gyvensenos sąlygomis.

   (b) Trigerio poveikį simuliuojantis modelis leidžia modeliuoti su trigerio poveikiu siejamas PV epizodų sekas. Remiantis moksliniais įrodymais, modeliu galima simuliuoti įvairių trigerių poveikį, tokių kaip alkoholis, didelis maisto kiekis, šalti gėrimai ar šaltas maistas, ūmus stresas ir nerimas. Modelis sprendžia anotuotų duomenų bazių trūkumo problemą, taip pat naudingas testuojant ryšio tarp potencialaus trigerio ir PV epizodų pasireiškimo vertinimo metodus.

   (c) Kiekybinis įvertis ryšio stiprumui tarp potencialaus trigerio ir PV epizodų atsiradimo įvertinti turi potencialo palengvinti ilgalaikių tyrimų įgyvendinimą ir gali būti naudojamas kaip mažiau šališka alternatyva klausimynais pagrįstam PV trigerių identifikavimui.

2. Šiame darbe pateikti sprendimai vystyti vykdant projektą „Personalizuotas paroksizminio priešírdžių virpėjimo trigerių atpažinimas ir valdymas naudojant dėvimas technologijas – TriggersAF“, kurį finansavo Europos regioninės plėtros fondas pagal sutartį su Lietuvos mokslo taryba (LMTLT), (01.2.2-LMT-K-718-03-0027), 2020–2023.

3. Europos patento paraiškoje „Priežastingumo balo tarp priešírdžių virpėjimo trigerių ir priešírdžių virpėjimo epizodų nustatymo metodas“ (Kauno technologijos universitetas, Vilniaus universitetas. EP21179681.8. 2021-06-16) aprašytos kai kurios disertacijoje naudojamų algoritmų dalys.

Tyrimo aprobavimas

Daktaro disertacija remiasi dviem pagrindiniais straipsniais, publikuotais tarptautiniuose moksliniuose žurnaluose, turinčiuose cituojamumo rodiklį „Clarivate Analytics Web of Science“ duomenų bazėje. Esminiai rezultatai pristatyti tarptautinėje pasaulyje pripažintoje konferencijoje: 49-oji ir 50-oji „Computing in Cardiology“ konferencijos.

Ginti teikiami teiginiai

1. Potencialūs PV trigeriai gali būti atpažįstami fiziologiniuose signaluose. EKG ir pagreičio signalai gali būti naudojami nuo laiko priklausomiems parametrams, kurių specifinės slenkstinės vertės naudojamos potencialiems trigeriams identifikuoti, apskaičiuoti.

2. Trigerio paveiktų PV epizodų pasireiškimą galima modeliuoti naudojant kintantį dviejų būsenų Hawkes procesą, atsižvelgiant į organizmo reaktyvumo funkciją, kuri apibūdina trigerio poveikį.

3. Ryšys tarp potencialaus trigerio ir PV epizodų pasireiškimo gali būti kiekybiškai įvertintas remiantis santykine PV trukme prieš ir po trigerio tam tikrame analizės laiko intervale, kuris priklauso nuo trigerio poveikio trukmės.

4. Siūlomas būdas ryšio stiprumui tarp potencialaus PV trigerio ir PV epizodų pasireiškimo įvertinti yra mažiau šališka alternatyva nei klausimynais pagrįsti metodai.

Bendradarbiavimas

Pasiūlytas metodas buvo sukurtas bendradarbiaujant su Leifu Sörnmo iš Lundo universiteto (Lundas, Švedija). Tyrime naudojami priešírdžių virpėjimo detektoriai buvo anksčiau sukurti Andriaus Sološenko [25] ir Andriaus Petrėno [34].

7.1 APŽVALGA

Prieširdžių virpėjimui būdingas nereguliarus ir itin greitas prieširdžių susitraukimų dažnis, kai depoliarizacija įvyksta 300–600 kartų per minutę. Tokiu atveju atrioventrikulinis mazgas veikia kaip filtras tarp prieširdžių ir skilvelių elektrinio laidumo sistemų, leisdamas tik daliai impulsų pasiekti skilvelius. Kol aritmija ankstyvų stadijų, PV epizodai dažnai būna trumpi ir savaime nutrūkstantys. Ilgainiui PV gali progresuoti į nuolatinį PV [37], kai epizodai trunka nepertraukiamai ilgiau nei 7 dienas. Galiausiai PV gali pereiti į nenutrūkstamą stadiją [38]. Pavojinga PV komplikacija – kraujo krešulių, kurie gali patekti į smegenis, plaučius, inkstus arba užkimšti arterijas, susidarymas [39].

Klinikinei PV diagnozei reikalingas dokumentuotas, ilgiau nei 30 sekundžių trunkantis PV epizodas, užregistruotas 12 derivacijų EKG [35, 36]. Pagrindiniai PV požymiai, matomi EKG, yra nereguliarus širdies ritmas, P bangų nebuvimas ir virpėjimo bangų atsiradimas.

Remiantis naujausiu PV mechanizmų supratimu, PV epizodai pasireiškia dėl aritmogeninio substrato, moduliuojančių ir potencialiai modifikuojamų veiksnių, dar vadinamų PV trigeriais, sąveikos [40, 41, 42]. Užsitęsęs PV sukelia elektrinius ir struktūrinius prieširdžių pokyčius, todėl svarbu kuo ilgiau išlaikyti pacientą ne PV būsenos [43].

Nepaisant pažangos gydant aritmijas, PV valdymas tebėra sudėtingas iššūkis [44]. Dabartinės gydymo galimybės daugiausia apsiriboja antikoaguliantais ir antiaritminiais vaistais, kurie siejami su pavojingais šalutiniais poveikiais, pvz., vidiniu kraujavimu, hipotenzija, hemodinamikos ir autonominės nervų sistemos (ANS) pokyčiais, ar net gali sukelti gyvybei pavojingas aritmijas [9, 10, 36, 45, 46]. Šiuolaikiniai gydymo metodai, tokie kaip abliacija, yra brangūs ir ne visada sėkmingi, nes po procedūros PV gali pasikartoti [47]. Veiksminga PV valdymo strategija galėtų apimti gyvenimo būdo pokyčius ir modifikuojamų veiksnių kontrolę kartu su farmakologiniu PV gydymu [12].

PV trigeriai sulaukia vis didesnio mokslininkų ir gydytojų susidomėjimo dėl galimos įtakos PV epizodams pasireikšti, todėl asmeninių potencialių trigerių kontrolė gali tapti svarbiu PV valdymo aspektu. Keletas tyrimų parodė, kad PV pacientai gali apibūdinti veiksnius, kuriems pasireiškus prasideda PV [11]. Tyrime, kuriame pacientai klausimynuose turėjo nurodyti potencialius PV trigerius [11], dauguma jų įvardijo bent po vieną, kurių dažniausi pavaizduoti 7.1 pav.

Iš išvardytų potencialių PV trigerių [11, 19] alkoholis labiausiai ištirtas [20]. Buvo parodyta, kad kelis mėnesius visiškai atsisakius alkoholio, PV epizodų sumažėja dvigubai [21]. Taip pat nustatyta, kad dviejų ar daugiau standartinių alkoholio vienetų suvartojimas siejasi su tris kartus padidėjusia PV epizodų pasireiškimo tikimybe per artimiausias keturias valandas [63]. Nors tikslus alkoholio poveikis, prisidedantis prie
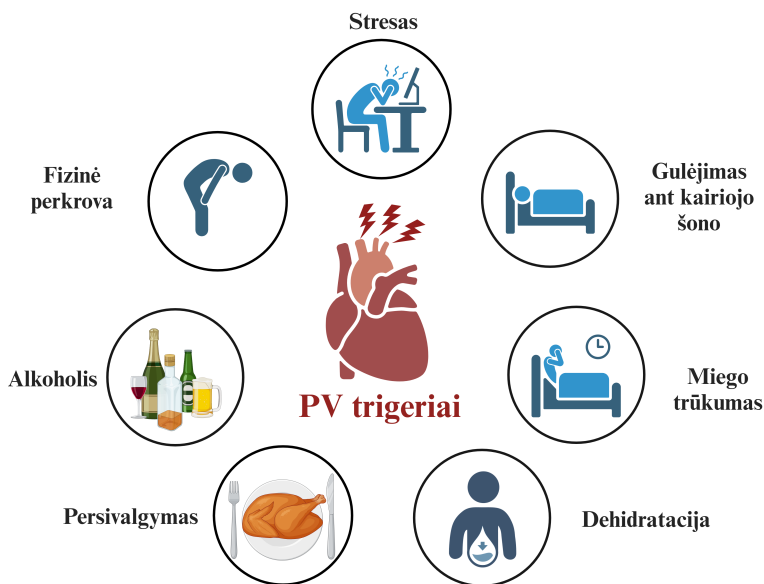
7.1 pav. Potencialūs PV trigeriai, dažniausiai nurodyti klausimynų pagrindu atliktuose tyrimuose

PV epizodų pasireiškimo, neišaiškintas, keliama hipotezė, kad alkoholis tiesiogiai veikia prieširdžių elektrines savybes dėl toksiško poveikio širdžiai arba ANS [14, 64].

Mokslinė literatūra nurodo J formos ryšį tarp fizinio aktyvumo ir PV, kas reiškia, jog lengvas ir vidutinio intensyvumo fizinis aktyvumas mažina PV riziką, o nejudrumas ir intensyvus fizinis krūvis – didina [16].

