Left Atrial Appendage morphology and silent cerebral ischemia in Atrial Fibrillation patients

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Abstract

Background. Left atrial appendage (LAA) is the major source of cardiac thrombi in atrial fibrillation (AF) and plays a major role in cardioembolic events.

Objective. To investigate the correlation between LAA morphology and the burden of silent cerebral ischemia (SCI) as a new thromboembolic risk marker in AF patients.

Methods: 348 AF patients undergoing trans-catheter ablation were enrolled. A cerebral MR was performed to assess SCI burden, while LAA morphology was studied by magnetic resonance (MR) or computed tomography (CT) and categorized as: Cactus in 52 (14.9%) patients, ChickenWing in 177 (50.9%), WindSock in 101 (29.0%), and Cauliflower in 18 (5.2%).

Results: SCIs were detected in 274 (84.8%) patients, with a median number of lesions of 23. SCI burden related to LAA complexity: 30.8% and 17.3% patients with Cactus, 30.5% and 22.0% with ChickenWing, 13.9% and 27.7% with Windsock, and 16.7% and 38.9% with Cauliflower LAA were in the first and fourth quartile of number of SCI per patient, respectively (p=0.035). Following adjustment for potential confounders, only age (beta 0.12, 95% CI 0.08-0.16; p<0.001), ChickenWing (beta [-0.28], 95%CI [-0.51]-[-0.04]; p=0.021), WindSock (beta 0.38, 95%CI 0.12-0.65; p=0.005) and Cauliflower (beta 0.61, 95%CI 0.07-1.14; p=0.026) LAA morphologies significantly related to SCI burden.

Conclusion. LAA morphology relates to the burden of SCI in AF patients. Future research should corroborate if accessible methods (e.g. echocardiography) are able to describe LAA morphology permitting its use within universal thromboembolic risk predictors in AF patients.

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List of abbreviations:

A-P: antero-posterior

AF: atrial fibrillation

CT: computed tomography

LA: left atrium

LAA: left atrial appendage

M-L: medial-lateral

MR: magnetic resonance

S-I: supero-inferior

SCI: silent cerebral ischemia

SD: standard deviation

TIA: transient ischemic attack

Authorôs role: MA, designed the study, performed statistical analysis, and revised the manuscript; MS enrolled patients; LDB enrolled patients and collected data; SG contributed to study design, analyzed LAA scans (MR), drafted the manuscript; PS analyzed LAA scans (CT); LC analyzed cerebral MR scans and drafted the manuscript;

MP analyzed LAA scans (MR); FC, RF and DR performed and analyzed all cardiac and cerebral scans; AN and FG coordinated the study and revised the manuscript.

Introduction

Independently from the presence of comorbidities AF relates to enhanced mortality and thromboembolism, particularly to the brain. In fact, patients with AF present an approximately five-fold higher risk of symptomatic cerebral events compared to the general population[1].

To predict the risk of thromboembolic events in AF patients a number of clinical scores have been evaluated[2]. However, the occurrence of an event, despite low risk score (e.g. CHA_2DS_2-VASc 0-1) unfortunately remains not unusual[3,4]. In this setting, the recently published data of a multicenter study showing a correlation between left atrial (LA) appendage (LAA) morphology and the risk of symptomatic stroke in patients with AF seems promising[5].

In the attempt to ameliorate thromboembolic event prediction, the present study aims to relate the morphology of the LAA, one of the major sources of cardiac thrombus responsible for cerebral embolism in patients with AF, to the burden of silent cerebral ischemia (SCI)[6,7,8].

Methods

Study population

In this multicenter retrospective study, 359 consecutive patients with AF referred for transcatheter ablation were enrolled from November 2008 to April 2010. For each patient cardiac magnetic resonance (MR) or computed tomography (CT) and cerebral MR were performed.

Exclusion criteria have been elsewhere reported[5]. In addition eleven patients (3.1%) were excluded due to low quality of the CT/MR scans not permitting LAA visualization.

All patients provided written informed consent and the study was conducted in accordance to the latest Declaration of Helsinki update.

Baseline evaluation

All subjects underwent extensive clinical assessment, including: medical history (targeted to presence of heart disease, comorbidities), thromboembolic risk assessment (CHA_2DS_2-VASc score[2]), physical examination and 12-lead electrocardiogram.

