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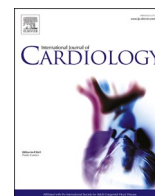
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Mobile app-based symptom-rhythm correlation assessment in patients with persistent atrial fibrillation

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ABSTRACT

Background: The assessment of symptom-rhythm correlation (SRC) in patients with persistent atrial fibrillation (AF) is challenging. Therefore, we performed a novel mobile app-based approach to assess SRC in persistent AF. **Methods:** Consecutive persistent AF patients planned for electrical cardioversion (ECV) used a mobile app to record a 60-s photoplethysmogram (PPG) and report symptoms once daily and in case of symptoms for four weeks prior and three weeks after ECV. Within each patient, SRC was quantified by the SRC-index defined as the sum of symptomatic AF recordings and asymptomatic non-AF recordings divided by the sum of all recordings. **Results:** Of 88 patients (33% women, age 68 ± 9 years) included, 78% reported any symptoms during recordings. The overall SRC-index was 0.61 (0.44–0.79). The study population was divided into SRC-index tertiles: low (<0.47), medium (0.47–0.73) and high (≥ 0.73). Patients within the low (vs high) SRC-index tertile had more often heart failure and diabetes mellitus (both 24.1% vs 6.9%). Extrasystoles occurred in 19% of all symptomatic non-AF PPG recordings. Within each patient, PPG recordings with the highest (vs lowest) tertile of pulse rates conferred an increased risk for symptomatic AF recordings (odds ratio [OR] 1.26, 95% coincidence interval [CI] 1.04–1.52) and symptomatic non-AF recordings (OR 2.93, 95% CI 2.16–3.97). Pulse variability was not associated with reported symptoms. **Conclusions:** In patients with persistent AF, SRC is relatively low. Pulse rate is the main determinant of reported symptoms. Further studies are required to verify whether integrating mobile app-based SRC assessment in current workflows can improve AF management.

1. Introduction

According to current atrial fibrillation (AF) guideline recommendations, AF management should focus on the comprehensive ABC (AF

Better Care) pathway incorporating anticoagulation therapy, better symptom management and comprehensive comorbidity treatment [1–3]. To improve symptom control and quality of life, the identification of AF-related symptoms is important as it guides personalized and joint

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decision making on either rate- or rhythm control. Particularly in patients with persistent AF (defined as continuously sustained AF beyond seven days, including episodes terminated by cardioversion after ≥ 7 days [1]) it is difficult to determine the association between patient self-reported symptoms and the underlying heart rhythm (symptom-rhythm correlation [SRC]) [4,5]. Differentiating between symptoms caused by AF (specific AF symptoms) and those caused by other underlying cardiovascular or non-cardiovascular conditions or risk factors (non-specific symptoms in AF) is often challenging, and no standardized strategy to assess SRC in AF patients is available [5]. Previously, we showed that symptom assessment around electrical cardioversion (ECV), once before ECV and once within 1-month follow-up, rarely identifies an SRC in persistent AF patients and often suggests changes in symptom pattern irrespective of changes seen in heart rhythm [6]. Mobile app-based simultaneous symptom and rhythm monitoring may improve SRC assessment but has not been described nor investigated before.

We hereby introduce a novel mobile app-based simultaneous symptom and rhythm monitoring approach to assess SRC in patients with persistent AF, which has been developed within the TeleCheck-AF project [7]. We aimed to 1) evaluate SRC and 2) establish related covariates for SRC in patients with persistent AF.

2. Methods

2.1. Project design

This is a substudy of the TeleCheck-AF project performed at the Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands, focusing on persistent AF patients monitored and managed around planned ECV. The TeleCheck-AF project is described in detail elsewhere [7]. Within this project, a uniform mobile health (mHealth) approach consisting of the on-demand use of a photoplethysmography (PPG)-based mobile app for remote rate and rhythm monitoring was introduced. This approach was set up around specific clinical scenarios and integrated into comprehensive AF management in several centres in Europe [8]. The TeleCheck-AF project was performed in compliance with the Declaration of Helsinki and approved by the Institutional Review Board at the MUMC+ (METC2020–1337).

2.2. Study population

From April 2020 to February 2021, consecutive patients (≥ 18 years) with persistent AF scheduled for ECV in the MUMC+ were included. Individuals were excluded if they did not have a smartphone, could not operate the mobile application system after instructions or had an implanted pacemaker.

2.3. Study procedures

Patients were provided with a Conformité Européenne (CE)-marked, on-demand mobile phone application monitoring heart rate and rhythm and symptoms (FibriCheck®, Qompium, Hasselt, Belgium). Access to this PPG-based application was prescribed in the form of a temporary QR code, and a short instruction for heart rate and rhythm measurements was provided. A case coordinator was responsible for sending the code and instructing the patients carefully on how to use the application. Within 24 h of sending the code, the case coordinator also evaluated whether the patients could activate the app and perform the measurements. Once the app was activated by the QR-code, the PPG recordings and corresponding symptom statuses were instantly synchronized to a secured and certified cloud (www.fibrichck.com), to which the treating physician and research team had access.

Patients were instructed to record a 60-s PPG through their smartphone's built-in camera once daily and additionally when experiencing symptoms for four weeks preceding ECV and three weeks following ECV. After completing a recording, patients were instructed to specify in the

mobile app if they experienced any of the following symptoms during the preceding PPG measurement: no symptoms, palpitations, chest pain, dyspnea, confusion, light-headedness, fatigue, and/or others. The app provided the patients with regular reminders to assess their heart rate/rhythm, to actively report the presence/absence of symptoms via pop-up notifications, and with precise instructions on how to improve the quality of measurements in case of insufficient signal quality [7].

2.4. Data collection

Baseline clinical characteristics (demographics and medical history) were retrieved from patients' medical records. Heart rhythm status and corresponding symptom status of each PPG-recording were retrieved from the secured and certified cloud. The raw waveforms of the PPG recordings were extracted from the FibriCheck cloud in European Data Format (EDF) format. The remaining data points were exported in comma-separated values (CSV) format.