Psichofiziologinis stresas neigiamai veikia širdies ir kraujagyslių sistemą bei gali padidinti PV epizodų pasireiškimo riziką [68]. Streso ir neigiamų emocijų metu organizmas išskiria streso hormonus, tokius kaip adrenalinas, noradrenalinas ir kortizolis, kurie veikia kraujotaką, suaktyvindami mechanizmus, tokius kaip padidėjęs širdies ritmas (ŠR) ir padidėjęs kraujospūdis.

Pacientai dažnai nurodo, kad gulėjimas ant kairiojo šono prisideda prie PV epizodų pasireiškimo [11]. Šis potencialus PV trigeris gali būti aiškinamas padidėjusiu tempimu plaučių venose.

Miego sutrikimai, įskaitant prastą miego kokybę, nepakankamą miego trukmę, knarkimą ir obstrukcinę miego apnėją, gali prisidėti prie PV vystymosi ir PV epizodų pasireiškimo [73, 74]. Vienas iš galimų mechanizmų yra kraujospūdžio padidėjimas dėl sumažėjusio deguonies lygio kraujyje, sukeliant chemorefleksą, galintį didinti tempimą kairiajame prieširdyje [75, 76].

Esami potencialių trigerių identifikavimo būdai remiasi savarankiškai identifikuotais trigeriais, naudojant iš anksto sudarytus sąrašus arba klausimynus, tačiau tokie metodai gali būti paveikti patvirtinimo šališkumo, kai pacientai mano, kad tam

tikri įvykiai lemia PV epizodų pasireiškimą. Be to, pacientai gali neprisiminti tam tikrų įvykių arba gali gėdytis pateikti informaciją apie žalingus veiksnius, pvz., alkoholio vartojimą. Dėl to prasminga klausimynus papildyti kiekybiniais potencialių trigerių identifikavimo metodais.

7.2 METODAI

7.2.1 Potencialių trigerių atpažinimo fiziologiniuose signaluose algoritmai

Šioje disertacijoje tirti trigeriai pasirinkti remiantis klausimynų pagrindu atliktais tyrimais [11, 19]. Kiekvienas potencialus trigeris remiasi susijusiu parametru, apskaičiuojamu nuosekliuose intervaluose EKG ir (arba) pagreičio signaluose. Dėl paprastumo fizinė perkrova, psichofiziologinis stresas, gulėjimas ant kairiojo šono ir miego sutrikimai įvardijami potencialiais trigeriais, neatsižvelgiant į tai, ar po jų pasireiškia PV.

7.2.1.1 Fizinė perkrova

Didelio intensyvumo fizinis krūvis laikomas veiksniu, galinčiu prisidėti prie PV epizodų pasireiškimo tiek sportininkams, tiek bendrai populiacijoje [91]. Fizinio krūvio intensyvumui įvertinti naudojamas metabolinio ekvivalento (MET) įvertis, kuris matuoja energijos sąnaudas, reikalingas įvairiomis fizinėmis veiklomis atlikti.

Dėl fizinio pasirengimo ir sveikatos būklės skirtumų pacientams būdingos skirtingos ŠR reakcijos į fizines veiklas. MET įvertis leidžia individualiai vertinti pacientų fizines pastangas atliekant tam tikras veiklas, lyginant su energijos sąnaudomis ramybės būsenoje. Fizinei perkrovai atpažinti naudojama regresijos lygtis ir skaičiuojamas y_{MET} įvertis, pasitelkiant pagreičio ir ŠR duomenis [92]:

$$y_{\text{MET}} = 0,0043 x_{\text{ACC}} + 0,047 x_{\text{HRR}} + 1,4238,$$

čia x_{ACC} yra trijų pagreičio ašių atstojamasis vektorius, x_{HRR} – ŠR rezervas, kuris priklauso nuo širdies gebėjimo reaguoti į fizinį aktyvumą.

Atstojamasis pagreičio vektorius x_{ACC} apskaičiuotas pašalinus gravitacinio pagreičio komponentę, filtruojant triašį pagreičio signalą aukštų dažnių filtru, kurio pjūvio dažnis 0,7 Hz [93], vidurkinant minutės trukmės intervaluose [94].

ŠR rezervas x_{HRR} apskaičiuotas pagal:

$$x_{\text{HRR}} = \frac{x_{\text{HR},a} - x_{\text{HR},r}}{x_{\text{HR},m} - x_{\text{HR},r}} \cdot 100,$$

čia $x_{\text{HR},a}$ – vidutinis ŠR 1 minutės intervale, $x_{\text{HR},r}$ – 5 minučių vidutinis ŠR dienos metu ramybėje, įvertintas iš nefiltruoto triašio pagreičio signalo vidutinės amplitudės nuokrypio 3–15 miligravitacijos jėgos vienetų intervale. $x_{\text{HR},m}$ yra didžiausias ŠR, apskaičiuotas naudojant standartinę formulę: 220 minus amžius.

Potencialus trigeris identifikuojamas, kai vidutinis y_{MET}, apskaičiuotas 1 minutės intervalui ne PV metu, viršija 5 MET vienetus. Atsižvelgiant į tai, kad dauguma pacientų vyresnio amžiaus, fizinės perkrovos atpažinimo slenkstis sumažintas iki 5 vietoje 6, kuris paprastai naudojamas jaunesnės populiacijos didelio intensyvumo fiziniam aktyvumui apibūdinti [95].

7.2.1.2 Psichofiziologinis stresas

Psichofiziologinio streso metu organizmas išskiria streso hormonus, todėl išauga ŠR ir širdis susitraukia stipriau, o tai gali turėti įtakos PV epizodų pasireiškimui [68]. Psichofiziologinio streso aptikimas remiasi prielaida, kad staigus ŠR padidėjimas, nesusijęs su reikšmingu fiziniu aktyvumu ar aritmija, gali atspindėti stresą sukeliančią situaciją.

Potencialus trigeris identifikuojamas, kai ŠR padidėja 15 dūžių per minutę vienos minutės intervale [97], jeigu tuo metu nebuvo reikšmingo fizinio aktyvumo ir per pastarąsias 4 valandas nebuvo aptiktas kitas potencialus trigeris. Fizinio aktyvumo nebuvimu laikoma, kai vidutinis 5 minučių intervalo ir analizuojamo 1 minutės intervalo vidutinis triašio pagreičio amplitudės nuokrypis mažesnis nei 22,5 miligravitacijos jėgos vienetai, kas atitinka sėdimą veiklą arba stovėjimą [98]. Vertinant ŠR padidėjimą ir siekiant sumažinti išskirčių poveikį, ŠR apskaičiuojamas 1 minutės ŠR verčių sekoje kaip pirmo laipsnio polinomo pirmos ir paskutinės verčių skirtumas.

7.2.1.3 Gulėjimas ant kairiojo šono

Tam tikri pacientai nurodo gulėjimą ant kairiojo šono kaip potencialų PV trigerį [11, 70]. Šis galimai aritmiją provokuojantis veiksnys aiškinamas tuo, kad kairioji gulima šoninė padėtis sukelia spaudimą prieširdžių ir plaučių venų sienelėse, o toks poveikis tam tikriems pacientams veikia proaritmiškai [71, 99, 100].

Potencialus trigeris atpažįstamas, kai įrenginio pagreičio vidurinės šoninės ašies (ACC_y) signalas, kuris geriausiai atspindi kairę šoninę gulėjimo padėtį, išlieka žemiau -600 miligravitacijos vienetų bent 1 valandą. Atsižvelgiant į tai, kad gulėjimo padėtis keičiasi kelis kartus per naktį, potencialiu trigeriu laikomas pirmasis įvykis 4 valandų intervale.

7.2.1.4 Miego sutrikimai

Miego sutrikimai, ypač obstrukcinė miego apnėja, gali prisidėti prie PV epizodų pasireiškimo [74, 101]. Atsižvelgiant į tai, kad obstrukcinės miego apnėjos epizodus dažnai lydi cikliški ŠR pokyčiai, ŠR variabilumo parametrai gali būti panaudoti sutrikusio miego epizodams aptikti [102]. ŠR pokyčiai nakties metu atpažįstami standartiniu normalių RR intervalų nuokrypio (SDNN) parametru, kuriuo galima spręsti apie dominuojančią ANS komponentę [103].

Prieš skaičiuojant SDNN, RR intervalų seka koreguojama atsižvelgiant į praleistus, klaidingai aptiktus ir priešlaikinius širdies susitraukimus [104]. Klaidingi RR intervalai pašalinami, praleistų atveju įterpiami nauji, o esant per ilgam RR intervalui, intervalas padalijamas į du tokio pat ilgio RR intervalus. Priešlaikiniai širdies susitraukimai pašalinami interpoliuojant gretimus RR intervalus.

Potencialiems miego sutrikimams atpažinti analizuojama naktis nuo 00.00 iki

7.00 val., apskaičiuojant SDNN vertes 1 valandos trukmės intervaluose. Kai SDNN viršija 116 ms slenkstį [102], intervalo pradžia laikoma potencialaus trigerio pradžia.

