

Clinical Study

Predictors of Occult Paroxysmal Atrial Fibrillation in Cryptogenic Strokes Detected by Long-Term Noninvasive Cardiac Monitoring

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Received 14 November 2010; Accepted 9 January 2011

Academic Editor: David S. Liebeskind

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Background and Purpose. Paroxysmal Atrial fibrillation/Flutter (PAF) detection rates in cryptogenic strokes have been variable. We sought to determine the percentage of patients with cryptogenic stroke who had PAF on prolonged non-invasive cardiac monitoring. *Methods and Results.* Sixty-two consecutive patients with stroke and TIA in a single center with a mean age of 61 (+/- 14) years were analyzed. PAF was detected in 15 (24%) patients. Only one patient reported symptoms of shortness of breath during the episode of PAF while on monitoring, and 71 (97%) of these 73 episodes were asymptomatic. A regression analysis revealed that the presence of PVCs (ventricular premature beats) lasting more than 2 minutes (OR 6.3, 95% CI, 1.11–18.92; $P = .042$) and strokes (high signal on Diffusion Weighted Imaging) (OR 4.3, 95% CI, 5–36.3; $P = .041$) predicted PAF. Patients with multiple DWI signals were more likely than solitary signals to have PAF (OR 11.1, 95% CI, 2.5–48.5, $P < .01$). *Conclusion.* Occult PAF is common in cryptogenic strokes, and is often asymptomatic. Our data suggests that up to one in five patients with suspected cryptogenic strokes and TIAs have PAF, especially if they have PVCs and multiple high DWI signals on MRI.

1. Introduction

Atrial fibrillation/flutter both persistent and paroxysmal are significant risk factors for cardioembolic ischemic stroke and is often asymptomatic [1, 2]. Atrial Fibrillation (both persistent and paroxysmal) are significant predictors of first and recurrent cerebrovascular and cardiac events, with more than 75 000 cases of stroke per year ascribed to AF (atrial Fibrillation) in the United States [3]. Oral anticoagulant therapy is the keystone of management of such patients, which reduces recurrences of stroke and stroke severity [4, 5]. A baseline electrocardiogram and routine Holter monitoring detects AF in up to 5–7 percent of patients with ischemic strokes within the first 72 hours [6, 7]. A large proportion of strokes, up to 40% in some reports, has no apparent etiology on routine diagnostic testing and is often classified as cryptogenic strokes [8]. The etiology of some of these strokes, however, may be cardioembolic even though the initial diagnostic evaluation may be negative.

Cardiac monitors have improved our capabilities to investigate the presence of paroxysmal atrial fibrillation or flutter (PAF) in patients with stroke for longer time periods. Higher detection rates of PAF have been reported with prolonged cardiac monitoring in patients with cryptogenic cerebrovascular events [9]. We investigated our cohort of cryptogenic stroke patients and sought to determine the percentage of patients who presented to our institution with cryptogenic strokes who have PAF on long-term monitoring. We also sought predictors of PAF in patients with cryptogenic strokes.

2. Methods

Between July 2007 to March 2010, we studied and retrospectively analyzed 62 consecutive patients with cryptogenic stroke ($n = 50$) or TIA ($n = 12$) who underwent prolonged non-invasive cardiac monitoring up to 28 days

TABLE 1: Patient characteristics.

Characteristics	Total N = 62	Afib N = 15	No-Afib N = 47
Mean age	61 years	64	59
Female ($n = 30$)	48%	52%	48%
HTN ($n = 16$)	26%	27%	23%
CAD ($n = 8$)	13%	20%	11%
DM ($n = 3$)	5%	6%	4%
Dyslipidemia ($n = 26$)	42%	45%	41%
Mean EF (ejection fraction)	58%	56%	59%
Percentage getting TEE ($n = 59$) (transesophageal echocardiogram)	95%	93%	96%
Percentage getting CTA (CTAngiogram)	100%	100%	100%

after discharge. These represented 10 percent of the total ischemic stroke and TIA population ($n = 629$). We sought to determine the percentage of patients with cryptogenic stroke (high signal on DWI) or TIA (symptoms lasting <24 hours and DWI imaging negative) who had PAF on prolonged outpatient non-invasive cardiac monitoring. This retrospective study was approved by IRB.

