Annals of Clinical and Medical Case Reports

ISSN 2639-8109

Research Article

The Association of Left Atrial Enlargement in Different Subtypes of Ischemic Stroke Based on Toast Classification

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Volume 3 Issue 4- 2020

Received Date: 01 Apr 2020

Accepted Date: 13 Apr 2020

Published Date: 18 Apr 2020

2. Key words

Atrium; Ischemic; TOAST; Atrial Cardiopathy

1. Abstract

1.1. Background and Purpose: LAE related rhythm disturbance that characterize atrial fibrillation is also associated with other atrial derangement such as endothelial dysfunction and impaired myocyte function. The role of LAE in acute cerebral infarction patient is not sufficiently described in literature. Hence of this study was undertaken to look for the frequency of left atrial enlargement in acute stroke subtypes.

1.2. Methods: 154 patients with acute ischemic stroke admitted during the study period (June 2016 to March 18) were included. Using clinical data, radiological images and investigation results, stroke subtype of each patient was determined based TOAST criteria. P wave morphology in lead V1 of ECG was evaluated in each patient to look for left atrial enlargement and PTFV1 > 4,000 microvolt ms was considered to be left atrial enlargement by ECG voltage criteria.

1.3. Results: Out of 154 patients, 64 (41.5%) had LAE. Indexed LA diameter was significantly (p=0.001) higher in Cardio embolic group (2.67±0.30) than other groups. LAE was most frequent in the cardio embolic group (40.6%) followed by undetermined cause group (35.9%).

1.4. Conclusions: Second Highest frequency of LAE found in undermined group raises the possibility cardiogenic origin of stroke, at least in some of these patients. Further studies may be worthwhile to determine optimal markers of atrial cardiopathy and the effect of anticoagulant therapy in patients with conclusive evidence of atrial cardiopathy, but no clear evidence of AF.

3. Introduction

Well known definitive modifiable risk factor for ischemic stroke include dyslipidemia, transient ischemic attack, prior stroke, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, valvular heart disease, carotid stenosis, cigarette smoking, obesity, alcohol consumption, increased fibrinogen, elevated homocysteine, low serum folate, oral contraceptive use and elevated anticardiolipin antibodies [1]. Even with full diagnostic evaluation, specific cause remains unidentified in upto 39% patient of acute infarct and are labeled as cryptogenic stroke [2]. Such patient of undetermined aetiology has significantly higher rate of recurrent stroke [3].

Out of these many modifiable risk factor, atrial fibrillation needs particular attention. Patient with atrial fibrillation have high risk of stroke. This risk has been ascribed to stasis of blood and thrombus formation resulting from the loss of an organized atrial contraction. Left atrial appendage is site for around 91% of non-rheumatic atrial fibrillation-related thrombi origin [4]. Although an single standard 12 lead ECG can pick up atrial fibrillation in some case but paroxysmal atrial fibrillation may be missed. In that case a standard 24 hours, 48 hours or even longer holter monitoring is used to diagnose paroxysmal atrial fibrillation. Long monitoring by Implantable loop recorders can also be helpful in detecting paroxysmal atrial fibrillation [5]. Some cardioembolic stroke may still be missed and labeled as stroke undetermined etiology. In a recent study, despite 3 years of heart monitoring 70% of patient with cryptogenic stroke had no evidence of atrial fibrillation [5]. While the role of atrial fibrillation in stroke is well established in literature, there are studies which are postulating that perhaps atrial fibrilla-

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Citation: Pushpendra N Renjen, The Association of Left Atrial Enlargement in Different Subtypes of Ischemic Stroke Based on Toast Classification. Annals of Clinical and Medical Case Reports. 2020; 3(4): 1-7.

tion is merely a marker or consequence of atrial disease and that it is actually atrial disease that is a risk factor for stroke [6, 7].

