Modeling of the Effect of Alcohol on Episode Patterns in Atrial Fibrillation

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Abstract

Growing evidence shows that alcohol triggers paroxysmal atrial fibrillation (PAF) in some patients. However, there is a lack of methods for assessing the causality between triggers and atrial fibrillation (AF) episodes. Accordingly, this work aims to develop an approach to episode modeling under the influence of alcohol for the purpose of evaluating causality assessment methods. The alternating, bivariate Hawkes model is used to produce episode patterns, where the conditional intensity function $\lambda_1(t)$ defines the transitions from sinus rhythm (SR) to AF. The effect of alcohol consumption is characterized by a body reactivity function, defined by the base intensity $\mu_1(t)$, which alters $\lambda_1(t)$. Different AF episode patterns were modeled for alcohol units ranging from 0 to 15. The mean AF burden without alcohol was 17.2%, which doubled with 9 alcohol units; the number of AF episodes doubled from 12.9 with 8 alcohol units. The aggregation of AF episodes tended to decrease after 6 alcohol units. The proposed model of alcohol-affected PAF patterns may be useful for assessing the methods for evaluation of causality between triggers and PAF occurrence.

1. Introduction

Alcohol is a common and well-established trigger of atrial fibrillation (AF) episodes [1, 2]. A recent study showed that abstinence from alcohol, even for several months, reduces the recurrence of arrhythmia twice for regular drinkers with diagnosed paroxysmal atrial fibrillation (PAF) [2]. Another study found that two or more alcoholic drinks are associated with a 3-fold greater odds of an AF episode within the following 4 hours [3]. Since PAF treatment is often restricted to oral anticoagulants and antiarrhythmic drugs, both associated with serious side effects [4], identification of PAF triggers for individual patients would empower patients to control their PAF triggers. This may be an effective strategy to achieve non-pharmacological AF management and supplement conventional pharmaceutical treatment [5].

Identification of individual triggers related to episode patterns is a difficult task since available approaches to causality 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 causality assessment is to employ simulated PAF signals that allow to control properties of generated signals. For instance, the simulator proposed for generating ECG signals accounts for atrial and ventricular activity morphologies during PAF and various types of noise encountered in ambulatory recordings [6]. The simulator was used to investigate algorithms for assessment of f-wave signal quality [7], estimate ECG-derived respiratory rate [8], f-wave extraction [9], and evaluate AF detectors [10].

Since switching between AF and sinus rhythm (SR) is modeled by a simple two-state continuous-time Markov chain, the simulator would benefit from more advanced modeling of episode patterns, here accomplished by the recently proposed alternating, bivariate Hawkes model [11]. The history-dependent modeling accounts for the alternating transition times from SR to AF and vice versa, thus allowing clustered episode patterns to be modeled. The model allows the modeling of a wide range of patterns and can be expanded to account for the effect of external triggers on the episode pattern.

This paper introduces an approach to modeling the effect of consumed alcohol on the AF episode pattern. The alternating, bivariate Hawkes model is modified to account for the alcohol body reactivity function, whose shape depends on consumed alcohol. The model can be useful for investigating methods for causality assessment between the different triggers and episode patterns.

2. Materials and methods

2.1. Alcohol transformation to body reactivity function

Alcohol pharmacokinetics (which include absorption, distribution, and elimination) can be characterized by a

body reactivity function, whose shape depends on the time needed for ethanol to be eliminated from the blood. The number of consumed units and consumption time must be known to model ethanol's function, absorption, and elimination rates. Typically alcohol consumption is described by standard alcohol units, which measure alcohol consumption by representing a beverage that contains a fixed amount of ethanol. For example, a shot (40 ml) of 40% alcohol (e.g., vodka) is about one alcohol unit, a glass (200 ml) of 10% wine contains about two alcohol units, a bottle (500 ml) of 5% beer contains about three alcohol units [12]. Absorption starts immediately after the alcohol reaches the stomach and can be as short as 10 min if the gastric emptying is rapid, but usually, the peak blood alcohol concentration is reached within an hour. Alcohol metabolism follows zero-order kinetics, with typically one alcohol unit metabolized per hour [13].

Several assumptions have to be made to model alcohol body reactivity function: 1) 30 min absorption time is assumed for one standard alcohol unit; 2) one hour elimination time of one alcohol unit under non-fasting conditions. Absorption and elimination rates are chosen considering standard male (70 kg weight) [13].

Alcohol drinking events, with the number of consumed alcohol units transformed from the time-stamped data to a time-series signal, increase the probability of a specific time window containing AF episodes. Alcohol absorption under the above assumptions will be characterized by a bounded exponential growth function defined as:

$$y(t) = b(1 - e^{a_0 \cdot t}), \tag{1}$$

where b is the alcohol unit, while a_0 is the growth parameter set to $-10.6/b$ units/h. The number of alcohol units determines the amplitude of alcohol absorption. Alcohol elimination from the body can be characterized by a linear function with a slope parameter a set to 1 unit/h. An alcohol body reactivity function is presented in Fig. 1, accounting for three alcohol drinking events, i.e., one alcohol unit at 18:00, 20:00, and 21:00.

