Original Paper

Detection of Paroxysmal Atrial Fibrillation in Acute Stroke Patients

T. Rizos[a]   C. Rasch[a]   E. Jenetzky[c]   C. Hametner[a]   S. Kathoefer[b]   R. Reinhardt[d]
T. Hepp[d]   W. Hacke[a]   R. Veltkamp[a]

Departments of [a]Neurology and [b]Cardiology, University of Heidelberg, and [c]Department of Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, and [d]apoplex medical technologies GmbH, Pirmasens, Germany

Abstract

Background: Atrial fibrillation (AF) is a frequent cause of stroke, but detecting paroxysmal AF (pAF) poses a challenge. We investigated whether continuous bedside ECG monitoring in a stroke unit detects pAF more sensitively than 24-hour Holter ECG, and tested whether examining RR interval dynamics on short-term ECG recordings using an automated screening algorithm (ASA) for pAF detection is a useful tool to predict the risk of pAF outside periods of manifest AF. *Methods:* Patients >60 years with acute ischemic stroke or transient ischemic attacks (TIA) were prospectively enrolled unless initial ECG revealed AF or they had a history of paroxysmal or persistent AF. ASA was performed on 1- to 2-hour ECG recordings in the emergency room and patients were classified into 5 risk categories for pAF. All patients underwent continuous bedside ECG monitoring for >48 h. Additionally, 24-hour Holter ECG was performed. *Results:* 136 patients were enrolled (median age: 72 years, male: 58.8%). In 29 (21.3%), pAF was newly diagnosed by continuous bedside ECG monitoring. pAF increased with age (p = 0.031). Median time to first pAF detection on continuous bedside ECG monitoring was 36 h. In 16 patients, pAF was detected by continuous bedside ECG monitoring prior to the performance of 24-hour Holter ECG. Thirteen of the remaining patients were pAF positive on continuous bedside ECG monitoring, but 24-hour Holter detected only 3 patients. Accordingly, the sensitivity of 24-hour Holter was 0.23. Sensitivity of higher-risk categories of ASA compared to continuous bedside ECG monitoring was 0.72, and specificity 0.63. *Conclusion:* Continuous bedside ECG monitoring is more sensitive than 24-hour Holter ECG for pAF detection in acute stroke/TIA patients. Screening patients for pAF outside AF episodes using ASA requires further development.

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Introduction

Nonvalvular atrial fibrillation (AF) is an important cause of ischemic stroke accounting for approximately 20–25% of all strokes [1–3]. The prevalence of AF increas-

Roland Veltkamp, MD
Department of Neurology, University of Heidelberg
INF 400, DE–69120 Heidelberg (Germany)
Tel. +49 6221 567 504, Fax +49 6221 565 654
E-Mail Roland.Veltkamp@med.uni-heidelberg.de

es with age; therefore, the contribution of AF to the overall stroke burden is expected to rise considerably because of ongoing demographic changes in our society [4, 5]. Moreover, strokes due to AF are associated with greater disability and mortality [6–9]. Importantly, effective measures for stroke prevention in AF have been established [1, 2, 10–14].

In the presence of highly effective preventive therapies, sensitive detection of AF is of utmost importance. Patients with ischemic stroke and transient ischemic attacks (TIA) must be thoroughly evaluated for AF, as preceding cerebral ischemia represents the strongest risk factor for subsequent cardioembolism in AF [15]. While it is simple to diagnose chronic AF, detecting paroxysmal AF – which accounts for about 30% of all AF patients in population-based studies [16] and carries the same risk of cardioembolism [17, 18] – can pose a challenge. Although recommendations for cardiological diagnostic work-up to detect paroxysmal AF (pAF) differ among current guidelines [10, 11, 19, 20], most acute stroke patients receive an electrocardiogram (ECG) and 24-hour Holter monitoring.

While pAF evades standard 12-channel ECG recording in many cases, 24-hour Holter ECG can identify pAF in 2–5% [21–23]. Extending the Holter ECG time to 48 h slightly increases pAF detection rates in stroke patients with initially inconspicuous ECG findings (1–5%) [23]. Continuous monitoring of the ECG on stroke units is considered a standard procedure [11], but prospective studies examining its value for the detection of manifest episodes of pAF are rare [24]. In particular, it is unclear whether continuous bedside ECG monitoring is equivalent to Holter ECG for detecting pAF [11].

