ORIGINAL ARTICLE

Incidence of Atrial Fibrillation in Hemodialysis Patients. A Prospective Long-Term Follow-Up Study

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Introduction and objectives. Although atrial fibrillation (AF) is the most commonly occurring arrhythmia in the general population and is a serious health problem, its incidence in patients on hemodialysis is unknown. Our objectives were to determine the incidence of AF in our hemodialysis patients, to investigate factors that predispose to its occurrence, and to assess the clinical implications of AF.

Methods. In total, 164 patients in sinus rhythm (SR) were followed for seven years. The occurrence of AF and its influence on mortality and on the occurrence of thromboembolic events were recorded.

Results. In a mean follow-up period of 47±29.5 months (i.e., 643.2 patient-years), 20 patients developed AF (3.1 per 100 patient-years). It was not possible to identify factors that predisposed to the arrhythmia. In patients aged ≥65 years, 1-year and 2-year mortality rates following the occurrence of AF were 38% and 53%, respectively, whereas the rates in those who remained in SR were 14% and 31%, respectively (*P*=NS). The development of AF was not found to be an independent predictor of mortality. Five patients in the AF group experienced 6 thromboembolic episodes in a follow-up period of 23.6 (21.4) months (i.e., 15 episodes per 100 patient-years), compared with 3 episodes per 100 patient-years in the SR group (relative risk=5.2; 95% CI, 2.1-12.4).

Conclusions. Each year, 3 in every 100 patients in our dialysis unit developed AF. The occurrence of AF increased the risk of a thromboembolic complication 5-fold. The use of anticoagulant treatment in these patients should be carefully evaluated.

Key words: *Arrhythmia. Kidney. Embolism.*

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Incidencia de la fibrilación auricular en los pacientes en hemodiálisis. Estudio prospectivo a largo plazo

Introducción y objetivos. Aunque la fibrilación auricular (FA) es la arritmia más frecuente en la población y constituye un relevante problema social y sanitario, su incidencia en los pacientes en hemodiálisis es desconocida. El objetivo es determinar la incidencia de FA en nuestra población en hemodiálisis, analizar los factores que condicionan su aparición y su influencia en la evolución clínica.

Métodos. Seguimos, durante 7 años, a 164 pacientes que se encontraban en ritmo sinusal (RS). Determinamos la aparición de FA y su influencia en la mortalidad y en la aparición de fenómenos tromboembólicos.

Resultados. Durante un seguimiento medio de 47 ± 29,5 meses (643,2 pacientes-año), 20 pacientes desarrollaron FA (3,1/100 pacientes-año), sin que se identificaran los factores que condicionaron la aparición de la arritmia. En el grupo ≥ 65 años, la mortalidad al primer y segundo año tras la aparición de FA fue del 38 y el 53%, respectivamente, mientras que en los pacientes que mantuvieron el RS fue del 14 y el 31% (p = NS); el desarrollo de FA no se mostró como factor predictor independiente de mortalidad. Cinco pacientes del grupo de FA desarrollaron 6 episodios tromboembólicos durante un seguimiento de 23,6 ± 21,4 meses (15 episodios/100 pacientes-año), mientras que el grupo que mantuvo el RS presentó 3 episodios/100 pacientes-año (riesgo relativo [RR] = 5,2; intervalo de confianza [IC] del 95%, 2,1-12,4).

Conclusiones. Tres de cada 100 pacientes desarrollaron, cada año, FA en nuestra unidad de diálisis. La aparición de FA incrementó en 5 veces el riesgo de presentar una complicación tromboembólica. La utilización del tratamiento anticoagulante en estos pacientes necesita ser cuidadosamente evaluada.

Palabras clave: *Arritmia. Riñón. Embolismo.*

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INTRODUCTION

The importance of atrial fibrillation (AF) as a growing public health problem is a well established

ABBREVIATIONS

AF: atrial fibrillation.
SR: sinus rhythm.

fact.[1,2] Its high prevalence, estimated to be 6.5% among individuals over 65 years of age and 0.9% among those over 20 years of age,[3] together with its influence on mortality[4,5] and on the presence of thromboembolic phenomena,[6] has aroused a great deal of interest in recent years. On the other hand, although cardiovascular disease in patients with chronic renal failure undergoing dialysis is well documented and constitutes the major cause of death in these patients,[7,8] the importance of AF in this population has only recently begun to be assessed,[9-14] and has been found to be a very prevalent arrhythmia that often leads to thromboembolic complications and results in a higher mortality rate.[9,10]

The fact that this disease is associated predominantly with the aged population, that this population is now the largest patient group in nearly all the dialysis units and that the treatment is particularly complex in these patients should lead us to consider AF to be a relevant problem of growing importance.

