Atrial Fibrillation and Cryptogenic Stroke: Role of Holter Monitoring – Reiterating the Fact and Applicability to Modern Medicine

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Abstract
Background: Cryptogenic strokes of the past are now sine qua non of atrial fibrillation. Yet, despite major advances in monitoring strategies for AF, there is no consensus regarding the optimal duration of monitoring. **Results:** This hospital based prospective clinical study screened 1000 stroke patients and included 142 patients in the study based on the exclusion and inclusion criteria . As per the current recommendations patients with cryptogenic stroke underwent 24 hour holter monitoring to detect atrial fibrillation. The mean age of patients was 68.5 years with increasing incidence of atrial fibrillation with increasing age. Out of the 142 patients included, 5 were identified to have atrial fibrillation, with paroxysmal variant being the most common type. The most frequent risk factors of stroke were type 2 diabetes mellitus (65%), hyperlipidemia (58%) , hypertension (39%) and smoking (42%). NIHS, MRS and KATZ score showed no statistical significant correlation with occurrence of atrial fibrillation in cryptogenic stroke. Analysis of the neuroradiological data revealed that 9.2% of strokes were large vessel, 24.6% were embolic, 11.3% were lacunar and 15.5% were subcortical infarcts. 19.7% had supratentorial bleed, 14.1% had infratentorial bleed and 2.1% had subarachnoid bleed. **Conclusions:** Atrial fibrillation is a leading avoidable cause of recurrent stroke for which early identification and prompt treatment are critical. However, due to the paroxysmal and asymptomatic presentation of atrial fibrillation, clinicians often tend to miss the diagnosis in cryptogenic stroke. Thus cost effective longer duration monitoring strategies are probably required to adequately detect AF in cryptogenic stroke as it has therapeutic implications in preventing recurrent stroke.
Keywords: Atrial fibrillation, cryptogenic stroke, holter monitoring, cerebrovascular accident , thrombotic stroke, hemorrhagic stroke

Background

The cause of 15% to 40% of all cerebrovascular accidents are unknown and these are termed as cryptogenic strokes (CS)[1,2]. Cryptogenic stroke is a diagnosis of exclusion. The diagnosis of cryptogenic stroke maybe considered in 3 situations (1) when the diagnostic evaluation is incomplete (2) when there are several plausible reasons and a single etiology cannot be identified (3) when there is no identifiable cause despite comprehensive assessment.According to recent studies atrial fibrillation may contribute to CS [3].

Evidence about the importance of atrial fibrillation (AF) load in CS as a frequent, potentially causal conditionand the advantages of anticoagulant therapy in preventing new strokes is growing

[4].Identification and prevention of AF related CS is a global health priority as 70-80% patients die or become disabled due to it[5].However paroxysmal AF is a silent risk factor in CS that is likely to go undetected in routine clinical care as it is asymptomatic [6]. Early detection and prompt treatment of AF is of utmost importance to prevent recurrence in CS [7].Timely anticoagulation therapy in these patients reduces the risk of stroke by 64% and mortality by 25% [8]. Despite these significant incidence rates, there is paucity of studies exploring the occurrence of non valvular AF in cryptogenic stroke with normal neck vessel doppler.

In this study we analysedthe possible relationship between atrial fibrillation and cryptogenic stroke and therole of 24hours Holter monitoring for detecting AF in CS.

Methods

Hospital based prospective clinical study over one and half yearscreening 1000 stroke patients being treated under the department of neurology in a tertiary care hospital. 142 patients fulfilled the criteria for cryptogenic stroke and were included in the study. Patients with co existing cardiac pathology, old cerebrovascular accidents, history of AF or atrial flutter, requiring or having a pacemaker or implantable cardioverter defibrillator and patients with permanent indication or contraindication to anticoagulation were excluded from the study.The objectives of the study was to