2.1. Non-Invasive Cardiac Monitoring. CardioNet MCOT (Conshohocken, PA), is a pocket-sized device worn by patients for up to 28 days for cardiac rhythm monitoring. Patients wear three chest leads attached to a small sensor that detects heartbeats and wirelessly transmits this information to the monitor. The monitor analyzes each heartbeat, detects arrhythmias, and transmits each event to the CardioNet monitoring center via a built-in cellular modem. Patients keep a log of their symptoms. Episodes of PAF were defined by duration of more than or 30 seconds [2]. The duration and frequency of PAF episodes were recorded. Manual review was done by 2 physicians to confirm the presence or absence of PAF episodes was recorded. The cardiologist report which was considered gold standard.

2.2. Statistical Analysis. Data was analyzed retrospectively. We performed logistic regression analysis ($P < .05$ with 95% CI) to determine factors predicting presence or absence of PAF. All analyses were done using (SPSSinc, IBM).

3. Results

Sixty-two consecutive patients (Table 1) with stroke ($n = 50$) and TIA ($n = 12$), with mean age of 61 (± 14) years, were analyzed. All patients underwent an MRI scan with DWI imaging. Ninety-five percent of patients had undergone TEE (transesophageal echocardiogram), TTE (transthoracic echocardiogram) with bubbles (5%), and a CT angiogram (100%). All these tests did not reveal a cause for the stroke. All patients had EKG on admission and at least 24 hours of cardiac telemetry. PAF was detected in 15 (24%) patients. The majority, 14 (93%), of the PAF was detected within the first 21 days (Figure 1). Median duration of non-invasive monitoring was 21 days (range 2–28) (Figure 2), and median day when the first PAF episode was detected was day 7.

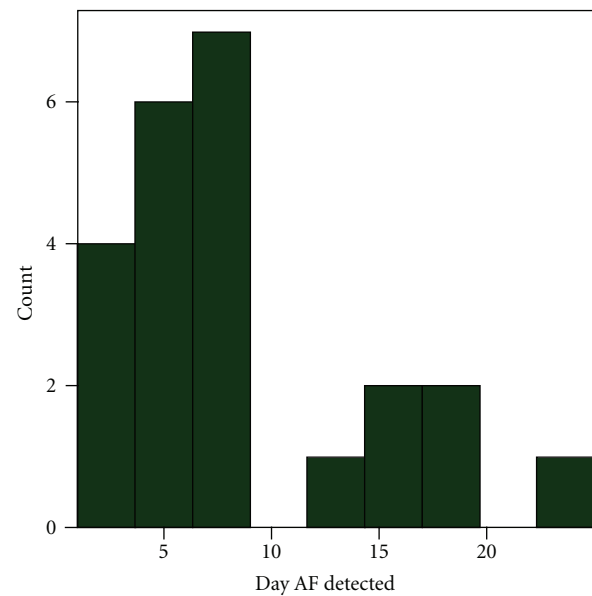


FIGURE 1: Day PAF detected on prolonged non-invasive cardiac monitoring.

There were 3 patients who underwent less than 7 days of monitoring. PAF was detected early in those patients, and monitoring was therefore terminated. A total of 73 episodes of paroxysmal PAF were detected among these 15 patients, with range (1–21) and median 5 episodes per patient. Only one patient reported symptoms of shortness of breath during the episode of PAF while monitoring, and 71 (97%) of these 73 episodes were apparently asymptomatic. In patients with PAF, mean maximum heart rate was 111 and mean minimum heart rate was 74. Median start date of non-invasive monitoring was day 29 (range 16–48) after discharge.

A logistic regression analysis revealed that the presence of PVCs lasting more than 2 minutes ($n = 12$, OR 6.32, 1.11–18.92, 95% CI, $P = .042$) significantly predicted PAF. In addition, strokes (high signal on diffusion weighted imaging) (OR 4.3, 95% CI, 5 to 36.3, $P = .041$) predicted PAF. There were 50 patients with high DWI signal (strokes) and 12 patients with TIA. Multiple DWI signals were observed

TABLE 2: Previous studies evaluating prolonged cardiac monitoring.