All patients underwent transthoracic and transesophageal echocardiography and the following parameters were measured[9]: left ventricle ejection fraction; LA antero-posterior (A-P), medial-lateral (M-L) supero-inferior (S-I) diameters; and LAA outflow velocity.

Imaging protocols

Cardiac MR and CT imaging of the LA was performed as previously detailed[5].

LAA morphology was categorized, based on previous literature[10], in one of the four progressively more complex types: Cactus, a dominant central lobe with small chambers extending in all directions; ChickenWing, an obvious bend in the proximal or middle part of the dominant lobe; WindSock, a dominant lobe plus secondary or even tertiary lobes arising from the dominant lobe; and Cauliflower, complex internal characteristics with lack of a dominant lobe. The total number of lobes for each LAA morphology was also recorded[11].

Cerebral scans were performed as previously detailed[12]. According to anatomo-pathological criteria[13] SCI were defined as focal, sharply demarcated, regularly or irregularly shaped areas hyperintense on T2-FLAIR or isointense in T1 weighted image. Each individual SCI detected was registered, independently from size.

All MR/CT scans were independently analyzed by two operators, blinded to clinical data; conflict was resolved by common agreement referring to a third expert.

Statistical analysis

Continuous variables, presented as means and standard deviations (SD), were compared by Student's t-test or analysis of variance (ANOVA) after normal distribution was assured by Shapiro-Wilk test. Number of SCI, instead, was presented as median and quartiles and compared by Kruskal-Wallis test. Categorical variables, presented as counts and percentages, were compared by cross tabulation tables by Pearson's chi-square or Fisher's exact tests, as appropriate. Interobserver agreement between readers (for each imaging modality) was evaluated by Cohen's kappa for LAA morphology classification and by coefficient of reproducibility (Bland-Altman analysis based on average and

difference of both examiners (100*SD(difference)/mean(average)) for SCI detection. A linear regression multivariate model, adjusted for all parameters emerged as potential confounders at univariate analysis (p-value below 0.1) was run to assess if LAA morphology (considered as each LAA morphology against all others by insertion in the model of an individual ñdummy variableò for each of the four morphologies) independently related to the number of SCI (regression coefficients [beta] and 95% confidence intervals [95%CI] reported).

All analyses were performed by 18.0 SPSS package for Windows (SPSS Inc, Chicago, IL, USA) and a two-sided p-value below 0.05 was considered as statistically significant.

Results

Baseline characteristics of the 348 patients enrolled are listed in Table 1.

Cactus type LAA was found in 52 patients (14.9%), ChickenWing in 177 (50.9%); WindSock in 101 patients (29.0%) and Cauliflower in 18 (5.2%; Figure 1). No significant bias was noted in classifying LAA morphology by operators both using MR (Cohenôs kappa 0.81, 95%CI 0.75-0.87) than CT (Cohenôs kappa 0.84, 95%CI 0.61-0.96).

At cerebral MR at least one SCI (Figure 2) was detected in 295 (84.8%) patients, with a median number of lesions in each patient of 23, inter quartiles (IQ) 6-43. Interobserver variability, expressed as coefficient of reproducibility assessed by Bland-Altman method, was 5.6% (from -3.8 to +4.0%; $p<0.01$).

Table 2 illustrates LA and LAA echocardiographic and MR/CT measurements stratified by SCI burden. Out of these, LA A-P and S-I diameters ($p=0.0035$ and $p=0.001$, respectively) related to SCI distribution in the population. The total number of lobes in each LAA - one lobe in 38.7% patients, while 2 or more lobes in the remaining cases (2 lobes, 42.6%; 3 lobes, 16,1%; 4 lobes, 2.3%; and 6 lobes, 0,3%) - instead, did not relate to SCI burden ($p=0.698$).

Eventually, the median number of SCI significantly differed by LAA morphology ($p=0.028$); the correlation between SCI quartiles and LAA type is illustrated in Figure 3. In fact, 30.8 and 17.3% patients with Cactus and 30.5 and 22.0% with ChickenWing, the simplest morphologies, compared to 13.9 and 27.7% with Windsock, and 16.7 and 38.9% with Cauliflower LAA, the most complex LAAs, were in the first and fourth quartile of number of SCI per patient, respectively ($p=0.035$).