Despite prolonged ECG recordings, pAF may escape diagnosis. A complementary approach to identify patients suffering from pAF outside of manifest fibrillation episodes is to analyze heart rate dynamics on the ECG so as to predict the individual risk of suffering from pAF [25, 26]. However, this technique has not yet been evaluated in acute stroke patients.

The aim of the present study was to evaluate different methods for screening and detecting pAF in patients with acute stroke or TIA. We examined whether prolonged continuous ECG monitoring detects pAF more sensitively than 24-hour Holter ECG. Furthermore, we tested the hypothesis that an automated screening algorithm (ASA) for pAF detection on 1- to 2-hour ECG recordings is a sensitive and sufficiently specific tool to identify patients at high risk of pAF.

Methods

Study Setting and Patient Selection

This prospective monocenter study was conducted in the Department of Neurology, University of Heidelberg, a tertiary care institution with a catchment area of approximately 850,000 inhabitants. Stroke patients in our institution are admitted via the neurological emergency room (ER) to a 20-bed stroke unit which provides continuous ECG monitoring with bedside and central display. The routine cardiac work-up for all patients admitted to our stroke unit suffering from stroke or TIA encompasses a baseline 12-channel ECG upon arrival, a 24-hour Holter ECG (unless AF has been identified early on) and continuous ECG monitoring for the time of the stay in the stroke unit. Additionally, echocardiography is performed on all patients.

Between July 2008 and March 2009, patients >60 years presenting with an acute ischemic stroke or TIA in the ER and who were subsequently admitted to the stroke unit of our hospital and underwent continuous ECG monitoring for a minimum period of 48 h were enrolled. Patients with AF on the initial 12-channel ECG (ELI 350; Mortara Instruments, Milwaukee, Wisc., USA) in the ER or a history of paroxysmal or persistent AF were excluded. All study procedures were approved by the local ethics committee. Informed consent was obtained from the patient or the patient's legal representative.

Data Collection

In parallel to the usual emergency work-up and treatment of the patients, a 12-bit resolution digital ECG recording (Lifecard CF, Spacelabs Healthcare) was made for 1–2 h in the ER. After completion, these ECG data were sent via internet to a computer where an unsupervised ASA was applied using the stroke risk analysis software (SRA; apoplex medical technologies, Pirmasens, Germany). The software employs an algorithm which creates an RR list of the ECG data, detects QRS complexes and then classifies atrial and ventricular beats. It performs time series analysis which includes 6 mostly nonlinear mathematical parameters. These parameters are derived from principle component analysis, RR difference plots, the ratio between shortest and longest interval of maximum 6 consecutive RR intervals, the number of atrial premature complexes, complexes without sinus nodal reset and approximate entropy of RR interval data [25–28]. Based on this ASA analysis, the risk of pAF was estimated by the software and each patient was assigned to 1 of 5 predefined categories: (1) continuous sinus rhythm; (2) ventricular rhythm disorders; (3) intermediate risk of pAF; (4) high risk of pAF; (5) manifest episodes of AF. Reports for each patient were created by the system and sent to the clinical investigators via e-mail. All employees of apoplex medical technologies were blinded to the patient's medical history, results of subsequent ECGs and other clinical data.