determine the incidence of paroxysmal AF in cryptogenic strokeand the contribution of atrial fibrillation to the causation of different types of stroke.Patients presenting to the neurology OPD with complains of weakness or numbness of one side of the body or diplopia, dysphagia, dysarthria, vertigo and suspected to have stroke were subjected to MRI Stroke protocol (Philips Achieva 3.0T, Nederlands). If MRI Stroke protocol showed features of cerebrovascular accident, they underwent bilateral neck vessel doppler (Philips EnVisor C, Philips Medical Systems, Nederlands). Patients were also screened for other common non-arrhythmic causes of cardiac thromboembolism by 2D Echocardiogram (Philips HD11 XE, Nederlands). Patients with MRI Stroke protocol suggestive of stroke with normal carotid vessel doppler and normal 2D Echocardiogram fulfilled the criteria for cryptogenic stroke and were included in the study. Baseline demographic data and associated comorbidities were analysed. Subjectswere monitored for paroxysmal atrial fibrillation by 24 hour holter monitoring(Philips Digitrak XT, Philips Healthcare) which was interpreted by a trained cardiologist. 12 lead electrocardiogram from a portable recorder (Page writer TC-30, Philips Healthcare) were also assessed manually by the cardiologist to identify any atrial fibrillation. AF was defined as an episode of irregular heart rhythm without detectable p-waves lasting for more than 30 seconds in duration. Katz index, NIHSS score and MRS score on admission were also correlated with the occurrence of AF. Study was approved by the institutional ethics committee.The data was transferred to the IBM SPSS Statistics 22.0 (2013, Chicago) program and the analysis was done. Mean, standard deviation, median, lowest-highest, frequency and ratio were included in the descriptive statistics of the data. A chi-square test will be applied to analyse the sensitivity and specificity of each clinical test. P value <0.05 was considered significant.

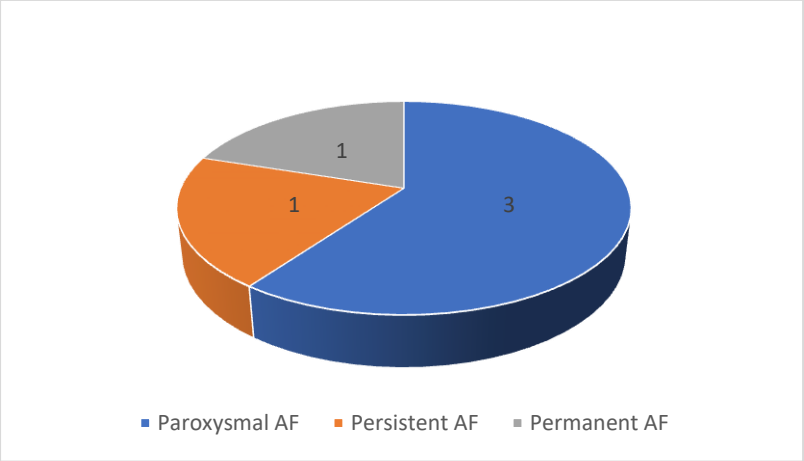
Results

Out of the total 1000 patients screened , 142 (14.2%)patients fulfilled the criteria for cryptogenic stroke and were included in the study. The mean age of the patients was 68.5 years (range 52 to 95 years).Only 5 out of the 142 patients (3.52%) were identified to have AF.Analysis of the demographic data showed that theoccurrence of AF was more common in males (4) compared to females (1).Correlation of age group with the occurrence of AF revealed increased occurrence of AF with increasing age and is as depicted in table 1.

Among all 142 patients, the most frequent risk factors of stroke were type 2 diabetes mellitus (65% of patients), hyperlipidemia (58%) , hypertension (39%) and smoking (42%). The Chi-square test showed that diabetes, hyperlipidemia, hypertension and smoking were not significantly different between the AF and no AF group (Table 2).

Patient's with CS had predominantly paroxysmal AF (60%) , when compared to persistent AF (20%) and permanent AF (20%) (figure 1).

Figure 1: Types of atrial fibrillation



Of the different types of stroke in patients with atrial fibrillation, 63.3% were thrombotic ,34.5% were hemorrhagic and 2.1% were subarachnoid bleed. However it was not statistically significant with a P value of 0.09(Table 3).

Overall the NIHSS score and the KATZ score was higher among the study population, with lower MRS scores. However there was no statistically significant difference in the scores when compared to the occurrence of AF (Table 4).