7.2.2 Trigerio paveiktų prieširdžių virpėjimo epizodų sekų modeliavimas

Identifikuoti asmeninius trigerius, susijusius su PV epizodų pasireiškimu, sudėtinga užduotis, nes esamiems kiekybiniams ryšio vertinimo metodams reikalingos didelės pacientų grupės (pvz., atsitiktinių imčių kontroliniai tyrimai), arba metodai turi esminių apribojimų, tokių kaip nepakankamas patikimumas esant nestacionariems ir dvejetainiams duomenims (pvz., Grangerio priežastinis ryšys). Vienas iš būdų, kuris leistų suprasti ryšio įvertinimo metodų tinkamumą, – naudoti simuliuotas duomenų bazes, kuriose žinomas trigerio poveikis PV epizodų pasireiškimui.

Žemiau aprašomas modelio įgyvendinimo principas, kuris iliustruojamas alkoholio poveikiu PV epizodų pasireiškimui. Alkoholio pasisavinimui ir pasišalinimui iš organizmo apibūdinti naudojama organizmo reaktyvumo funkcija, kuri priklauso nuo kelių veiksnių: suvartotų standartinių alkoholio vienetų skaičiaus, laiko, reikalingo etanoliui iki galo pasišalinti iš organizmo, bei pasisavinimo ir pašalinimo greičio.

Alkoholio suvartojimas paprastai įvertinamas standartiniais alkoholio vienetais, atsižvelgiant į gryno etanolio kiekį alkoholiniuose gėrimuose [106]. Organizmas pradeda pasisavinti alkoholį, kai jis pasiekia skrandį, ir tai vidutiniškai gali trukti nuo 10 minučių iki valandos [107]. Šiame darbe priimama, kad vienas standartinis alkoholio vienetas atitinka 10 ml gryno etanolio [108].

Remiantis alkoholio kiekiu galima sudaryti organizmo reaktyvumo funkciją, kurią modeliuojant daroma keletas prielaidų [109]: vidutiniam 70 kg svorio vyrui vieno standartinio alkoholio vieneto pasisavinimas užtrunka 30 minučių, o visiškas pašalinimas – vieną valandą. Šiame darbe alkoholio pasisavinimas modeliuojamas naudojant apribotą eksponentinę augimo funkciją, kuri aprašoma:

$$y(t; u) = u(1 - e^{-at}), \quad a > 0,$$

čia u – alkoholio vienetų skaičius, o a – eksponentės augimo parametras $10{,}6/u$ vnt./val. [109]. Alkoholio pašalinimas iš organizmo modeliuojamas tiesine funkcija, kurios nuolydis b atitinka 1 vnt./val. [107].

Trijų standartinių alkoholio suvartojimo laike organizmo reaktyvumo funkcija pavaizduota 7.2.1 pav. Svarbu atkreipti dėmesį, kad trečiasis alkoholio vartojimas, kurio pradžia 21.30 val., yra anksčiau nei baigiasi antrojo alkoholio vieneto pašalinimas. Dėl šios priežasties organizmo reaktyvumo funkcija prasideda nuo 0,5 ir pakyla iki 1,5 alkoholio vienetų.

Kiti dažnai literatūroje minimi trigeriai, kurie taip pat gali būti modeliuojami organizmo reaktyvumo funkcijomis, yra fizinis krūvis, persivalgymas, šalti gėrimai ir šaltas maistas [11].
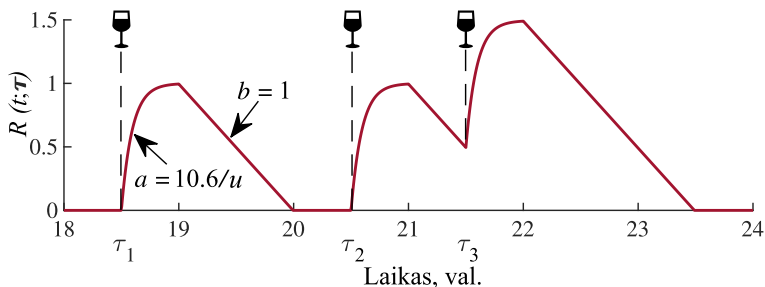
7.2.1 pav. Trijų standartinių alkoholio vienetų suvartojimo laike organizmo reaktyvumo funkcija

Nors žinios apie ryšio tarp alkoholio vartojimo ir PV epizodų pasireiškimą gana ribotos, manoma, kad egzistuoja tiesinis ryšys [63]. Kitas tyrimas parodė, kad alkoholio vartojimas padidina santykinę PV trukmę ir PV epizodų pasireiškimo riziką. Remiantis tuo, kuriant modelį daroma prielaida, kad PV epizodų pasireiškimo tikimybė tiesiškai didėja, augant suvartotam standartinių alkoholio vienetų skaičiui.

Kintantis dviejų būsenų Hawkes modelis leidžia simuliuoti įvairius PV epizodų pasireiškimo profilius [105]. Šioje disertacijoje modelis patobulintas integruojant trigerio poveikį apibūdinančią organizmo reaktyvumo funkciją, kuri padidina PV epizodų pasireiškimo tikimybę trigerio poveikio laiko intervaluose. 7.2.2 pav. pateikti simuliuoti PV epizodų pasireiškimo profiliai: (a) be trigerio įtakos ir (b) su trigerio įtaka, kai pridėtas trijų alkoholio vienetų poveikis ties 10.00. Čia $\mu_1(t)$ yra laike kintantis Hawkes modelio parametras, kuris modifikuojamas pagal organizmo reaktyvumo funkciją, o $\lambda_1(t)$ – modelio funkcija, kuri nulemia būsenos persijungimus iš ne PV ritmo į PV.

7.2.3 Ryšio stiprumo tarp potencialaus trigerio ir prieširdžių virpėjimo epizodų pasireiškimo įvertinimas ir interpretavimas

Potencialių trigerių identifikavimo būdas remiasi prielaida, kad PV santykinė trukmė po trigerio didesnė nei prieš trigerį. Analizės laiko intervalas T, naudojamas skaičiuojant santykinę PV trukmę po trigerio $B_{1,n}$, parenkamas atsižvelgiant į numanomą trigerio efekto trukmę. Dėl paprastumo toks pat intervalo ilgis naudojamas skaičiuojant PV santykinę trukmę po trigerio $B_{0,n}$. Ryšio stiprumo įvertis γ, kuris susieja santykines PV trukmes prieš ir po trigerio, randamas pagal:

$$\gamma = \sum_{n=1}^{N_t} \frac{B_{1,n}}{1 + B_{0,n}} H(B_{1,n} - B_{0,n}),$$

čia N_t yra trigerių skaičius stebėjimo intervale. Hevisaido žingsnio funkcija $H(\cdot)$ panaudota siekiant atmesti atvejus, kai santykinė PV trukmė prieš trigerį didesnė nei po trigerio ($B_{0,n} > B_{1,n}$), nes tokiais atvejais negalima daryti prielaidos, kad trigeris darė poveikį PV epizodų pasireiškimui.
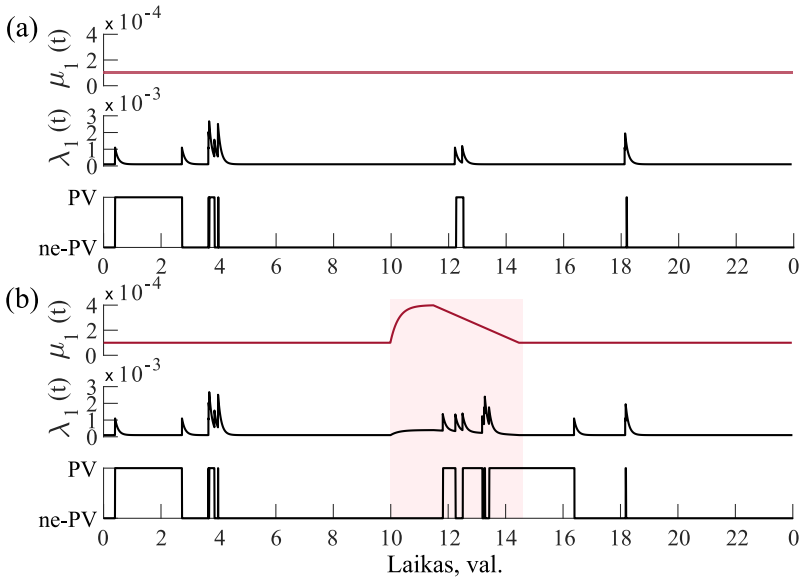
7.2.2 pav. Simuliuoti PV epizodų pasireiškimo profiliai (a) be ir (b) su alkoholio poveikiu. Raudoname fone parodomas trigerio poveikio intervalas

Ryšio stiprumo įverčiui skaičiuoti taikomas kaupiamasis principas, nes nėra pagrindo manyti, kad trigeris visada paveiks santykinę PV trukmę. Labiausiai tikėtina, kad trigeris tik kartais darys įtaką PV epizodų pasireiškimui, taip pat priklausomai nuo kitų lygiagrečiai veikiančių veiksnių, didinančių PV epizodų pasireiškimo tikimybę [40, 42]. 7.2.3 pav. parodytas sąryšio stiprumo įvertis γ skirtingų PV epizodų pasireiškimo profilių atveju.

