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Refinement of detecting atrial fibrillation in stroke patients: Results from the TRACK-AF-Study

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Abstract

Background: Detection of occult atrial fibrillation (AF) is crucial for optimal secondary prevention in stroke patients. We determined the AF detection rate by implantable cardiac monitor (ICM) compared to the prediction rate of the probability of incident AF by software based analysis of continuously monitored ECG at follow up (Stroke risk analysis=SRA) and propose an optimized AF detection algorithm by combining both tools.

Methods: In a monocentric prospective study we investigated 105 out of 389 patients with cryptogenic stroke despite extensive diagnostic workup with two additional cardiac monitoring tools: (a) 20 month monitoring by ICM and (b) SRA during hospitalization at the Stroke Unit.

Results: The detection rate of occult AF was 18% by ICM (n=19) (range 6-575 days) and 62% (n=65) had an increased risk for AF predicted by SRA. When comparing the predictive accuracy of SRA to ICM, the sensitivity was 95%, specificity 35%, positive predictive value 27% and negative predictive value 96%. In 18 patients with AF detected by ICM, SRA showed also a medium risk for AF. Only one patient with a very low risk predicted by SRA developed AF revealed by ICM monitoring after 417 days.

Conclusions: Combination of SRA and ICM is a promising strategy to detect occult AF. SRA is reliable in predicting incident AF with a high negative predictive value. Thus, SRA may serve as a cost-effective pre-selection tool identifying patients at risk for AF who may benefit from further cardiac monitoring by ICM.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02641678

Introduction

AF is associated with a two- to fivefold increase in stroke risk [1,2,3,4]. Many patients with acute stroke do not show AF in the standard 12 lead ECG or Holter recordings but suffer from paroxysmal AF (pAF) [2]. pAF increases stroke risk and is one of the main causes for "cryptogenic" stroke [5,6].

The optimal diagnostic approach in cryptogenic stroke is debatable but mainly consisting of 12-lead ECG, 24h-Holter ECG, and continuous ECG monitoring [7]. The low yield of AF detection rates even with 24h Holter ECG is known [8,9] and extension of the monitoring time increases AF detection rate [9,10,11].

We investigated cryptogenic stroke patients by two extended ECG monitoring tools (SRA and ICM). The objective was to assess the ability of software based analysis of continuously monitored ECG during hospital stay at the stroke unit to estimate the probability of AF in comparison to the AF detection rate based on ICM after a negative comprehensive clinical work up. Moreover, we aimed to develop a cost effective strategy to optimize the detection of occult AF.

Methods

We performed a prospective, monocentric study at our Stroke Unit. The study was approved by the local ethics committee and registered at ClinicalTrials.gov.

From March 2013 until December 2014, 1153 patients (539 female, 47%) were admitted with diagnosis of transient ischaemic attack (TIA) or ischaemic stroke. The target population had been patients with cryptogenic stroke who underwent accurate diagnostic workup in order to determine stroke etiology according to TOAST classification [12]. These patients received MRI or CCT; standard 12-lead ECG upon admission, 24h-Holter ECG, ultrasound of the brain supplying arteries and a transesophageal echocardiography (TEE). If there was *no* explaining pathology, the stroke was classified as cryptogenic (TOAST 5b) [12]. Exclusion criteria were incomplete workup and competing sources of embolism.

The patients' ECGs were monitored throughout their stay at the stroke unit with standard monitoring (Draeger Infinity Delta© Luebeck, Germany). The ECG data was continuously sent encrypted via internet to a server (Apoplex Medical Technologies, Pirmasens, Germany). For any individual patient, ECG analysis was performed software based (stroke risk analysis, SRAclinic©, version 2.7.0) for every hourly ECG period and the resulting report was sent daily to corresponding patient's electronic health record. SRA results were integrated into the electronic health record and could be obtained bedside no later than 24h after start of the monitoring. The conventional ECG monitoring with Draeger Infinity Delta at the Stroke Unit and investigational SRA monitoring obtained simultaneously. Also the 24h Holter ECG had been performed in the same time window than the conventional ECG monitoring. No episodes of AF were detected during conventional monitoring with Draeger Infinity Delta and 24-hour Holter-ECG in the simultaneous time window which was used for SRA.

The software measures the R-R-range-intervals of the ECG since increased or irregular R-R interval dynamics are more frequent in patients with AF even in periods with sinus rhythm [13,14]. Afterwards, the R-R intervals are used to calculate various, mostly nonlinear, mathematical parameters. These parameters are used as fundament for support vector machine-based risk probability of AF. The algorithm was trained in a neural network setup with several hundred datasets from patients with paroxysmal AF and subjects without AF. The determination of AF risk by the software is not limited to a defined duration. It works from a minimum of about 15 seconds and therefore includes all episodes > 30s. Further details of the software based algorithm have been published elsewhere [15] but the exact classification algorithms have not been published by the manufacturer.