2.5. Data analysis

2.5.1. Symptom-rhythm correlation assessment

Patients could report more than one symptom experienced during the PPG recording. For SRC assessment, the predominant symptom per measurement chosen from the symptoms list was included in the analysis. The chronologic order of the annotated symptoms per recording was used to determine the predominant symptom.

The PPG recordings were interpreted by the FibriCheck® algorithm as follows: 1) regular rhythm, 2) warning, 3) possible AF ('AF-rhythm'), and 4) insufficient quality. 'Regular rhythm' was defined as a recording presenting sinus rhythm. A measurement labelled as 'warning' implied that the algorithm detected some abnormalities that could not be classified as AF (e.g. extrasystoles, bradycardia or tachycardia), and there was no interference. For this study, regular and warning rhythms were further considered as 'non-AF rhythm'. An 'insufficient quality' recording indicated that too much interference was detected to perform a detailed rhythm analysis. The treating physician and research team had access to the raw data of the PPG signals together with the RR-tachogram and Poincaré plot. Additionally, certified technicians reviewed all algorithm analysis-based irregular PPG recordings, and the results were integrated into the secured cloud. This could have further increased the accuracy to detect AF episodes [9].

For this study, only measurements classified as non-AF rhythm (non-AF PPG recordings including regular and warning rhythms) and AF-rhythm (AF PPG recordings) were considered in the SRC assessment. AF recordings with the presence of self-reported symptoms were defined as symptomatic AF PPG recordings, AF recordings without symptoms as asymptomatic AF PPG recordings, non-AF recordings with the presence of symptoms as symptomatic non-AF PPG recordings, and non-AF recordings without self-reported symptoms as asymptomatic non-AF PPG recordings (Fig. 1).

We assessed the SRC by considering the association between self-reported symptoms and rhythm status. The SRC per patient was quantified by the SRC-index, defined as the number of symptomatic AF recordings and asymptomatic non-AF recordings divided by all recordings regardless of symptom status (Fig. 1).

2.5.2. Pulse rate variability assessment

60-s PPG recordings were processed in Matlab® (The MathWorks, USA) for pulse rate variability assessment. Baseline wander was removed using a high-pass filter with a cutoff frequency of 0.5 Hz. Motion artifacts were automatically identified using a 10-s sliding window, in which the peaks were detected and assessed for outliers. Segments containing artifacts were rejected from the analysis. From the time series of pulse intervals, we calculated the mean pulse interval, the standard deviation (SD) of pulse intervals, the root-mean-square of successive pulse interval differences (RMSSD) and the standard

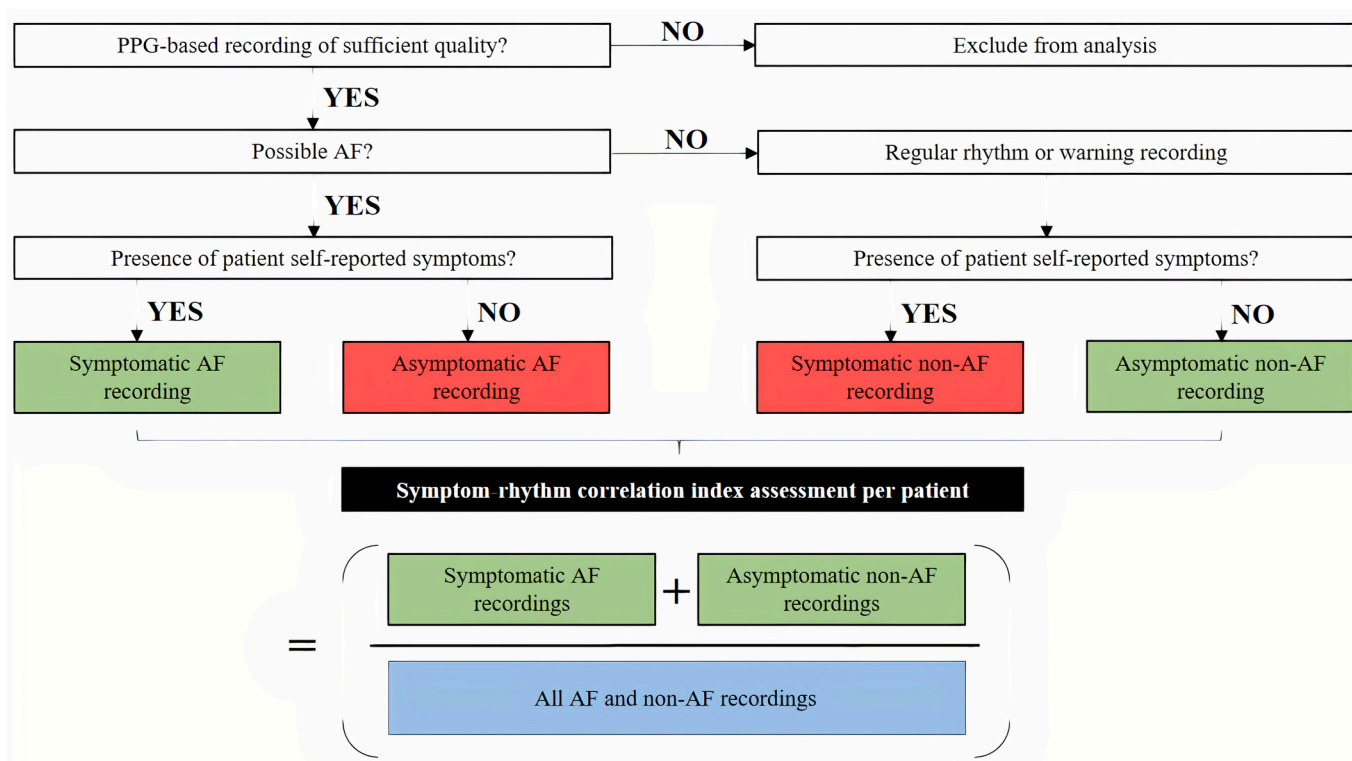


Fig. 1. Flow chart symptom-rhythm correlation index assessment. Abbreviations: AF, atrial fibrillation; PPG, photoplethysmography.

deviation of successive pulse interval differences (SDSD) as these are the most common parameters used for pulse rate variability assessment [10].