Continuous bedside ECG monitoring on the stroke unit was carried out using the Infinity® Delta monitoring system (Dräger, Lübeck, Germany) and started immediately after the patient was admitted to the stroke unit. The monitoring system includes different cardiac rhythm alarms: (1) alarm in case of flatline ECG; (2) alarm for ventricular fibrillation; (3) alarm in the presence of couplets or bigeminus, and (4) an alarm when the heart rate exceeds preset upper and lower frequency thresholds. During the study, frequency thresholds were set to 130 and 40 beats per min,
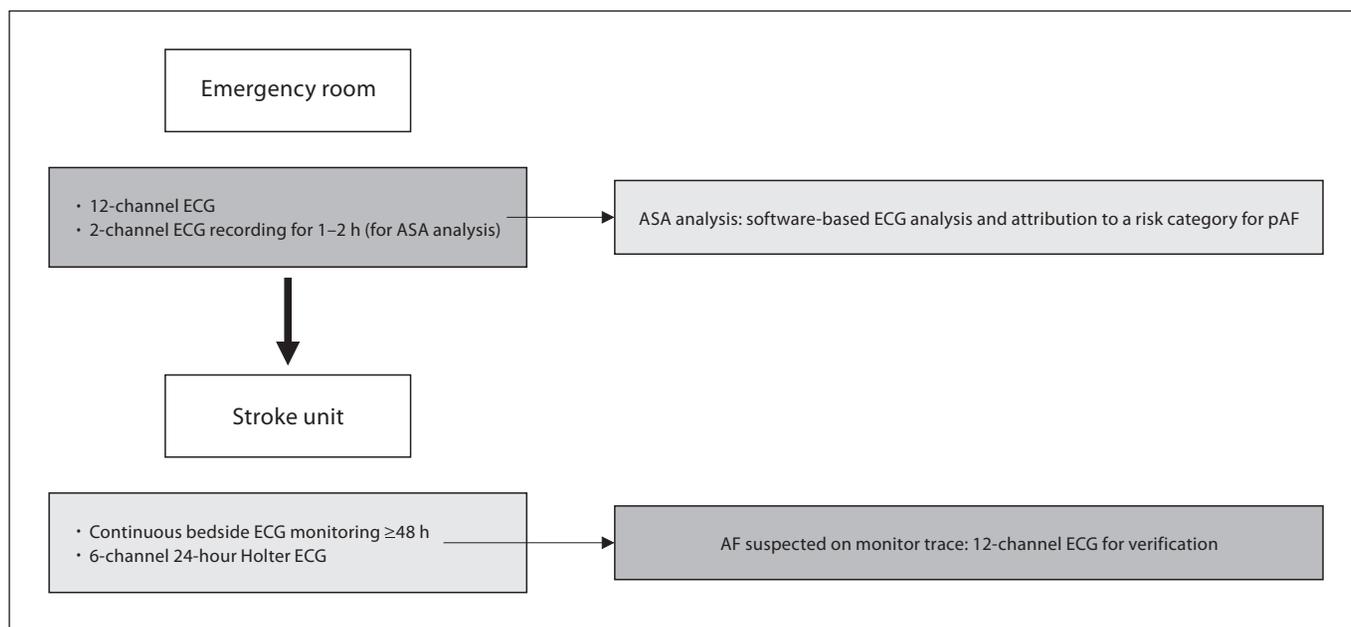
Fig. 1. Flowchart of procedures carried out in this study to detect and ascertain the risk of pAF.

respectively. However, the system is not capable of automatically sounding an alarm in case of AF. When AF was suspected from the monitor trace, a 12-channel ECG (ELI 350; Mortara Instruments) was conducted and presumed AF was ascertained by a cardiologist. Time of starting continuous ECG monitoring and time of first pAF detection were recorded for all patients.

During hospitalization, a 6-channel Holter ECG was performed for 24 h (H12+; Mortara Instruments). The results were analyzed and interpreted by a cardiologist using the H-SCRIBE software (version 4.0; Mortara Instruments). The cardiologist was blinded to the patient's medical history and the results of any other ECG recordings of the patient.

AF was diagnosed when AF episodes lasted at least for 30 s. All nurses and physicians involved in patient care were blinded to the study procedures. A synopsis of the study procedure is given in figure 1.

Statistical Analysis
For basic demographic results and the results of ECG and ASA, descriptive data analysis was performed using the Statistical Package for the Social Sciences (SPSS 17.0). Normal distribution was tested using the Kolmogorov-Smirnov test. For non-normally distributed data, median and interquartile ranges are presented. To compare different methods for screening and detecting pAF, sensitivity and specificity were calculated. To test associations between age and pAF detection rates, a t test was performed. A potential relationship between the results of ASA analysis results and pAF detection during continuous ECG monitoring was evaluated using Fisher's exact test. Cohen's κ was used to test the reliability of the ASA analysis results between the first and second hour of recording; κ was interpreted according to Landis and Koch [29].

Results

A total of 136 patients presenting in our ER fulfilled all predefined criteria and were therefore enrolled in this study (male: 58.8%). Median age of the study population was 72 years (IQR 66–78; fig. 2a). In 120 patients (88.2%) a manifest stroke was diagnosed, and in 16 (11.8%) a TIA; 27.2% of patients had a medical history of previous stroke or TIA. Median duration of continuous bedside ECG monitoring was 97 h. Baseline characteristics and cardiovascular risk factors are summarized in table 1.

Detection of pAF by Continuous ECG Monitoring
In 29 patients (21.3%), pAF was newly diagnosed by continuous ECG monitoring. Prevalence of pAF increased significantly with age (p = 0.031; fig. 2b). The median interval to first detection of pAF was 36 h (IQR 10.5–73.5; fig. 3). In 21 patients (72.4%), pAF was detected within the first 72 h of continuous bedside ECG monitoring, in 6 (20.7%) between 72 and 120 h and in 2 (6.9%) even after a period of >120 h (fig. 3).