Interpretuojant ryšio stiprumo įvertį γ, reikia atsižvelgti į tai, kad vieno trigerio atveju, kai PV epizodas prasideda iškart po trigerio ir nesibaigia per visą analizės laiko intervalą ($B_{1,n} = 1$), o analizės laiko intervale prieš trigerį nebuvo nė vieno PV epizodo ($B_{0,n} = 0$), tuomet $\gamma = 1$, o tai priskiriama vidutiniam ryšio stiprumui. Atvejais, kai $B_{1,n} = 1$, o $B_{0,n} > 0$, tada įvertis gali įgyti vertes nuo 0,5 iki < 1, o tai rodo silpną sąryšį. Kai $B_{1,n}$ ir $B_{0,n}$ artėja prie 0, tada $\gamma < 0,5$, o tai rodo labai silpną ryšį. Atvejais, kai yra bent du trigeriai ir jiems abiem esant santykinė PV trukmė po trigerio yra didesnė nei prieš trigerį ($B_{1,n} > B_{0,n}$), laikoma, kad ryšys stiprus.

7.2.4 Prieširdžių virpėjimo epizodų atpažinimas fiziologiniuose signaluose

Siekiant įvertinti nešiojamųjų įrenginių panaudojimo galimybes vertinant ryšį tarp potencialių trigerių ir PV epizodų pasireiškimo, pasitelkti EKG ir FPG pagrindu veikiantys PV detektoriai.

EKG analizuojantis detektorius remiasi tuo, kad PV metu padidėja ŠR ir RR intervalai tampa nereguliarūs [34]. Detektorius sukurtas ypač trumpiems PV epizo-
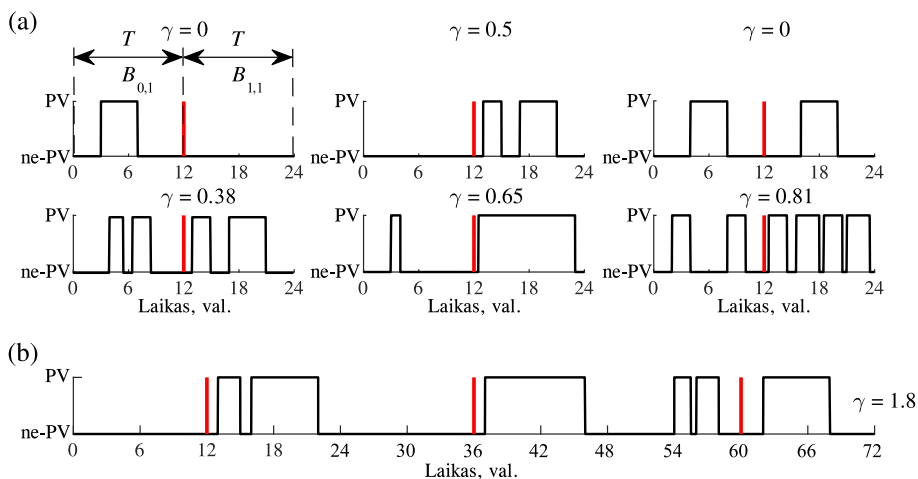
7.2.3 pav. Ryšio stiprumo įvertis γ skirtingiems PV epizodų pasireiškimo profiliams, kai (a) šešiuose skirtinguose PV epizodų pasireiškimo profiliuose per parą buvo vienas trigeris ir (b) trys trigeriai įvyko tuo pačiu paros metu trijų dienų laikotarpiu. Trigerio pradžios laikas pažymėtas raudonai. Visais atvejais prieš ir po trigerio analizės laiko intervalas T parinktas 12 valandų

dams atpažinti, o klaidingų aliarmų skaičiui mažinti įgyvendinti priešlaikinių širdies susitraukimų ir bigeminų poveikį slopinantys blokai. Analogišku principu veikia ir FPG signalą analizuojantis detektorius, tačiau papildomai įgyvendintas signalo kokybės vertinimo algoritmas [25].

7.3 DUOMENŲ BAZĖS

7.3.1 Simuliuoti duomenys

Dėl duomenų bazių su anotuotais trigeriais ir PV epizodais trūkumo šioje disertacijoje panaudota modeliuota signalų su įvairiu trigerio poveikiu duomenų bazė. Ši duomenų bazė ypač vertinga, tiriant siūlomą ryšio tarp trigerio ir PV epizodų pasireiškimo įvertinimo metodą dėl galimybės turėti informaciją apie trigerio pasireiškimo trukmę. Trys PV epizodų pasireiškimo tipai panaudoti trigeriu paveiktų PV epizodų pasireiškimo profiliams modeliuoti, žr. 7.3.1 pav.:

1. daug epizodų klasteryje, kurių kiekvienas trunka keletą minučių,

2. daug epizodų klasteryje, kurių kiekvienas trunka nuo keliolikos minučių iki kelių valandų,

3. keli epizodai, kurių kiekvienas trunka keliolika valandų.
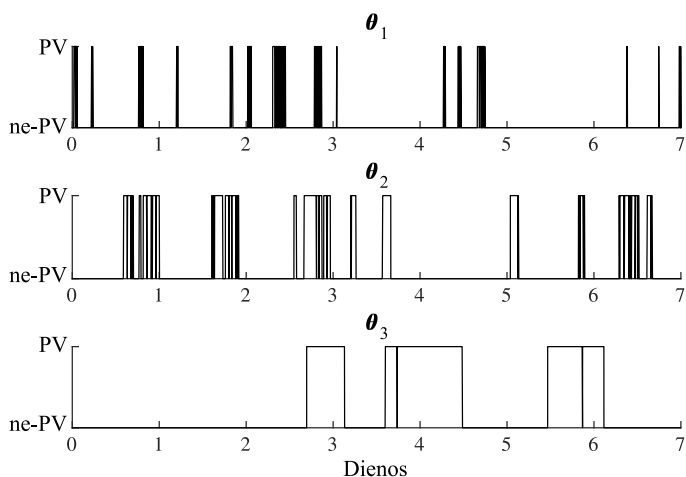
7.3.1 pav. Modeliuotų PV pasireiškimo profilių tipų pavyzdžiai be pridėto trigerio poveikio. Iliustracijoje pavaizduota tik pirmoji simuliuotų PV epizodų pasireiškimo profilių savaitė

Kiekvienam PV epizodų pasireiškimo tipui sumodeliuota po 100 vieno mėnesio trukmės PV epizodų pasireiškimo profilių, iš kurių kiekvienas rinkinys su skirtingu trigerių (0, 2, 4, 6, 8 ir 10) ir alkoholio vienetų (3, 6, 9, ir 12) skaičiumi. Iš viso sumodeliuotame duomenų rinkinyje yra $3 \cdot 100 \cdot 6 \cdot 4 = 7200$ mėnesio trukmės PV epizodų pasireiškimo profilių. Siekiant išvengti analizės laiko intervalų T persidengimo, PV epizodų pasireiškimas modeliuotas darant prielaidą, kad kitas trigerio įvykis pasireikš praėjus mažiausiai 12 valandų po ankstesnio trigerio. PV epizodų

pasireiškimą paveikę trigeriai laike išdėstyti generuojant atsitiktinius skaičius iš toly-giojo skirstinio.

Siekiant ištirti alkoholiu paveikto PV epizodų pasireiškimo modelio veikimą, buvo susimuliuota mažesnė, 24 valandų trukmės PV epizodų pasireiškimo profilių duomenų bazė. Čia kiekvienam alkoholio vienetų skaičiui, nuo 0 iki 15, simuliuota po 50 paros trukmės profilių. Iš viso susimuliuota 300 PV epizodų pasireiškimo profilių.

7.3.2 Klinikiniai duomenys

Vilniaus universiteto ligoninės Santaros klinikų Kardiologijos skyriaus pacien-tai, kuriems diagnozuotas paroksizminis PV, buvo pakviesti dalyvauti tyrime. Prieš dalyvavimą pacientai pateikė rašytinį sutikimą dalyvauti tyrime. Tyrimui pritarė re-gioninis bioetikos komitetas (leidimo numeris 158200-18/7-1052-557). Iš viso tyrime dalyvavo 182 pacientai, tačiau tolesnei analizei naudoti 35 pacientų, kuriems per stebėjimo laikotarpį pasireiškė bent vienas PV epizodas, duomenys.

Duomenų bazę sudaro fiziologiniai signalai, užregistruoti nevaržomos kasdienės veiklos metu naudojant Bittium OmegaSnap™ vienos derivacijos pleistro tipo EKG įrašymo įrenginį „Bittium", Suomija) ir Kauno technologijos universitete, Biomedici-nos inžinerijos institute, sukurtą ant riešo dėvimą įrenginį [58]. EKG įrenginys buvo uždėtas tiesiai ant krūtinkaulio ir registravo nepertraukiamą EKG 500 Hz diskretiza-vimo dažniu bei trijų ašių pagreičio signalus 25 Hz dažniu. Ant riešo dėvimas įrenginys registravo nuolatinę FPG 100 Hz dažniu. Pacientai taip pat suvedė, jų manymu, PV epizodų pasireiškimui įtaką darančius trigerius, naudojant išmaniajam telefonui sukurtą programėlę. Duomenų bazė laisvai prieinama Zenodo duomenų saugyklo-je [118].

Atraminiai PV epizodų pasireiškimo profiliai gauti naudojant EKG detektorių ir kardiologijos rezidentams rankiniu būdu atliekant signalo peržiūrą, taip patikslinant anotacijas surandant neaptiktus PV epizodus, neįtraukiant klaidingai aptiktų epizodų ir patikslinant PV epizodų pradžias ir pabaigas. Rezidentai neaiškiais atvejais konsul-tavosi su patyrusiu kardiologu. Tokiu pačiu būdu suanotuoti priešlaikiniai prieširdžių susitraukimai, prieširdžių tachikardija ir prieširdžių plazdėjimas.