The Framingham study was one of the earliest studies to observe left atrial enlargement as a risk factor for ischemic stroke in men [8]. Later numerous studies found similar association in women also. However, the role and basic characteristic of left atrial enlargement in acute cerebral infarction patient have not been sufficiently described in literature; especially the relation between stroke subtype and left atrial enlargement is not clear in patient with acute ischemic stroke. The relationship between LA enlargement and stroke is complex. Rhythm disturbance that characterize atrial fibrillation is also associated with other atrial derangement such as endothelial dysfunction [9], fibrosis [10], impaired myocyte function [11] and chamber dilation. Greater LA volume and reduced LA reservoir function are associated with subclinical cerebrovascular disease in subjects without history of stroke also [12]. These derangements can play an independent role in formation of thrombus and its embolization and the dysrthymia that define atrial fibrillation is not always necessary for left atrial thrombus formation and embolization to occur [13,14]. In the light of fact that recurrent strokes are more likely among patients with cardioembolic stroke than among patients with stroke of other cause [15,16], role of left atrial dilatation as risk factor for ischemic stroke become more important. This study we analyzed the association of left atrial enlargement in various acute stroke subtypes.

4. Methodology

Patients who were admitted in the Indraprastha Apollo Hospital during the study period (June 2016 to March 2018) with a diagnosis of acute ischemic stroke were screened according to our inclusion and exclusion criteria, and those found suitable were enrolled for the study. It was a prospective, hospital based, observational study. We included all the cases of first time acute ischemic stroke defined as "abrupt onset of neuronal death due to vascular compromise causing neurological deficit lasting more than 24 hours associated with CT/MRI features of infarction" admitted in IAH, Delhi during the study period. Patients with hemorrhagic stroke, Transient Ischemic Attack (TIA), and those with history of previous ischemic, hemorrhagic stroke or sinus thrombosis were excluded from the study. Patients detailed history and thorough physical examination was performed and his/her demographic data, complete clinical profile, drug history and traditional stroke risk factors were noted.

Routine hematological (CBC), biochemical analysis (RFT, Serum Electrolytes, RBS, Lipid profile), 12 lead ECG, Trans-thoracic Echocardiography were performed within 24 hours of admission. Neuro-radiological analysis that were required to diagnose stroke and related to aetiology determination [Brain CT, Brain MRI, Brain MRI Angiography, Carotid MRI Angiography], as required were performed. Other investigation like Carotid Doppler, 24 hours holter, HbA1C, Serum Homocysteine level, PT and other lab test for thrombophilia were performed in selected patient to establish aetiology of stroke. Using clinical data, radiological images and investigation results, stroke subtype of each patient was determined based on Modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) Classification system [17].

P wave morphology in lead V1 of ECG was evaluated in each patient to look for left atrial enlargement and PTFV1 > 4,000 microvolt ms were considered to have left atrial enlargement by ECG voltage criteria [18, 19]. Trans Thoracic Echocardiography was performed by cardiologist in every patient to determine left atrial enlargement. Left atrial diameter (cm) in parasternal long axis view (at the level of aortic valve) was noted. Left atrial diameter was indexed to Body Surface Area (BSA) (m^2). Indexed Left atrial diameter (cm/m^2) more than or equal to 2.4 cm/m^2 was considered as left atrial enlargement by echo criteria [20]. Body Surface Area was calculated according to Du Bois formula. Patient who fulfilled left atrial enlargement criteria both by ECG criteria and by Trans Thoracic Echocardiography criteria defined earlier were considered to have left atrial enlargement. After classifying patients in groups according to Toast criteria, distribution of left atrial enlargement in each group was analyzed and inference was drawn pertaining to the aims and objectives of the study.

5. Statistical Analysis

Categorical variables were present as frequency and percentages whereas linear variables were expressed as mean and standard deviation. The chi-square test was used to compare the categorical variables. Unpaired t test and ANOVA test followed by Tukey's post hoc tests were used to compare linear variables. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

6. Results and Observations

The present study was conducted in the Department of Neurology, Indraprastha Apollo Hospital, and New Delhi with the objective to study the frequency of left atrial enlargement in different subtypes of ischemic stroke. A total of 154 stroke patients were included in the study. The mean age of male and female stroke patients was 61.13±14.51 years and 62.11±13.34 years respectively. Overall mean age of patients was 61.52±14.02 years. There was no significant (p>0.05) association of age with stroke subtype. Figure 1

shows the distribution of stroke subtype. Cause was undetermined in 36.4% of patients. Cardioembolic stroke was noted among 22.1% patients and small artery was among 20.1% patients. Large artery occlusion was found among 17.5% patients (Figure 1). The presence of LAE was lower among males (31.2%) than females (57.4%), the association was statistically significant (p=0.001) (Figure 2).