Study	Design	Patient selection	N	Device/Days	Percent with PAF/Outcome definition
Barthelemy et al, 2003 [10]	Observational	Ischemic stroke or TIA	60	Cardiac monitoring 4 days	7.7% with PAF \geq 30 secs
Jabaudon et al, 2004 [11]	Observational	Ischemic stroke or TIA	88	Cardiac monitoring 7 days	5.7% with PAF
Tayal et al, 2008 [9]	Retrospective	Cryptogenic stroke or TIA	56	Cardiac monitoring 21 days	23% with any PAF
Elijovich et al, 2009 [12]	Retrospective	Cryptogenic stroke or TIA	20	Cardiac monitor 30	20% with PAF \geq 30 secs
Zeigler et al, 2010 [13]	Observational	Stroke or TIA	183	Implantable defib/pacer \geq 21 days	29% with PAF/AT \geq 5 mins
Gaillard et al. 2010 [14]	Observational	Cryptogenic strokes or TIA	98	Cardiac monitor 30 days	9.2% with PAF \geq 32 secs
Dion et al. 2010 [15]	Observational	Cryptogenic strokes or TIA	24	Implantable defib/pacer \geq 21 days	4% with PAF \geq 30 secs

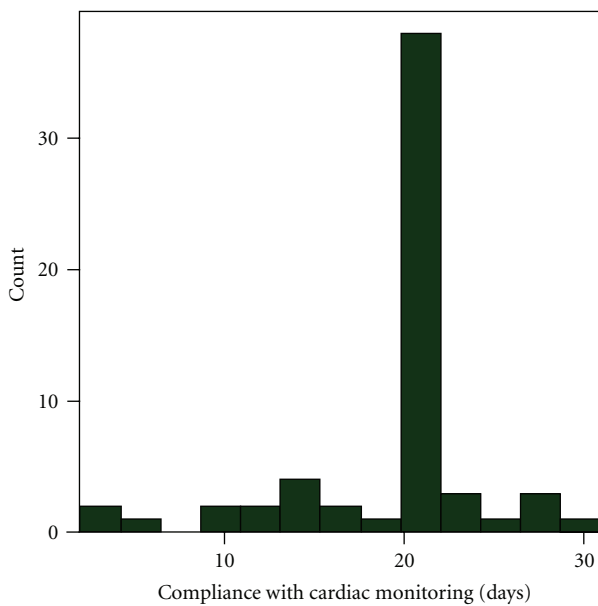


FIGURE 2: Compliance in days by patients with non-invasive cardiac monitoring.

in 20 out of 50 patients. There were 14 patients with high DWI signal with PAF and 1 patient with TIA with PAF. Out of the 14 patients with high DWI signals, 11 had multiple signals and 3 had solitary signals. Patients with multiple DWI signals were more likely than solitary signals to have PAF (OR 11.1, 95%CI, 2.5–48.5, $P < .01$). Other factors such as age, sex, diabetes, hypertension, and heart disease were not significantly associated with PAF detection.

4. Discussion

Our findings indicate that around 25% of patients with cryptogenic stroke had PAF, and most (97%) of these PAF

episodes were silent (absence of symptoms suggestive of arrhythmia). If we used the 5-minute definition, 6 patients (9%) had PAF. Previous studies (Table 2) reported PAF detection rates ranging from 4% to 29% on prolonged cardiac monitoring which ranged from 4 to 30 days in patients with strokes or TIAs. However, there was significant heterogeneity in the design and outcomes of those studies. In 4 studies, [9, 12, 14, 15] which specifically studied cryptogenic strokes, the PAF detection rate was 4–23%. Different types of cardiac monitors were used with variable duration of monitoring (4–30 days). In fact, two studies [13, 15] used implantable devices to evaluate for PAF, and found variable results (4% to 29% detection) on longer term monitoring (up to 1.4 years). A recent cost-effective analysis showed that non-invasive outpatient cardiac monitoring is a cost-effective option for detection of PAF in patients with stroke [16].