On analysis of neuroradiological data, 9.2% of strokes were large vessel, 24.6% were embolic, 11.3% were lacunar and 15.5% were subcortical infarcts. 19.7% had supratentorial bleed, 14.1% had infratentorial bleed and 2.1% had subarachnoid bleed. However their correlation with the occurrence of AF showed no statistical significance (Table 5).

Discussion

About 15–18% of individuals have AF at the time of a cerebrovascular accident and in majority of these patients stroke is attributed to their AF . A first episode of AF is found in 4–13% of cryptogenic stroke patients without prior AF at the time of stroke, compared to around 30% of all patients with pre - existing AF prior to the stroke[9].

Evaluating patients for the occurrence of atrial fibrillation following cryptogenic stroke is important because of its therapeutic implications[6]. Even in the presence of a strong suspicion, AF may not be detected in the acute phase of ischemic stroke, due to its paroxysmal and asymptomatic nature [10]. In our study the incidence of AF in CSafter 24 hours of holter monitoring was observed to be 3.52% which correlates with the review conducted by Carmona-Puertaand colleagues [3] and David J and colleagues[6].

The incidence of AF among patients in the age group of 50 -60 years was observed to be 0 , 61-70 years it was 3, 71 – 80 years it was 1 and 81 -90 years it was 1 (P value 0.329) (table 1). It was observed that the occurrence of AF was higher with advancing age, which though was not statistically significant, correlated with the study conducted by Thijs and colleagues[11]. The review article by Essa Hariri and colleagues also revealed that the prevalence of AF increases from 0.5% in the 50–59 age group to more than 8% in the 80–89 age group[12].This highlights thatan ageing population will make it more crucial than ever to improve atrial fibrillation detection[13].

The occurrence of AF was more common in males (4) compared to females (1) which correlates with the findings of CRYSTAL- AF study by Susan X. Zhao and colleagues[14].

Patients detected to have AF were initiated on anticoagulation therapy , while the rest were continued on antiplatelet therapy.

It was observed in our study that most frequent risk factors for stroke were diabetes (65%), hyperlipidemia (58%), hypertension (39%) and smoking (42%), with no significant correlation with the occurrence of AF , which correlated with the observations of Maria Vittoria De Angelisand colleagues[15].
On analysis of the index event it was observed that majority of patients had an ischaemic stroke (n = 90) when compared to hemorrhagic stroke (n=49) or subarachnoid bleed (n=3), which correlated with the findings of David.J.Gladstone and colleagues were 62.9% patients had an ischaemic stroke [6]. This suggests that patients with cryptogenic stroke and AF are more likely to have thrombotic than hemorrhagic stroke.
Among the 5 patients with AF, 4 were identified to have a left atria size of greater than 45mm, which has been recently identified as a positive predictor for AF [16].
This study had several limitations. The main drawback was the short duration of AF monitoring which was not sufficiently sensitive for the detection of paroxysmal AF. This was also observed by Kishore A and colleagues in his metaanalysis [17].The detection rates of AF in CS can probably be improved by long term monitoring as observed by the meta analysis conducted by Dahal and colleagues[18] (2.5% in short term monitoring of≤ 48hours versus 13.8% in long term monitoring of ≥7 days). Hence we suggest that the recommendations to monitor for AF post CS should be increased to atleast 72hours from the current recommendation of 24hours. The advantage of long term AF monitoring was also highlighted by the CRYSTAL-AF study [19]. Long term AF monitoring can reduce overdiagnosis of CS and enableadequate secondaryprevention of recurrent stroke with anticoagulants, the occurrence of which is as high as 3-6% [20]. Oral anticoagulation is observed to be highly effective and reduce the risk of recurrence by almost 70% [21]. However it is of utmost importance to document AF after an ischaemic stroke because current American and European Stroke Guidelines still recommend secondary prevention with only antiplatelet agents in the absence of documented AF. Oral anticoagulation is recommended only when AF is detected[22].
Also our study likely enrolled patients with other causes of stroke, lowering the incidence of atrial fibrillation, in comparison to a group of more thoroughly evaluated patients with truly cryptogenic stroke. This is because cryptogenic stroke is a diverse entity that has lacked a rigorous standardised definition and not all of our patient population underwent intracranial vascular imaging or transesophageal echocardiography.