2.5.3. Patient compliance and motivation assessment

Patient compliance and motivation were calculated to assess adherence to the study protocol. Compliance was defined as the number of PPG measurements per number of expected PPG measurements (at least one daily) over the entire study period (from three weeks before ECV until four weeks after ECV). Motivation was defined as the number of days in which the expected number of PPG measurements (at least one daily) were performed per number of days over the entire study period.

2.6. Statistical analyses

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean \pm SD. Nonparametric variables were presented as median [interquartile range (IQR)] and categorical variables as numbers (n) with percentages (%). Differences in continuous parameters were compared using one-way ANOVA and nonparametric Kruskal-Wallis test, as applicable. For the comparison of categorical data, the Pearson's chi-squared tests were used. A binary logistic generalized estimating equation was used to develop a model for the dichotomous symptom outcome (odds ratio [OR] for symptomatic PPG recordings and OR for asymptomatic PPG recordings with their 95% confidence interval [95% CI]) using the within-patient standardized pulse rate and pulse rate variability data in AF and non-AF. Statistical significance was assumed at a 5% level. For database management and statistical analysis, we used IBM SPSS Version 25 (IBM Corporation, Somers, New York, USA).

3. Results

Data from 88 consecutive persistent AF patients (age 68 ± 9 years, 33.0% women) referred for ECV in the MUMC+ were analysed (Table 1). Of these patients, 11.4% suffered from diabetes mellitus, 48.9% from hypertension and 25.0% from chronic heart failure. The prevalence of obesity (body mass index [BMI] ≥ 30 kg/m² was 33.3% and a history of myocardial infarction was present in 11.4%. In 60.2% of patients, thromboembolic risk was increased (CHA₂DS₂-VASc score ≥ 2 in men or ≥ 3 in women), and all were anticoagulated. Antiarrhythmic drugs were used in 23.9% of patients, 69.3% received beta-blockers, 7.0% non-dihydropyridine calcium channel blockers and 25.0% digoxin. The overall median patient compliance and motivation to use the mobile app-based simultaneous symptom and rhythm monitoring approach were high, with 164% and 92%, respectively.

3.1. Rhythm and symptom variability

ECV was performed in 77 patients (87.5%) among all included patients. In 11 patients (12.5%), the scheduled ECV was cancelled as these converted to sinus rhythm spontaneously (of these, nine patients had a paroxysmal AF pattern, and two patients were in stable sinus rhythm throughout the remaining monitoring period). ECV was successful in 74 patients (96.1%) and unsuccessful in three patients (3.9%). Within three weeks after ECV, 48 out of 77 patients (62.3%) had PPG-documented recurrence of AF.

In total, 6359 separate PPG recordings were analysed (mean number of PPG recordings per patient 72 ± 43 ; mean number of monitoring days per patient 46 ± 7 ; mean number of recordings per day per patient 1.6 ± 0.91). Of these PPG recordings, 1964 (31%) were symptomatic AF recordings, 1843 (29%) asymptomatic non-AF recordings, 1993 (31%) asymptomatic AF recordings and 559 (9%) symptomatic non-AF recordings. The majority of patients (78%) reported symptoms during their PPG recordings and 22% of patients were completely

Table 1
Clinical characteristics of included patients, divided in tertiles according to symptom-rhythm correlation index.