Detection of pAF by Holter ECG
Median time of starting 24-hour Holter ECG recording after admission to the stroke unit was 49 h (IQR 25–141). The median duration of Holter recording was 24 h
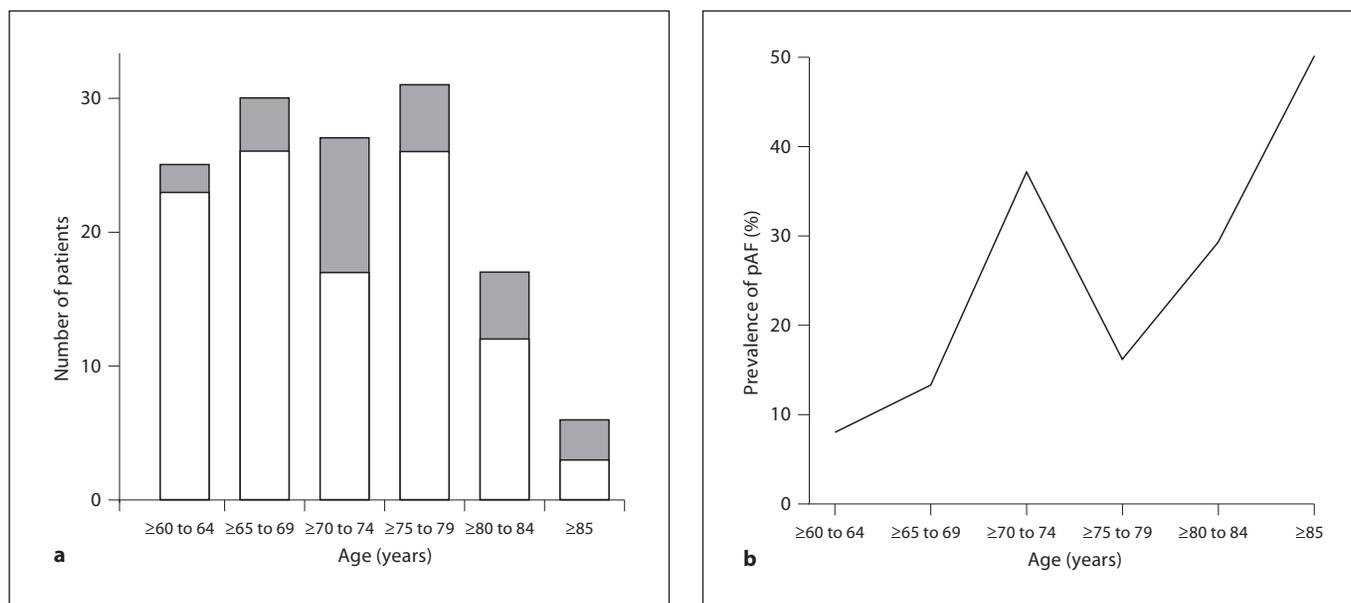
Fig. 2. a Age distribution of the study population in 5-year intervals (grey: patients with newly detected pAF during continuous ECG monitoring). **b** Age and pAF prevalence in the study population. Prevalence of pAF significantly increased with age (p = 0.031).

(IQR 22–24). In 16/136 patients, pAF had been detected already by continuous ECG monitoring prior to connecting the Holter recorder. These patients did not undergo subsequent Holter ECG. Therefore, Holter ECG was not carried out in these patients and test results were available for 120/136 patients (88.2%). Holter ECG detected pAF in only 3 patients, whereas continuous ECG monitoring provided a diagnosis of pAF in 13/120 patients (10.8%). Accordingly, the sensitivity of detecting newly diagnosed pAF by delayed Holter ECG was 0.23 in this patient cohort (table 2). None of the patients found to be suffering from pAF by 24-hour Holter ECG escaped diagnosis by continuous ECG monitoring.