Dar vykstant klinikiniam tyrimui, 37 pacientų savarankiškai suvesti trigeriai ir duomenys buvo naudojami tiriant santykinę PV trukmę prieš ir po trigerio anotuo-tuose ir iš FPG gautuose PV epizodų pasireiškimo profiliuose. Iš šių pacientų 15-kai pasireiškė bent vienas PV epizodas stebėsenos laikotarpiu. 7.3.2 pav. pateikti anotuoti ir FPG atpažinti PV epizodai kartu su pacientų įvestais trigeriais.
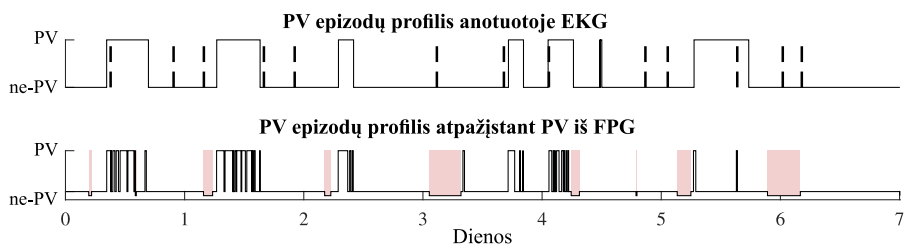
7.3.2 pav. Anotuoto EKG ir iš FPG gauto PV epizodų pasireiškimo profilių pavyzdžiai. Juodos brūkšninės linijos rodo paciento įvestus trigerius. Raudona sritis atspindi ant riešo dėvimo įrenginio nedėvėjimą. Pateiktame pavyzdyje žema signalo kokybė (nerodoma) 63%, o įrenginio nedėvėjimo laikas 12,7%

7.4 REZULTATAI

7.4.1 Potencialių trigerių atpažinimas fiziologiniuose signaluose

Pavyzdyje 7.4.1 pav. parodyti potencialūs trigeriai, atpažinti fiziologiniuose signaluose. Šio paciento atveju dažniausiai atpažintas gulėjimas ant kairiojo šono ir miego sutrikimai.

7.4.2 pav. (a) pateiktas kiekvieno atpažinto potencialaus trigerio skaičius atskiriems pacientams. Bent vienas fizinės perkrovos, psichofiziologinio streso, gulėjimo ant kairiojo šono ir miego sutrikimų potencialus trigeris atpažintas atitinkamai 80%, 74%, 71% ir 89% pacientų, o potencialių trigerių mediana atitinkamai 2 (tarpkvartilinis plotis: 1–3), 2 (1–5), 4 (1–6) ir 5 (4–7), žr. 7.4.2 pav. (b).

7.4.2 Trigerio paveiktų prieširdžių virpėjimo epizodų pasireiškimo modelis

Tiriant PV pasireiškimo modelį, nustatyta, kad santykinė PV trukmė didėja beveik tiesiškai didinant alkoholio kiekį, žr. 7.4.3 pav. (a). Be pridėto alkoholio poveikio, santykinė PV trukmė 17,2%, o pridėjus 9 alkoholio vienetus – padidėja du kartus. Panaši tendencija matoma vertinant PV epizodų skaičių (7.4.3 pav. (b)) – be alkoholio poveikio vidutiniškai sugeneruoti 12,9 epizodo, o esant 8 alkoholio vienetams epizodų skaičius padidėja du kartus. PV epizodų agregacija pradeda mažėti po 6 alkoholio vienetų (7.4.3 pav. (c)), kas rodo, kad PV epizodai mažiau klasterizuoti.

7.4.3 Ryšio tarp trigerio ir prieširdžių virpėjimo epizodų pasireiškimo stiprumo tyrimas naudojant modeliuotus duomenis

7.4.4 pav. pateiktos PV santykinės trukmės po trigerio $B_{1,n}$ ir ryšio stiprumo γ vertės didžiausioms galimoms modelio parametro $\mu_1(t)$, kuris nulemia PV epizodo pasireiškimo tikimybę, reikšmėms. Ryšio stiprumas γ proporcingai didėja didėjant $B_{1,n}$ visų tipų PV profilių atveju. PV epizodų pasireiškimo profilio tipo $\boldsymbol{\theta}_2$ atveju matomas didžiausias γ pokytis, kai naudojami modeliuoti PV profiliai be pridėto alkoholio poveikio ir su 12 alkoholio vienetų.

7.4.5 pav. iliustruoja ryšį tarp analizės laiko intervalo T, PV epizodų pasireiškimo profilio tipo ir alkoholio vienetų skaičiaus. Ryšio stiprumas γ θ_1 profilio tipui padidėja 3–10 kartų esant 12 alkoholio vienetų, palyginti su γ, kai alkoholio poveikio nėra (0 a.v.). θ_2 ir θ_3 tipų PV epizodų profiliams ryšio stiprumas γ padidėja tik 1,5–3,5 karto, o tai rodo, kad γ jautresnis, kai epizodų daug.

Ryšio stiprumo įverčio γ priklausomybė nuo trigerių skaičiaus esant skirtingiems alkoholio vienetams pateikta 7.4.6 pav. Priklausomai nuo PV epizodų pasireiškimo profilio tipo, naudojant modeliuotus profilius su mažesniu alkoholio vienetų skaičiumi, gautas 3–6 kartus mažesnis ryšio stiprumas γ.

PV epizodų pasireiškimo profiliui įtaką darančio trigerio identifikavimo principas iliustruojamas 7.4.7 pav. Principo esmė – vykdyti stebėseną ir skaičiuoti γ dviem
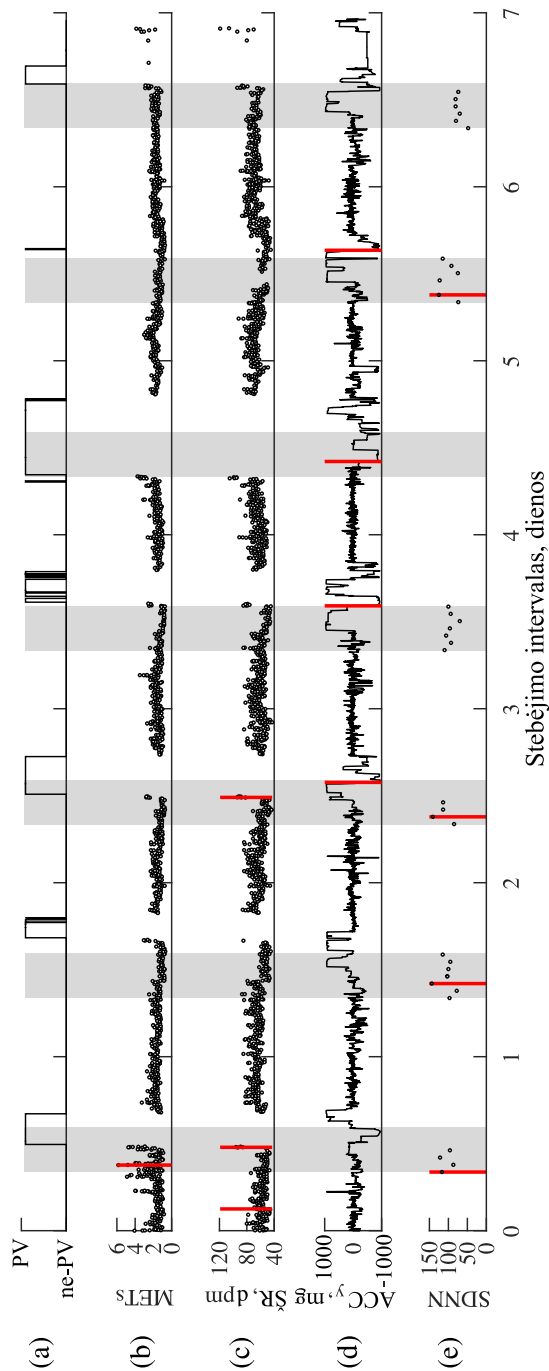
7.4.1 pav. Pavyzdys su (a) anotuotais PV epizodais ir skirtingomis laike kintančių parametrų verčių sekomis, kuriose atpažinti potencialūs trigeriai dėl (b) fizinės perkrovos, (c) psichofiziologinio streso, (d) gulėjimo ant kairiojo šono, (e) miego sutrikimų. Atpažinti potencialūs trigeriai trigeriai pažymėti raudonomis vertikaliomis linijomis. Pilka spalva nurodo nakties laikotarpį nuo 00.00 iki 7.00 val.
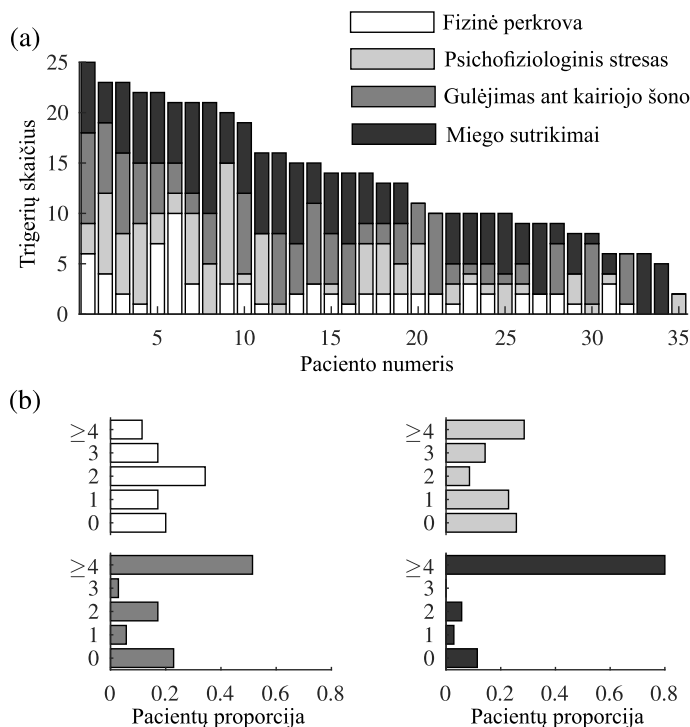
7.4.2 pav. (a) Atskiriems pacientams atpažintų potencialių trigerių skaičius pateiktas sudėtinėmis diagramomis, išrikiuojant pacientus mažėjančia tvarka pagal bendrą atpažintų potencialių trigerių skaičių. (b) Pacientų, kuriems aptiktas tam tikras trigerių skaičius, proporcija