The objective of our study was to establish the incidence of new cases of AF in our dialysis unit and analyze the factors that play a role in its onset and its influence on the clinical outcomes of the patients.

METHODS

In January of 1998, we established, by means of cross-sectional analysis, the prevalence of AF in our hemodialysis patient population. All the patients who had undergone this treatment in our center for a period of over three months and had not been diagnosed as having rheumatic valve disease were included in the analysis. Of the 190 patients included, 26 (13.6%) presented AF, and the course of this group had been the object of previous analyses.[9,10] The 164 patients who were in sinus rhythm at that time were followed for seven years and the incidence of new cases of AF was established. A patient was considered to present AF when the presence of the arrhythmia was detected by electrocardiography for the first time, and the pattern of the arrhythmia was subsequently classified according to the guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology (ACC/AHA/ESC).[15] We analyzed the factors associated with or that played a role in the presence of AF, including: age; sex; length of time on dialysis; diabetes; systemic hypertension; dyslipidemia; previous ST-elevation acute myocardial infarction; anemia; urea, creatinine and albumin concentrations; protein catabolic rate; Kt/V; parathyroid hormone; calcium and phosphorus. In those cases in which an echocardiogram was available at the start of the study (68 patients), the presence of left ventricular systolic dysfunction or left ventricular hypertrophy was also recorded.

We considered a patient to be diabetic or dyslipidemic if he or she was receiving drug treatment to control blood glucose levels or cholesterol or triglyceride concentrations.

Patients were considered to be hypertensive if, at the time of inclusion in the study, they were taking medication to achieve an arterial pressure of less than 140/90 mm Hg. Left ventricular systolic dysfunction or left ventricular hypertrophy was considered to be present if these conditions were expressly mentioned in the echocardiographic report or if the ejection fraction was less than 50%, the wall thickness was greater than 12 mm or the ventricular mass was greater than 120 g/m^2. All the patients were followed until death, the discontinuation of dialysis due to transplantation or a change in technique or until 1 December 2004. No therapeutic recommendations were established and antiarrhythmic therapy, monitoring frequency and antithrombotic therapy were left to the criteria of the physicians responsible for each patient. No patient was lost to follow-up.

The mortality and the presence of thromboembolic phenomena among the patients who presented AF were compared with those of the patients who maintained sinus rhythm.

Thromboembolic phenomena were considered to be the occurrence of ischemic stroke, transient ischemic attack or systemic embolism. Ischemic stroke was defined as the sudden onset of a focal neurological deficit that persisted for more than 24 hours, with confirmation of the absence of hemorrhage by means of imaging techniques (computerized tomography or magnetic resonance). Transient ischemic attack was defined as the sudden onset of a focal neurological deficit, diagnosed by a neurologist, that resolved spontaneously within 24 hours. Systemic embolism was defined as the presence of acute ischemia in any territory with clinical or radiological evidence of arterial embolism.

Statistical Analysis

Univariate analysis was performed using a nonparametric test (Mann-Whitney) for quantitative variables and Fisher's exact test for qualitative variables. For the multivariate analysis, logistic regression analysis was utilized. Survival was calculated according to the Kaplan-Meier method. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. For hypothesis testing, *P* values of less than .05 were considered to be statistically significant.

RESULTS

In all, 38 patients underwent transplantation, three were transferred to peritoneal dialysis and 75 died. None of the patients with AF became transplant recipients or were transferred to peritoneal dialysis. Twenty of the 164 patients (12.2%) developed AF during the seven years of follow-up. The cumulative incidence of AF during follow-up is shown in Figure 1. The mean follow-up was 47±29.5 months, corresponding to 643.2 patient-years. Thus, the incidence of new cases of AF in our population was 3.1 per 100 patient-years.

The clinical characteristics of the patients and the differences between those patients who developed AF and those who maintained sinus rhythm appear in Table. As can be seen, significant differences were only observed with respect to the sex, while age was near the borderline of statistical significance. The multivariate analysis identified no independent predictors of a higher probability of developing AF.

The mean age of the patients at the onset of AF was 72 years (mean, 68.5±11 years).

