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Does Duration of Symptoms Reliably Predict Detection of Left Atrial Thrombus in Newly Diagnosed Atrial Fibrillation

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Abstract

Background: Large prospective trials attribute minimal thromboembolic risk for cardioversion of atrial fibrillation (AF) when duration of symptoms is shorter than 48 hours. Our goal is to compare the prevalence of left atrial appendage (LAA) thrombus as demonstrated by a Trans esophageal echocardiography (TEE) exam between patients presenting with less or more than 48 hours of AF symptoms.

Method: Observational cohort study including consecutive patients hospitalized with primary diagnosis of new onset AF, not previously treated with oral anticoagulation. All patients underwent TEE to exclude LAA thrombus, regardless of symptoms duration. Patients were divided into two groups based on AF duration: 1) early presenters: up to 48 hours, 2) later presenters: longer than 48 hours.

Results: The study included 122 patients mean age 65.8 years). The "early presenters" were younger, with less co-morbidities. LAA thrombus was detected in 13(21%) of 62 early presenters, compared to 20 (33%) of 60 patients of the second group (P=0.12). Significant predictors of LAA thrombus in the whole cohort by univariate analysis were ≥65 years of age (1.051, P=0.017), acute heart failure (2.394, P=0.038), and history of coronary artery/ peripheral vascular disease (2.7, P= 0.019). Notably neither duration of symptoms nor CHA2DS2-VASc score significantly predicted LAA thrombus. Inmultivariate analysis, only age ≥65 was found to be a significant predictor of LAA thrombus.

Conclusion: LAA thrombus in patients presenting within 48 hours of AF symptoms onset is not uncommon. Duration of symptoms is not reliable for excluding LAA thrombus.

Introduction

There is strong evidence confirming the relation between left atrial appendage (LAA) thrombus and cardioembolic events. Atrial fibrillation (AF) autopsy studies showed high frequency of LAA thrombus and embolism in deceased AF patients [1-3]. Early transoesophageal echocardiography (TEE) studies demonstrated a much higher prevalence of LAA thrombus in newly diagnosed AF patients in the setting of cerebro-vascular accident (CVA) or transient ischemic attack (TIA) [4]. Prospective studies following AF patients with confirmed LAA thrombus showed increased risk for thromboembolic events [5]. Cardioversion when not preceded by adequate anticoagulation therapy is associated with increased risk for stroke [6-8], however, exclusion of LAA thrombus minimizes this risk [9-10].

Patients presenting with new onset AF have increased risk for thromboembolic events [11]. Conventionally, patients presenting within 48 hours of symptoms onset deemed to be in lower risk and cardioversion may be attempted [12,13]. However, cardioversion is not risk-free, as 6.4% of strokes related to AF occur after cardioversion [14]. Demonstration of LAA thrombus by TEE, usually performed prior to cardioversion in patients presenting beyond 48 hour of symptoms onset, is associated with significant risk of thromboembolic events and prohibits cardioversion [15].

Earlier studies showed that LAA thrombus in acute AF (less than 48hours of duration) is not uncommon and thromboembolism among uncoagulated patients undergoing cardioversion is not negligible, especially when presenting later than 12 hours of symptoms onset in patients with risk factors [7,16,17]. International Guidelines recommendations are permissive for cardioversion in patients presenting early (symptoms less than 48 hours), when anticoagulation is started before cardioversion [12,13]. However, the short time between anticoagulation and cardioversion might not be enough for thrombus resolution, supposed LAA thrombus is present, and these patients' risk for thromboembolism might be significantly high.

Key Words

Atrial Fibrillation, Duration, Thrombus.

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Table 1: Baseline characteristics

		Duration of AF symptoms before presentation		
	All (n= 122)	≤48 Hours (n= 62)	>48 Hours (n= 60)	p value
Sex (female) n. (%)	68 (55.7)	32 (51.6)	36 (60)	0.35
Age (mean) (years)	65.8	63.1	68.8	0.003
Hypertension n. (%)	86 (70.5)	38 (61.3)	48 (80)	0.023
Diabetes mellitus n. (%)	47 (38.5)	18 (29)	29 (48.3)	0.028
History of heart failure n. (%)	28 (23)	11 (17.7)	17 (28.3)	0.164
Acute heart failure n. (%)	33 (27)	6 (10)	27 (45)	0.00001
History of stroke/TIA n. (%)	11 (9)	5 (8)	6 (10)	0.27
History of CAD/PVD n. (%)	32 (26.2)	15 (24.2)	17 (28.3)	0.6
CKD (eGFR≤ 60 ml/min) n. (%)	14 (11.5)	4 (6.5)	10 (16.6)	0.08
Smokers n. (%)	20 (16.4)	9 (14.5)	11 (18.3)	0.57
Hyperlipidemia n. (%)	78 (63.9)	36 (58)	42 (70)	0.17
CHA2DS2-VASc (mean)	3.2	2.60	3.8	0.0003
CHA2DS2-VASc >1 in men or >2 in women	88 (72)	37 (60)	51 (85)	0.002