Conclusions

Despite establishment of atrial fibrillation as one of the most important risk factors of cryptogenic stroke , the optimal duration for monitoring of AF is still a matter of debate. Our study revealed that the current guidelines of 24 hour holter monitoring may not be sensitive enough to detect AF and longer monitoring strategy maybe required to enhance the detection rates of AF as it has therapeutic implications. Further studies will be required to establish the cost effectiveness of long term monitoring for AF.

Abbreviations

CS : Cryptogenic stroke
AF : Atrial fibrillation
CRYSTAL-AF : The CRYptogenic STroke And underLying Atrial Fibrillation Study

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Table file :

Correlation of age group with the occurrence of AF revealed increased occurrence of AF with increasing age and is as depicted in table 1.

Table 1: Age distribution and occurrence of Atrial fibrillation

Age group	Number (n)	With Atrial fibrillation	Without Atrial fibrillation
50 – 60 years	32	0	32
61 – 70 years	68	3	65
71 – 80 years	37	1	36
81 – 90 years	5	1	4
Chi -square test : 3.43 (p-value: 0.33).			

Among all 142 patients, the most frequent risk factors of stroke were type 2 diabetes mellitus (65% of patients), hyperlipidemia (58%) , hypertension (39%) and smoking (42%). The Chi-square test showed that diabetes, hyperlipidemia, hypertension and smoking were not significantly different between the AF and no AF group (Table 2).

Table 2: Medical risk factors correlation with Atrial fibrillation

	Number (n)	With Atrial fibrillation	Without Atrial fibrillation
Hypertension	55	4	51
Type 2 Diabetes	92	2	90
Hyperlipidemia	82	3	79
Chi-square test: 2.40 (p-value: 0.30).			
Smoking status			
Current smoker	34	2	32
Reformed smoker	25	0	25
Chi -square test : 0.11 (p-value: 0.75).			

Of the different types of stroke in patients with atrial fibrillation, 63.3% were thrombotic ,34.5% were hemorrhagic and 2.1% were subarachnoid bleed. However it was not statistically significant with a P value of 0.09(Table 3).

Table 3: Type of stroke distribution with relation to Atrial fibrillation

Type of stroke	Number (n)	With Atrial fibrillation	Without Atrial fibrillation
Thrombotic	90	4	86
Hemorrhagic	49	1	48
Subarachnoid bleed	3	0	3
Chi -square test : 4.89 (p-value: 0.09).			

Overall the NIHSS score and the KATZ score was higher among the study population, with lower MRS scores. However there was no statistically significant difference in the scores when compared to the occurrence of AF (Table 4).

Table 4: Comparison of NIHSS , MRS and KATZ score on admission with risk of AF :

Score	With Atrial fibrillation	Without Atrial fibrillation
NIHSS* score		
4 or less	1	38
5 or more	4	99
Chi -square test : 0.12 (p-value: 0.70).		
MRS† score		
2 or less	3	85
3 or more	2	52
Chi -square test : 0.01 (p-value: 0.93).		
Katz ADL‡ score		
2 or less	1	44
3 or more	4	93
Chi -square test : 0.33 (p-value: 0.57).		

*NIHSS: National Institute of Health Stroke Scale
†MRS : Modified Rankin Scale
‡KATZ: Katz Activities of Daily Living

On analysis of neuroradiological data, 9.2% of strokes were large vessel, 24.6% were embolic, 11.3% were lacunar and 15.5% were subcortical infarcts. 19.7% had supratentorial bleed, 14.1% had infratentorial bleed and 2.1% had subarachnoid bleed. However their correlation with the occurrence of AF showed no statistical significance (Table 5).

Table 5: CT / MRI finding in relation to Atrial fibrillation

CT / MRI finding	Number	With Atrial fibrillation	Without Atrial fibrillation
Supratentorial bleed	28	1	27
Embolic infarct	35	3	32
Subcortical infarct	22	0	22
Lacunar infarct	16	1	15
Infratentorial bleed	20	0	20
Large vessel infarct	13	0	13
Subarachnoid bleed	3	0	3
Chi-square test : 0.50 (p-value : 0.92).			