To detect if LAA morphology relates to SCI burden independently from other clinical or

instrumental variables recorded and possibly involved, a multivariate model, adjusted for all parameters emerged as potential confounders at univariate analysis (p-value below 0.1), was computed. By this analysis, only age (beta 0.12, 95% CI 0.08-0.16; p<0.001), ChickenWing (beta [-0.28], 95%CI [-0.51]-[-0.04]; p=0.021), WindSock (beta 0.38, 95%CI 0.12-0.65; p=0.005) and Cauliflower (beta 0.61, 95%CI 0.07-1.14; p=0.026) LAA morphologies resulted as independently related to SCI burden (Table 3).

Discussion

The main results of the present study are that age and LAA morphology independently relate to SCI burden in AF patients referred for transcatheter ablation. If the fact that advancing age is linked to an increasing risk of cerebrovascular events is well known[14], the role of the LAA, although a recognized source of cardiac thrombi has not been sufficiently investigated.

Based on previous literature LAA morphology has been standardized in four different types, characterized by increasing complexity (Cactus, ChickenWing, WindSock, Cauliflower)[10]. LAA type is to date easily recognized by commonly performed imaging techniques in patients referred for AF transcatheter ablation, as CT and MR.

On the other side, evaluation of the thromboembolic risk was based on the presence of SCI, evaluated by cerebral MR. Silent ischemic cerebral damage potentially includes a broad spectrum of lesions determined by several ethio-pathological causes. In the last years, however, several Authors have analyzed in post mortem studies the relationship between MR findings and the neuro-pathological specimens aiming to optimize a SCI definition able to selectively describe the small cerebral hyperintensities, as those described in the present study and highlighted in Figure 2, most likely related to embolic causes[13]. In fact, the MR imaging protocol hereby performed allows to differentiate, by T2-FLAIR cerebral MR weighted sequences, AF related gliotic ischemic lesions (hyperintense on T2-FLAIR weighted sequences and isointense in T1 sequences) from other unspecific findings as perivascular spaces and lacunes (hypointense on T2-FLAIR weighted sequences)[15,16].

The sensitivity of this recently introduced MR technique is, therefore, the most plausible

cause of the high SCI prevalence reported. In fact, our data seem more in agreement with MR based studies reporting SCI in AF patients ranging from 75 to 86%[17,18] compared to those based on cerebral CT scans ranging from 13% to 48%[19,20].

Thromboembolic events in AF patients are known to be due to endothelial dysfunction, abnormal blood stasis and hypercoagulable state (the Virchowôs triad)[21,22] resulting in gliotic ischemic lesions. The silent lesions detected by cerebral MR, deriving from microembolization of multiple small platelet thrombi in the terminal brain vessels (especially the leptomeningeal arteries), therefore represent a quantifiable measure of the thromboemoblic risk of the patient. Not surprisingly SCI have widely proved to predict the subsequent risk of symptomatic strokes[23,24]. Although no strong evidence exists in favor of a prevention or reduction of SCI by antiaggregants/anticoagulation it is reasonable (and supported by small previous studies[17,25]) to suppose that these therapies may prevent events also in the early stages of the AF-related cerebral damage, including cognitive impairement[6].

The observation that different LAA morphologies relate to SCI burden may hence be explained assuming that a more complex internal anatomical structure, such as that of the WindSock and Cauliflower LAAs, more intensively promotes local blood stasis and thrombogenesis compared to a simpler structure, as the ChickenWing LAA. The correlation between LAA morphology and thromboembolic risk in patients with AF is an original topic. To the best of our knowledge the first time this relationship was investigated was in a multicenter study, performed by the same centers involved in the present study, reporting a protective odds ratio for symptomatic stroke and TIA in AF patients with ChickenWing, compared to other LAA morphologies[5]. The latter report,

although performed on a considerable number of patients (932), relied on the distribution of symptomatic cerebrovascular events, suffered by a small proportion of the population (8%). This, together with the low prevalence of the Cactus LAA (30% and 15%, respectively in these two experiences), are the most plausible reasons explaining the lack of a protective effect proved by the simplest LAA morphology itself. Given these limitations, in the attempt to strengthen previous findings, the present work assessed, in a population at lower risk, the correlation between LAA morphology and burden of SCI, a more prevalent incident within AF patients.