TIA: transient ischemic attack, CAD: coronary artery disease, PVD: peripheral vascular disease, CKD: chronic kidney disease

This study aims to evaluate the presence of LAA thrombus in all AF patients who were admitted to our department and were candidate for cardioversion regardless of symptoms duration, and to characterize early presenting patients with LAA thrombus, for whom cardioversion might be risky.

Methods

All patients who were admitted to the cardiology department in Poriya Medical Centre, in the north of Israel, between 01.2016 and 01.2019, hospitalized for newly diagnosed AF and not treated with anticoagulation and were candidates for cardioversion, underwent a TEE study to exclude LAA thrombus, regardless of AF symptoms duration, as defined by local policy, contrast was not routinely injected. We retrospectively queried our local hospital digital data base for patient's medical background and TEE reports. Symptom's duration was determined by reviewing emergency room records and admission records. Patients whom symptoms duration were undetermined (e.g., asymptomatic patients), or unmentioned in the medical records were excluded. Patients were divided to 2 groups: patients with symptoms ≤48 hours (early presenters) and patients with symptoms > 48 hours (late presenters). In addition, digital medical records were followed up retrospectively for 12 months after admission, all cerebrovascular accidents, transient ischemic attacks, or peripheral arterial emboli, as determined by using clinical and imaging data (at discretion of neurologists or vascular surgeons)were included.

Statistical analysis

Data were analyzed with SPSS software, Version 18.0 (SPSS Inc.; Chicago, IL, USA). Categorical variables were expressed as percentages and continuous variables as means ± standard deviations. Chi-Square was applied for categorical variables, and Independent T test for continuous variables as appropriate to assess the differences between patients with AF duration of ≤48 hours versus those with >48 hours before presentation to the hospital. Statistical significance was defined by a $p < 0.05$.

A univariate logistic regression model was used to predict the presence of LAA thrombus. A multivariate logistic regression was performed, using the backwards model. All covariates whose univariate statistical significance was < 0.05 were forced into a multivariate model. Backwards variable elimination was then used to develop a parsimonious regression model. These variables include in the multivariate logistic regression were age ≥65, history of coronary artery disease (CAD) or peripheral vascular disease (PVD), and acute heart failure. Those variables whose adjusted statistical significance was < 0.1 were retained in the final model. Odds Ratio (OR) with a 95% CI and p-values were derived from the Wald chi-square test.

We assessed the differences in the rate of systemic emboli (CVA/TIA) during the first year of follow-up between patients with and patients without LAA thrombus. Statistical significance considered to be two-sided p-values of <0.05.

Results

After querying our echo database for AF and TEE for LAA thrombus exclusion before cardioversion between 01/2016 and 01/2019, 136 patients were located. Reviewing of emergency room and admission records revealed that among them 62 patients presented up to 48 hours of symptoms, and 60 patients with symptoms lasting longer than 48 hours. In 14 patients, symptoms duration could not be ascertained, either due to lack of proper recording, or patients were not aware of any symptoms; this group was excluded from the final analysis. Mean age of the cohort was 65.8 years. Patients presenting beyond 48 hours of symptoms were older (68.8 vs. 63.1 years, p=0.003), had significantly more comorbidities, including hypertension (80% vs 61.3%, P=0.023) and diabetes mellitus (48.3% vs. 29%, p=0.028). Chronic kidney disease (CKD) was more common in patients presenting lately but the difference did not reach statistical significance(16.6% vs. 6.5%, respectively, P=0.08). Notably, sex, hyperlipidemia, coronary CAD)/PVD, heart failure, history of CVA/TIA, and smoking status were not significantly different among the two groups as described in table 1. Acute heart failure was more common among late presenters (45%) compared to early presenters (10%, p=0.00001). Mean CHA_2DS_2-VASc [Congestive heart failure, hypertension, Age ≥75 years, diabetes mellitus, stroke, vascular disease, Age 65-74, sex category (female)] score was 3.2. Later presenters had significantly higher CHA_2DS_2-

