

Risk factors, atrial fibrillation and thromboembolic events

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Aim. The aim of this study was to evaluate the relation between risk factors for atrial fibrillation (AF) and thromboembolic complications.

Methods. We studied 480 patients (mean age: 71.2±11.6 years): 240 with paroxysmal AF, 240 with permanent AF. The association between AF and the presence of risk factors, cardiac and systemic disease was observed and the correlation with the occurrence of complications analyzed.

Results. Patients with AF had a high prevalence of the following conditions: hypertension, hypertensive heart disease (HHD), coronary artery disease, hyperthyroidism. Thromboembolism was observed in 26.6% of the patients. A correlation between the occurrence of a thromboembolic complication and the presence of one of the following risk factors for thromboembolism was observed: older age, diabetes mellitus, HHD and hyperfibrinogenemia. No correlation was detected between: female sex, arterial hypertension, hypercholesterolemia, smoking, and obesity. Exitus was observed in 7 patients with permanent AF.

Conclusion. Older age, diabetes mellitus, HHD and hyperfibrinogenemia were strongly associated with the occurrence of thromboembolic complications. Patients with effectively pharmacologically controlled hypertension had not more frequently thromboembolic complications. A strict blood pressure control may prevent thromboembolic complications of AF.

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Key words: Atrial fibrillation - Hypertension - Thromboembolism - Postoperative complications.

Atrial fibrillation (AF) is the most common cardiac arrhythmia with incidence and prevalence increasing with age.¹ Because of the increasing mean age in the general population, the number of patients with AF is expected to increase up to 2.5 times, in the next 5 years,² and the phenomenon may assume the dimension of a real epidemic.

For this reason our attention was drawn to AF and the aim of our study was to evaluate the relationship between risk factors for this arrhythmia, such as arterial hypertension (AH), diabetes mellitus, smoking, obesity, hyperfibrinogenemia,^{3, 4} and thromboembolic complications (either cerebral or peripheral).

Materials and methods

Patient's characteristics

We studied 480 patients, aged between 21 and 97 years (mean age: 71.2±11.6 years): 232 male (48.3%), and 248 female (51.6%), admitted to hospital with AF.

A total of 240 patients (50%), of the 480 enrolled, had paroxysmal AF (PAF) and 240 (50%) had permanent or chronic AF (CAF).

Most of the patients were between the 5th and the 8th decade of life, with a peak incidence in the 6th decade for PAF and in the 8th decade for CAF.

Diagnosis of PAF or CAF was made from the history, clinical and electrocardiographic data. Patients were considered to have PAF if the arrhythmia was started less than 7 days prior to admission, and more frequently within 24 h, and was self terminating.⁵ They were considered to have CAF, if it was lasting from at least 1 month and continuing despite suitable therapeutic interventions or if the restoration of sinus rhythm was never attempted.⁵ The patient's characteristics are summarized in Table I.

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TABLE I.—Patient characteristics.

	No. of patients (N.=480)	Percentage
Age (y)	71.2±11.6	
Males	232	48.4
Females	248	51.6
PAF	240	50
CAF	240	50

PAF: paroxysmal atrial fibrillation; CAF: chronic atrial fibrillation.

Data collection

All data have been collected by asking the patients or examining the clinical notes, and then analyzed for the computerized statistical calculation.

The association between AF and risk factors, cardiac and systemic disease and complications was analyzed.

The following risk factors were considered: AH; diabetes mellitus; hypercholesterolemia; smoking; obesity; hyperfibrinogenemia.

Patients were considered to be hypertensive if systolic blood pressure was >140 mmHg or diastolic blood pressure >90 mmHg.⁶

Patients were considered diabetic if fasting plasma glucose was >126 mg%;⁷ hypercholesterolemic if cholesterol plasma levels were >220 mg% in more than one sample, and obese if waist-hip ratio was >0.9.

A patient was considered to be a smoker if he smoked more than 10 cigarettes per day for at least 10 years.

The diagnosis of hyperfibrinogenemia was made if fibrinogen plasma levels were >350 mg%.

