Discriminating atrial flutter from atrial fibrillation using a multilevel model of atrioventricular conduction

Eberhard P. Scholz, MD,[*] Florian Kehrle, MSc,[†] Stephan Vossel, BSc,[*] Alexander Hess, MD,[*] Edgar Zitron, MD,[*‡] Hugo A. Katus, MD,[*‡] Sebastian Sager, PhD[†]

From the [*]Department of Internal Medicine III, University Hospital Heidelberg, Heidelberg, Germany, [†]Faculty of Mathematics, University of Magdeburg, Magdeburg, Germany, and [‡]DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Heidelberg, Germany.

BACKGROUND The discrimination between atrial flutter (AFlu) and atrial fibrillation (AFib) can be made difficult by an irregular ventricular response owing to complex conduction phenomena within the atrioventricular (AV) node, known as multilevel AV block. We tested the hypothesis that a mathematical algorithm might be suitable to discriminate both arrhythmias.

OBJECTIVES To discriminate AFlu with irregular ventricular response from AFib based on the sequence of R-R intervals.

METHODS Intracardiac recordings of 100 patients (50 patients with AFib and 50 patients with AFlu) were analyzed. On the basis of a numerical simulation of variable flutter frequencies followed by 2 levels of AV block in series, a given sequence of R-R intervals was analyzed.

RESULTS Although the ventricular response displays absolute irregularity in AFib, the sequences of R-R intervals follow certain rules in AFlu. We find that using a mathematical simulation of multilevel AV block, based on the R-R sequence of 16 ventricular beats, a stability of atrial activation could be predicted with a sensitivity of 84% and a specificity of 74%. When limiting the ventricular rate to 125 beats/min, discrimination could be performed with a sensitivity of even 89% and a specificity of 80%. In cases of AFlu, the atrial cycle length could be predicted with high accuracy.

CONCLUSION On the basis of the electrophysiological mechanism of multilevel AV block, we developed a computer algorithm to discriminate between AFlu and Afib. This algorithm is able to predict the stability and cycle length of atrial activation for short R-R sequences with high accuracy.

KEYWORDS Atrial flutter; Atrial fibrillation; Atrioventricular conduction; Multilevel AV block; AV node

ABBREVIATIONS **Δ** = increment in atriventricular block–type Wenckebach; **θ** = refractory period; **AFib** = atrial fibrillation; **AFlu** = atrial flutter; **AV** = atrioventricular; **AV_M** = atrioventricular conduction time in atrioventricular block–type Mobitz; **AV_{max}** = maximum atrioventricular conduction time; **AV_W** = atrioventricular conduction time in atrioventricular block–type Wenckebach; **CL** = cycle length; **ECG** = electrocardiogram/electrocardiographic; **LSQ** = least squares–type difference between simulation and measurements; **MAVB** = multilevel atrioventricular block; **ROC** = receiver-operating-characteristic; **$R\text{-}R_{ECG}$** = sequence of R-R intervals taken from the surface electrocardiogram; **$R\text{-}R_{SIM}$** = sequence of simulated R-R intervals

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Introduction

The correct discrimination between atrial fibrillation (AFib) and regular atrial arrhythmias including atrial flutter (AFlu) and focal atrial tachycardia poses a diagnostic challenge to both physicians and computerized algorithms.[1,2] As a result, misinterpretation rates of up to 80% have been reported in clinical practice.[1] AFib represents a high-frequency chaotic electrical activation of the atria exhibiting electrocardiographic (ECG) signs of fibrillation waves in combination with an absolutely irregular ventricular response. In contrast, electrical activation follows defined reentrant circuits in AFlu, resulting in regular flutter waves in the surface ECG. In the case of isthmus-dependent AFlu (typical AFlu), electrical activation produces a characteristic sawtooth pattern in the surface ECG. However, the discrimination between AFib and AFlu from the surface ECG can be made difficult by several factors. On one hand, AFib may present with coarse fibrillatory waves, which are reminiscent of AFlu.[3,4] On the other hand, AFlu may display atypical characteristics in the surface ECG, including hardly discernible low-voltage flutter waves as well as an irregular ventricular response, thereby mimicking AFib. However, the exact differentiation between AFib and AFlu is imperative with respect to treatment modalities as the effectiveness of antiarrhythmic agents is generally lower in AFlu and catheter ablation is

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often the superior option. Furthermore, atypical forms of AFlu are becoming increasingly important in clinical practice as a complication of left atrial ablation.

The objective of this study was to develop a computer algorithm for an automated discrimination between AFib and regular atrial arrhythmias (AFlu and atrial tachycardia). Our algorithm is based on the observation that the irregularity of ventricular activation in AFib and AFlu follows two distinct electrophysiological mechanisms. Although irregularity is caused by chaotic atrial activation in AFib, a serial arrangement of atrioventricular (AV) block levels (multilevel AV block [MAVB]) is causative in AFlu.[5] The description of this type of AV block dates back to the 1960s when Watanabe and Dreifus[6] identified multiple block levels in series within AV nodes of rabbit hearts. Similar results could be obtained later in humans using intracardiac recordings.[7] Ventricular activation patterns resulting from MAVB are often complex for visual recognition (Online Supplemental Figure 1). However, a computer algorithm should be able to identify the underlying levels of AV block. On the basis of the electrophysiological mechanism of MAVB, we developed a computer algorithm for the automated discrimination between AFib and AFlu. We show that our algorithm is able to predict the stability and cycle length (CL) of atrial activation even for short sequences of R-R intervals with high accuracy.