Table 2: Logistic regression model for predicting left atrial appendage thrombus

	Odd ratio	95% CI	p value
Symptom's duration > 48 hours	1.063	0.598-1.890	0.835
Age ≥ 65 years	1.051	1.009-1.095	0.017
CHA2DS2-VASc >1 in men or >2 in women	1.18	0.958-1.454	0.119
Sex (male)	0.689	0.317-1.499	0.348
Acute heart failure	2.394	1.049-5.462	0.038
Hypertension	1.692	0.667-4.295	0.268
History of Heart failure	2	0.856-4.673	0.109
History of stroke/TIA	0.818	0.212-3.158	0.771
Diabetes Mellitus	0.61	0.271-1.382	0.237
History of CAD/PVD	2.7	1.18-6.26	0.019

Table 3: multivariate logistic regression model for predicting left atrial appendage thrombus

	Odd ratio	95% CI	p value
Age ≥65	1.05	1.000-1.089	≤0.05
Acute heart failure	1.76	0.738-4.216	0.20
History of CAD/PVD	2.197	0.928-5.199	0.07

VASc scores compared to early presenters, however mean scores of both groups, separately, were high (3.8 vs. 2.6, respectively, P=0.003). CHA_2DS_2-VASc >1 in men or >2 in women was more common among patients presenting beyond 48 hours (85%) compared to ≤48 hours (60%, p=0.002).

LAA thrombus was detected in 13(21%) of 62 early presenters, compared to 20 (33%) of 60 patients with longer than 48 hours symptoms duration (P=0.12). Average CHA_2DS_2-VASc score in early presenters who had LAA thrombus was 3.2, compared to 2.4 in early presenters without LAA thrombus (p=0.06). Three (12.5%) of 24 patients who had CHA_2DS_2-VASc score of 0 or 1 had LAA thrombus. Univariate logistic regression analysis for predicting LAA thrombus in the whole cohort found the following variables significantly related to LAA thrombus detection: Age ≥65 (OR=1.051, P=0.017), acute heart failure (OR= 2.394, P=0.038), and history of CAD/PVD (OR= 2.7, P=0.019).

Neither symptoms duration, CHA_2DS_2-VASc, sex, hypertension, history of heart failure, history of CVA/TIA, nor diabetes mellitus, were found to be significant predictors of LAA thrombus, as described in table 2. In multivariate analysis including age ≥65, history of CAD/PVD, and acute heart failure at presentation, only age ≥65 was found to be a significant predictor of LAA thrombus (OR= 1.05, P≤0.05) (table 3).

Detection of LAA thrombus was significantly related to a cardioembolic event in the first year (OR= 14.4, P=0.001), but not in the first month of follow up (OR=2.8, P=0.26) (table 4).

Discussion

The main result we found is the surprisingly high prevalence of LAA thrombus among AF patients, presenting within 48 hours of symptom onset, compared to previously reported data. In our study, 21% of AF patients, presenting within 48 hours of symptoms onset, had LAA thrombus. Interestingly, this rate is not statistically different compared to AF patients presenting beyond 48 hours (33%, p=0.12) despitesignificantly higher mean CHA_2DS_2-VASc score among the latter group. Age ≥65, history of CAD/PVD, and acute heart failure were found to be significant predictors of LAA thrombus in univariate analysis, among which only age ≥ 65 stayed significant after multi variate analysis, even though there was a trend to significance regarding CAD/PVD.

In one study comparing thromboembolic events in short term AF, 4% of AF patients, not pre-treated with anticoagulation, had LAA thrombus [7]. Reduced left ventricular function and increased left atrial volume were significantly associated with increased risk for LAA thrombus [7]. In a study evaluating the clinical outcome of stroke/TIA at 30 days after cardioversion in acute AF patients, thromboembolic events were rare (0.2%) [8]. However, risk increased significantly (9.8%) when adjusted for heart failure and diabetes [8]. In another study, 14% of 63 patients presenting within 72h of symptom onset had LAA thrombus, that was the highest prevalence reported thus far [16].

In univariate logistic regression, age ≥65, acute heart failure, and history of CAD/PVD were related to LAA thrombus detection. Patients presenting with acute heart failure are usually older, with more co morbidities including CAD/PVD. Heart remodeling, structural and valvular abnormalities are more common among these patients, being a substrate for LAA thrombus formation and increasing risk for thromboembolism. This subgroup should be treated with extra vigilance, as on one hand, urgent cardioversion might be indicated if tachyarrhythmia is thought to be major contributor to deteriorating hemodynamics, overweighing the risk of thromboembolism. On the other hand, when mechanisms other than AF prevail, thorough considerations should be made before cardioversion as increased risk for LAA thrombus and hence thromboembolic event exists, regardless of symptoms duration. We believe every effort should be done to postpone cardioversion until proven safe either by ruling out LAA thrombus or allowing sufficient time for anticoagulation, except in cases when hemodynamic instability is present.