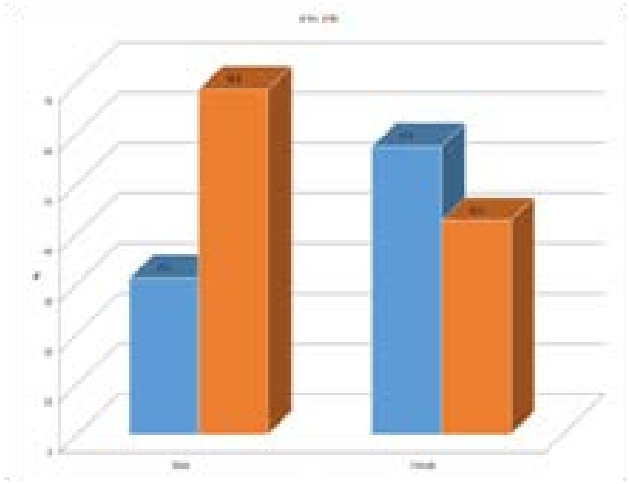

Figure 1: Distribution of stroke subtype

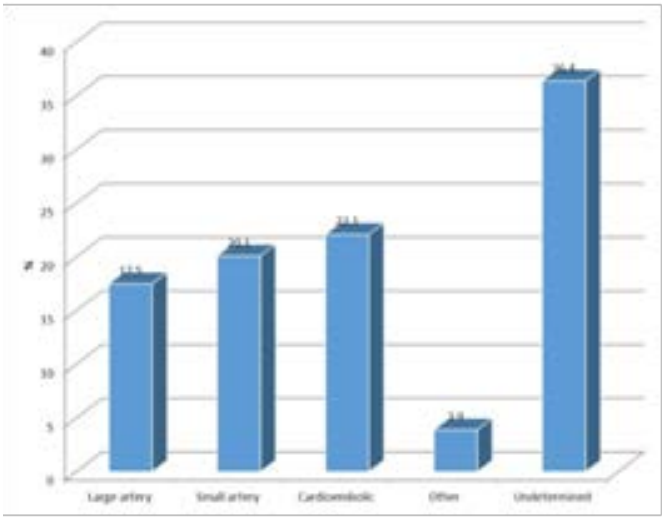

Figure 2: Comparison of LAE with gender

Table 1: Comparison of Indexed LA diameter among male and females

Gender	Indexed LA diameter (in cm)
Male	2.27±0.26
Female	2.48±0.34
p-value[#]	0.03*

[#]Unpaired t-test, *Significant

Indexed Left atrial diameter (cm/m^2) more than or equal to 2.4 cm/m^2 was considered as left atrial enlargement by echo criteria [20]. Study revealed, indexed LA diameter was significantly (p=0.03) lower among males (2.27±0.26) than females (2.48±0.34) (Table 1).

Table-2 shows the comparison of LAE by voltage and ECHO criteria. Both voltage and ECHO criteria for LAE was positive in 41.6% patients (Table 2). The percentage of positivity by voltage and ECHO criteria was almost similar constituting 42.9% and 42.2% respectively. LA diameter was significantly (p=0.002) higher among hypertensive (4.24±0.54) patients than non-hypertensive (3.96±0.48). LA diameter was insignificantly (p>0.05) higher among diabetic patients than non-diabetics. The percentage of AF was 25% among whom LAE was present and the association was statistically insignificant (p>0.05).

Table 2: Comparison of LAE by voltage and ECHO criteria

Voltage	ECHO				Total		p-value[#]
	Yes		No				
	No.	%	No.	%	No.	%	
Yes	64	41.6	2	1.3	66	42.9	0.001*
No	1	0.6	87	56.5	88	57.1	
Total	65	42.2	89	57.8	154	100.0	

[#]Chi-square test, %age is from total no. of cases, *Significant

Comparison of AF among different stroke subtype showed highest percentage of AF (85%) in cardioembolic stroke followed by stroke of undermined cause (15%). This association of AF with stroke subtype was significant (p=0.0001). Upon comparison of LA diameter among different stroke subtype, the one-way analysis of variance showed that there was significant (p=0.001) difference in LA diameter among stroke subtype. The post hoc tests revealed that LA diameter was significantly (p=0.0001) lower in large artery (3.93±0.54) than Cardioembolic (4.48±0.46). The post hoc tests also revealed that LA diameter was significantly (p=0.023) lower in small artery (4.10±0.48) than Cardioembolic (4.48±0.46). The significant (p=0.002) difference was also found between Cardioembolic and undetermined.