Methods

Recording and processing of electrophysiological data

Electrophysiological data were obtained retrospectively from patients exhibiting AFib or AFlu with irregular ventricular response during invasive electrophysiological testing or catheter ablation. All procedures were performed without continuous sedation. Diagnostic catheters were inserted through the right or left femoral vein. Depending on the type of the procedure, atrial electrograms were recorded either using a duodecapolar or quadripolar catheter placed in the right atrium or using a decapolar or quadripolar catheter placed in the coronary sinus. Electrophysiological signals were processed and stored using a commercially available electrophysiological recording system (BARD Clearsign, C. R. Bard Inc, Lowell, MA). Segments of 40 seconds were selected manually from the data files for further analysis. Segments containing premature ventricular beats were excluded. The discrimination between AFib and AFlu was performed using electrical signals measured at the atrial electrodes by an expert in the field of cardiac electrophysiology. For AFib, we found that all examples exhibit highly irregular intervals of atrial activation (qualitative assessment) in combination with a short mean atrial CL (182 ms). These data correspond well with the threshold of 200 ms that is referred to in the European guideline for the management of AFib.[8] In contrast, intracardiac recordings taken from patients with AFlu exhibited highly regular intervals in combination with a mean atrial CL of 240 ms. In many cases, the correct rhythm diagnosis could be proved further by evaluating the reaction of the arrhythmia to catheter ablation. Among the group of AFlu cases, further quantitative assessment revealed an AA variation below 5 ms. The exact timing of the R-R intervals was determined carefully from the surface ECG ($R\text{-}R_{ECG}$) using built-in calipers and transferred to a data sheet. Forty-second segments of 50 patients presenting with AFlu and 50 patients presenting with AFib were extracted. The study design was approved by the ethics committee of the University of Heidelberg and conforms to the standards defined in the Helsinki Declaration.

Mathematical model of MAVB

MAVB was simulated by a combination of 2 levels of second-degree AV block in series (Figure 1A). Combinations that were allowed included AV block–type Mobitz followed by AV block–type Wenckebach or vice versa. All signals leaving the first block level served as input for the second block level. Figure 1B displays a typical example of MAVB exhibiting AV block–type Mobitz on the first level and AV block–type Wenckebach on the second level. For the simulation of AV block–type Mobitz, a first incoming signal was conducted through the block level with a conduction time (AV_M). As soon as this signal traversed the block level, a refractory period (θ) was initiated. All following signals entering the block level during this period were dropped (Figure 1C). As soon as the refractory period timed out, the next signal was again conducted with the conduction time AV_M. For the simulation of AV block–type Wenckebach, a first incoming signal was subjected to a fixed conduction time (AV_W). The conduction time of the next incoming signal was determined by adding an increment (Δ) to the conduction time AV_W (Figure 1D). This increment was added from beat to beat until the total conduction time exceeded a predefined margin (AV_{max}). As soon as the total conduction time exceeded this threshold, the beat was dropped and the next signal was again conducted with the conduction time AV_W. For a given CL, conduction time AV_M and refractory period θ (Mobitz) or threshold AV_{max}, and conduction time AV_W and an increment Δ (Wenckebach), a forward simulation can be performed as described above. This yields a series of time points of signals exiting the second block level. We used it to define the sequence of simulated R-R intervals ($R\text{-}R_{SIM}$) that can be compared with $R\text{-}R_{ECG}$.

Discrimination between regular and irregular atrial activation

For each data instance, we used mathematical optimization to determine the values of the patient-specific parameters AV_M, AV_W, CL, θ, AV_{max}, Δ with simulation results that had the smallest difference between $R\text{-}R_{SIM}$ and $R\text{-}R_{ECG}$. The latter was analyzed blinded to all clinical data and served as the input of our discrimination algorithm. We used a least