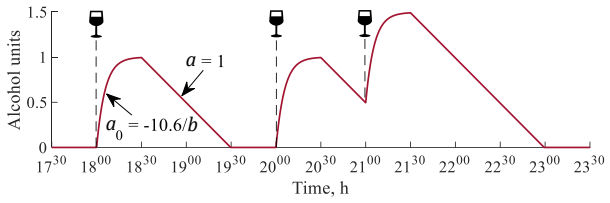

Figure 1. Alcohol body reactivity function of three alcohol drinking events of one alcohol unit each.

2.2. Modeling AF episode patterns

The alcohol body reactivity function allows modeling of how a certain amount of alcohol influences episode patterns. The bivariate Hawkes model can produce such patterns. The counting processes $N_1(t)$ describing transitions from SR to AF and $N_2(t)$ describing transitions from AF to SR are associated with the conditional intensity functions $\lambda_1(t)$ and $\lambda_2(t)$, respectively, defined by [11]:

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

where $\mu_m > 0$, $\alpha_{m,n} \geq 0$, $\beta_{m,n} \geq 0$ for $m, n = 1, 2$, and $t_{n,k}$ the transition times.

Assuming for simplicity that $\beta_{1,1} = \beta_{1,2} = \beta_1$ and $\beta_{2,1} = \beta_{2,2} = \beta_2$, the bivariate 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 parameters of the model can be compactly represented by the vector:

$$\boldsymbol{\theta} = [\mu_1, \mu_2, \alpha_{1,1}, \beta_1, \alpha_{1,2}, \alpha_{2,1}, \beta_2, \alpha_{2,2}]. \tag{3}$$

There is no clear information in the literature on how episode patterns relate to alcohol consumption; therefore, it is unclear what specific AF burden or episodes clustering patterns alcohol induces. Having information about reduced AF burden and recurrence [2] of AF episodes due to abstinence implies that alcohol should increase AF burden and possibly also the degree of episode clustering.

Episode patterns were modeled using the parameter values $\boldsymbol{\theta} = [0.1, 0.5, 2, 2.5, 2, 1, 5, 2] \cdot 10^{-3}$, estimated from a database obtained from AF patients [11]. Alcohol influence is reflected by an increase in the base intensity $\mu_1(t)$. Since $\lambda_1(t)$ is responsible for transitions from SR to AF, increasing the background intensity increases the transition probability. If alcohol is consumed, the peak value of $\mu_1(t)$ changes over time according to the alcohol body reactivity function, e.g., with one alcohol unit, it doubles; with two, it triples. According to the number of consumed alcohol units, $\mu_1(t)$ increases over time with alcohol absorption and slowly returns to its initial value with alcohol elimination from the body.

2.3. Performance evaluation

AF episodes may manifest in clusters or aggregate within a specific time interval, e.g., during the night. Therefore, AF episode patterns may be translated to pattern-characterizing parameters, e.g., accounting for episode clustering or aggregation over time, to provide additional information on the influence of a specific trigger on AF progression.

Fifty 24-h long episode patterns for each number of alcohol units, ranging from 0 to 15, were simulated. The results were determined in terms of AF burden, defined as the percentage of time spent in AF during the monitored