Variable	Study group (n = 88)	Low [<0.47] SRC-index (n = 29)	Moderate [$0.47-0.73$] SRC-index (n = 30)	High [≥ 0.73] SRC-index (n = 29)	P-value
Demographics					
Age (years) – mean \pm SD	68 \pm 9	68 \pm 10	68 \pm 9	68 \pm 7	0.918
Female sex	29 (33.0%)	8 (27.6%)	10 (33.3%)	11 (37.9%)	0.703
BMI (kg/m ²) – mean \pm SD	28.2 \pm 4.7; n = 87	27.9 \pm 4.7; n = 29	28.8 \pm 4.5; n = 30	27.9 \pm 4.8; n = 28	0.686
AF					
First-detected AF	19 (21.6%)	7 (24.1%)	2 (6.7%)	10 (34.5%)*	0.032
Current AF episode duration >6 months**	53 (91.4%); n = 58	17 (85.0%); n = 20	24 (96.0%); n = 25	12 (92.3%); n = 13	0.422
Current AF episode duration >12 months**	45 (77.6%); n = 58	13 (65.0%); n = 20	21 (84.0%); n = 25	11 (84.6%); n = 13	0.249
Previous CV (electrical and/or pharmacological)**	41 (59.4%); n = 69	14 (63.6%); n = 22	20 (71.4%); n = 28	7 (36.8%); n = 19	0.054
Ablation therapy for AF**	17 (24.6%); n = 69	4 (18.2%); n = 22	8 (28.6%); n = 28	5 (26.3%); n = 19	0.685
Cardiovascular diseases					
Myocardial infarction	10 (11.4%)	3 (10.3%)	1 (3.3%)	6 (20.7%)	0.108
PCI/PTCA	9 (10.2%)	2 (6.9%)	2 (6.7%)	5 (17.2%)	0.314
CABG	3 (3.4%)	2 (6.9%)	1 (3.3%)	0 (0.0%)	0.351
Peripheral vascular disease	1 (1.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0.376
Diabetes mellitus	10 (11.4%)	7 (24.1%)	1 (3.3%)	2 (6.9%)	0.027
Hypertension	43 (48.9%)	15 (51.7%)	13 (43.3%)	15 (51.7%)	0.757
Chronic heart failure	22 (25.0%)	7 (24.1%)	13 (43.3%)	2 (6.9%)*	0.005
Obesity (BMI ≥ 30 kg/m ²)	29 (33.3%); n = 87	9 (31.0%); n = 29	10 (33.3%); n = 30	10 (35.7%); n = 28	0.932
Stroke/TIA/pulmonary embolism	5 (5.7%)	0 (0.0%)	3 (10.0%)	2 (6.9%)	0.238
Device therapy (PM/CRT/ICD)	5 (5.7%)	0 (0.0%)	2 (6.7%)	3 (10.3%)	0.226
Transthoracic echocardiographic parameters					
LVEF (%) – median (IQR)	52 (45–59); n = 77	55 (45–61); n = 26	50 (45–55); n = 27	52 (43–59); n = 24	0.374
Left atrial volume – mean \pm SD	96 \pm 30; n = 76	102 \pm 27; n = 25	92 \pm 32; n = 28	95 \pm 30; n = 23	0.448
Valvular heart disease	6 (7.1%); n = 84	1 (3.7%); n = 27	3 (10.0%); n = 30	2 (7.4%); n = 27	0.653
Thromboembolic risk					
CHA ₂ DS ₂ -VAsC score = 0 (if male), = 1 (if women)	14 (15.9%)	5 (17.2%)	5 (16.7%)	4 (13.8%)	0.928
CHA ₂ DS ₂ -VAsC score = 1 (if male), = 2 (if women)	21 (23.9%)	7 (24.1%)	6 (20.0%)	8 (27.6%)	0.791
CHA ₂ DS ₂ -VAsC score ≥ 2 (if male), ≥ 3 (if women)	53 (60.2%)	17 (58.6%)	19 (63.3%)	17 (58.6%)	0.912
Medications					
Oral anticoagulants	88 (100.0%)	29 (100.0%)	30 (100.0%)	29 (100.0%)	NA
Antiplatelet drugs	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	0.125
Beta-blockers	61 (69.3%)	21 (72.4%)	18 (60.0%)	22 (75.9%)	0.379
Antiarrhythmic drugs	21 (23.9%)	4 (13.8%)	12 (40.0%)	5 (17.2%)	0.037
Diuretics	29 (33.0%)	11 (37.9%)	9 (30.0%)	9 (31.0%)	0.782
Dihydropyridine-CCB	17 (19.8%)	8 (28.6%)	2 (6.9%)	7 (24.1%)	0.093
Non-dihydropyridine-CCB	6 (7.0%)	1 (3.6%)	3 (10.3%)	2 (6.9%)	0.604
ACEI	24 (27.3%)	7 (24.1%)	10 (33.3%)	7 (24.1%)	0.656
ARB	18 (20.5%)	5 (17.2%)	7 (23.3%)	6 (20.7%)	0.845
MRA	2 (2.3%)	0 (0.0%)	1 (3.3%)	1 (3.4%)	0.604
Digoxin	22 (25.0%)	11 (37.9%)	5 (16.7%)	6 (20.7%)	0.136

The number provided after the semicolon indicates the total number of patients available for that variable. Values are depicted as the number of patients (n) with percentages unless indicated otherwise. * P-value ≤ 0.05 for comparison between moderate vs high symptom-rhythm correlation. The Bonferroni correction was applied to address the multiple comparison issues.** Results after excluding patients with first-detected AF.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass surgery; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; CV, cardioversion; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not applicable; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack.

asymptomatic. Fatigue (30%) was the most common reported symptom, followed by palpitations (17%), chest pain (9%), shortness of breath (8%), other (7%), light-headed (5%) and several (3%). Among all patients with PPG-documented AF (n = 86), 77% reported symptoms and 23% were completely asymptomatic during AF PPG recordings. In AF PPG recordings, fatigue (30%) was the most common reported symptom, followed by palpitations (19%), shortness of breath (8%), other (8%), chest pain (7%), light-headed (2%) and several (2%). Of all

patients with PPG-documented non-AF (n = 79), nearly half of patients (48%) reported symptoms and 52% were completely asymptomatic during non-AF PPG recordings. In non-AF PPG recordings, fatigue (16%) was the most common reported symptom, followed by palpitations (10%), light-headed (6%), several (4%), chest pain (4%), shortness of breath (4%) and other (4%). In the 66 patients who reported any symptoms during AF PPG recordings, the mean percentage of symptomatic AF PPG recordings per patient was 56%. In the 40 patients who

reported any symptoms during non-AF PPG recordings, the mean percentage of symptomatic non-AF PPG recordings per patient was 43%. There was no difference in patient-reported predominant symptom type during non-AF and AF PPG recordings per patient based on comorbidities, such as chronic heart failure and diabetes mellitus, of which symptoms often overlap with those associated with AF (**Supplementary Table S1**).

Symptom burden (defined as the proportion of symptomatic PPG recordings per all PPG recordings) was 42% prior to ECV compared to 31% after ECV. Symptomatic AF PPG recordings comprised 59% ($n = 66$) of all AF PPG recordings preceding ECV and 57% ($n = 41$) following ECV, while asymptomatic non-AF PPG recordings made up 82% ($n = 73$) of all non-AF PPG recordings before ECV and 82% ($n = 73$) after ECV. Preceding and following ECV, the most common predominant self-reported symptom was fatigue, comprising 38% and 33% of symptom measurements, respectively. About 67% of patients reported ≥ 2 types of symptoms pre-ECV, and 64% did this post-ECV. Interestingly, intra-individually variable symptom patterns, defined as changes in predominant self-reported symptoms within patients around ECV, were present in 37 patients (42%) (**Supplementary Fig. S1**).

3.2. Symptom-rhythm correlation

The proportion of symptomatic AF PPG recordings for all AF PPG recordings was low (40% [5–83%]), whereas the proportion of asymptomatic non-AF PPG recordings per all non-AF PPG recordings was high (92% [67–100%]). Therefore, mainly driven by a large number of asymptomatic AF PPG recordings, the overall SRC-index was 0.61 (0.44–0.79).

