

Atrial Fibrillation and Dialysis. A Convergence of Risk Factors

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Although end-stage chronic renal failure (ESCRF) is not a highly prevalent disease, it poses a health care problem of the utmost importance due to the high rates of morbidity and mortality and considerable economic cost involved. Renal transplantation and dialysis are, to date, the only available options for renal replacement (RRT) therapy. In 2005, the Spanish Society of Nephrology published the data on RRT in Spain corresponding to the year 2002.¹ The overall prevalence in Spain was 895 patients per million population, 50% of whom were undergoing hemodialysis, 5% were receiving peritoneal dialysis and 45% had functioning renal transplants. This prevalence is increasing progressively at an annual rate of 4%. Likewise, the incidence, which was 131 patients per million population in 2002, has risen continuously over the years. This incidence also increases as the population ages and is 10 times more frequent among individuals over 65 years of age as compared to those under the age of 45. Thus, on the basis of these data, we can affirm that there are around 40 000 patients receiving RRT, half of whom are on hemodialysis, and that the mean age of these patients is over 65 years.

Atrial fibrillation (AF) is the arrhythmia most frequently encountered in routine clinical practice. It is epidemic in nature, going beyond the sphere of cardiology, and is of great importance not only in terms of health care, but in social and economic terms as well. Its incidence and prevalence increase very significantly with age; thus, if we take into account the progressive aging of the population, it is hardly surprising that it has been defined as one of the epidemics of the end of the twentieth century, a situation that persists today.² Moreover, this state of

affairs is not static; there are studies that show that, in recent years, the prevalence of AF is increasing in different age-matched groups.³ This circumstance could be related to the fact that the population now lives to increasingly advanced ages, but with a greater number of cardiovascular risk factors in comparison with preceding years and decades. According to the findings of the Framingham study, the prevalence of this arrhythmia in the general population is 0.4%, that is, 4000 patients per million population.⁴ However, this prevalence is nearly 2% among individuals in their sixties, reaches 4% among those in their seventies and surpasses 8% in those over the age of 80 years.⁴ Thus, this disease is seen to be concentrated in the final decades of life, as was the case in patients receiving hemodialysis.

In recent years, the association between renal failure and cardiovascular disease has become especially relevant. This is due not only to the fact that they share a good number of common cardiovascular risk factors, such as age, hypertension, diabetes mellitus, etc, but also to the fact that renal failure is now considered to be an important prognostic factor for cardiovascular morbidity and mortality and that the 2 entities maintain a relationship of reciprocal influence.⁵⁻⁷

In the article that appears in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, Vázquez et al⁸ analyze the incidence of AF in hemodialysis patients. They report the results of a long-term (7-year) prospective study of 164 patients on hemodialysis. The major findings of the study are: the mean annual incidence is 3.1%, it was not possible to identify factors implicating the onset of AF and that the arrhythmia was not an independent factor affecting mortality. Finally, the onset of AF was associated with a 5-fold increase in the risk of developing a thromboembolic complication.

The mean annual incidence of AF in the article by Vázquez et al⁸ was 3.1%. This represents roughly a 15-fold higher incidence than that reported for the general public of the same age. Specifically, in the Framingham study,⁹ the incidence of AF was 0.2% in a population ranging between 55 and 64 years of age, which is comparable to the mean age of the patients in this study (62 years). There are only a few articles in the literature that analyze the incidence of AF in hemodialysis patients. Abbott et al¹⁰ report an

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incidence of AF episodes requiring hospitalization of 1.25%. This rate is considerably lower than that of the present article. This may be due to the fact that they only consider the patients who required hospital admission and, thus, did not count the milder or self-limited episodes of AF that did not require admission. On the other hand, in the article by Abbott et al,¹⁰ half of the patients were undergoing peritoneal dialysis, which is associated with a considerably lower rate of AF than that reported for hemodialysis, the technique employed in all of the patients described in the article by Vázquez et al.⁸

The reason for this marked difference between patients on hemodialysis and the normal population of the same age lies in several determining factors: *a)* the most common known causes of ESCRF involve 2 of the most important risk factors for the development of AF, diabetes mellitus and hypertension; in the aforementioned registry of the Spanish Society of Nephrology,¹ the origin of ESCRF was diabetes mellitus in 21% of the cases, followed by vascular nephropathy in 17%, while in 22% of the cases, the etiology remained unknown; this proportion varied according to patient age, with disease of vascular origin being more predominant in groups of more advanced age;¹ *b)* ESCRF in itself acts as a risk factor for the development of AF (volume overload, hypertension, uremia, anemia, electrolyte disturbances, pericardial involvement, development of hyperparathyroidism,¹¹ etc); and *c)* hemolysis in itself can be considered a risk factor for the development of AF. Harnett et al¹² found that many episodes of paroxysmal AF in patients undergoing hemodialysis occur between 3 and 4 hours after the session is initiated. This circumstance has been related to the changes in electrolytes produced during dialysis,¹³ especially to the abrupt decrease in potassium concentrations.¹⁴ There are also significant changes in the extravascular volume, with significant decreases in systemic and pulmonary arterial pressure.¹⁵ Finally, electrocardiography has shown there to be a prolongation and increased dispersion of P wave duration during dialysis, which could play an important role in the onset of AF during the sessions.¹³

In the article by Vázquez et al,⁸ of the 20 patients who developed AF, in 8, the arrhythmia became permanent from the very onset, 5 maintained a paroxysmal pattern at first, which subsequently became permanent and, in the remaining 7, the paroxysmal pattern persisted. The article does not mention the frequency with which electrocardiograms were performed to detect possible asymptomatic AF episodes or the temporal relationship between the episodes of AF and the dialysis sessions. The latter aspect may be important since, in addition to the classification of AF as paroxysmal, persistent or permanent, we could consider other types of AF,

characterized by an episodic behavior, triggered a few hours after the initiation of dialysis, which usually abate rapidly without specific treatment. It may be of interest to separate this type of AF, which is not uncommon in routine clinical practice, from the paroxysmal fibrillation that occurs outside the dialysis sessions, since it may require a different clinical treatment.