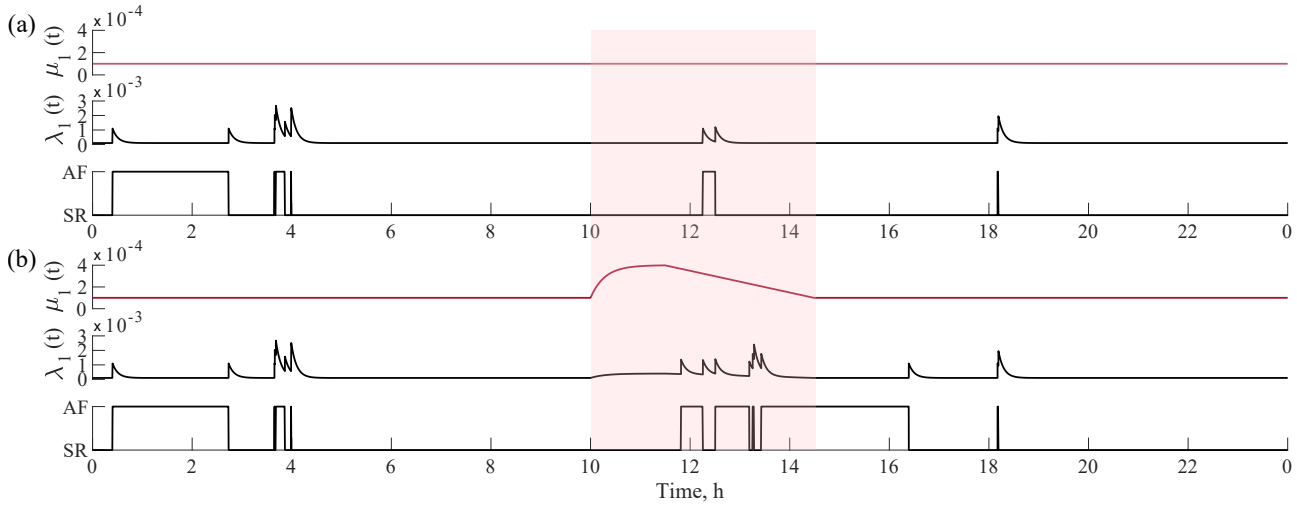

Figure 2. An example of episode pattern modeling: (a) without added alcohol component and (b) with added alcohol component. In each case, the base intensity $\mu_1(t)$, the conditional intensity function $\lambda_1(t)$, and the episode pattern are shown.

period, the number of AF episodes, and the aggregation of AF episodes. The aggregation takes values between 0 and 1. Values close to 1 indicate high temporal aggregation, inherent for patterns with a single short continuous AF episode. While values close to 0 indicate low aggregation, this applies to AF patterns with episodes evenly spread over the monitoring period. All parameters were computed for all simulated episode patterns [14]. In this work, it is assumed that all drinks were consumed at once.

3. Results

Simulated AF episode patterns are illustrated in Fig. 2, where the upper panel in (a) and (b) show $\mu_1(t)$, which is constant as long as there is no alcohol drinking event (a), 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 middle panel in (a) and (b) show $\lambda_1(t)$, which is responsible for transitions from SR to AF. The resulting episode pattern is shown in the lower panel, where the high level corresponds to AF and the low level to SR. The episode patterns, Fig. 2 (a) and (b), are the same until the alcohol drinking event occurs; after it, due to the effect of alcohol, patterns start to differ.

Figure 3(a) shows that the AF burden increases almost linearly by increasing alcohol consumption. Without added alcohol AF burden was 17.2%, increasing twice with 9 alcohol units. A similar tendency can be seen with the number of AF episodes (Fig. 3(b)): without added alcohol the mean was 12.9 episodes, whereas it increases by a factor of two with 8 alcohol units. The aggregation tends to decrease after 6 alcohol units (Fig. 3 (c)), which means that episodes tend to occupy a large part of the monitoring

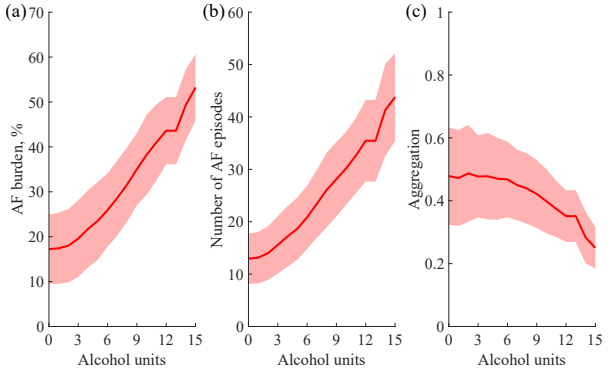

Figure 3. Fifty 24-h long PAF patterns for the different number of alcohol units: (a) AF burden, (b) number of AF episodes, and (c) aggregation. Results are given as mean and standard deviation.

duration. As expected, alcohol consumption increased the likelihood of AF episodes to occur.

4. Discussion

Modeled 24-h long AF patterns show quite a high AF burden (17.2%); this was expected because model parameters were obtained from AF databases with more exceptional cases of PAF patients with relatively many AF episodes. The present choice of $\boldsymbol{\theta}$ exemplifies clustered PAF pattern, previously used in [11]. Other choices of $\boldsymbol{\theta}$ would give PAF patterns with different characteristics. In this case, the most important thing was to obtain a change in the AF parameters after alcohol consumption.

Since alcohol intake levels and the consequences of al-

cohol use differ between men and women, it is important to analyze men and women separately, including age and environmental factors [15, 16]. Specifically, only average non-obese male alcohol pharmacokinetics was used in this study for simplicity.

Alcohol is one of many PAF triggers. Other triggers, e.g., caffeine, physical load, large meals, cold beverages, emotional stress [1], can also be represented as signals and used to influence $\lambda_1(t)$. Other triggers, same as with alcohol, should be transformed to body reactivity functions, i.e., starting at the time instances where the triggers are timestamped by the person and are characterised by the growth function with the growth rate parameter and by the slope function with the slope rate parameter. Parameters must be determined specifically for each AF trigger based on the clinically established properties. Modeling more than one trigger would be more realistic.

5. Conclusions

The modified alternating, bivariate Hawkes model is useful for generating alcohol-affected episode patterns and thus may be useful for assessing methods for causality assessment between triggers and PAF occurrence. The model can be improved by individualizing alcohol body reactivity function to account for gender, weight, and age.

Acknowledgments

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