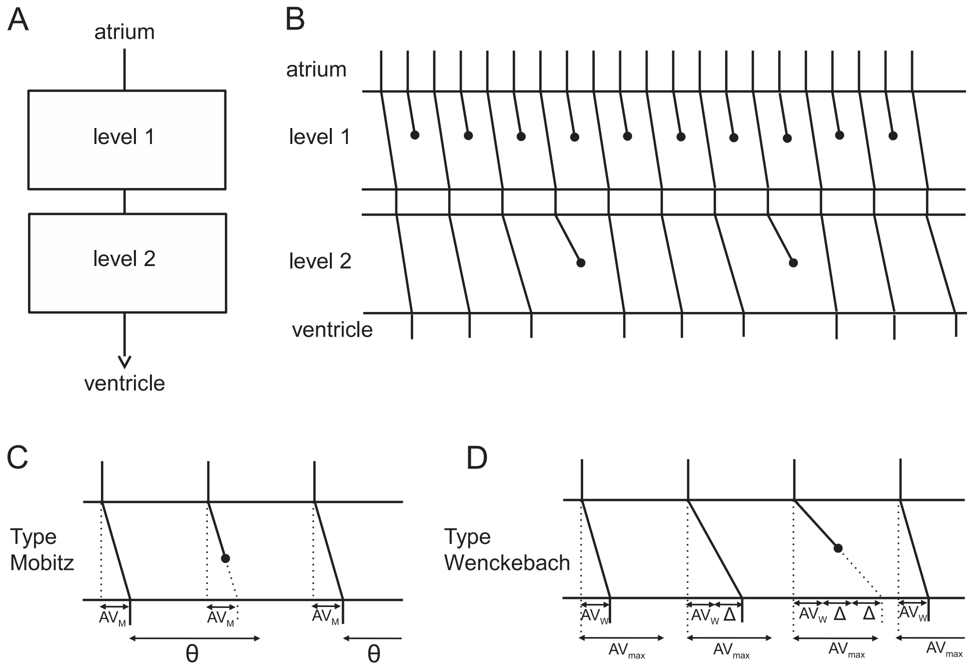

Figure 1 Mathematical model of multilevel atrioventricular (AV) block. **A:** The discrimination algorithm was based on a mathematical model of AV conduction consisting of 2 levels of second-degree AV block in series. **B:** Typical example of Mobitz-type block on the first level resulting in a 2:1 conduction ratio, followed by a Wenckebach-type conduction with a fixed ratio of 4:3. **C:** Mobitz-type conduction was simulated with a conduction time AV_M and a refractory period θ. **D:** The mathematical formulation of Wenckebach-type block consisted in an initial conduction delay AV_W of the first conducted beat. For every following beat, a fixed increment Δ was added. The maximum AV conduction time AV_{max} determined the conduction ratio.

squares (LSQ) type of function to measure the difference between the 2 time series:

$$LSQ = \frac{\sum_{i=1}^{n} \delta_i^2}{\alpha n} \tag{1}$$

where δ_i is the time difference between a simulated ventricular activation (R_{SIM}) and the corresponding ventricular activation obtained from surface ECG (R_{ECG}), α is a scaling factor of 10,000 ms^2, and n is the number of R waves.

The likelihood between R-R_{SIM} and R-R_{ECG} in terms of the LSQ value of the best solution found by our algorithm was used to discriminate between AFib and AFlu, with 0 being an exact match. The watershed value for the LSQ value was determined empirically and a posteriori by analysis of a receiver-operating-characteristic (ROC) curve.

Mathematical optimization

We implemented and compared different algorithms to find the parameter values that minimize the LSQ value defined above. Among them were brute-force simulation by enumeration on a fixed discretization grid for the parameters (with an exponential explosion of the runtime), the stochastic particle swarm approach[9] (with high runtimes and the lack of a guaranteed global solution), and local heuristics based on the NEWUOA software[10] (which often got stuck in local minima). For the given reasons, they were not suited for our task.

We developed a problem-specific algorithm, which allows a calculation of an approximate and physically meaningful solution within a computing time of around 1 minute and which was used for the following analysis. It is approximated in the sense that it works on a discretized grid for possible parameter values, as does the brute-force approach. However, it uses logical arguments to avoid a full enumeration of parameter values on the grid. Also, we reverse the enumeration order. Instead of enumerating over all parameter values in an outer loop and simulating for all time points in the inner loop, we now iterate over all time points in an outer loop. In the inner loop, we enumerate over all parameter values that have not been discarded yet. Parameter values can be discarded whenever the simulation of an early time signal already leads to a mismatch to the R-R_{ECG} data. In addition, the parameter values can be varied within given bounds, which allows for changing Wenckebach ratios. Our algorithm does not guarantee to find the global solution to the optimization problem, but it does guarantee to find the global optimum on the given grid if the corresponding LSQ value is below a threshold. The lower and upper margins as well as the step size of all variable parameters are summarized in Table 1. For Mobitz-type block, the upper margin of the θ was set to the longest R-R_{ECG} interval. Note that the values allow Wenckebach-type block with a conduction ratio between 2:1 and 8:7.

Statistical analyses

For patient characteristics, statistical significance was evaluated using the independent Student *t* test. Data are expressed as mean ± standard error of the mean. Differences were considered to be statistically significant when the *P* value was $< .05$.

Table 1 Range of model parameters

Parameter	Lower margin	Upper margin	Increment
CL	198 ms	350 ms	1 ms
θ	50 ms	NA	20 ms
Δ	20 ms	100 ms	20 ms
AV_M	50 ms	50 ms	—
AV_{max}	50 ms	500 ms	20 ms
AV_W	50 ms	50 ms	—

Δ = increment in atrioventricular block–type Wenckebach; θ = refractory period; AV = atrioventricular; AV_M = atrioventricular conduction time in atrioventricular block–type Mobitz; AV_{max} = maximum atrioventricular conduction time; AV_W = atrioventricular conduction time in atrioventricular block–type Wenckebach; CL = cycle length; NA = not available.

Results

Discrimination between AFib and AFlu using a multilevel model of AV conduction

The discrimination between AFib and AFlu with irregular ventricular response based on the surface ECGs remains challenging and is associated with a high rate of misdiagnoses in clinical practice.[1,11,12] Figure 2 displays 2 typical examples of surface ECGs with corresponding intracardiac recordings taken from a patient with AFib (Figure 2A) and a patient with AFlu (Figure 2B) during an invasive electrophysiological study. Both examples exhibit irregularity of the R-R intervals, thereby underlining the low diagnostic value of R-R periodicity in the discrimination between both arrhythmias.[12] Although irregular high-frequency fibrillatory waves might be identified in the surface ECG of the patient with AFib (Figure 2A, upper panel), flutter waves are barely visible in the ECG of the patient with AFlu (Figure 2B, upper panel). Synchronously recorded intracardiac signals reveal irregular high-frequency atrial activation with variable CL in AFib (Figure 2A, lower panel) as compared with regular atrial activation in AFlu with a CL of 240 ms (Figure 2B, lower panel).