Associated cardiac diseases were detected by clinical examination, electrocardiogram, echocardiogram, chest X-ray and specific blood tests.

The associated cardiac diseases were: coronary artery disease (CAD); hypertensive heart disease (HHD); rheumatic cardiac disease (RCD); cor pulmonare (CP); Wolff-Parkinson-White syndrome (WPW); dilated cardiomyopathy (DC); thyrotoxic cardiomyopathy.

The occurrence of the following complications of AF was evaluated: cardiogenic thromboembolism (either cerebral or peripheral); heart failure; CAD; death.

Such complications were considered to be acute, if occurring during in-hospital stay or previously, if revealed by the history.

TABLE II.—Risk factors.

	No. of patients (N.=480)	Percentage
Arterial hypertension	237	49.3
Diabetes mellitus	137	28.5
Hypercholesterolemia	49	10.2
Smoking	28	5.8
Obesity	55	11.4
Hyperfibrinogenemia	107	22.2

TABLE III.—Associated systemic and cardiac disease.

	No. of patients (N.=480)	Percentage
AHHD	201	41.8
CAD	142	29.5
RHD	50	10.4
CP	8	1.6
WPW	7	1.4
DC	13	2.7
Hyperthyroidism	16	3.3

HHD: hypertensive heart disease; CAD: coronary artery disease; RHD: rheumatic heart disease; CP: cor pulmonare; WPW: Wolff-Parkinson-White syndrome; DC: dilatative cardiomyopathy.

Statistical analysis

Differences among groups were evaluated, using the χ^2 test; differences between ages have been calculated using the Student's *t*-test. P values <0.05 were considered statistically significant.

Results

Risk factors

A percentage of 75.4 of the patients had at least one risk factor and particularly: 237 (49.3%) AH; 137 (28.5%) diabetes mellitus; 49 (10.2%) hypercholesterolemia; 28 (5.8%) smoking; 55 (11.4%) obesity; 107 (22.2%) had hyperfibrinogenemia.

The patient's risk factors are summarized in Table II.

Associated cardiac disease

AF was associated with (Table III): HHD, in 41.8% of the patients (N.=201), with a peak of incidence in the 8th decade; CAD, in 29.5% of the patients (N.=142), with a peak of incidence in the 8th decade; RCD in 10.4% of the patients (N.=50), with a peak of incidence in the 6th decade; hyperthyroidism in 3.3% of the patients (N.=16),

TABLE IV.—Adverse events.

	No. of patients (N.=480)	Percentage
Acute thromboembolic stroke	36	7.5
Previous thromboembolic stroke	67	13.9
Acute peripheral embolism	8	1.6
Previous peripheral embolism	17	3.5
Acute heart failure	52	10.8
Previous heart failure	136	28.3
Acute myocardial infarction	0	0
Previous myocardial infarction	26	5.4
Exitus	7	1.4

with a peak of incidence in the 5th decade; DC in 2.7% of the patients (N.=13), with a peak of incidence in the 6th decade; CP in 1.6 % of patients (N.=8), with a peak of incidence in the 7th and 8th decade; WPW, in 1.4% of patients (N.=7), with a peak of incidence in the 4th decade; 7.9% of patients (N.=38) had no associated cardiopathies, detectable by blood and instrumental tests. This subgroup of patients had a peak of incidence in the 5th decade of life.

Adverse events

A total of 128 patients (26.6%) had a thromboembolic complication. The peak of incidence was in the 7th decade of life and particularly: 36 patients (7.5%) had an acute ischemic stroke; 67 patients (13.9%) had a previous ischemic stroke; 8 patients (1.6%) had an acute peripheral thromboembolism; 17 patients (3.5%) had a previous peripheral thromboembolism.

Heart failure had been diagnosed in 188 patients (39.1%) and particularly: 136 patients (28.3%) had a history of heart failure; 52 patients (10.8%) experienced heart failure during hospitalization.

Twenty-six patients (5.4%) had a previous myocardial infarction; no patients experienced an acute myocardial infarction during in hospital stay.

Death occurred in 7 patients (1.4%), with CAF, and in no patient with PAF.