Automated Screening to Assess the Risk for pAF in the ER

ASA analysis yielded 'continuous sinus rhythm' (i.e. ASA category 1) in 70/136 patients (51.5%; table 3). However, in 7/70 of these patients, paroxysmal AF was detected during subsequent continuous ECG monitoring (i.e. 10% false-negative results). Paroxysmal AF was identified in 21/61 patients classified in the incremental higher ASA risk categories 3–5 (i.e. 3 = intermediate risk of pAF; 4 = high risk of pAF; 5 = manifest AF) during subsequent continuous ECG monitoring. In contrast, in 40/61 patients with categories 3–5, no pAF was detected by the

Table 1. Baseline characteristics of the study population

	All patients (n = 136)
Age, years	72 (66–78)
Male sex	80 (58.8)
Manifest stroke	120 (88.2)
TIA	16 (11.8)
Duration of bedside ECG monitoring, h	97 (82–144)
Bedside ECG monitoring	
48–71 h	17 (12.5)
72–95 h	44 (32.4)
96–119 h	31 (22.8)
≥120 h	44 (32.4)
Time of ECG recordings for ASA analysis	
1 h	136 (100)
2 h	132 (97.1)
Congestive heart failure	49 (36.0)
Prior myocardial infarction	31 (22.8)
Hypertension	108 (79.4)
Diabetes mellitus	41 (30.1)
TSH suppression <0.1 mU/l	1 (0.7)

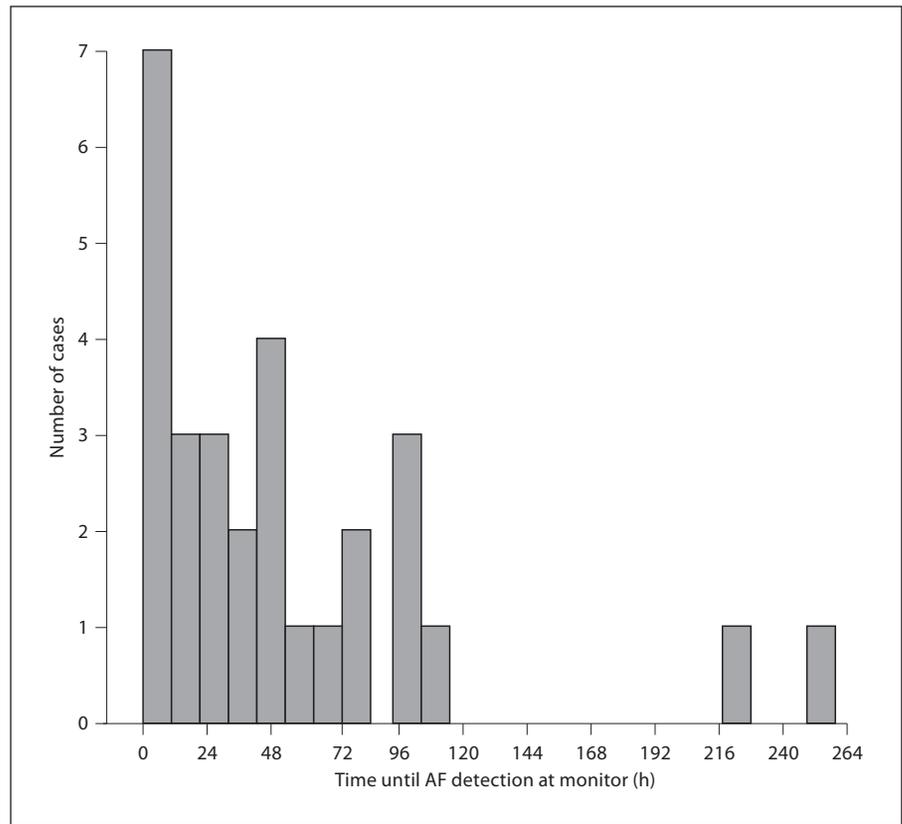Data presented as n (%) or medians (IQR). TSH = Thyroid-stimulating hormone.

Fig. 3. Interval to first detection of pAF during continuous bedside ECG monitoring on the stroke unit.

Table 2. Sensitivity and specificity for 24-hour Holter ECG and ASA analysis high-risk categories for pAF versus continuous bedside ECG monitoring (CEM)

	Holter vs. CEM (n = 120)	ASA vs. CEM (n = 136; categories 3–5)
Sensitivity	0.23	0.72
Specificity	1	0.63

ASA categories: 3 = intermediate risk of pAF; 4 = high risk of pAF; 5 = manifest AF.

Table 3. Results of continuous bedside ECG monitoring (CEM) compared to ASA analysis results to assess the risk of pAF outside manifest AF episodes (n = 136)

	ASA results					Total
	continuous sinus rhythm	ventricular rhythm disorders	intermediate risk of pAF	high risk of pAF	manifest AF	
pAF during CEM						
Yes	7	1	5	14	2	29
No	63	4	20	20	0	107
Total	70	5	25	34	2	136

other diagnostic modalities. Therefore, for the categories 3–5, sensitivity was 0.72 and specificity 0.63 as compared to the findings of continuous ECG monitoring (table 2). ASA analysis results and pAF detection during continuous bedside ECG monitoring correlated significantly (p = 0.031).