Figure 3 displays a typical example of AFlu with irregular ventricular response due to MAVB. The simulation indicates AFlu with a CL of 233 ms followed by an MAVB consisting of a Mobitz block (2:1) in the upper level and a Wenckebach block (from 2:1 to 4:3) in the lower level (Figure 3). As can be seen from the intracardiac recording, the predicted CL of atrial activation matched the recorded CL (Figure 3).

Considering that AV conduction follows no systematic rules in AFib, we next tested the hypothesis that the minimum attainable average deviation should be significantly lower in AFlu than in AFib. The database of our electrophysiological laboratory was browsed for patients presenting with either AFib or AFlu with irregular ventricular response. Patient characteristics are summarized in Table 2. Intracardiac recordings of 50 patients with AFib and 50 patients with AFlu that met the above-mentioned requirements could be retrieved. For further analysis, time intervals of 40 seconds were extracted. Atrial CL and the timing of the recorded R waves were measured from intracardiac recordings and surface ECG ($R\text{-}R_{ECG}$).

Diagnostic accuracy of the algorithm

R-R sequences of all patients with AFlu (n = 50) and AFib (n = 50) were further analyzed systematically using the described algorithm. Figure 4 displays examples of MAVB predicted by the algorithm. The best solution of the first example (Figure 4A) consisted of a Wenckebach-type conduction on the first level with varying conduction ratios between 6:5 and 3:2 followed by a Mobitz-type block on the second level with varying refractory periods between 1000 and 1650 ms. The CL was 340 ms, and the LSQ of the solution was 0.040. Figure 4B displays an example with a Wenckebach-type conduction on the first level ranging between conduction ratios of 7:6 and 3:2 followed by a Mobitz-type block on the second level (θ 300–900 ms). The atrial CL was 237 ms, and the LSQ was 0.041. The third

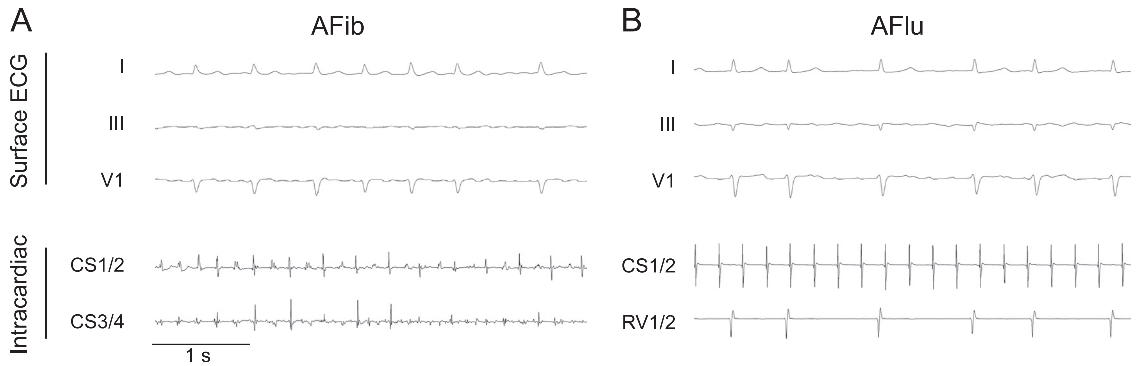

Figure 2 Exemplary surface ECGs and intracardiac recordings from AFib and AFlu. **A:** Surface ECG (leads I, III, and V_1) from a patient suffering from AFib (upper panel) and simultaneously obtained intracardiac tracings recorded in the CS. The surface ECG exhibits high-frequency variable atrial activation in combination with an irregular ventricular response. Atrial electrograms reveal high-frequency signals (CL < 200 ms) with marked irregularity. **B:** Surface ECG (upper panel) and simultaneously recorded electrograms (lower panel) taken from a patient with atypical (non-isthmus–dependent) atrial flutter. The ECG shows merely discernible flutter waves in combination with an irregular ventricular response due to multilevel AV block. Simultaneously obtained intracardiac recordings show regular atrial activation (CS). AFib = atrial fibrillation; AFlu = atrial flutter; AV = atrioventricular; CL = cycle length; CS = coronary sinus; CS1/2 = electrograms obtained between the distal pair of electrodes of the coronary sinus catheter; CS3/4 = electrograms obtained between the proximal pair of electrodes of the coronary sinus catheter; ECG = electrocardiogram; RV1/2 = electrograms obtained between the proximal pair of electrodes of the right ventricular catheter.