Interestingly, CHA_2DS_2-VASc >1 (>1 in men or >2 in women) was not found to be a significant predictor of LAA thrombus. This does not mean that CHA_2DS_2-VASc > 1 is not a risk factor for thromboembolic events, but it shouldn't be used to predict LAA thrombus in these group of patients. Mean CHA_2DS_2-VASc score was high in both groups(2.8% Vs. 3.8%, P=0.0003). High CHA_2DS_2-VASc score (>2 for males, and >3 for females) among early presenters in our cohort may blurred the real impact of CHA_2DS_2-VASc score upon LAA thrombosis. Furthermore, our cohort included only patients who were hospitalized for AF that was not resolved spontaneously in the emergency department, or within several hours of admission. In our experience, most of the patients with acute AF, that resolved spontaneously, are younger and have less comorbidities, and therefore likely have less risk for LAA thrombus.

AF duration was not a significant predictor of LAA thrombus detection. This finding should be kept in mind when addressing patients presenting acutely within 48 hours of symptoms, as in contrary to general practice which refer low thromboembolic risk for cardioversion of short duration AF. Indeed, according to the recently published 2020 ESC guidelines, it may be ideal to perform elective cardioversion after 3 weeks of anticoagulation or after TEE excluding LAA thrombus in patients with AF duration 12-48 hours and CHA_2DS_2-VASc ≥2 in males and ≥ 3 in females even it is a IIa indication according to this guideline for early cardioversion without TEE in patients with an AF duration of < 48 hours [18]. Furthermore, a wait-and-watch approach with rate control medication only and cardioversion when needed within 48 h of symptom onset should be considered as it was found to be as

Table 4: Pearson chi square testing LAA thrombus as predictor for cardioembolic events

	OR	p value
1 month follow up	2.796	0.265
1 year follow up	14.419	0.001

safe as and non-inferior to immediate cardioversion of recent-onset AF, which often resolves spontaneously within 24 h [19].

An association between LAA thrombus and a thromboembolic event (TIA, stroke, systemic embolism) at first year after admission was demonstrated. Interestingly, such an association was not found for events in the first month. LAA thrombus may perform as a general predictor of thromboembolic risk, rather than just a harbinger for a threatening event. A challenging scenario that may clarify this point is detecting LAA thrombus in low thromboembolic risk, as determined by a CHA_2DS_2-VASc score. We believe such patients should be treated chronically with anticoagulation.

Limitations

First, it is single center observational study. Second, the study is limited by the retrospective methodology and relatively small sample size. Univariate, and multivariate analysis for predictors of LAA thrombus should be cautiously interpreted. The small sample size, not powered to detect difference, may explain the reason that CHADS-VASc score was not associated with LAA thrombus, and age>65 had increased risk for LAA thrombosis by only 5%. Unfortunately, data regarding anticoagulation status for 1 month and 1 year after admission was not reliably found for all patients; if it was, this would have provided perspective as to why there is an increased risk of cardio embolic event in this population at one year. Although symptoms duration was determined after careful review of emergency room and admission records, the reporting was not homogenous, and symptoms were diverse, limiting the possibility to further subdivide early presenters into groups of 24 hours and 48 hours. Another drawback, most patients in the study didn't have transthoracic echo performed in hospital as local policy doesn't mandate it for AF patients planned for cardioversion. Data regarding actual atrial size is lacking and association of left atrial size and LAA thrombosis could not be assessed. Mean LAA velocity was not routinely assessed during TEE and relation between this variable and LAA thrombosis could not be assessed. Determination of thromboembolic events was based on clinical and imaging data at discretion of neurologists and vascular surgeons. Head MRI, head and neck MRA/CTA were not regularly performed, and some events could be an atherothrombotic complication rather than cardioembolic etiology. Finally, the study population was characterized by high CHA_2DS_2-VASc, which may contribute to the high prevalence of LAA thrombus and diminish generalizability.

Conclusion

LAA thrombus is not uncommon in patients not treated with anticoagulation presenting with acute AF, even when assumed for a short duration (less than 48 hours). Attempts to clarify LAA thrombus may be needed before cardioversion is performed in high-risk patients, mainly patients ≥65 years of age, presenting with acute heart failure, and history of CAD/PVD.

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