Of note, in the present study, hypertension, contrary to other previous reports[14], did not emerge as a predictor of SCI. The SCI definition and MR protocol, in fact, prevented from including perivascular lacunar lesions, closely related to the hypertension-related microvascular damage. In addition, the present is a relatively young population (mean age 57 years) hypothetically not yet suffering the typical detrimental effects of long-term hypertension.

In the present population, no peri-procedural overt cerebrovascular accident was encountered. During a clinical follow-up of about three years, instead, overt cerebrovascular accidents occurred in two (0.6%) patients, both presenting a ChickenWing LAA (the most prevalent morphology). This low incidence of overt events, surely influenced by the high rate of conversion and maintenance of sinus rhythm following AF ablation and by the fact that the majority of the patients were kept on oral anticoagulants after the procedure, does not permit any statistical inference computation but surely inspires further studies on the subject. Future research should also corroborate if LAA morphology results reproducibly assessable by easily available imaging methods

(e.g. bi and/or three dimensional echocardiography), to consider if its routine evaluation could improve the traditional thrombembolic risk assessment, especially in ñlow riskò AF patients.

Limitations

The following limitations need to be pointed out. In our analysis we excluded patients with history of prior TIA and or stroke to avoid including individuals with an evident high thromboembolic risk; generalization of our results to these patients is therefore not plausible. Patients with LAA spontaneous echo contrast/thrombi (an exclusion criteria) did not undergo cardiac MR; correlation between LAA morphology and this finding is hence unknown. As in previous studies on this topic an accurate measurement of the effective period of anticoagulant or antiaggregant therapy during exposure to the arrhythmia is lacking. Any retrospective correlation between pharmacological treatment and cerebral MR findings is therefore avoided. The present study does not present a matched control group; comparisons between AF and non-AF matched controls have, however, previously been conducted clearly reporting that non-AF patients are less prone to SCI (e.g. SCI prevalence of 53.8% and mean number of lesions 11.8 ± 20.4[17]). Eventually, heart rhythm at the moment of the MR/CT scans was not recorded: presence of AF/sinus rhythm could have therefore hypothetically influenced quantitative measures of the LAA and left atrium (Table 2), but it is not expected to alter morphology description, being LAA morphology preserved through the different phases of the cardiac cycle.

Conclusion

Age and LAA morphology relate to SCI burden in AF patients. If confirmed, LAA morphology would allow to refine thromboembolic risk prediction and treatment especially in patients with low CHA_2DS_2-VASc score.

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Legend

Figure 1. Examples of the four progressively more complex left atrial appendage morphologies: Cactus (A), ChickenWing (B), WindSock (C), and Cauliflower (D).

Figure 2. Axial FLAIR T2 images demonstrating a total of 33 silent ischemic lesions: 25 subcortical (8 in A, 7 in B, 10 in C, respectively), seven deep white matter (3 in A, 4 in B, respectively) and one nucleus caudate (A) lesions. Clusters of lesions are indicated by arrows.

Figure 3. Quartile distribution of silent cerebral ischemia (SCI) by left atrium appendage (LAA) morphology (1st quartile, Ò6 SCI: white; 2nd quartile, 7-23 SCI: light grey; 3rd quartile, 24-43 SCI: dark grey; 4th quartile, Ó44 SCI: black; p=0.035).

Table 1. Baseline characteristics of the study population stratified by quartiles of silent cerebral ischemia (ANOVA p-value for continuous variables and Pearson's chi-square or Fisherôs exact* p-value for categorical variables).