Table-3 shows the comparison of Indexed LA diameter among different stroke subtype. The one-way analysis of variance showed that there was significant (p=0.001) difference in Indexed LA diameter among stroke subtype {{Table 3}}. The post hoc tests revealed that indexed LA diameter was significantly (p=0.001) lower in large artery (2.20±0.22) than Cardioembolic (2.67±0.30). The post hoc tests also revealed that Indexed LA diameter was signifi-

cantly (p=0.001) lower in small artery (2.29±0.20) than Cardioembolic (2.67±0.30). The significant (p=0.002) difference was also found between Cardioembolic and undetermined.

Table 3: Comparison of Indexed LA diameter among stroke subtype

Stroke subtype	Indexed LA diameter (in cm)
Large artery	2.20±0.22
Small artery	2.29±0.20
Cardioembolic	2.67±0.30
Other	2.03±0.16
Undetermined	2.31±0.29
p-value#	0.001*

#ANOVA test, *Significant

6.1. LAE by ECHO Criteria: Analysis of LAE by ECHO criteria among different stroke subtype showed the percentage of Cardioembolic (40%) was higher than large (9.2%) and small (15.4%) artery, among whom LAE was present according to ECHO criteria and the association was statistically significant (p=0.001). The percentage of undetermined cases was 35.4% in whom LAE was detected by ECHO criteria.

6.2. LAE by voltage criteria: LAE by voltage criteria among different stroke subtype showed that percentage of Cardioembolic (39.4%) was higher than large (9.1%) and small (16.7%) artery among whom LAE was detected by ECG voltage criteria and the association was statistically significant (p=0.001). The percentage of undetermined cases was 34.8% in whom LAE was detected by voltage criteria.

6.3. LAE among different stroke subtype:

Upon comparison of LAE (positive by both voltage and echo criteria) with stroke subtype, the percentage of Cardioembolic (40.6%) was higher than undetermined (35.9%) among whom LAE was present by both echo and voltage criteria and the association was statistically significant (p=0.001) (Figure 3).