We grouped patients into tertiles using the SRC-index; in low (<0.47), moderate (0.47–0.73) and high (≥ 0.73) (**Table 1**). Detailed distribution of patients regarding the SRC-index is provided in **Supplementary Fig. S2**. Patients in the highest SRC-index tertile more often had first-detected AF (34.5% vs 6.7% of patients in moderate tertile vs 24.1% of patients in low tertile, $P = 0.032$) and were less often diagnosed with chronic heart failure (6.9% vs 43.3% vs 24.1%, respectively, $P = 0.005$). Moreover, patients in the low (vs moderate and high) SRC-index tertile were more frequently diagnosed with diabetes mellitus (24.1% vs 3.3% and 6.9%, $P = 0.027$) and less often received antiarrhythmic drugs (13.8% vs 40.0% and 17.2%, $P = 0.037$). No statistically significant differences in duration of current AF episode, the use of rate control drugs such as beta-blockers with the highest contribution of metoprolol, as well as in echocardiography-derived cardiac dimensions or functional parameters were observed between the low, moderate and high SRC-index group. Although 24.6% of patients had a previous AF ablation, what could influence the symptom burden as patients with previous AF ablation are more prone to have asymptomatic AF events and therefore have lower SRC-index as compared to patients without previous AF ablation [11], we found no statistically significant difference between the low, moderate and high SRC-index group according to prevalence of previous AF ablation as well as between patients with and without previous AF ablation according to type of recordings (**Supplementary Table S2**).

SRC in the pre-ECV and post-ECV period were compared. After exclusion of the PPG recordings performed at the day of ECV, the overall SRC-index in the pre-ECV period ($n = 3199$ recordings) was 0.49 (0.03–0.88), whereas the overall SRC-index in the post-ECV period ($n = 2983$ recordings) was 0.73 (0.40–0.92). In additional analysis restricted to post-ECV period, we divided patients into tertiles using the post-ECV SRC-index; in low (<0.55), moderate (0.55–0.88) and high (≥ 0.88) SRC-index (**Supplementary Table S3**). Within three weeks after ECV, 48 out of 77 patients (62.3%) had PPG-documented recurrence of AF. In patients with AF recurrence, median pulse rate per patient in AF prior and after ECV was 78 bpm (73–85) and 76 bpm (72–83), respectively, $P = 0.008$. There was no statistically significant difference between the low, moderate and high SRC-index group according to the time to AF

recurrence (3 days [2–5]; $n = 21$ vs 4 days [3–10]; $n = 17$ vs 1 day [1–8]; $n = 9$, $P = 0.110$). Patients in the high SRC-index tertile more often used dihydropyridine calcium channel blockers compared to those in the moderate and low SRC-index tertiles (35.5% vs 10.3% vs 10.7%, respectively, $P = 0.018$).

3.3. Extrasystoles, pulse rate and pulse rate variability as determinants of symptoms

Of all non-AF PPG recordings, 22% were symptomatic. Extrasystoles occurred in 12% of all non-AF PPG recordings. The proportion of all symptomatic non-AF PPG recordings with extrasystoles was 19%, while extrasystoles just occurred in 10% of all asymptomatic non-AF PPG recordings (**Fig. 2**). The proportion of all non-AF PPG recording per patient classified as extrasystoles, bradycardias and tachycardias was 4.7%. There was no statistically significant difference in the proportion of ‘warning’ recordings in patients with low vs moderate vs high SRC-index (3% [0–7] vs 2% [0–10] vs 2% [0–6], $P = 0.784$).

The median pulse rate during symptomatic AF PPG recordings was 78 bpm (72–86) with a range of 41–119 bpm and during asymptomatic AF PPG recordings 77 bpm (70–85) with a range of 36–121 bpm. Pulse rate during symptomatic and asymptomatic non-AF PPG recordings ranged between 40 and 109 bpm (median 65 bpm [59–72]) and between 35 and 152 bpm (median 61 bpm [55–67]), respectively (**Supplementary Fig. S3**). There was a significant increase in the percentage of symptomatic AF and non-AF PPG recordings with increasing pulse rates, but not with increasing pulse rate variabilities (**Supplementary Table S4**). Especially the percentage of light-headedness and palpitations as self-reported symptom increased with increasing pulse rate in AF, while in non-AF PPG recordings, increasing pulse rate was related to increasing percentage of chest pain, fatigue, light-headedness and palpitations as self-reported symptom (**Supplementary Table S5**). To exclude the eventual risk of the biases associated with an unequal number of performed recordings per patient, we sub-analysed 20 patients with ≥ 45 AF PPG recordings (**Supplementary Fig. S4**). Within each patient, PPG recordings with the highest (vs lowest) tertile of pulse rates conferred an increased risk for symptomatic AF recordings (OR 1.26, 95% CI 1.04–1.52) and symptomatic non-AF recordings (OR 2.93, 95% CI 2.16–3.97) (**Fig. 3**). **Fig. 4** represents the percentage of symptomatic AF and non-AF PPG recordings per pulse rate tertile (low, moderate, high) within a particular patient. An example of recordings showing pulse rate variability based on increasing individual pulse rate (tertiles) is presented in **Supplementary Fig. S5**. There were no statistically significant differences in mean pulse rate and pulse rate variability between the low, moderate and high SRC-index group (**Supplementary Table S6**).