periodais: kai potencialus trigeris nepašalinamas (patikros periodas) ir kai nurodoma potencialaus trigerio vengti (patvirtinimo periodas). Vykdant stebėseną patikros ir patvirtinimo periodais, skaičiuojamas γ ir jei γ viršija slenkstį σ, kuris turėtų būti nustatytas klinikinėse studijose, trigeris laikomas įtaką darančiu. Naudojant modeliuotus duomenis susimuliuoti atvejai, kai trigeris nedaro įtakos PV epizodų pasireiškimo profiliui (7.4.7 pav. (a)) ir kai įtaka daroma (7.4.7 pav. (b)). 7.4.7 pav. (a) atveju tiek patikros, tiek patvirtinimo periodais γ gautas panašus, todėl potencialus trigeris laikomas nedarančiu įtakos PV epizodų pasireiškimo profiliui. 7.4.7 pav. (b) atveju patvirtino periodo γ gautas kur kas mažesnis, o tai gali reikšti, kad potencialus trigeris prisideda prie PV epizodų atsiradimo.

7.4.4 Ryšio tarp potencialių trigerių ir prieširdžių virpėjimo epizodų pasireiškimo tyrimas

7.4.4.1 Savarankiškai identifikuoti potencialūs trigeriai

Naudojant išmaniajam telefonui sukurtą programėlę, 37 pacientai suvedė 288
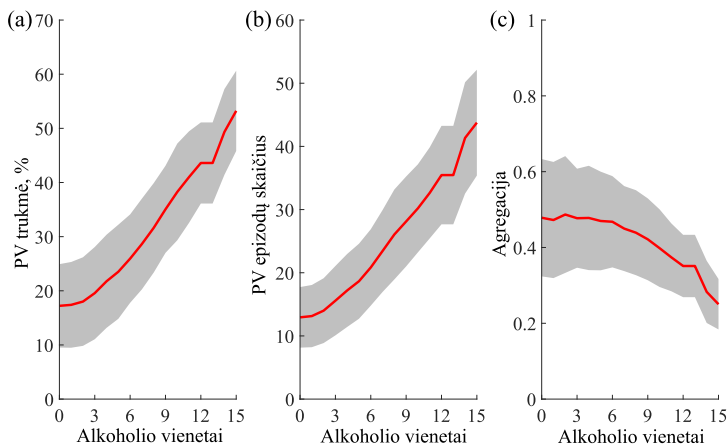
7.4.3 pav. Paroksizminio PV epizodų pasireiškimo profilių charakteristikos esant skirtingam alkoholio vienetų skaičiui: (a) santykinė PV trukmė, (b) PV epizodų skaičius ir (c) PV epizodų agregacija. Rezultatai gauti naudojant 50 paros trukmės modeliuotų PV epizodų pasireiškimo profilių ir pateikti vidurkiu ir standartiniu nuokrypiu
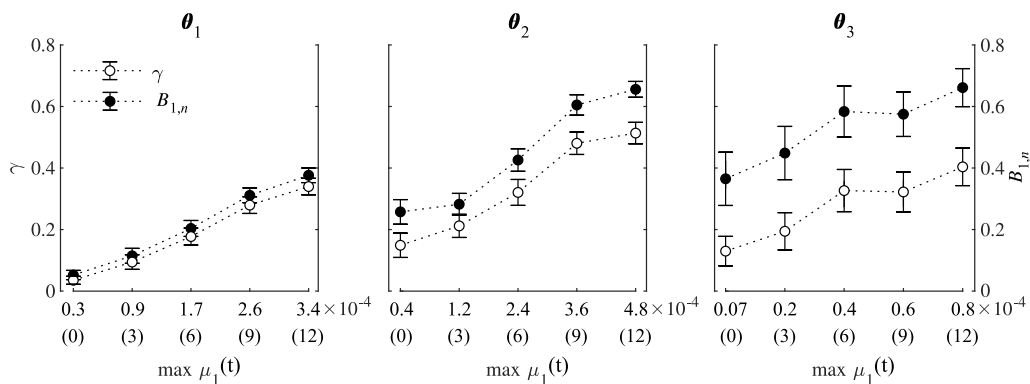
7.4.4 pav. Ryšio stiprumo įverčio γ ir PV santykinės trukmės po trigerio $B_{1,n}$ priklausomybės nuo maksimalios $\mu_1(t)$ vertės, kai $T = 12$ val. Skliausteliai nurodo alkoholio vienetų skaičių modeliuotuose PV epizodų pasireiškimo profiliuose. Rezultatai pateikiami vidurkiu ir pasikliautinuoju intervalu (95%)

potencialius trigerius (7.4.1 lentelė), tačiau tik 15-kai pasireiškė bent vienas PV epizodas. Skaičiuojant iš anotuotų PV epizodų pasireiškimo profilių vidutinė santykinė PV trukmė buvo 0,15. Vidutinė PV epizodo trukmė – 54,7 min. Dažniausiai nurodyti potencialūs PV trigeriai – kava (126), miego trūkumas (43), fizinė perkrova (38), psichofiziologinis stresas (36) ir alkoholis (33).

7.4.8 pav. pateikta santykinė PV trukmė skirtinguose analizės laiko intervaluose T prieš ir po nurodyto potencialaus trigerio, kai naudojami anotuoti PV profiliai
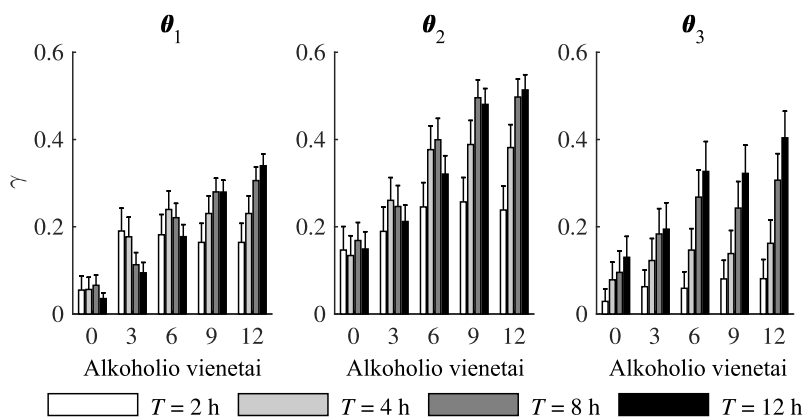
7.4.5 pav. Ryšio stiprumo įvertis γ kaip alkoholio vienetų skaičiaus funkcija skirtingiems analizės laiko intervalams T. Rezultatai pateikiami vidurkiu ir 95% pasikliautinuoju intervalu. Skaičiavimams naudotas tik pirmas simuliuojant pridėtas trigeris

7.4.1 lentelė Įvestų potencialių trigerių skaičius

Potencialus trigeris	Bendras skaičius
Kava	126
Miego trūkumas	43
Fizinė perkrova	38
Psichofiziologinis stresas	36
Alkoholis	33
Šaltas maistas / gėrimas	6
Persivalgymas	6

ir PV profiliai, gauti naudojant PV epizodų atpažinimo FPG signaluose detektorių. Rezultatai rodo, jog vidutinė santykinė PV trukmė po potencialių trigerių didesnė tiek anotuotuose, tiek detektoriumi gautuose PV epizodų pasireiškimo profiliuose. Tačiau vidutinė santykinė PV trukmė FPG pagrindu veikiančiu PV detektoriumi gautuose profiliuose yra perpus mažesnė nei anotuotuose.

7.4.4.2 Fiziologiniuose signaluose atpažinti potencialūs trigeriai

Ryšio stiprumas tarp fiziologiniuose signaluose atpažintų potencialių trigerių ir PV epizodų pasireiškimo vertintas 4 valandų analizės laiko intervale T. Ryšio stiprumo įvertis žymimas γ_d, kai vertinamas ryšys tarp atpažintų potencialių trigerių ir detektoriumi gauto PV epizodų pasireiškimo, o γ_a – kai vertinamas ryšys tarp atpažintų potencialių trigerių ir anotuoto PV epizodų pasireiškimo.