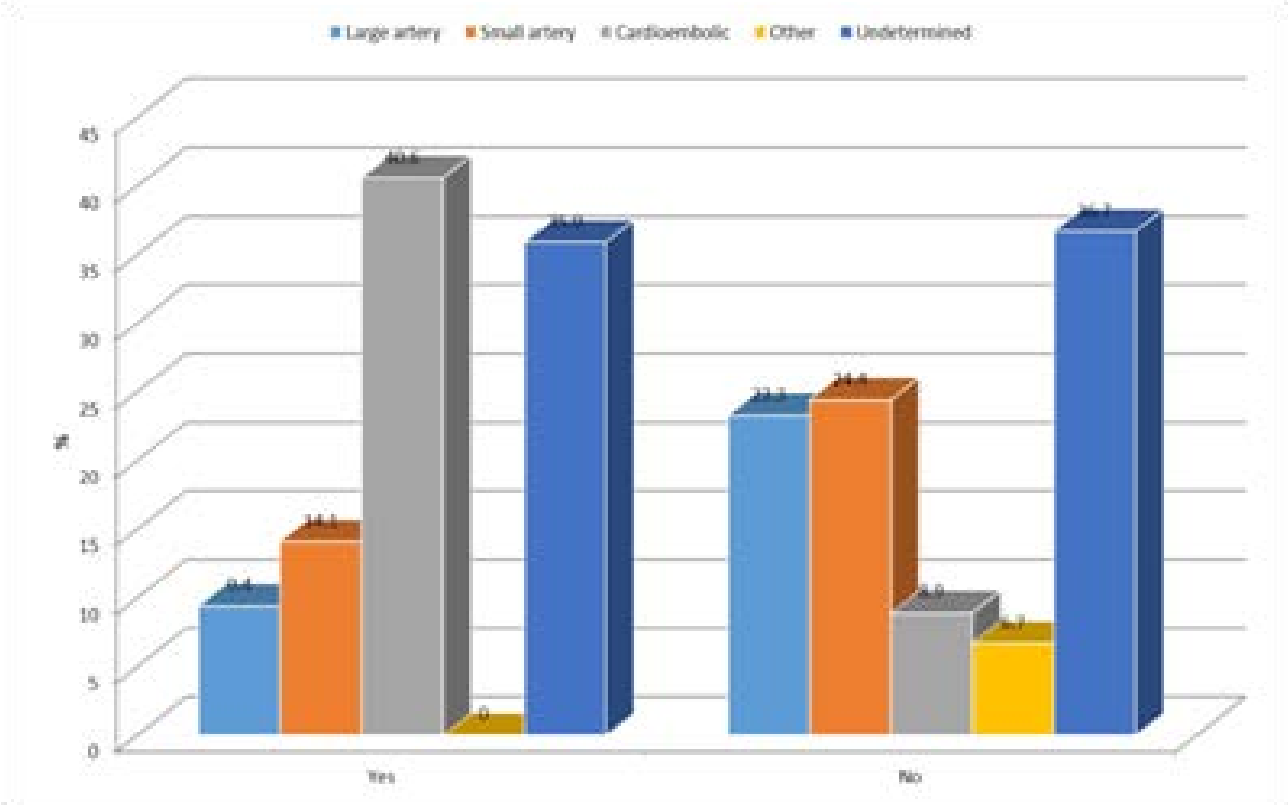

Figure 3: Comparison of LAE among different stroke subtype

7. Discussion

Cardioembolic strokes usually have more severe clinical status and a higher recurrence risk in the short term compared to other stroke groups [21]. Echocardiography and ECG serves as the cornerstone in evaluating patients who may have had a cardioembolic stroke. Although there are many studies done on echocardiogram findings and acute stroke diagnosis, they were all focused on echocardiogram findings. We included ECG criteria also to define LAE in this study.

In this study, percentage of stroke due to undermined aetiology was highest (36.4%) followed by cardioembolic stroke (22.1%). Small artery occlusion was among 20.1% patients and large artery atherosclerosis was found among 17.5% of stroke patients. Stroke of other determined aetiology was noted in only 3.9% of stroke patient. The reason for having a higher number of patients in the undetermined group in this study could be due to inclusion in this group, of patients with cursory evaluation and those with two or more potential cause of stroke. In this study, 154 patients were distributed in 5 groups as per TOAST criteria. Out of 154 patients, 64 (41.5%) had LAE by both voltage and echo criteria. Patients with LAE composed of 29 males (31.2%) and 35 females (57.4%). Presence of LAE was lower among males than females, the association was statistically significant (p=0.001). Contrary to this Misirli et al [22], found no significant difference between left atrial dilatation and gender. Indexed LA diameter was also found significantly (p=0.03) lower among males (2.27±0.26) than females (2.48±0.34) in this study. This may be because of higher cardioembolic stroke found among females in this study.

Both voltage and ECHO criteria for LAE was positive in 41.6% patients. The percentage of positivity by voltage and ECHO criteria for LAE was almost similar constituting 42.9% and 42.2% respectively. Batra et al [23], also found ECG to be a reasonable indicator of left atrial enlargement and suggested, electrocardiography can be used for diagnosis of left atrial enlargement, In case of non-availability of echocardiography. Similar observation was noted by khoska et al [19]. Because Echo-LAE measurements carry certain limitations because of irregular LA geometry, ECG-LAE, which reflects global electrophysiological changes secondary to atrial remodeling, could overcome these limitations.

Hypertension was most common risk factor among the stroke patient in this study (61.6%), followed by Left atrial enlargement (41.5%) and diabetes mellitus (38.3%). In previous studies also, it was considered that there could be a relationship between left atrial dilatation and HT [24]. It is not so clear if this relates to left ventricular hypertrophy or there is a direct relationship between HT and left atrial dilatation. With its thin wall, left atrium dilates easily. As a result of this, LA dilatation in echocardiography may be evaluated as an early finding of hypertensive heart disease. In this study also, indexed left atrial diameter was significantly (p=0.02) higher among hypertensive (2.45±0.32 cm) patients than non-hypertensive (2.20±0.24 cm) highlighting relationship between hypertension and left atrial enlargement. No such relation was noted with D.M. in this study. In this study, we detected significant involvement of AF in cardioembolic strokes. This is expected also as Atrial fibrillation disturbs synchronous mechanical atrial activity and impairs the hemodynamics which can give rise to thrombus formation and embolism to the systemic circulation leading to cardioembolic stroke. Similar observations were noted by Misirli et al [22].