None of the patients underwent electrical cardioversion to restore sinus rhythm. Eight of the 20 patients (40%) did not recover sinus rhythm after the detection of the first episode of AF. Five patients (25%) presented recurrent, paroxysmal episodes until the arrhythmia became permanent. At the end of the follow-up period, 7 (35%) presented a clinical pattern of recurrent paroxysmal AF. Three of the 12 patients who had developed recurrent AF were treated at some point with antiarrhythmic drugs.

Twelve patients (60%) in the group that developed AF and 63 (43%) of those who maintained sinus rhythm died during follow-up. In the former group, the mean time to new-onset AF (from January 1998 to the detection of AF) was 40 months (mean, 40±23 months). The overall survival curves corresponding to the two groups, after including the AF-free follow-up period, are shown in Figure 2. The mortality 1 and 2 years after the detection of AF among patients aged 65 years or over was 38% (5 of 13) and 53% (7 of 13), respectively, whereas the mortality in the same age group among those who maintained sinus rhythm was 14% (8 of 57) and 31% (18 of 57), respectively, rates that were not significantly different. These data show the trend toward a higher mortality associated with AF and reduce the bias that results from the analysis of survival in the AF group, including the period prior to the onset of the arrhythmia; nevertheless, AF was not an independent predictor of mortality.

Five patients (20%) in the AF group presented 6 thromboembolic episodes during follow-up.

The mean follow-up of the patients after the detection of AF was 23.6 months, corresponding to 39.3 patient-years, with an incidence of thromboembolic phenomena of 15 episodes per 100 patient-years. The 6 episodes involved 3 systemic embolisms, 2 strokes and 1 transient ischemic attack.

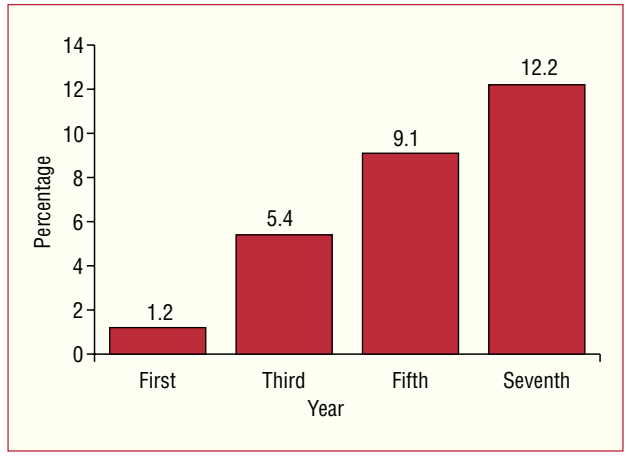
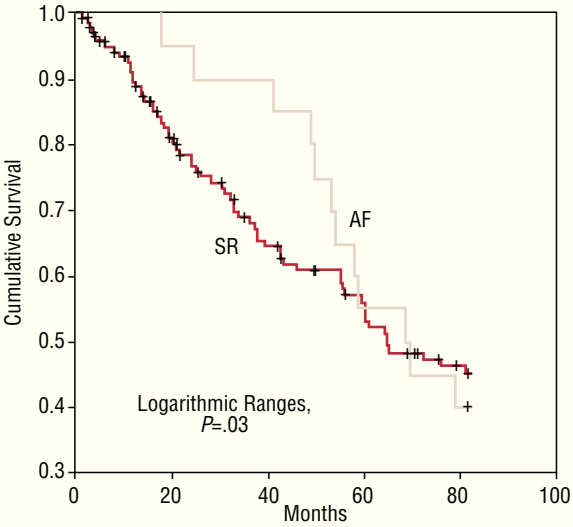


Figure 1. Cumulative incidence of atrial fibrillation during follow-up.