SRA categorizes the risk for AF in five levels from 0= very low risk for AF; 1=low risk for AF; 2=medium risk for AF; 3=high risk for AF; 4=very high risk for AF. The results are displayed by a Lorenz Plot (see figure 1). As ICM we used the REVEAL XT (Medtronic, Minneapolis, MN) [16]. The ICM has been further refined to detect AF as it applies specific algorithms to the monitored ECG [16]. Its detection rate of pAF is significantly higher compared to Holter ECG in patients with cryptogenic stroke [17,18]. The monitoring period of the patients with ICM was 20 months. All ECG data were analyzed by experienced cardiologists.

In summary, the participating patients received the two additional AF detection tools, (a) 20 month monitoring by ICM and (b) a software based analysis of continuously monitored ECG during hospitalization at the Stroke Unit.

The primary endpoint was the detection rate of AF (>30s) by ICM compared to the categorial probability of AF determined by the SRA. Secondary endpoint was creating a cost-benefit equation in relation to the detection rate and to develop new strategies in the detection of AF by combining the different methods.

Results

Out of 389 patients with TOAST 5b classification 105 patients took part (27%). Patients´ characteristics are displayed in table 1. In these subjects 12-lead ECG upon admission and 24h-Holter ECG showed no AF, the median analysis time of the 24h-Holter ECG was 23h36min (IQR 20h18min-23h48min).

ICM implantation had been performed within 4 weeks after stroke onset without any side effects. ECG data of the ICM revealed AF in 19 patients (18%, 9 men, 10 women) after a median of 217 days (31 weeks) (IQR 72.5-338 days) (figure 2). These patients had a significantly higher CHA_2DS_2 Vasc score of 5 compared to 4 in the patient group without AF (p=0.011).

SRA levels were level 0 (very low risk for AF) in 26 cases (25%), level 1 (low risk for AF), in 0 cases, level 2 (medium risk for AF) in 39 cases (37%), level 3 (high risk for AF) in 22 cases (21%) and level 4 (very high risk for AF). in 4 cases (4%). This results in 65 patients (62%) with relevant probability for possible paroxysmal or permanent AF (figure 3). In 12 patients (11%), the SRA analysis could not be obtained but in these patients the results of ICM ECG data revealed no AF. The median ECG monitoring time was 12 hours (IQR 6h-31h). The median SRA level in patients without AF studied with ICM was 2 whereas it was 3 in patients with AF detected by ICM (p=0.0236). In the 19 patients with AF detected by ICM

the SRA level was at least 2 in 18 patients (level 2 in 7 patients, level 3 in 10 patients and level 4 in one patient) and level 0 in one patient.

To calculate the accuracy of the SRA software algorithm compared to ICM by cross tab analysis we determined cut off values for the SRA and considered classification level 0 and 1 as negligible risk for AF and level 2-4 as significant risk for AF. Thereafter, SRA displayed a sensitivity of 94.8% a specificity of 35.1 %, a positive predictive value of 27.3% (PPV) and a negative predictive value of 96.3% (NPV) (see table 2).

The costs of SRA software analysis per patient per year vary from 12.6 -36.2 . The costs for the implantation of an ICM in patients with cryptogenic stroke are different between the healthcare systems. In Germany, the reimbursement is regulated by the diagnosis related group (DRG) system and varies each year. In 2016, the average costs for implantation were 2.157 in our department.

Discussion

In the present study the detection rate of occult AF in 105 patients with cryptogenic was 18% by ICM. In 62% of the patients, SRA revealed an increased risk for AF. We were able to show a low positive but a high negative predictive value for SRA analysis, which may therefore serve as a promising tool for pre-selection of patients before ICM implantation.

Extended ECG monitoring increases the chance to detect AF. By using 7 d Holter ECG studies reported additional AF detection rates between 13% [9] and 17.5% [10]. Beside, numerous studies found increased detection rates of AF by ICM leading to ICM as current standard of occult AF detection after cryptogenic stroke in many centers. The main advantage of ICM obviously is the long-term monitoring period, as in many cases AF is detected after a

30-day monitoring period [16-20]. Hindricks et al. [16] reported a sensitivity of 96.1%, a specificity of 85.4%, a PPV of 79.3% and a NPV of 97.4%, in detecting paroxysmal AF.

In non-randomised studies the detection rate of occult AF in patients with cryptogenic stroke was 25.5% and 17%, respectively [17,18]. The randomized Crystal AF study [19] demonstrated an AF detection rate of 12.4% within a monitoring period of 12 months. Thus, monitoring with an ICM leads to an eightfold higher detection rate of AF than using conventional methods [19,20]. The 18% AF detection rate in our study is in line with previous studies keeping in mind the longer monitoring period of 20 months.

There has not been a prospective study investigating and comparing clinical benefits of SRA versus ICM. In previous studies SRA showed a high accuracy with AF detection rates of 90% during a monitoring time of 4 days in patients with stroke [8].