Similarly, there was significant difference in Indexed LA diameter among stroke subtype in this study. Indexed LA diameter was significantly (p=0.001) higher in Cardioembolic (2.67±0.30) than large artery, small artery and undetermined stroke group. This higher LA diameter can result in new onset AF and thus explains association of AF with cardioembolic stroke. Hye Young shin et al [25], also found higher mean indexed LA volume (ml/m^2) in cardioembolic group and increased indexed LA volume was noted to associated with cardioembolic stroke. LA volume measurement is more accurate estimate of true LA size, however, in this study left atrial volume was not measured.

When TOAST classification [17] was followed, it was found that left atrial enlargement was most frequent in the cardioembolic group (40.6%). This was quite expected finding since left atrial dilatation was observed together with AF in the cardioembolic group. However, left atrial dilatation had the second highest frequency in the undetermined cause group (35.9%), after the cardioembolic group, which was bit surprising. one probable explanation to this finding can be occult paroxysmal atrial fibrillation (AF) which is found in a substantial minority of patients with cryptogenic stroke. Similar observation was noted by Takoglu et al [26], in his study, who found left atrial enlargement most frequently in cardioembolic group followed by undermined cause group and further suggested that having only left atrial dilatation in the undetermined cause group should be evaluated as a risk factor.

Contrary to this, Misirli et al [22], noted frequency of LA enlargement in the Cardioembolic group only, was significantly higher (p<0.01) compared to the other groups. However higher frequency in the undetermined cause group is consistent with recent studies that call into question whether AF—the dysrhythmia itself—is always a necessary step in the pathogenesis of left atrial thrombo-embolism [13] and Left atrial abnormality as indicated by left atrial enlargement can itself lead to thrombus formation and embolism, in which case, because of absence of AF, stroke would be likely labeled as cryptogenic and thus stroke of undetermined aetiology and would be prone to recurrent stroke. Such a condition may explain some proportion of the ischemic strokes that currently lack a known cause. It would be ideal to perform further studies with larger number of patients with special emphasize on atrial volume.

Following are the salient findings of the present study:

1. Of 154 stroke patients, percentage of undermined group (36.4%) was highest followed by cardioembolic group (22.1%). Small artery occlusion was found among 20.1% patients and large artery atherosclerosis was seen among 17.5% patients. Stroke of other determined aetiology was noted in only 3.9% of stroke patient.
2. Hypertension was most common risk factor among the stroke patient in this study (61.6%), followed by Left Atrial enlargement (41.5%) and Diabetes mellitus (38.3%).
3. Indexed left atrial diameter was significantly (p=0.02) higher among hypertensive (2.45±0.32) patients than non-hypertensive (2.20±0.24).
4. Indexed LA diameter was significantly (p=0.001) higher in Cardioembolic group (2.67±0.30) than large artery, small artery and undetermined stroke group.
5. Left atrial enlargement was most frequent in the cardioembolic group (40.6%) followed by undetermined cause group (35.9%).

This study had following limitations:

1. We didn't evaluate left atrial volume indexes relative to body surface area or body height, since recent literatures concerning left atrial size have emphasized the importance of the left atrial volume rather than the left atrial dilatation.
2. Our study protocol did not include follow up of the patients to recognize increased risk for atrial arrhythmias, thrombi or recurrent stroke.

8. Conclusion

Second Highest frequency of LAE found in undermined group raises the possibility cardiogenic origin of stroke, at least in some of these patients. Paroxysmal AF or left atrial pathology without AF may explain this phenomenon. As these patient would be prone to recurrent stroke, stroke patients of undermined aetiology with left atrial enlagement should be evaluated in detail including more prolonged holter. Further given the proven benefit of anticoagulant therapy in preventing left atrial thromboembolism in patients with AF, further studies may be worthwhile to determine optimal markers of atrial cardiopathy and the effect of anticoagulant therapy in patients with conclusive evidence of atrial cardiopathy, but no clear evidence of AF.

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