	OVERALL n=348	Ò6 SCI n=87	7-23 SCI n=92	24-43 SCI n=86	Ó44 SCI n=83	*p*
Gender (n, %)						
Male	274(78.7)	66(75.9)	76(82.6)	69(80.2)	63(75.9)	0.622
Age (years)	57.4(±10.6)	52.5(±12.4)	56.7(±10.5)	58.0(±9.0)	62.8(±7.2)	<0.001
AF duration (months)	79.4(±71.2)	62.2(±56.7)	88.7(±90.4)	81.3(±65.9)	85.4(±63.8)	0.065
Smoking habit (n,%)	72(20.7)	13(14.9)	20(21.7)	16(18.6)	23(27.7)	0.580
Comorbidities (n,%)						
Hypertension	178(51.1)	36(41.4)	46(50.0)	47(54.7)	49(59.0)	0.119
Diabetes	18(5.2)	6(6.9)	5(5.4)	4(4.7)	3(3.6)	0.832*
Hypercholesterolemia	86(24.7)	15(17.2)	19(20.7)	25(29.1)	27(32.5)	0.071
Underlying heart disease (n,%)	51(14.7)	19(21.8)	13(14.1)	11(12.8)	9(10.8)	0.809*
coronary artery disease	25(7.2)	9(10.3)	4(4.3)	6(7.0)	6(7.2)	
Hypertrophic cardiomiopathy	8(2.3)	2(2.3)	3(3.3)	1(1.2)	2(2.4)	
Congenital heart disease	2(0.6)	1(1.1)	0(0)	1(1.2)	0(0)	
Hypocinetic cardiopathy	16(4.6)	6(6.9)	6(6.5)	3(3.5)	1(1.2)	
CHA_2DS_2-VASc (n,%)						0.240
0-1	241(69.3)	63(72.4)	63(68.5)	63(73.3)	52(62.7)	
Ó2	107(30.7)	24(27.6)	29(31.5)	23(26.7)	31(37.3)	

Table 2. Left atrium and left atrial appendage parameters by echocardiography and magnetic resonance stratified by quartiles of silent cerebral ischemia.

	OVERALL n=348	Ò6 SCI n=87	7-23 SCI n=92	24-43 SCI n=86	Ó44 SCI n=83	*p*
TRANSTHORACIC ECHOCARDIOGRAPHIC DATA						
Ejection Fraction (%)	46.6(±7.8)	46.8(±6.6)	47.0(±8.6)	46.9(±7.5)	45.9(±8.4)	0.865
A-P diameter (mm)	39.8(±15.9)	34.8(±15.7)	41.0(±15.9)	42.1(±16.6)	40.6(±15.0)	0.035
S-I diameter (mm)	45.3(±6.2)	43.3(±5.6)	46.9(±6.2)	45.0(±6.0)	46.2(±6.5)	0.001
M-L diameter (mm)	60.6(±7.8)	59.1(±7.5)	60.1(±8.4)	61.3(±7.8)	61.8(±7.2)	0.214
TRANSESOPHAGEAL ECHOCARDIOGRAPHIC DATA						
LAA Peak Flow speed (cm/s)	61.4(±7.1)	61.1(±7.1)	61.3(±7.8)	62.1(±7.1)	61.0(±6.4)	0.737
Sinus Rhythm (60.9%)	63.0(±5.6)	62.6(±5.4)	63.1(±5.4)	64.3(±6.3)	62.1(±5.3)	0.310
Atrial Fibrillation (39.1%)	58.8(±8.4)	58.2(±9.0)	58.4(±9.9)	59.7(±7.3)	58.8(±7.6)	0.883
MRA/CT DATA						
LA volume (cm^3)	89.2(±32.8)	83.8(±30.8)	87.0(±28.7)	95.8(±34.5)	91.6(±36.6)	0.119
LAA volume (cm^3)	8.0(±4.4)	8.5(±5.2)	7.7(±3.5)	8.0(±4.6)	8.0(±4.2)	0.784
LAA ostium						
Area (cm^2)	5.3(±1.8)	5.1(±2.0)	5.5(±1.7)	5.4(±1.8)	5.3(±1.8)	0.474
Perimeter (cm)	8.9(±1.6)	8.7(±1.7)	9.1(±1.3)	9.0(±1.8)	8.8(±1.7)	0.465
Dmax (mm)	32.8(±6.5)	32.3(±6.7)	33.6(±5.6)	33.5(±7.3)	31.7(±6.12)	0.203
dmin (mm)	20.1(±4.6)	19.1(±4.7)	20.7(±4.8)	20.0(±4.7)	20.5(±4.3)	0.120

Dmax, maximum diameter; dmin, minimum diameter

Table 3. Multivariate analysis investigating the correlation between recorded clinical and echocardiographic parameters (unit for continuous variables reported in brackets), left atrial appendage morphology and number of silent cerebral ischemia (unit=10 lesions) expressed by regression coefficients (beta) and 95% confidence intervals (95%CI). For example, subjects with Cauliflower LAA (beta=0.605) present in mean 0.605*10 = 6.05 lesions more than those presenting other LAA morphologies.