Observed adverse events are summarized in Table IV.

Thromboembolic events

The 480 studied patients were divided into two groups: with (N.=128, 26.6%) and without (N.=352, 73%) thromboembolic complications. Differences between the two groups, in respect to the pre-

TABLE V.—Thromboembolic complications, risk factors and associated cardiac or systemic disease.

	Patients with TC (128/480)	Patients without TC (352/480)	P value
Mean age (y)	74.8±8.3	70±12.4	<0.0001
Diabetes mellitus	39%	24.7%	<0.02
Hyperfibrinogenemia	39.8%	15.9%	<0
HHD	49.2%	39.2%	<0.05
CAD	35.1%	27.5%	0.1
Male Sex	42.8%	50.2%	0.18
Female Sex	57%	49.7%	0.18
AH	56.2%	46.8%	0.07
Hypercholesterolemia	11.7%	9.6%	0.5
Smoking	4.6%	6.2%	0.5
Obesity	13.2%	10.8%	0.4
RHD	10.1%	10.5%	0.9
CP	0.7%	1.9%	0.4
WPW	0%	1.9%	0.1
DC	0.7%	3.4%	0.1
Hyperthyroidism	2.3%	3.6 %	0.5

TC: thromboembolic complications; HHD: hypertensive herat disease; CAD: coronary artery disease; AH: arterial hypertension; RHD: rheumatic heart disease; CP: cor pulmonare; WPW: Wolff-Parkinson-White syndrome; DC: dilatative cardiomyopathy

sence of risk factors for thromboembolism, were evaluated (Table V).

Patients with embolic events, when compared with those without, had the following characteristics: older age (mean age: 74.8±8.3 years vs 70±12.4) (P<0.0001); diabetes mellitus (50/128, 39% vs 87/352, 24.7%; P<0.002); hyperfibrinogenemia (51/128, 39.8% vs 56/352, 15.9%; P<0.0001); HHD (63/128, 49.2% vs 138/352, 39.2%; P<0.05).

No differences between the two groups were detected concerning: male sex (55/128, 42.9%, vs 177/352, 50.2%; P=NS); female sex (73/128, 57% vs 175/352, 49.7%; P=NS); AH (72/128, 56.2% vs 165/352, 46.8%; P=NS); CAD (45/128, 35.1% vs 97/352, 27.5%; P=NS); hypercholesterolemia (15/128, 11.7% vs 34/352, 9.6%; P=NS); smoking (6/128, 4.6% vs 22/352, 6.2%; P=NS); obesity (17/128, 13.2% vs 38/352, 10.8%; P=NS); rheumatic heart disease (13/128, 10.1% vs 37/352, 10.5%; P=NS); CP (1/128, 0.7% vs 7/352, 1.9%; P=NS); WPW (0/128 vs 7/352, 1.9%; P=NS); dilatative cardiomyopathy (1/128 vs 12/352; P=NS); hyperthyroidism (3/128, 2.3% vs 13/352, 3.6%; P=NS).

Summary of main results

The study showed an equivalent prevalence of PAF and CAF. Most of the cases were elderly, and

there was a peak of incidence in the 6th decade, for PAF, and in the 8th decade for CAF; 25% of the patients had at least one cardiovascular risk factor and most of them were hypertensive.

Complication of AF was frequent, and our attention was drawn especially to thromboembolism, that was observed in 26.6% of our population of patients (34.3% of cases were acute and 65.7% previous). Thromboembolic strokes or transient ischemic attacks were more frequent than peripheral thromboembolisms. A correlation between the occurrence of a thromboembolic complication and the presence of one of the following risk factors for thromboembolism was observed: older age, diabetes mellitus, HHD and hyperfibrinogenemia. No correlation was found concerning: sex, AH, CAD, hypercholesterolemia, and smoking cigarettes. Other complications observed were heart failure, and more rarely, coronary artery disease. Death was observed in 7 patients, all with CAF.