With an increased risk for AF (minimum level 2= medium risk for AF) in 62% of the patients with cryptogenic stroke, SRA was over-sensitive as compared to the 18% AF detection rate by ICM. However, in only one patient in whom the SRA showed sinus rhythm AF was later detected by ICM after a period of 417 days. Thus, with a negative predictive value of 96% it seems possible to select patients who most likely will not benefit from ICM. On the other hand, the low specificity of 35% and the very low positive predictive value of 27% do not allow diagnose AF by SRA. This finding is underlined by the fact that only in 11 of 19 patients (58%) SRA diagnosed AF by level 3 or 4 in comparison to ICM. Therefore SRA´s strength was found to be the valid and reliable exclusion of AF. We also found a higher CHA_2DS_2 Vasc score and more supraventricular premature atrial beats as predictive for AF diagnosis and patients with AF were between 65-74 years (mean 72) compared to non-AF patients who were younger than 65 (mean 64). Therefore, the use of invasive ECG

monitoring via ICM should be well-considered in younger patients with a low CHA_2DS_2 Vasc score.

Implantation of ICM in patients with cryptogenic stroke is cost-effective due to preventing recurrent strokes by anticoagulation compared to standard workup [21]. In our study at least 25% of patients with cryptogenic stroke have a SRA level of 0 and will hardly benefit from ICM implantation. With average costs of 25 per patient SRA is hundredfold cheaper compared to ICM implantation. Therefore, it seems highly cost effective to combine both methods SRA and ICM than using ICM alone in patients with cryptogenic strokes.

Limitations

The main limitation of the study is its monocentric design and the limited size of the study cohort. Furthermore, the inclusion quote of 27% seems to be rather low. Another limitation is the use of SRA as a single method of AF prediction in comparison to ICM. Other predictive values like atrial tachycardia, left atrial volume and prolonged PR interval have not been considered. At last, the significance of AF detection by continuous monitoring with Draeger Infinity Delta is unknown since it is based on a proprietary algorithm which is highly susceptible to faults. Its sensitivity and specificity have not been analyzed so far.

Conclusion

With the use of two diagnostic tools to detect AF in patients with cryptogenic stroke, SRA and ICM, it is possible to optimize AF detection in patients with cryptogenic stroke. Due to its high negative predictive value (96%) but rather low positive predictive value (27%) SRA software analysis cannot replace ICM as current gold standard for detecting AF. However, it

may provide as a valuable pre-selection tool. It enables the clinician to select patients in whom the implantation of an ICM is reasonable because they are at risk to develop AF while sparing other patients who most likely do have AF in a cost effective way.

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Table 1: Patient's characteristics of the included 105 patients, AF diagnosis by implantable cardiac monitor (ICM)

Characteristics	**All (n=105)**	**No AF (n=86)**	**AF (n=19)**	**p-value**
Age; y (SD)	64.4 (12.6)	63.6 (13)	72.2 (7.7)	< 0.001
female; n (%)	46 (43.8)	36 (41.9)	10 (52.6)	
CHA_2DS_2 Vasc Score (IQR)	4 (3-6)	4 (3-6)	5 (4-6)	0.011

NIHSS at admittance (IQR)	2 (1-5)	2 (0.5-4)	5 (2-8)	0.249
TIA (%)	19 (18.1)	16 (18.6)	3 (15.8)	
Infarction (%)	86 (82.9)	70 (81.4)	16 (84.2)	
Supraventricular premature atrial beats; n (SD)		486 (1987)	2243 (3110)	<0,05

Abbreviations: AF= Atrial fibrillation; TIA= Transient ischaemic attack,

NIHSS=National Institutes of Health Stroke Scale

Table 2: Sensitivity, Specificity, NPV and PPV of Software based analysis of continuous ECG monitoring levels (SRA) in 105 patients with cryptogenic stroke compared AF diagnosis by implantable cardiac monitor (ICM)

level 0=very low risk for AF, level 1= low risk for AF, level 2=medium risk for AF, level 3=high risk for AF to level 4=very high risk for AF

ICM	**No AF**	**AF**
SRA level 0-1 =negligible risk for AF	26	1
SRA level 2-4 =significant risk for AF	48	18

sensitivity: 94.8% (95% CI: 74%-99.9%)

specificity: 35.1 % (95% CI: 24.4%-47.1%),

positive predictive value 27.3% (PPV) (95% CI: 17%-39.6%)

negative predictive value 96.3% (NPV) (95% CI: 81%-99.9%)

Figure 1: Example of a construction of a Lorenzplot (upper part of the figure). Successive R-R intervals are displayed in a coordinate system with the first interval on the y-axis and the second interval on the x-axis and so forth. The underpart of the figure shows Lorenzplots of a patient with sinusrhythm (A), with pAF (B) and with permanent AF (C). (Publication on the authority of Apoplex Medical Technologies)

Figure 2: Timespan of detection of AF after implantation of ICM in weeks in the 19 patients (f=female, m=male) (median 31 weeks, IQ 1=10 weeks, IQ 3=48 weeks)

Figure 3: Software based analysis of continuous ECG monitoring levels (SRA) during hospitalization at the Stroke Unit in 105 patients with cryptogenic stroke.

level 0=very low risk for AF, level 1= low risk for AF, level 2=medium risk for AF, level 3=high risk for AF to level 4=very high risk for AF