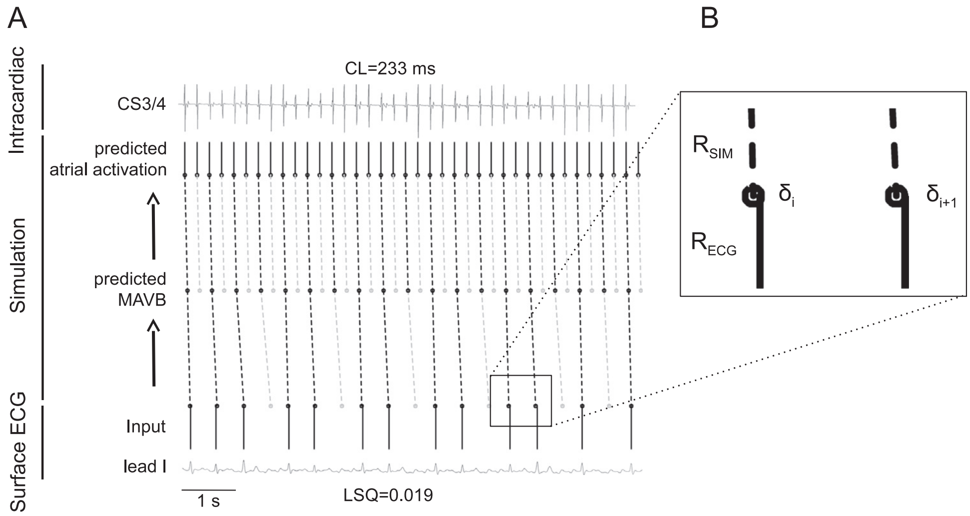

Figure 3 Diagnostic workflow of the algorithm. A sequence of R-R intervals that was obtained from the surface ECG served as an input to our algorithm (lowest panel, lead I). The algorithm calculated a set of model parameters; among them are the atrial CL and a characterization of the specific multilevel AV block. These parameters minimized the difference (LSQ) between the series of simulated time points R_{SIM} and the measurements R_{ECG}. The predicted atrial CL of 233 ms matches the measured CL (uppermost panel, CS3/4), which was only compared a posteriori and is usually not available for decision making. The proposed multilevel AV block consists of a Mobitz-type block on the first level followed by a Wenckebach-type conduction on the second level with a conduction ratio between 4:3 and 2:1. AV = atrioventricular; CL = cycle length; CS3/4 = electrograms obtained between the proximal pair of electrodes of the coronary sinus catheter; ECG = electrocardiogram; LSQ = least squares type difference between simulation and measurements; MAVB = multilevel atrioventricular block.

example (Figure 4C) exhibits Mobitz-type block with a fixed refractory period on the first level resulting in 2:1 block, followed by Wenckebach-type conduction on the second level (conduction ratios 5:4 to 3:2). The atrial CL was 258 ms, and the LSQ was 0.068. Figure 4D displays the best solution for an example of AFib, yielding a relatively high LSQ value of 0.22.

In order to identify the best discriminatory cutoff, the minimal LSQ was determined for every example. Next, the LSQ distribution for all AFib and AFlu examples was plotted. Figure 5A exemplarily displays the average deviation for 16 R-R intervals. In order to establish an ROC curve from these data, sensitivity and specificity for any given LSQ cutoff between 0 and 1 was calculated. Figure 5C displays the corresponding ROC curve for 16 R-R intervals, yielding an area under the curve of 0.83. Optimal discrimination could be obtained by identifying the LSQ, with the largest difference between sensitivity and (1 − specificity). For 16 R-R intervals, an optimal cutoff of 0.08 could be identified. Next, to determine the ideal segment length for discrimination, a full analysis of performance vs number of R-R intervals was performed (Figure 5E). Between a segment length of 6 and 36 R-R intervals, highest diagnostic accuracy could be obtained for 16 R-R intervals, yielding a sensitivity of 84% and a specificity of 74%. In 30 cases (60%), the correct atrial CL ($\leq$2 ms) was found as the best solution and in 2 other cases (4%) among the best 3 solutions. Thirteen of the remaining patients (72%) contained deviations in the atrial CL of approximately 1–5 ms. Those were mostly classified correctly as AFlu by the algorithm, but with a wrong atrial CL, probably owing to variations in atrial CL.

It is well recognized that in AFib, R-R variability decreases with an increase in heart rate, a phenomenon commonly referred to as pseudoregularization.[13] Considering that this regularization might result in misclassifications by the algorithm, we tested whether the diagnostic accuracy might be improved when limiting the mean heart rate to 125 beats/min. A total of 44 patients with AFlu and 41 patients with AFib exhibited a heart rate below this threshold. Again, 16 R-R intervals were used for further analysis. As expected, when limiting the heart rate to 125 beats/min, the diagnostic accuracy of the algorithm could be further increased, yielding a sensitivity of 89% with a specificity of 80% and an area under the curve of 0.90 (Figures 5B and 5D).

Discussion

In contrast to previously published approaches, the algorithm presented here offers 2 main advantages: (1) As discrimination is solely based on a sequence of R-R intervals, it is likely to be less susceptible to artifacts or the presence of small flutter waves that might impede discrimination. (2)

Table 2 Patient characteristics

Characteristic	Atrial flutter (n = 50)	Atrial fibrillation (n = 50)	*P*
Age (y)	68 ± 1.6	63 ± 1.7	.05
Sex: male/female	33/17	32/18	
Ejection fraction (%)	52.0 ± 1.7	52.8 ± 2.0	.97
LA diameter (mm)	42.9 ± 0.7	44.3 ± 0.8	.92
Antiarrhythmic agents	40 (80)	34 (68)	
β-Blocker	33 (66)	28 (56)	
Amiodarone	4 (8)	2 (4)	
Dronedarone	2 (4)	5 (10)	
Digitalis	7 (14)	8 (16)	
Others	7 (14)	2 (4)	

LA = left atrium.