Discussion

It is well known that patients with AF are more prone to thromboembolism because of the loss of atrial contraction that promotes stasis and the increase in left atrial pressure, which may induce endocardial damage and consequently activation of the coagulation cascade and hemoconcentration due to the release of atrial natriuretic factor.^{5, 8}

Our data, according to the international literature, confirm that patients with diabetes mellitus, advanced age, HHD and hyperfibrinogenemia have thromboembolic complications more frequently.⁹⁻¹⁵

DM is a condition of increased thromboembolic risk: it impairs endothelial function and microcirculation, and oxidative stress induced by hyperglycemia reduces nitric oxide bioavailability.¹⁴⁻¹⁷

Older age is also a well-known thromboembolic risk factor: age increases AF prevalence. Moreover, in the elderly, diastolic function is often impaired,^{18, 19} left atrial appendage velocity may be reduced and it is possible to detect smoke effect at TEE.^{20, 21} The SPAF study demonstrated that age is the most important risk factor for thromboembolism, often associated with other risk factors such as hypertension and female sex.²² Expe-

perimental studies have shown that levels of F 1.2 fragment, an index of thrombin generation, increases with age.²²⁻²⁵

Age is also a risk factors for non-cardiogenic stroke (embolism from the aortic arch), because it increases the risk of atherosclerosis.²⁶

Hyperfibrinogenemia is a marker of contrast effect in left atrium and of intravascular thrombogenesis together with D-dimer.^{13, 27, 28}

Our study did not find relation between thromboembolism and gender, AH, CAD, hypercholesterolemia, obesity, smoking, RHD, WPW, hyperthyroidism, CP, DC, that are usually considered risk factors.⁵

Patients with hypertension and with HHD may be predisposed not only to AF,²⁸ but also to its thromboembolic complications because of the occurrence of anatomical and functional cardiac modifications such as left atrial enlargement, left ventricular hypertrophy and consequently impaired relaxation, and sometimes systolic dysfunction.^{29, 30} The increased left atrial pressure may induce endocardial damage and fibrosis²⁹ that together with stasis may predispose to thrombus formation, as well as diastolic dysfunction, by impairing atrial hemodynamics.³¹ On the other hand, AH, such as elderly, increases the risk of atherosclerosis and consequently of ischemic stroke, independently of AF.^{26, 32}

We found a trend, but not a statistically significant relation, between AH and thromboembolic complications, probably because all the studied hypertensive patients were on optimized antihypertensive therapy and had well controlled blood pressure levels. For this reason, we believe, according to some other authors, that a strict blood pressure control may not only prevent the development of cardiac damage, but also thromboembolic complications.^{29, 33}

In patients with CAD, ischemia is a well-known trigger for the development of AF and the presence of a procoagulant state or an eventually reduced ejection fraction may predispose to thrombus formation.^{10, 13, 34} Nevertheless there were not, in the studied population, patients with active ischemia or with acute MI, moreover patients with previous MI were on antithrombotic and anti-ischemic drugs and this may have influenced our results.

Regarding hypercholesterolemia, obesity, smoking, RHD, WPW, hyperthyroidism, CP, DC,

a possible explanation is that statistical analysis did not reach significance because these conditions were not very frequent in our population of patients.

In fact, it is well known that patients with RHD have a 17-fold increased risk when compared to the general population.³⁵ Scientific studies have demonstrated increased levels of the fibrin peptide A, the complex thrombin/antithrombin IIIC and the prothrombin F1.2 fragment, in the left atrium of patients with rheumatic mitral stenosis, which may be due to the elevation of left atrial pressure.^{36, 37}

Smoking and hypercholesterolemia are risk factors for atherosclerosis and for this reason are more likely to be related to atherothrombotic stroke and to stroke derived from embolism of the aortic arch than to cardiogenic stroke.³⁸

Conclusions

Older age, diabetes mellitus, HHD and hyperfibrinogenemia were, in our population of patients, strongly associated with the occurrence of thromboembolic complications.

AH is the most important risk factor for AF. It has a deep social and economical impact. We believe that a strict control of blood pressure is today mandatory to prevent systemic and cardiac damage due to hypertension. It may also be an effective tool not only to reduce the prevalence of AF, but also of its thromboembolic complications.

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