TABLE 1. **Clinical Characteristics of the Patients at the Start of the Study**

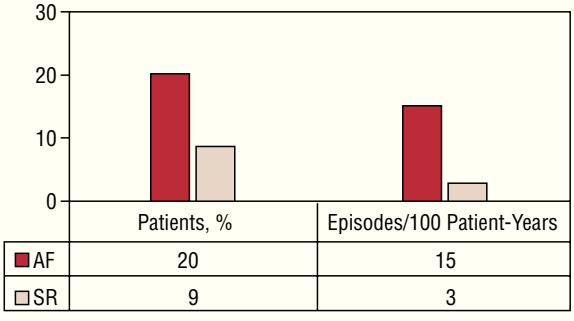
	AF (n=20)	SR (n=144)	*P*
EAge, median (mean±SD), y	68 (64±11)	62 (56±20)	.07
Time on dialysis, median (mean±SD), m	34 (42±36)	46 (75±111)	NS
Men, n (%)	17 (85)	75 (52.1)	.007
Hypertension, n (%)	8 (40)	47 (32.6)	NS
Diabetes, n (%)	3 (15)	13 (9)	NS
Dyslipidemia, n (%)	3 (15)	26 (18.3)	NS
Myocardial infarction, n (%)	2 (10)	10 (6.9)	NS
Left ventricular systolic dysfunction, n (%)	4/13 (30.8)	7/55 (12.7)	NS
Left ventricular hypertrophy, n (%)	10/13 (76.9)	42/55 (76)	NS
Hematocrit, median (mean±SD), %	31 (32±4)	32 (32±5)	NS
Urea, median (mean±SD), mg/dL	139 (139±35)	149 (159±102)	NS
Creatinine, median (mean±SD), mg/dL	9 (9±1.6)	9 (9±2.3)	NS
Protein catabolic rate, median (mean±SD), g/kg/dL	1 (0.9±0.25)	1 (1±2.4)	NS
Albumin, median (mean±SD), g/dL	4.3 (4.3±0.2)	4.4 (4.4±0.4)	NS
Kt/V, median (mean±SD)	1.2 (1.2±1.4)	1.2 (1.3±0.9)	NS
Parathormone, median (mean±SD), pg/mL	307 (350±312)	217 (329±431)	NS
Calcium, median (mean±SD), mg/dL	10 (10±1.1)	10 (10±0.9)	NS
Phosphorus, median (mean±SD), mg/dL	5.8 (5.5±1.3)	5.5 (6.2±4.8)	NS

*AF indicates atrial fibrillation; NS, not significant; SD, standard deviation; SR, sinus rhythm.
The quantitative variables are expressed as the median, with the mean plus or minus the standard deviation in parentheses.



SR (n)	144	119	100	91	81
AF (n)	20	19	18	11	8

Figure 2. Survival curves, according to the method of Kaplan-Meier, of the patients who developed atrial fibrillation and those who maintained sinus rhythm from the start of follow-up (January 1998). The mean time to onset of arrhythmia in the atrial fibrillation group was 40 months. AF indicates atrial fibrillation; SR, sinus rhythm; n, number of living patients plus those who had undergone transplantation or a change in type of dialysis.



	Patients, %	Episodes/100 Patient-Years
AF	20	15
SR	9	3

Figure 3. Incidence of thromboembolic complications in patients with and without atrial fibrillation. The patients with complications are expressed in percentages and episodes per 100 patient-years of follow-up. Relative risk =5.2; 95% confidence interval, 2.1-12.4. AF indicates atrial fibrillation; SR, sinus rhythm.

In the group that maintained sinus rhythm, 13 patients presented 16 episodes (4 strokes), corresponding to 3 episodes per 100 patient-years. The difference between the 2 groups is shown in Figure 3.

None of the patients who developed thromboembolic complications were receiving anticoagulants, and all of them were being treated with antiplatelet agents. Four patients (20%) received anticoagulant therapy at some point of follow-up.

DISCUSSION

Our study shows that, each year, 3 of every 100 patients treated in our dialysis unit developed AF. The probability of new-onset AF after 5 years of follow-up in a population with the clinical characteristics of the patients included in our study is approximately 10% (Figure 1). This finding can not be compared with the results of other studies as it had not been documented previously. Although the patients who developed AF were older than those who maintained sinus rhythm, the small number of patients results in a difference that only comes near the borderline of statistical significance. While in population-based studies, the prevalence of AF is higher among men, who represent 56.6% of the patients,[3] the predominance of men of 85% in our study does not agree with previous reports by other authors[3-6] or earlier work carried out by us,[9] and we can provide no explanation for it. On the basis of our multivariate analysis, we have been unable to identify independent predictors of a higher probability of the development of AF.

The clinical course in the patients who developed AF was worse than that of the patients who maintained sinus rhythm. The present study did not identify AF as an independent predictor of mortality, although we did observe a trend that we consider noteworthy. Figure 2 shows that the survival decreased abruptly from 40 months of follow-up on, coinciding with the mean time to onset of the arrhythmia. Thus, the mortality at 40 months was 10% (2 of 20) in the group that developed AF and 30% (44 of 144) in the group that maintained sinus rhythm, whereas, at the end of the follow-up period, the rates were 60% (12 of 20) and 43.7% (63 of 144), respectively. However, it must be taken into account that every one of the 41 patients who underwent transplantation or a change in the dialysis technique, and thus were not included in the final analysis, belonged to the arrhythmia-free group. When we analyze the survival rates one year and two years after the onset of AF in the group of patients aged 65 years or over and compare them with the rates in patients who did not develop AF, we also observe differences between the two groups, although they are still nonsignificant.