Cohen's κ between the 1st and 2nd hours of ASA was 0.61, which is considered borderline for a substantial agreement between the ASA results.

Discussion

It is of utmost importance to detect pAF early after acute cerebral ischemia because patients suffering from stroke/TIA and AF are at a particularly high risk of stroke recurrence, which can frequently be prevented by initiating adequate treatment measures. The major new find-

ings of our study are that: (1) continuous bedside stroke unit ECG monitoring (>48 h) detects pAF much more frequently than 24-hour Holter ECG; (2) screening patients for pAF outside manifest AF episodes using an automated algorithm for pAF detection is currently not sufficiently sensitive and specific to be used as a routine method in the emergency setting of acute stroke.

Prospective studies evaluating the benefit of continuous ECG monitoring in stroke units for detecting pAF in patients with acute stroke/TIA are rare, and presently it is not known whether continuous ECG monitoring at the bedside is equivalent to Holter ECG for detecting pAF [11]. Therefore, recommendations for cardiac evaluation in acute stroke patients differ among guidelines [10, 11, 19, 20].

In the present study, pAF was newly diagnosed by continuous ECG monitoring in 21% of acute stroke patients with initially inconspicuous ECG and no history of AF, emphasizing the usefulness of continuous ECG monitoring for pAF detection in the acute stroke phase. Vivanco Hidalgo et al. [24] reported a pAF detection rate of 7% using a continuous ECG monitoring approach; however, the median time of continuous ECG monitoring was considerably shorter than in the present study. The different methods for identifying pAF used in the present and previous studies [21–24, 30] and limiting enrollment to patients older than 60 years may be partially responsible for the high incidence of newly diagnosed pAF in our population. On the other hand, an even higher detection rate of pAF in our cohort is conceivable if continuous ECG monitoring had been performed for even longer periods. Remarkably, no sophisticated automatic system was used to discover pAF during continuous ECG monitoring.

A key finding of our study is the much higher sensitivity of prolonged continuous ECG monitoring compared to 24-hour Holter ECG. In accordance with the existing literature [21–23], 24-hour Holter ECG only discovered pAF in 2.5% of 120 patients. The true prevalence of pAF in our cohort remains unknown, but 24-hour Holter ECG alone would have failed to diagnose pAF in many patients in whom prolonged continuous ECG monitoring provided evidence of pAF. Because 50% of pAF episodes had already been captured by continuous ECG monitoring within the first 36 h after admission to the stroke unit, delay in placing the Holter recorder presumably prevented more frequent detection of pAF by 24-hour Holter ECG. Hence, the sensitivity of 24-hour Holter ECG may be underestimated in our study because patients with early evidence of pAF based on continuous ECG monitoring were not subsequently subjected to 24-hour Holter

ECG. Whether earlier initiation and prolonged duration of the Holter recordings or the use of cardiac event recorders [31–34] are more sensitive than continuous ECG monitoring is currently unknown. Providing early and prolonged Holter ECG routinely for all patients would be demanding for most stroke units, and may be unnecessary in view of the diagnostic yield of continuous ECG monitoring.

Complementary techniques that have a high sensitivity for detecting patients suffering from pAF even outside of manifest fibrillation episodes would greatly improve the often elusive diagnostic work-up for this condition. Recently, the STAF score was introduced to target stroke patients at risk for pAF [35] and frequent premature atrial beats have been reported to be an independent predictor of paroxysmal AF in patients with ischemic stroke [36]. The ASA algorithm to screen patients suffering from pAF even outside AF episodes was tested for the first time in a high-risk population of acute stroke patients in our prospective study. Subsequent detection of pAF by continuous ECG monitoring in the present cohort (see above) was taken for comparison to assess the quality of this new procedure. Sensitivity for the combined higher-risk categories 3–5 was 0.72, indicating that this method can give cues to identify patients at risk for pAF who should receive further extensive work-up for pAF. However, false-positive predictions were made rather frequently. Moreover, agreement between the 2 subsequent hours of ASA classifications was only borderline [29].

In conclusion, the present study strongly supports the usefulness of continuous ECG monitoring on stroke units compared to 24-hour Holter ECG in acute stroke and TIA patients. Screening patients for pAF outside of AF episodes using ASA requires further development.

Acknowledgments

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