4. Discussion

The assessment of SRC in AF patients has been addressed and discussed in previous analyses [6,12], and is frequently used in the clinic to guide AF management decision-making. To the best of our knowledge, the present study is the first to assess SRC in persistent AF patients using a mHealth approach of simultaneous PPG-based heart rhythm/rate monitoring and active interrogation of patient-reported symptoms, which provides a novel approach to systematically assess SRC in persistent AF. Despite the relatively low SRC, the established association of symptom burden with comorbidities and the greater risk of symptoms with higher ventricular response rates are all well recognized features of AF. Most evidence on SRC in AF populations comes from patients in post-ablation period [12]. Semi-continuous longitudinal assessment of symptomatic and asymptomatic AF episodes around ECV adds novel findings in patients with persistent AF. Interestingly, the strategy of how sinus rhythm is restored may impact SRC by differentially influencing the perception of AF after ablation compared to ECV. SRC assessment around ECV by inducing immediate restoration of sinus rhythm allows

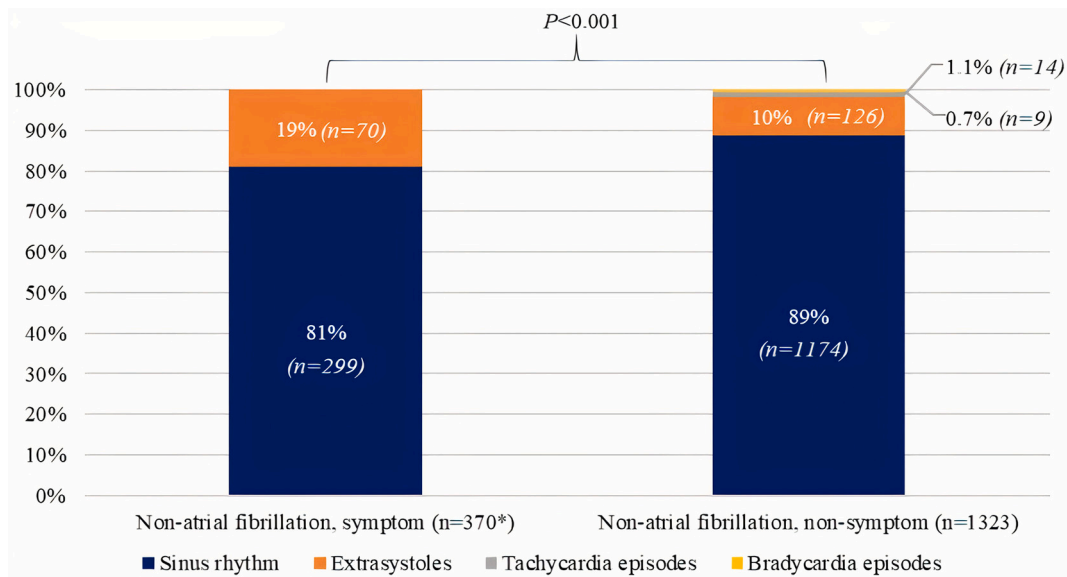


Fig. 2. Occurrence of specific rhythms within non-atrial fibrillation recordings depending on the presence and absence of symptoms. * + 1 recording presenting atrial flutter.

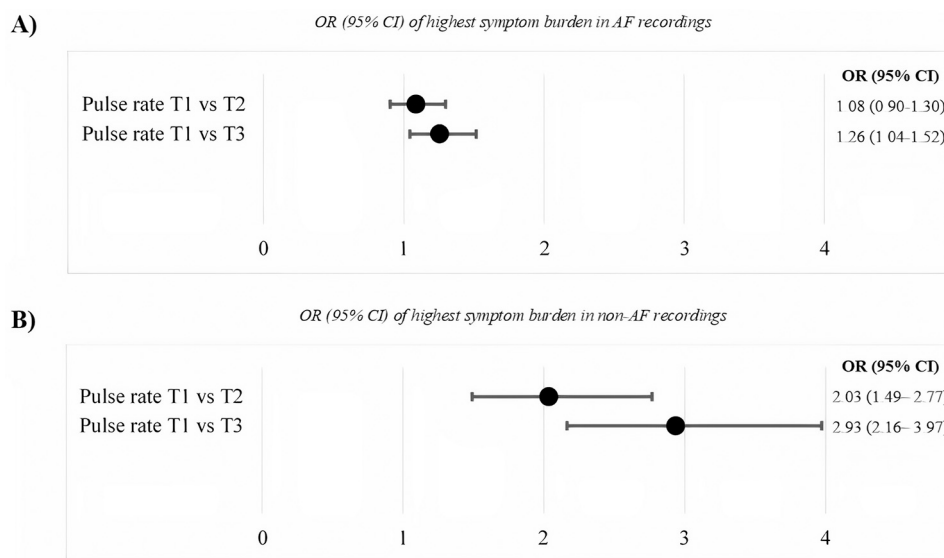


Fig. 3. Symptom burden depending on increasing tertiles of pulse rate in symptomatic photoplethysmography recordings both representing atrial fibrillation (Panel A) and non-atrial fibrillation (Panel B). Abbreviations: AF, atrial fibrillation; CI, coincidence interval; OR, odd ratio; T, tertile.

the evaluation whether symptoms improve or whether symptom burden remains unaffected [13].

The main findings of our study are as follows. First, a low proportion of all rhythm recordings with simultaneous symptom monitoring were in line with an SRC, resulting in an overall low SRC-index (defined as the sum of symptomatic AF recordings and asymptomatic non-AF recordings divided by the sum of all recordings). Second, patients with the lowest degree of SRC-index more frequently suffered from chronic heart failure and diabetes mellitus as compared to those with the highest degree of SRC-index. Third, extrasystoles can explain a minority of symptomatic non-AF PPG recordings. Finally, a higher pulse rate, but not a higher pulse irregularity, was associated with a higher probability of a symptomatic recording during AF and non-AF PPG recordings in persistent AF patients.