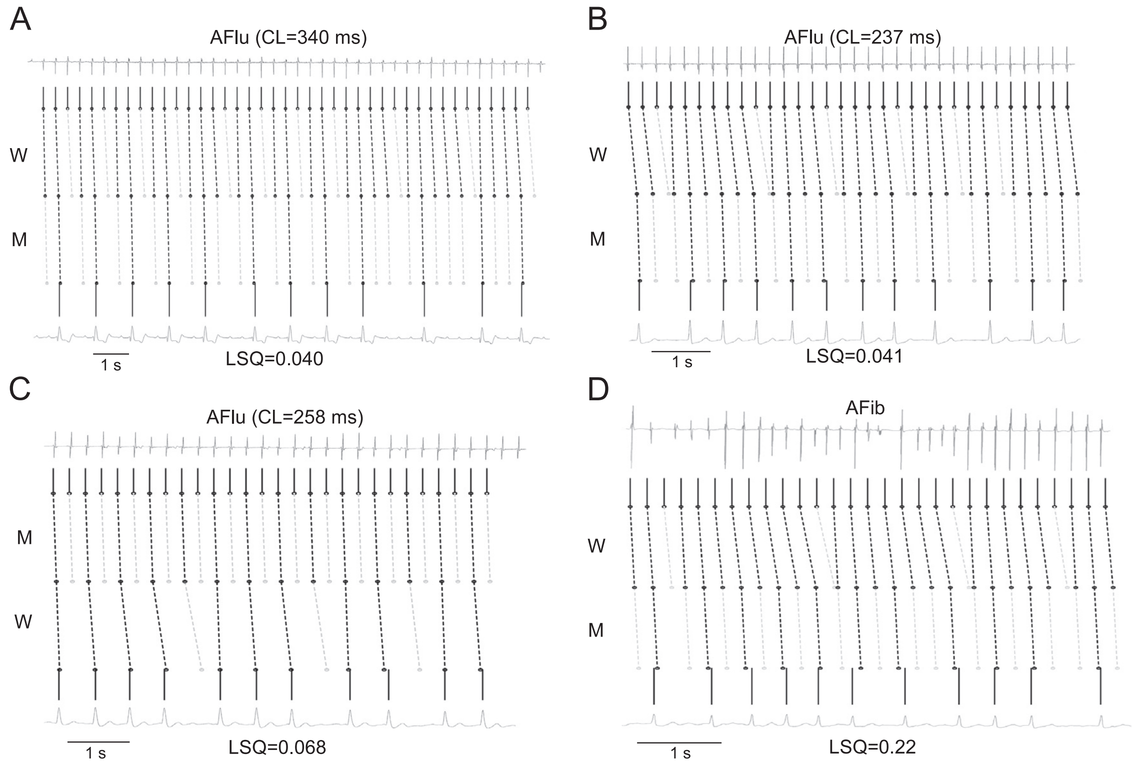

Figure 4 Prediction of atrial activation based on a sequence of R-R intervals. Panels A-D show the predicted multilevel AV block and the predicted atrial CL of 4 examples. **A, B:** Predicted MAVB with Wenckebach-type conduction on the first level and Mobitz-type block on the second level. **C:** Predicted MAVB with Mobitz-type block (2:1 ratio) on the first level and Wenckebach-type conduction on the second level. **D:** Best solution of an example correctly classified as AFib (LSQ $>$ 0.08). AFib = atrial fibrillation; AFlu = atrial flutter; AV = atrioventricular; CL = cycle length; LSQ = least squares type difference between simulation and measurements; MAVB = multilevel atrioventricular block.

Based on the diagnostic approach, differentiation can be performed even with short ECG strips.

In silico model of MAVB

Considering the short sequence of R-R intervals used for the analysis, the discrimination rate offered by the algorithm seems relatively good. Better test values were precluded by AFlu examples yielding high LSQ values as well as AFib examples yielding relatively low LSQ values.

The existence of AFlu examples with high LSQ values might be explained by the simplicity of the model and the coarse discretization of possible parameter values (see Table 1). As a consequence, rare electrophysiological phenomena, such as complex concealed conduction mechanisms or atypical Wenckebach periodicity,[14–16] could not be reproduced with our model. It is tempting to speculate that refinements might improve the quality of our approach. Further research in optimization algorithms and an increase in computational power will help us to address this question in the future. As initially published by Kosowsky et al,[5] MAVB might theoretically consist of up to 3 block levels in series. They further found that most examples could be explained sufficiently by the existence of 2 block levels.[5] However, we cannot exclude that some of the AFlu examples might be better explained with 3 or more block levels. As expected, the more the degrees of freedom were included in the model, the more the AFib examples with low LSQ could be observed. In contrast, the existence of AFib examples with low LSQ values can be partly attributed to simulated sequences of R-R intervals that accidentally matched with the sequence of R-R intervals taken from ECG. In addition, it is well recognized that in AFib, R-R variability decreases with an increase in heart rate, a phenomenon commonly referred to as pseudoregularization.[13] As a consequence, AFib examples with high ventricular rates might be more likely to match a simulated MAVB, thereby yielding a relatively low LSQ value.

Furthermore, the simulation process is based on a rapid atrial activation with a fixed CL. However, it is well recognized that the CL of AFlu might exhibit small variations. All AFlu examples yielded a variation of the atrial CL below 5 ms. However, when analyzing AFlu examples with high LSQ values, we found that even variations in CL within a range of 1–3 ms resulted in an impaired discrimination. These results underline that diagnostic accuracy is best for AFlu examples with low variation in CL.