It has been pointed out elsewhere[16] that it is important to distinguish between AF as a "risk factor" for mortality and morbidity and AF as a "risk marker" for comorbidity, meaning that the arrhythmia can develop as a consequence of a serious and complex disease in susceptible patients and, thus, can not be considered a determining factor of the outcome. In our study, two patients died within less than a month after the onset of the arrhythmia and only one of them was

64 or more years old. Thus, even their exclusion from the analysis of survival does not significantly modify the results.

Given that it is only possible to establish the presence of AF once documented, but the time of onset is unknown, the thromboembolic events, in both groups, were considered throughout the entire follow-up period; nonetheless, the incidence of thromboembolism was significantly higher among the patients who developed the arrhythmia (Figure 3).

With respect to both mortality and thromboembolic phenomena, the results of the present study should be related to the findings in the general population. A review of studies analyzing the influence of AF on mortality in the general population shows that the risk is between 1.4 and 2.5-fold higher.[4,5,17] In one of our earlier works,[10] AF resulted in a 2.1-fold higher risk of mortality and, in the present study, the mortality at one year and two years was 38% and 53%, respectively, in the AF group, whereas it was 14% and 31%, respectively, in the group that maintained sinus rhythm, a finding that indicates that the situation is not very different from that observed in the general population.

The probability of presenting a thromboembolic phenomenon was 4.6-fold higher in patients with AF according to our earlier study[10] and 5.2-fold higher in the present report, findings that do not differ significantly from those observed in the Framingham study of the general population.[6]

Thus, the importance of AF in patients on dialysis lies is due to the fact that it multiplies risks that are already elevated and in the high prevalence and incidence of this arrhythmia in this patient population. The incidence of 3.1 per 100 patient-years and the prevalence of 13.6% in our entire patient population and of 16.4% in patients aged 64 years or over[9] result in percentages that are much higher than those of the general population, which are estimated to be 9.0% in individuals aged 80 years or over[3] and 4.7%[18] or 5.9%[19] in those aged 65 or over. Given that the age at which dialysis is started is increasing, we consider that the problem of AF in the dialysis patient population will require more attention in the future and that it will be necessary to establish the treatment of this condition.

Our patients were treated according to the criteria of the responsible physician, without any specific recommendations. As we mentioned above, none of the patients underwent electrical cardioversion, all of them received antiplatelet therapy and 20% of them, anticoagulant therapy with coumarins. The fact that there were no attempts to restore sinus rhythm by electrical or drug therapy can be attributed only to the responsible physicians, who did not consider it to be indicated. Nevertheless, although cardioversion is applicable in certain groups of patients with AF, despite the results of recently published studies,[20,21] we believe that the characteristics of the dialysis patient population (high prevalence of structural heart disease which makes antiarrhythmic strategies difficult and favors the recurrence of the arrhythmia) raise doubts as to the benefits of said procedure in these patients. However, the more widespread use of anticoagulant therapy with coumarin derivatives is an aspect that should be carefully evaluated. Although, classically, renal failure and anticoagulant therapy have been associated with a higher risk of bleeding, and renal failure is even considered to be an absolute contraindication to the use of oral anticoagulants,[22] this risk has not been established within the current conditions for efficacy and quality in dialysis. Although the use of coumarins has been associated with increased survival,[13] studies have not been carried out to determine whether the efficacy demonstrated by anticoagulant therapy in the general population can be extrapolated to dialysis patients; on the other hand, the risk of hemorrhage in these patients is much higher than that observed in the general population,[23] and is considerably increased when they receive anticoagulant or antiplatelet therapy.[24,25] In a retrospective study carried out at our institution,[24] the utilization of anticoagulant therapy resulted in a 2.3-fold increase in the risk of bleeding, although there were no cases of fatal or intracranial hemorrhage or hemorrhage-related sequelae. Nevertheless, we feel that the risk of thromboembolic complications is greater than the risk of hemorrhage[24] and, thus, that individualized risk-benefit assessment regarding antithrombotic therapy in patients with AF undergoing dialysis, while difficult and complex, should be considered indispensable in the therapeutic approach to this situation.

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