Although most patients in our study reported symptoms during AF, a

remarkable number of AF PPG recordings during the same persistent AF episode were not associated with self-reported symptoms assessed through active interrogation of patient-reported symptoms. Additionally, in line with previous observation, patients experienced a wide variety of symptoms during persistent AF episodes, including fatigue, chest pain, palpitations, light-headedness and shortness of breath [4,6], and there was high variability in patient-reported predominant symptoms before and after ECV [6]. Interestingly, fatigue was the most common reported symptom in patients with persistent AF, whereas individuals with paroxysmal AF are more likely to experience palpitations [14]. This heterogeneity in terms of symptom presentation may be explained by high variability in symptom perception [1,5] and affected by several sociodemographic characteristics such as the level of anxiety and depression as well as multiple pathophysiologic mechanisms [14]. Psychological aspect assessment around mHealth use would be an

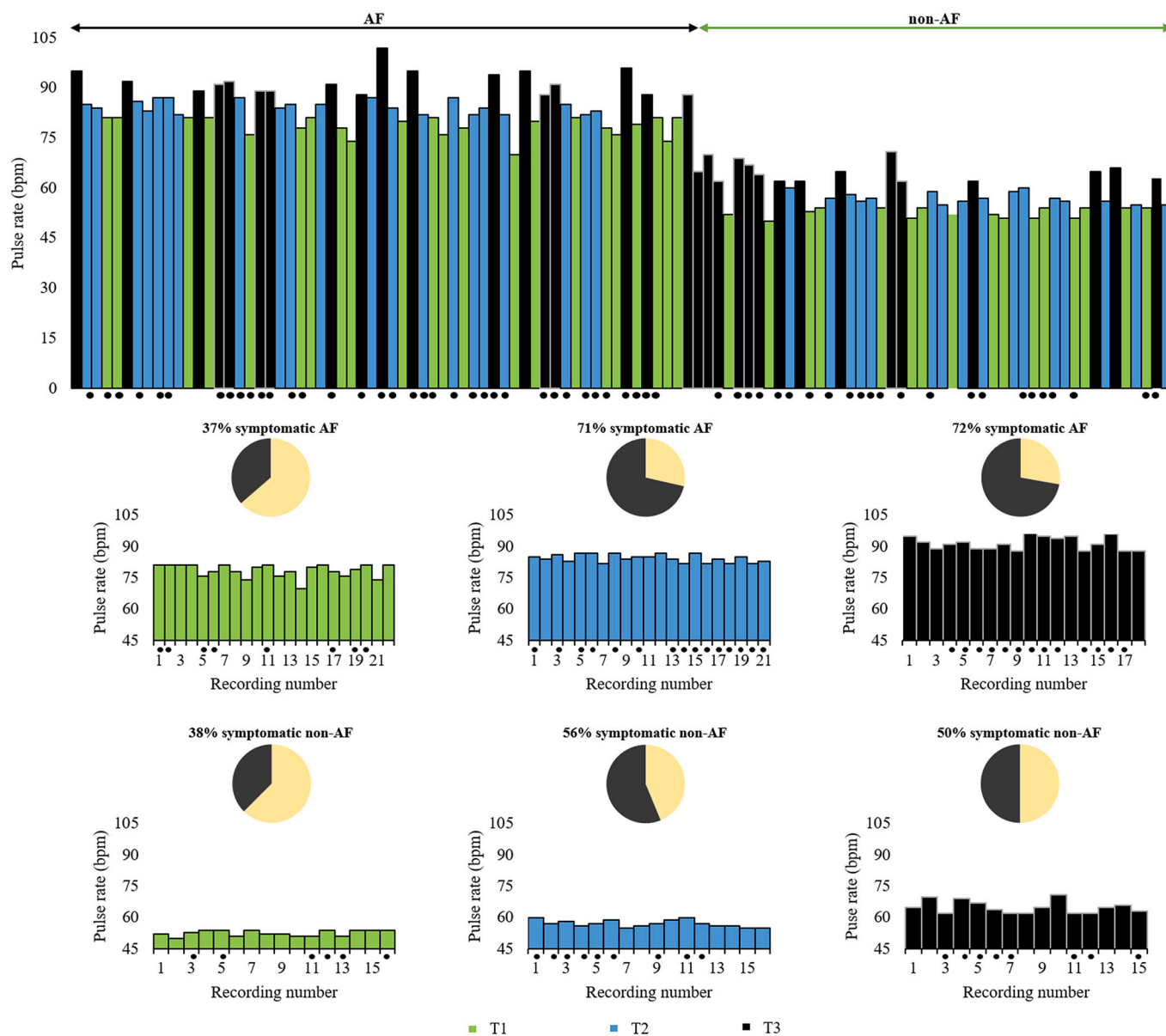


Fig. 4. The percentage of symptomatic atrial fibrillation and non-atrial fibrillation photoplethysmography recordings per pulse rate tertile (low, moderate, high) within a particular patient. Green, blue and black bars indicate individual low, moderate and high tertile of patient’s pulse rate, respectively. Black dots below the particular bars indicate symptomatic recordings. *Upper panel:* Pulse rate during recordings performed by a particular patient. *Middle and low panels:* Column bars representing individual low, moderate and high tertiles of patient’s pulse rate during recordings with atrial fibrillation (middle panel) and non-atrial fibrillation (low panel). Pie graphs above column-graphs represent the percentage of symptomatic recordings in each pulse rate tertile group (low, moderate and high). Abbreviations: AF, atrial fibrillation; bpm, beats per minute; T, tertile. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interesting component to improve SRC measurement in the near future. Additionally, concomitant cardiovascular or non-cardiovascular conditions and risk factors as well as the number of underlying comorbidities may contribute to altered self-reported symptom perception in AF patients [15]. The central role of somatosensory and insula cortices in interoceptive attention endorses their proposed contribution to subjective emotional feeling states arising from representations of bodily responses [16]. Importantly, this variability in symptoms, overall symptom burden and SRC in patients with persistent AF cannot be adequately assessed by spot assessment in outpatient AF clinics [6], and therefore may require approaches of simultaneous rhythm monitoring and active interrogation of patient-reported symptoms as introduced in this study.