Comparison with alternative approaches

On the basis of the spectra of F waves obtained from atrial ECGs, Hoppe et al[4] developed a diagnostic algorithm that is able to discriminate between both arrhythmias with high accuracy. They find that, compared with AFib, AFlu is associated with dominant and narrow peaks reflecting single

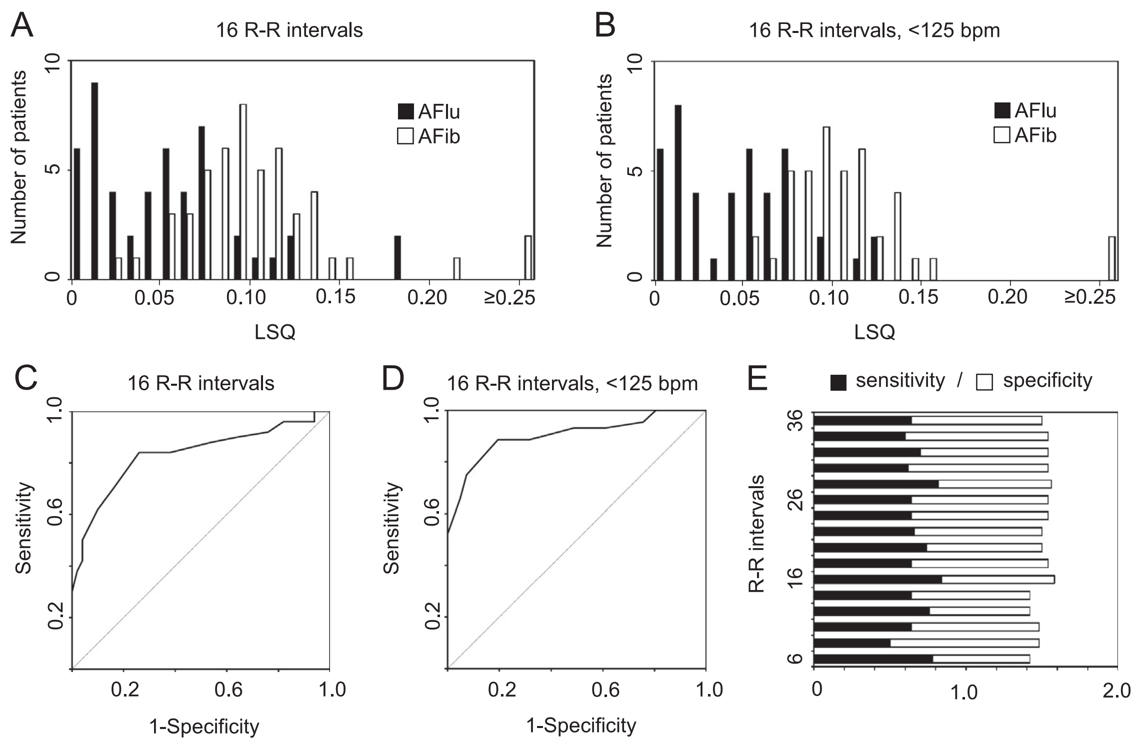

Figure 5 Diagnostic accuracy of the algorithm. **A:** Distribution of LSQ values of the best solution for 16 R-R intervals of 50 patients with AFlu and MAVB (solid bars) and 50 patients with AFib (open bars). **B:** Limiting the ventricular rate to 125 beats/min reduces the number of pseudoregularized AFib solutions with low LSQ (AFlu: n = 44; AFib: n = 41). **C, D:** Corresponding ROC curves for 16 R-R intervals and 16 R-R intervals with limited ventricular rate, yielding an area under the curve of 0.83 and 0.90, respectively. Highest diagnostic accuracy could be observed for 16 R-R intervals with limited ventricular rate (sensitivity 89%; specificity 80%). **E:** Systematic analysis of sensitivity and specificity depending on the segment length. AFib = atrial fibrillation; AFlu = atrial flutter; LSQ = least squares type difference between simulation and measurements; MAVB = multilevel atrioventricular block; ROC = receiver operating characteristic.

macroreentrant wave fronts. Even though patients were enrolled in a prospective manner, the study is based on a relatively small number of individuals (18 of 21). Furthermore, all ECGs were recorded under artificial conditions, namely, in the sedated state and using a high-quality physiological recorder.[4] In addition, regions of extreme noise were excluded from the analysis. As expected, when applying this algorithm to a real-world population, discrimination was considerably lower, even though 11% of the ECGs had been excluded from the analysis owing to poor quality.[17] These results underline the clinical observation that a discrimination based on atrial activation is often impossible due to the absence of unambiguously identifiable flutter waves. A similar detection algorithm based on the analysis of spectral entropy has been published earlier by Taha et al.[11] Analyzing more than 4000 QRST-subtracted ECGs, they find that the analysis of spectral peak frequencies significantly improved the discrimination rate between AFib and AFlu. However, no invasive measurements, that are considered the gold standard for rhythm diagnosis, were available to validate the suggested diagnosis.

Although the discrimination between AFib and AFlu based on the analysis of atrial activation can be performed with short ECG strips, it exhibits a high degree of susceptibility to artifacts. In contrast, the analysis of R-R intervals may represent a more reliable technique. However, determining the diagnostic utility of R-R regularity for the discrimination between AFib and AFlu, Krummen et al[12] found that R-R periodicity (<50 ms) can only be observed in 62% of typical and 10% of atypical AFlu. As a consequence, they show that R-R periodicity only poorly separated both arrhythmia. Similar results could be obtained when applying the algorithm published by Krummen et al to our data (sensitivity 58% and specificity 24%) (Figure 6). However, it is well recognized that the diagnostic utility of R-R intervals can be improved when analyzing long time intervals. By

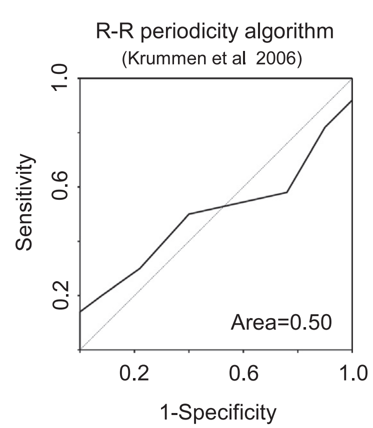

Figure 6 ROC curve of the R-R periodicity algorithm. An algorithm based on R-R periodicity[12] failed to discriminate between AFib and AFlu when analyzing a segment length of 16 R-R intervals. AFib = atrial fibrillation; AFlu = atrial flutter; ROC = receiver operating characteristic.