The use of the term “cryptogenic” has been variable among stroke physicians. A recent study [15] found very low incidence of PAF on long term monitoring (1/24) in a population of cryptogenic stroke patients. However, in that study, not all patients underwent evaluation of the intracranial and extracranial vasculature and it is possible that the etiology of stroke was due to atherosclerosis. In fact, some patients only had carotid Doppler imaging. All stroke or TIA patients in our study had a CT angiogram to visualize the aortic arch, extracranial, and intracranial blood vessels. In addition, 95% of patients had a TEE and 5% had surface echo with agitated saline injection for detection of right-to-left shunt. We believe the term “cryptogenic” stroke should be reserved for patients who have undergone a comprehensive cardiac and vascular work up.

The duration of monitoring may be important. In our study, although patients were prescribed monitoring for 21–28 days, not all patients were able to complete the full duration of prescribed monitoring (Figure 2). Monitoring was discontinued in three patients who underwent less than

7 days of monitoring, as PAF was detected early. Although previous studies have focused on monitoring for 30 days, existing data indicate that PAF detection is possible even beyond this time period. In a pooled estimate of stroke patients from the Virtual International Stroke Trials Archive data of more than 2504 patients [7], new PAF was detected in 6.9% patients, of which in 68% of patients, PAF was detected after 48 hours of presentation. Another study [17] evaluating long-term monitoring in stroke patients for more than 21 days showed that 62% of PAF cases were detected beyond the initial 21 days of monitoring.

Previous studies used different definitions for PAF (Table 2). We used the ACC/AHA definition of paroxysmal PAF [2] which is self-terminating PAF episodes lasting 30 seconds or longer. In fact, 85% of the episodes of PAF in the study by Tayal et al. [9] did not meet the current criteria of paroxysmal PAF. Zeigler et al. defined paroxysmal PAF as self-terminating episodes lasting 5 minutes or longer, but did not differentiate between PAF and other atrial tachycardias. In our study, all 15 patients satisfied the current ACC/AHA definition of PAF. In addition to the 15 patients, 8 patients had less than 30-second episodes of PAF, which did not satisfy criteria of PAF by AHA.

Multiple high signals on DWI MRI and runs of PVCs may help to predict PAF. In a recent study [14] using transtelephonic evaluation, where EKGs were obtained every day for 30 days, the detection rate was 9% (9/98). This study also showed that positive DWI signal on MRI scan ($P = .042$) and presence of >100 premature atrial contractions ($P = .007$) predicted the presence of PAF. Our study, however, showed for the first time that presence of PVCs for more than 2 minutes and multiple high signals on DWI were predictive of higher detection rates of paroxysmal PAF. A recent analysis of ARIC (atherosclerosis risk in communities) study showed that presence of frequent PVCs lasting more than 2 minutes were associated with increased risk of stroke in participants free of hypertension and diabetes [18]. In conclusion, although limited to a single center retrospective sample, our study suggests that PAF is common in cryptogenic stroke patients. In addition, it is always difficult to include cryptogenic TIA patients, as some of these patients may not represent true cerebrovascular events. However, we used traditional definition of TIA and we acknowledge that the low number of TIA patients may result in possibility of bias. Also, five percent ($n = 3$) of patients did not have TEE in our population. They were evaluated with TTE with bubbles (agitated saline) which is a relatively sensitive test to detect shunt. Patients with multiple DWI signals on MRI and PVCs lasting longer than 2 minutes may have higher PAF prevalence rates—this novel finding warrants further study. The majority of the PAF episodes are asymptomatic. Whether detecting PAF in these patients warrants change in therapy needs further study. Further studies using larger patient population are necessary. Sensitivity and specificity of these devices to detect PAF needs to be evaluated in a systematic fashion. In addition, role of implantable devices to detect PAF may facilitate longer duration of monitoring, which needs to be investigated.

Conflict of Interests

There is no conflict of interests to declare.

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