The notion that a persistent AF episode is not always symptomatic is

interesting. It may depend on the pulse rate and activation of the autonomic nervous system, as these may influence the patient’s perception of AF episodes [14]. We thereby show that within each patient, PPG AF recordings with the individually highest pulse rates conferred a 1.26-fold increased risk of being associated with symptoms compared with the individually slowest AF PPG recordings, which is in line with prior work [17]. Interestingly, the extent of pulse irregularity in the PPG signal did not relate to symptoms. This supports the potential role of effective rate control in improved symptom management of persistent AF patients. Although we found no association between symptoms and overmedication (usage of >2 of the following cardiovascular drugs: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiarrhythmic drugs, beta-blockers, calcium channel blockers, digoxin, diuretics, mineralocorticoid receptor antagonists) or

usage of a particular cardiovascular drug (**Supplementary Table S7**), we cannot exclude the influence of cardiovascular drugs on the occurrence of side effects in the form of symptoms due to the small size of the study group.

Additionally, our data showed that half of the patients were symptomatic during non-AF PPG recordings, which is in line with previous study [18]. A small proportion of all non-AF PPG recordings per patient (4.7%) were classified as extrasystoles, bradycardias and tachycardias which may explain symptoms reported by patients during non-AF PPG recordings. However, there was no statistically significant difference in the proportion of ‘warning’ recordings in patients with low vs moderate vs high SRC-index. Interestingly, also during non-AF PPG recordings, increased pulse rates were associated with increased symptom burden. An explanation might be the presence of non-specific disease-related symptoms related to other comorbidities and risk factors or anxiety. However, the cause-effect relationship remains unclear.

Related covariates of SRC may identify the patients who could profit the most from heart rhythm control in regard to symptom reduction. The current study found that patients with poor SRC were more often diagnosed with comorbidities, including chronic heart failure and diabetes mellitus, which is in line with previous work [19,20]. Diabetic patients could have problems with AF symptom discrimination regarding frequently occurring neuropathic pain [19]. In contrast, heart failure patients share common symptoms with AF, which makes it difficult to separate symptoms caused by heart failure from those caused by AF [20]. These findings highlight the challenge in symptom management in multi-morbid AF patients and may partly explain the sub-optimal improvement in symptoms when solely focussing on rhythm control in patients with persistent AF and comorbidities. Therefore, following current AF-guidelines, an integrated and multidisciplinary care approach focused on comprehensive treatment including optimal and personalized management of underlying conditions and risk factor management may be required to achieve optimal symptom control in persistent AF patients [1–3]. Moreover, the recommended patient-centred focus, as part of an integrated approach, requires active involvement of the patient, which includes education and clear instruction on e.g. the use of mHealth and the reporting of symptoms. However, this requires further investigation.

The low SRC described by this study as well as the notion that many persistent AF patients still perceived symptoms even after restoration of sinus rhythm through ECV indicate that patient self-reported symptoms alone are not an accurate and reliable means of assessing the current rhythm status. This could also explain the relatively low SRC in this analysis and has important implications for several clinical scenarios, including assessing AF patients exclusively during teleconsultations and evaluating AF recurrences and AF burden during follow-up after rhythm control strategy approaches. Implementation of on-demand mHealth approaches, e.g. around teleconsultation (TeleCheck-AF [7]), around ECV (TeleWAS-AF [21]) or for follow-up after AF ablation [22], may provide better heart rhythm monitoring with simultaneous symptom assessment and allow informed decision making and integration of the data into clinical workflows [23].

Despite the fact that most patients were reporting symptoms during AF, a remarkable number of AF PPG recordings were not associated with self-reported symptoms. Nevertheless, the number of patients in whom all AF PPG recordings were asymptomatic was very low. Therefore, instead of categorising patients into symptomatic versus asymptomatic AF patients, we introduced the mobile app-based SRC-index as a continuous variable. Although recent studies suggest that asymptomatic AF patients profit from rhythm control comparable to symptomatic patients [24], the implication of SRC assessment for managing AF patients needs to be investigated in future studies.

4.1. Limitations

Our study had several limitations. Firstly, due to the subjective

symptom evaluation by AF patients, we could not determine whether symptoms were causally linked to AF or whether they are just associated with AF. Secondly, symptom severity assessment, a primary endpoint of AF management, was not considered. Secondly, symptom severity and quality of life assessment, both important endpoints of AF management [1,25], were not incorporated in the current mobile application used in our study. Patient education on symptom quality and development is required to assess symptom severity better [26]. The best way how to educate and involve patients in the assessment of symptom quality and severity requires further study. Thirdly, there may be selection bias, as only persistent AF patients with symptoms that are severe enough for ECV indication and those willing to use the mobile app were included. Therefore, caution should be taken before generalizing our findings to all patients with AF. Also the number of recruited patients was limited, which may impact the statistical power. Fourthly, as patients were instructed to perform a PPG recording once daily as well as when experiencing symptoms, SRC analysis might be influenced by more symptom positive recordings. Fifthly, the possibility that patients did not perform PPG recordings every time they experienced symptoms might have influenced our SRC findings by less symptom positive recordings. Additionally, as we were not able to completely separate scheduled recordings from patient-initiated recordings, the interpretation of patient-reported symptoms might have been influenced. Finally, the monitoring periods pre- and post-ECV were not equal (four weeks vs three weeks, respectively), and based on this, the number of PPG recordings was skewed towards AF presence which might also have impact on SRC analysis.

5. Conclusions

In persistent AF patients, simultaneous mobile app-based symptom and rhythm monitoring revealed a relatively low overall SRC, which was mainly driven by a majority of AF recordings which were asymptomatic. Extrasystoles can explain a minority of symptomatic non-AF PPG recordings. Pulse rate, but not pulse variability, is the main determinant of reported symptoms during AF and non-AF PPG recordings. Further studies are required to test whether mobile app-based SRC assessment can be implemented in current workflows and integrated into a personalized symptom and rhythm control AF management approach.

Author statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2022.08.021>.

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