analyzing R-R intervals obtained from 24-hour Holter recordings using 2-dimensional Lorenz (Poincaré) plots, Esperer et al[18] observed characteristic patterns that allowed the discrimination between AFib and AFlu with high accuracy. Although the Lorenz plot method offers a reliable technique for the discrimination between AFib and AFlu, its diagnostic value is strongly dependent on a large number of R-R intervals. In order to compare our algorithm to this approach, all examples (16 R-R intervals length) were divided into distinct morphological classes using the spreading ratio of Poincaré data points as well as geometrical characteristics of central and eccentric clusters, as described by Esperer et al.[18] However, when carefully analyzing the plots, we found that only 15 cases exhibited characteristic AFlu morphology. For all other 85 cases, a discrimination based on the Poincaré plots was not possible owing to the limited number of data points. Exemplary Poincaré plots of AFib and AFlu are displayed in Online Supplemental Figure 2.

Study limitations

All data presented in this study are based on a patient collective that was analyzed retrospectively. In order to further underline the relevance of our findings, this diagnostic approach should be further validated within a prospective study. Furthermore, ECG samples containing ventricular premature beats were excluded from the analysis.

Conclusions

On the basis of a multilevel model of AV conduction, we developed an algorithm for the discrimination between AFlu and AFib. This algorithm is able to predict the stability and CL of atrial activation for short R-R sequences with high accuracy.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.02.013.

References

1. Shiyovich A, Wolak A, Yacobovich L, Grosbard A, Katz A. Accuracy of diagnosing atrial flutter and atrial fibrillation from a surface electrocardiogram by hospital physicians: analysis of data from internal medicine departments. Am J Med. Sci 2010;340:271–275.
2. Bogun F, Anh D, Kalahasty G, Wissner E, Bou Serhal C, Bazzi R, Weaver D, Schuger C. Misdiagnosis of atrial fibrillation and its clinical consequences. Am J Med 2004;117:636–642.
3. Knight BP, Michaud GF, Strickberger SA, Morady F. Electrocardiographic differentiation of atrial flutter from atrial fibrillation by physicians. J Electrocardiol 1999;32:315–319.
4. Hoppe BL, Kahn AM, Feld GK, Hassankhani A, Narayan SM. Separating atrial flutter from atrial fibrillation with apparent electrocardiographic organization using dominant and narrow F-wave spectra. J Am Coll Cardiol 2005;46:2079–2087.
5. Kosowsky BD, Latif P, Radoff AM. Multilevel atrioventricular block. Circulation 1976;54:914–921.
6. Watanabe Y, Dreifus LS. Second degree atrioventricular block. Cardiovasc Res 1967;1:150–158.
7. Young ML, Gelband H, Wolff GS. Atrial pacing-induced alternating Wenckebach periodicity and multilevel conduction block in children. Am J Cardiol 1986;57:135–141.
8. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31:2369–2429.
9. Vaz AIF, Vicente LN. PSwarm: a hybrid solver for linearly constrained global derivative-free optimization. Optim Methods Softw 2009;24:669–685.
10. Powell MJD. The NEWUOA software for unconstrained optimization without derivatives. In: Di Pillo G, Roma M, eds. Large-Scale Nonlinear Optimization. Boston: Kluwer Academic Publishers; 2006:255–297.
11. Taha B, Reddy S, Xue Q, Swiryn S. Automated discrimination between atrial fibrillation and atrial flutter in the resting 12-lead electrocardiogram. J Electrocardiol 2000;33:123–125.
12. Krummen DE, Feld GK, Narayan SM. Diagnostic accuracy of irregularly irregular RR intervals in separating atrial fibrillation from atrial flutter. Am J Cardiol 2006;98:209–214.
13. Kettering K, Dörnberger V, Lang R, Vonthein R, Suchalla R, Bosch RF, Mewis C, Eigenberger B, Kühlkamp V. Enhanced detection criteria in implantable cardioverter defibrillators: sensitivity and specificity of the stability algorithm at different heart rates. Pacing Clin Electrophysiol 2001;24:1325–1333.
14. Jørgensen P. A mathematical model of human atrioventricular nodal function incorporating concealed conduction. Bull Math Biol 2002;64:1083–1099.
15. Katoh T, Kinoshita S, Tsujimura Y, Sasaki Y. Alternating reversed Wenckebach periodicity: concealed electrotonic conduction as a possible mechanism. J Electrocardiol 2003;36:81–84.
16. Barold SS, Hayes DL. Second-degree atrioventricular block: a reappraisal. Mayo Clin Proc 2001;76:44–57.
17. Krummen DE, Patel M, Ngyen H, Ho G, Kazi DS, Clopton P, Holland MC, Greenberg SL, Feld GK, Faddis MN, Narayan SM. Accurate ECG diagnosis of atrial tachyarrhythmias using quantitative analysis: a prospective diagnostic and cost-effectiveness study. J Cardiovasc Electrophysiol 2010;21:1251–1259.
18. Esperer HD, Esperer C, Cohen RJ. Cardiac arrhythmias imprint specific signatures on Lorenz plots. Ann Noninvasive Electrocardiol 2008;13:44–60.