7.4.9 pav. pateikti ryšio stiprumo įverčiai fiziologiniuose signaluose atpažintiems potencialiems trigeriams γ_d ir kontroliniams trigeriams γ_c, kurie stebėsenos
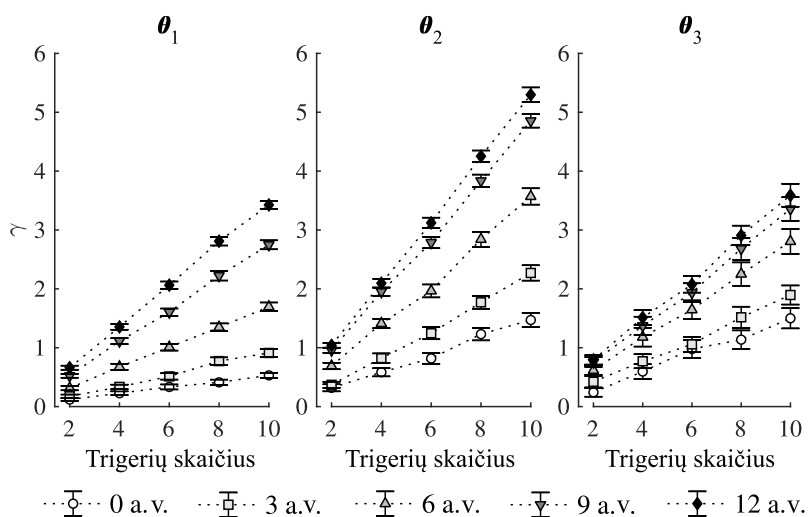
7.4.6 pav. Ryšio stiprumo įverčio γ priklausomybė nuo trigerių skaičiaus esant skirtingiems alkoholio vienetams (a.v.). Rezultatai pateikiami vidurkiu ir 95% pasikliautinuoju intervalu. 0 a.v. reiškia, kad PV epizodų pasireiškimo profiliai modeliuoti be trigerio poveikio
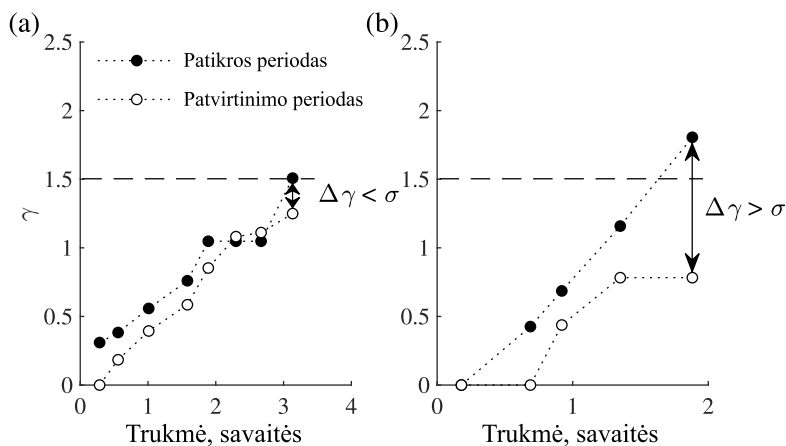
7.4.7 pav. Siūlomo būdo identifikuoti asmeninius PV trigerius taikymo praktikoje pavyzdys: kai potencialus trigeris (a) daro įtaką PV epizodų pasireiškimui ir (b) nedaro įtakos. Rodyklė rodo γ pokytį tarp patikros ir patvirtinimo periodų

intervale paskirstyti atsitiktiniu būdu. Rezultatai rodo, kad kai kuriems pacientams γ_d smarkiai padidėja, palyginti su kontroliniu ryšio stiprumu γ_c. Didžiausias ryšio stiprumo padidėjimas gautas fizinei perkrovai ($p < 0,01$). Reikšmingų skirtumų psichofiziologinio streso ir miego sutrikimų atvejais nepastebėta. Taip pat nerasta
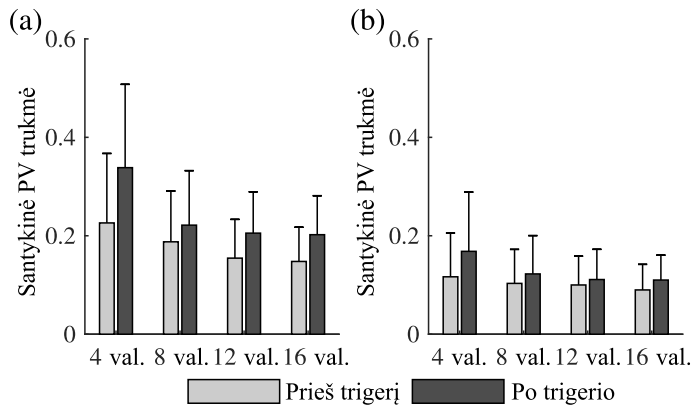
7.4.8 pav. Santykinė PV trukmė prieš ir po potencialių trigerių, kai naudojami skirtingi analizės laiko intervalai: (a) anotuotas PV epizodų pasireiškimo profilis, (b) profilis, gautas naudojant FPG pagrindu veikiantį PV epizodų detektorių. Rezultatai pateikiami vidurkiu ir 95% pasikliautinuoju intervalu

reikšmingų skirtumų tarp γ_d moterų ir vyrų grupėse: esant fizinei perkrovai, psichofiziologiniam stresui, gulėjimui ant kairiojo šono ir miego sutrikimams, atitinkamai gautos p vertės 0,06, 0,34, 0,49 ir 0,66.

7.4.10 pav. pateikta koreliacija tarp ryšio stiprumo įverčio γ, skaičiuojant anotuotuose PV epizodų pasireiškimo profiliuose γ_a ir detektoriumi gautuose PV epizodų pasireiškimo profiliuose γ_d. Rezultatai rodo, kad γ_a vidutiniškai koreliuoja su γ_d. Spearmano koreliacijos koeficientai gauti atitinkamai $r = 0,66$ naudojant EKG analizės pagrindu veikiantį PV detektorių ir $r = 0,62$ FPG pagrindu analizės pagrindu veikiantį detektorių.
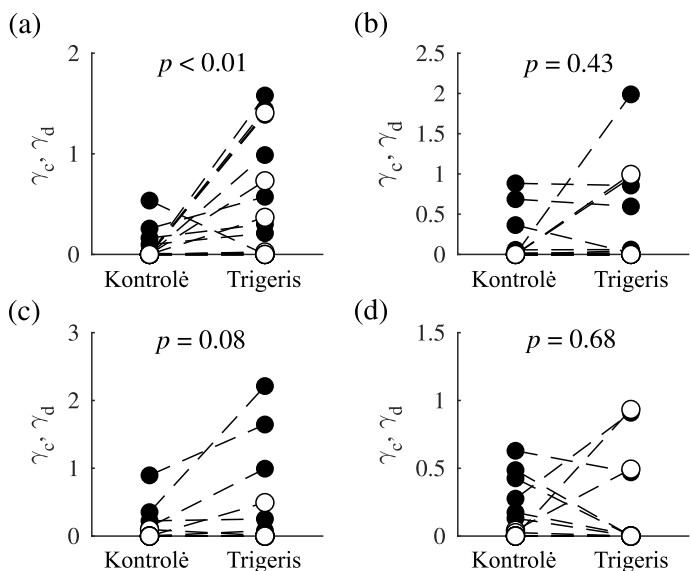
7.4.9 pav. Kiekvieno paciento ryšio stiprumo įverčiai γ_c ir γ_d: (a) fizinė perkrova, (b) psichofiziologinis stresas, (c) gulėjimas ant kairiojo šono ir (d) miego sutrikimai. Balti apskritimai žymi moterų γ vertes
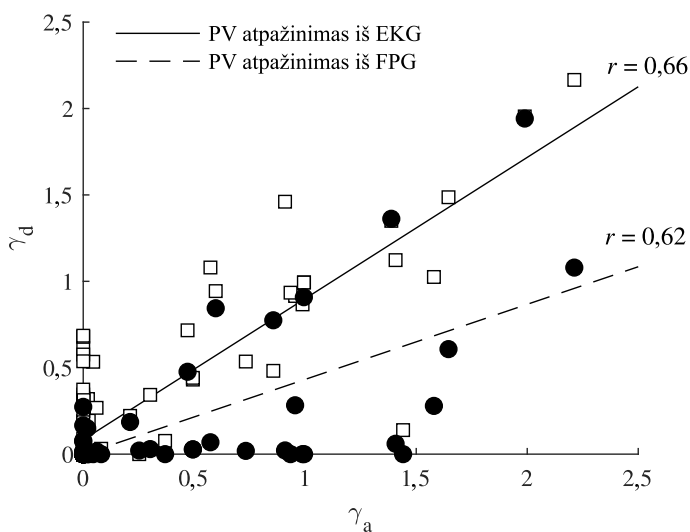
7.4.10 pav. Ryšio stiprumo įverčių γ_a ir γ_d koreliacija. Šviesūs kvadratai – γ įverčiai, apskaičiuoti tarp atpažintų potencialių trigerių ir iš EKG atpažintų PV epizodų pasireiškimo profilių; tamsūs apskritimai – γ įverčiai, apskaičiuoti tarp atpažintų potencialių trigerių ir iš FPG gautų PV epizodų pasireiškimo profilių

7.5 IŠVADOS

1. Pasiūlyta ir ištirta metodika, skirta potencialiems trigeriams atpažinti fiziologiniuose signaluose dėl fizinės perkrovos, psichofiziologinio streso, gulėjimo ant kairiojo šono ir miego sutrikimų. Paroksizminio PV pacientų signalų analizė parodė, kad miego sutrikimai atpažinti dažniausiai, pasireiškę vidutiniškai 5 kartus per savaitę (tarpkvartilinis plotis: 4–7).