It was not possible to identify any risk factors that predisposed patients to this arrhythmia. In other works in the reported studies, age, the presence of coronary heart disease, the size of right atrium, maximum and minimum systolic arterial pressures prior to the initiation of the dialysis session, hemodialysis versus peritoneal dialysis, the use of digoxin and peripheral vascular disease were proposed as independent factors associated with the development of AF in dialysis patients.^{10,16,17} Given the small number of patients in the series, all these findings should be considered with certain reservations. Vázquez et al⁸ observed no statistically significant relationship between the onset of AF and mortality. The mortality 1 year and 2 years after the development of AF is compared with that of a group of patients of the same age who had maintained sinus rhythm. The article does not specify whether the 2 groups also presented the same clinical characteristics, time on dialysis, etc. We should also comment on the survival curve, where it is interesting to observe that, during the first 40 months of follow-up, the survival rate was higher in the group of patients who developed AF and that it is only at that point, which corresponds to the median time to onset of AF, that there is an increase in mortality among these patients that reaches and surpasses that of the patients in sinus rhythm, although the difference is not statistically significant. This finding is difficult to explain. In a previous work published by these authors involving a series of 190 patients, there was a significant difference in the mortality rate in patients with AF, in whom it was 23%, versus the 6% reported in the patients who maintained sinus rhythm, although AF did not appear to be an independent predictor.¹⁸ However, in another study, the same group of authors did identify the presence of AF as an independent predictor of mortality when multivariate analysis was employed.¹⁹ There are no other reports in the literature with which to compare these results in patients undergoing hemodialysis. The discrepancy between these data may be related to the relatively small number of patients being studied, and it could be that, with a larger number of patients, the role of AF as an independent factor of increased mortality would have been demonstrated, as occurs in the general population.²⁰

One of the most important aspects of this article is the incidence of thromboembolic phenomena and their therapeutic implications. Five of the 20 patients with

AF presented 6 thromboembolic episodes within a mean follow-up time of 23 ± 21 months (15 episodes per 100 patient-years), an incidence that is 5-fold higher than the rate observed in the group that maintained sinus rhythm. None of the patients were receiving anticoagulant therapy at the time of the thromboembolic episode. This increase in risk appears to be similar to that reported in the general population. In the Framingham study, the presence of AF multiplied the probabilities of developing stroke by 4.8.²¹ However, when this phenomenon was analyzed according to age group, the risk among the population aged 60 to 69 years (an age group similar to that of the present study), it was "only" 2.6-fold higher, and it increased very significantly in groups of more advanced age.²¹ These data indicate that the presence of AF increases the risk of thromboembolic phenomena to a greater extent in patients receiving hemodialysis than in the general population (5 vs 2.6). This finding contrasts with the data of Wiesholzer et al,²² for whom the presence of AF in patients on hemodialysis was not associated with an increased risk of stroke. On the other hand, anticoagulant therapy is not free of serious complications in these patients and, according to at least one clinical practice guideline,²³ is contraindicated in the presence of AF. In this respect, there are too few studies that analyze this treatment in the literature. In 2003, Vázquez et al published an article²⁴ in which they assessed 29 patients on hemodialysis treated with oral anticoagulants. These patients presented a 2.3-fold higher risk of hemorrhage than hemodialysis patients who were not receiving anticoagulant therapy. There were no fatal or intracranial hemorrhages. In the same year, Abbott et al¹⁰ published an observational study in which treatment with oral anticoagulants reduced the mortality rate among patients on hemodialysis who were admitted to the hospital for AF. Thus, in view of the lack of large-scale controlled studies that analyze the safety and efficacy of this treatment, the only option is to manage each case on an individual basis and, in those patients presenting a high risk for thromboembolic phenomena (a large majority of the patients undergoing hemodialysis), start anticoagulant therapy with close monitoring of the anticoagulation to avoid increases of the International Normalized Ratio.

Finally, it is surprising that, in the clinical management of the patients, in no case was the attempt made to restore sinus rhythm in the patients with "permanent" AF by means of electrical or pharmacological cardioversion, and that only three patients with recurrent AF received antiarrhythmic drugs at some point for their stabilization. It is true that the use of this medication in patients on hemodialysis is associated with added risks over and above the usual ones, but the proper selection of the

antiarrhythmic drug, as well as careful dosage adjustment, should make it possible to attempt to maintain sinus rhythm in certain patients, especially since AF is often difficult to control because of poor tolerance, hypotension during dialysis, etc.²⁵

In conclusion, this article by Vázquez et al⁸ demonstrates that there is a high incidence of AF in patients on hemodialysis, that surpasses that observed in the general public and is associated with high rates of morbidity and mortality and a considerable increase in the incidence of thromboembolic phenomena. More studies with a larger number of patients will be needed to enable us to address the remaining doubts concerning the clinical medical management of these patients in terms of antiarrhythmic and anticoagulant therapy.

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