	Beta	95% CI	*p*
Age (years)	0.124	0.084ï 0.163	**<0.001**
AF duration (months)	-0.005	(-0.011)ï 0.001	0.077
Hypercholesterolemia	0.942	(-0.011)ï 1.895	0.053
A-P diameter (mm)	$0.45*10^{-4}$	(-0.025)ï 0.026	0.994
S-I diameter (mm)	-0.024	(-0.090)ï 0.042	0.471
Cactus LAA	-0.051	(-0.390)ï 0.289	0.770
ChickenWing LAA	-0.275	(-0.507)ï (-0.043)	**0.021**
WindSock LAA	0.384	0.116ï 0.652	**0.005**
Cauliflower LAA	0.605	0.073ï 1.138	**0.026**

Figure 1.

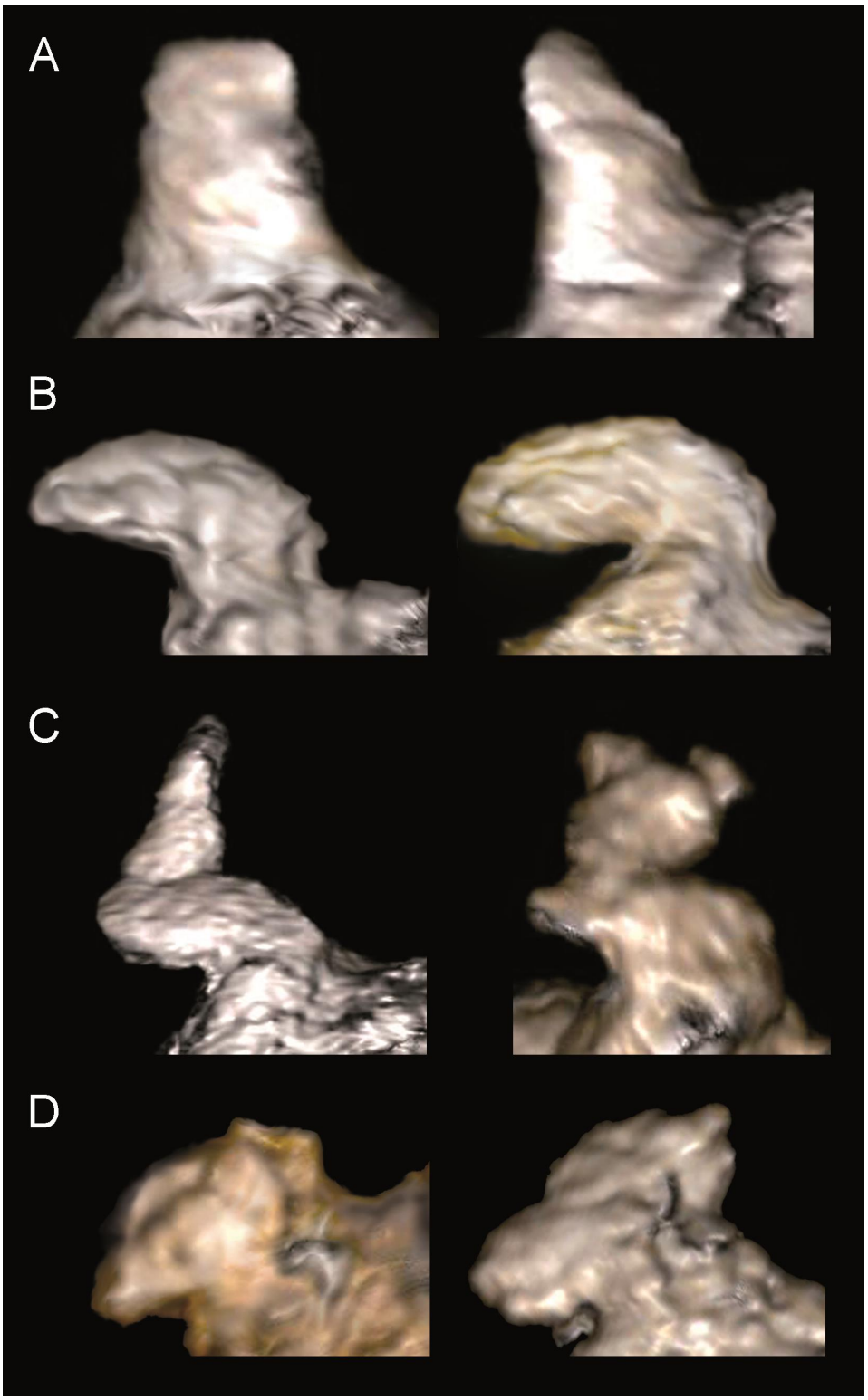


Figure 2.

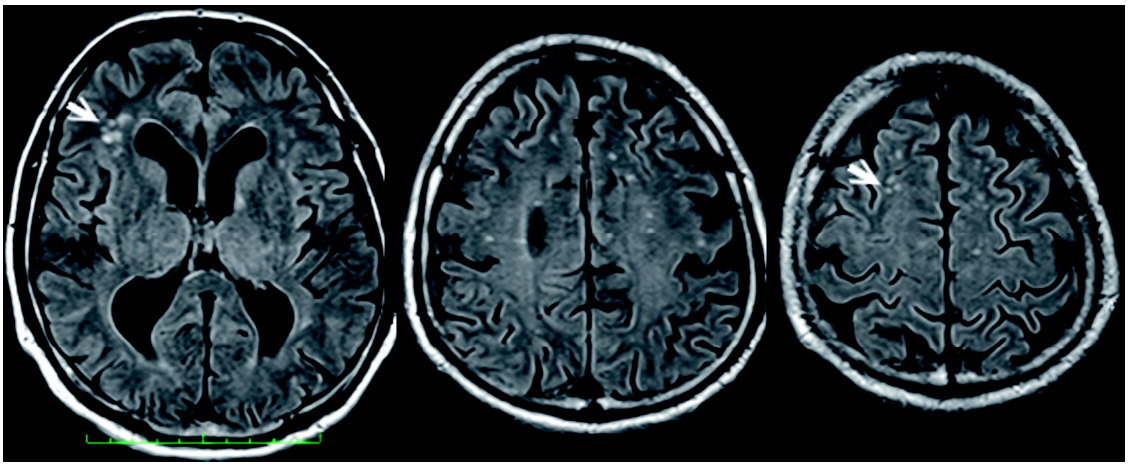
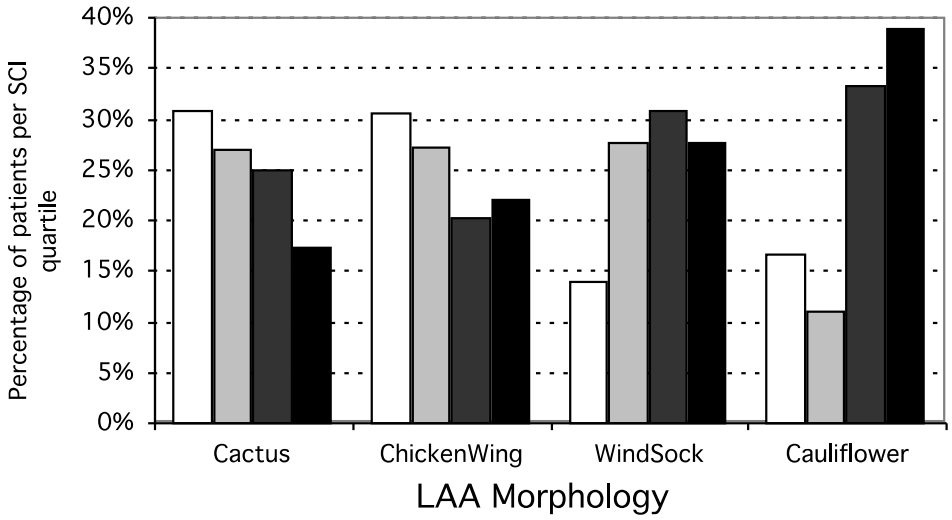


Figure 3.


40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients per SCI quartile
Cactus
ChickenWing
WindSock
Cauliflower
LAA Morphology