2. Pasiūlytas modelis, skirtas trigerio paveiktiems PV epizodų pasireiškimo profiliams simuliuoti, kuris vertingas tiriant ryšio vertinimo metodus. Hawkes procesu pagrįstas modelis papildytas alkoholio poveikio organizmo reaktyvumo funkcija. Modelio tyrimas parodė, kad be pridėto alkoholio poveikio santykinė PV trukmė 17,2%, o 9 alkoholio vienetų atveju padidėjo du kartus. Trigerio poveikio PV epizodų pasireiškimo modelis gali būti tobulinamas adaptuojant organizmo reaktyvumo funkciją, atsižvelgiant į lytį, svorį ir amžių.

3. Pasiūlytas kiekybinis PV trigerių ir PV epizodų pasireiškimo ryšio stiprumo įvertinimo būdas, kuris remiasi santykinės PV trukmės prieš ir po potencialaus trigerio vertinimu. Tyrimas, naudojant skirtingo tipo simuliuotus PV epizodų pasireiškimo profilius, parodė, kad, priklausomai nuo PV epizodų profilio tipo, ryšio stiprumas su pridėtu trigerio poveikiu padidėja 3–6 kartus, palyginti su profiliais be trigerio poveikio. Pasiūlytas būdas gali palengvinti ilgalaikių tyrimų, skirtų PV trigeriams identifikuoti, įgyvendinimą ir papildyti esamus, klausimynais pagrįstus būdus.

4. Naudojant paroksizminiu PV sergančių pacientų fiziologinius signalus ir anotuotus PV epizodų pasireiškimo profilius, didžiausias ryšio stiprumo padidėjimas didžiausiam pacientų skaičiui gautas esant fizinei perkrovai ($p < 0,01$); reikšmingų skirtumų psichofiziologinio streso ir miego sutrikimų atvejais nepastebėta. Tiriant dėvimų įrenginių naudą vertinant ryšio stiprumą PV epizodams atpažinti naudoti elektrokardiogramos ir fotopletizmogramos analizės pagrindu veikiantys PV detektoriai. Atpažintų PV epizodų ryšio stiprumo įvertis vidutiniškai koreliuoja su anotuotu PV epizodų įverčiu: $r = 0,66$ atpažintų iš elektrokardiogramos ir $r = 0,62$ atpažintų iš fotopletizmogramos.

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CURRICULUM VITAE

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Qualifications:
Bachelor of Biomedical Electronics, Kaunas University of Technology (2014-2018), Master of Biomedical Engineering, Kaunas University of Technology (2018-2020), PhD studies in Electrical and Electronics Engineering, Biomedical Engineering Institute, Kaunas University of Technology (2020-2024), PhD topic *A method for identifying personal triggers of paroxysmal atrial fibrilaltion*.
Supervisor: Andrius Rapalis (2020-2023); Andrius Petrėnas (2023-2024).

Employment history:
Junior Researcher, Biomedical Engineering Institute, Kaunas University of Technology (2023 - present), Administrator, Biomedical Engineering Institute, Kaunas University of Technology (2018-2020), Project Analyst, Biomedical Engineering Institute, Kaunas University of Technology (2020), Junior Project Researcher, Kaunas University of Technology (2020-2023).

Research:
Relation assessment approach: With my supervisor, Dr. Andrius Petrėnas, I have developed and tested an approach for identifying the relation between suspected AF triggers and the occurrence of atrial fibrillation episodes.
Atrial fibrillation mechanisms: I am currently investigating arrhythmogenic chains in paroxysmal atrial fibrillation. Understanding the individual mechanisms that lead to atrial fibrillation episodes may help identify specific treatment targets to interrupt arrhythmia recurrence. This, in turn, could reduce the frequency of episodes and help prevent blood clot formation in the atria.
Signals obtained from wearable devices: I am currently working with electrocardiogram signals obtained from wearable devices and exploring ways to improve their quality for diagnostic purposes.

LIST OF PUBLICATIONS ON THE SUBJECT OF THE DOCTORAL THESIS

Publications in the journals referred in the *Clarivate Analytics Web of Science* database with impact factor

1. **Pluščiauskaitė, Vilma**; Butkuvienė, Monika; Rapalis, Andrius; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. An Objective Approach to Identifying Individual Atrial Fibrillation Triggers: A Simulation Study. *Biomedical Signal Processing and Control*. 2023, vol. 87, pt. A, art. no. 105369, p. 1-8. [IF: 5.000; Q1, 2023].

2. **Pluščiauskaitė, Vilma**; Sološenko, Andrius; Jančiulevičiūtė, Karolina; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. Assessment of the Relational Strength Between Triggers Detected in Physiological Signals and the Occurrence of Atrial Fibrillation Episodes. *Physiological Measurement*. 2024, vol. 45, iss. 9, p. 095011. [IF: 2.300, Q3, 2023].

Publications referred in the *Clarivate Analytics Web of Science* database without impact factor

1. **Pluščiauskaitė, Vilma**; Rapalis, Andrius; Butkuvienė, Monika; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. Modeling of the Effect of Alcohol on Episode Patterns in Atrial Fibrillation. *Computing in Cardiology (CinC)*: September 4-7, 2022, Tampere, Finland. 2022, vol. 49, p. 1-4.

2. **Pluščiauskaitė, Vilma**; Butkuvienė, Monika; Sološenko, Andrius; Jančiulevičiūtė, Karolina; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. Detection of Pre- and Post-Trigger Atrial Fibrillation in Long-Term Photoplethysmogram Signals Acquired in Free-Living. *Computing in Cardiology (CinC)*: October 1-4, 2023, Atlanta, Georgia, USA. 2023, vol. 50, p. 1-4.

Conference presentation abstracts

1. **Pluščiauskaitė, Vilma**. Alkoholio įtakos paroksizminio prieširdžių virpėjimo profiliams modelis. *Bioateitis: gamtos ir gyvybės mokslų perspektyvos: 15-oji Lietuvos jaunųjų mokslininkų konferencija: pranešimų tezės.* 2022, p. 39.

List of attended conferences

1. **Pluščiauskaitė, Vilma**; Rapalis, Andrius; Butkuvienė, Monika; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. Modeling of the Effect of Alcohol on Episode Patterns in Atrial Fibrillation. *49th International Computing in Cardiology (CinC) Conference*: September 4-7, 2022, Tampere, Finland.

2. **Pluščiauskaitė, Vilma**. Alkoholio įtakos paroksizminio prieširdžių virpėjimo profiliams modelis. *Bioateitis: gamtos ir gyvybės mokslų perspektyvos 2022: 15-oji Lietuvos jaunųjų mokslininkų konferencija*: November 24, 2022, Vilnius, Lithuania.

3. **Pluščiauskaitė, Vilma**; Butkuvienė, Monika; Sološenko, Andrius; Jančiulevičiūtė, Karolina; Marozas, Vaidotas; Sörnmo, Leif; Petrėnas, Andrius. Detection of Pre- and Post-Trigger Atrial Fibrillation in Long-Term Photoplethysmogram Signals Acquired in Free-Living. *50th International Computing in Cardiology (CinC) Conference*: October 1-4, 2023, Atlanta, Georgia, USA.

Patent applications

1. Method for Establishing a Causality Score Between Atrial Fibrillation Triggers and Atrial Fibrillation Pattern: European patent specification / inventors: A. Petrėnas, M. Butkuvienė, B. Paliakaitė, J. Bacevičius, **V. Pluščiauskaitė**, A. Sološenko, S. Daukantas, D. Sokas, A. Rapalis, A. Aidietis, V. Marozas, applicants: Kaunas University of Technology, Vilnius University. EP21179681.8. 2021-06-16.

Open access databases

1. Bacevičius, Justinas; **Pluščiauskaitė, Vilma**; Abramikas, Žygimantas; Badaras, Ignas; Butkuvienė, Monika; Daukantas, Saulius; Dvinelis, Ernestas; Gudauskas, Modestas; Jukna, Edvardas; Kiseliūtė, Margarita; Kundelis, Ričardas; Marinskienė, Julija; Paliakaitė, Birutė; Petrėnas, Andrius; Petrylaitė, Marija; Pilkienė, Aistė; Pudinskaitė, Gintarė; Radavičius, Vytautas; Rapalis, Andrius; Sokas, Daivaras; Sološenko, Andrius; Staigytė, Justina; Stankevičiūtė, Guostė; Taparauskienė, Neringa; Zarembaitė, Gintarė; Aidietis, Audrius; Marozas, Vaidotas. Long-term electrocardiogram and wrist-based photoplephysmogram recordings with annotated atrial fibrillation episodes. *Zenodo*, 2024.

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Nuoširdžiausia padėka mano mamai ir mano vaikino tėvams, jūs mane visada palaikėte ir skatinote judėti pirmyn. Net jei ne visada supratote, ką darau, jūsų parama ir tikėjimas manimi reiškia daugiau, nei galiu išreikšti žodžiais. Myliu jus!