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Atrial fibrillation: still a benign condition in the elderly?

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Evaluation of: Vesin C, Protogerou AD, Lieber A *et al.*: Predictive factors for all-cause mortality in the hospitalized elderly subject: the importance of arrhythmia. *Atherosclerosis* 207, 507–513 (2009). A recent study demonstrated that the presence of an atrial arrhythmia, mainly atrial fibrillation, in a hospitalized elderly population (mean age: 85 years) was an independent predictor of all-cause mortality during follow-up. This association persisted in multivariable analyses, even after adjustment for several social, clinical and laboratory variables. The great complexity of a 'real-world' geriatric population, which is the result of the coexistence of comorbidities, mood disorders, poor social networks and reduced homeostasis, may explain these results. New age-oriented guidelines are necessary in order to effectively manage atrial fibrillation in elderly individuals who are most exposed to the severe complications of arrhythmia.

In a recent study, Vesin and colleagues demonstrated that the presence of an atrial arrhythmia found in a standard 12-lead resting ECG in a hospitalized elderly population was an independent predictor of all-cause mortality during follow-up [1]. This result is particularly intriguing from a geriatric point of view if we consider that atrial fibrillation (AF) and flutter, which are very similar [2] and are often considered clinical signatures of the aging process [3], were the most represented types of arrhythmia, with atrial tachycardia being diagnosed in only a minority of cases [1]. The close link between age and AF was recently confirmed in the Framingham Study, in which it was found that the 10-year risk for developing arrhythmia increased from approximately 15% in subjects younger than 65 years to 27% in subjects older than 65 years [4]. From an economic point of view, AF represents a significant health problem since it is responsible for 350,000 hospitalizations, 5 million office visits, 276,000 emergency department visits and 234,000 outpatient visits each year in the USA alone, with a total estimated cost of US\$6.65 billion [5].

Summary of methods & results

The Vesin *et al.* study included 331 consecutive patients aged older than 70 years (mean age: 85 years) with a history of cardiovascular disease, who were admitted to the geriatric department of two French hospitals involved in the Pronostic Cardiovasculaire et Optimisation Thérapeutique en Geriatrie (PROTEGER) study between May 2000 and November 2001. Exclusion criteria were the presence of severely impaired cognitive status (Mini Mental State Examination <15), fatal illness (life expectancy <1 month), cachexia, advanced

cancer or severe renal failure. The patients underwent an extensive social and clinical evaluation. The instrumental assessment provided data regarding cardiac structures and left ventricular performance, common carotid artery intima-media thickness and wall motion, and aortic pulse wave velocity. Atrial arrhythmias had a prevalence of 25%. The follow-up was completed in April 2004. After approximately 1 year (mean length of follow-up: 380 days), 33% of patients had died. The authors demonstrated that the presence of an atrial arrhythmia at baseline was significantly correlated with mortality, entailing a risk of dying two-times higher than that observed in sinus rhythm patients (relative risk: 2.40; 95% CI: 1.41–4.07). This association was so strong that it persisted even after adjustment for age, gender and the presence of lower values of diastolic blood pressure and in a series of multivariable models with progressively increasing complexity, including almost all of the most important social, clinical and laboratory variables (i.e., educational level, neuropsychological function, reason for hospitalization, main comorbidities, drug therapy, some metabolic indicators and parameters associated with vascular and cardiac function). Only when the models were adjusted for structural cardiac parameters was the independent predictive value of atrial arrhythmia on mortality lost, being then replaced by left atrium diameter.

Discussion

The results obtained by Vesin and colleagues are of great interest, even though they seem to be in conflict with the findings of some important studies. In fact, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

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investigators demonstrated that no survival benefit was associated with a rhythm-control strategy for AF when compared with rate-control in a large series of patients aged 70 years at a high risk for stroke and death [6]. Similarly, no difference in mortality between these two types of treatment was observed in patients aged 67 years with a history of AF and congestive heart failure (left ventricular ejection fraction $\leq 35\%$), who were enrolled in the Atrial Fibrillation in Congestive Heart Failure (AF-CHF) trial [7]. The results of these studies appear to suggest that the clinical impact of AF is negligible when an optimal control of heart rate is reached. How can we explain these apparently conflicting results? They are probably due to the clinical characteristics of the populations studied. In fact, as Vesin and colleagues acknowledge in the discussion section of their article, their dataset consisted of very old and complex subjects with a history of cardiovascular disease and with a medical condition severe enough to require hospitalization [1]. The main clinical causes of admission to the hospital in this 'real-world' geriatric population, along with cardiovascular diseases (19%), were falls (36%), dementia or neuropsychological problems (14%) and infections (10%). Medical conditions were so severe that 1-year mortality was approximately 33%, while it was only 4 and 10% in the AFFIRM and the AF-CHF trials, respectively [1,6,7].

Moreover, the presence of AF greatly influences many important aspects of geriatric medicine apart from mortality. First, in the Rate Control Versus Electrical Cardioversion (RACE) study, the health-related quality of life (HRQL), assessed with the generic instrument SF-36, was impaired in patients with arrhythmia when compared with healthy controls. After a follow-up of 2.3 years, the persistence of sinus rhythm was associated with a significant improvement in HRQL [8]. These results were further strengthened by the Sotalol

Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), which demonstrated that cardioversion significantly enhances HRQL in the absence of arrhythmia relapses [9]. Mood disorders are also important in subjects with arrhythmia. In fact, the presence of depressive symptoms predicted cardiovascular and all-cause mortality in the AF-CHF trial patients, with adjusted hazard ratios of 1.57 (95% CI: 1.20–2.07) and 1.38 (95% CI: 1.07–1.77), respectively [10]. However, the most fascinating aspect related to AF in the elderly is the association between the arrhythmia and cognitive decline. It was first reported by the investigators of the Rotterdam Study who demonstrated that both vascular and Alzheimer's dementia may be determined by AF, even in the absence of a history of stroke [11]. More recently, in the 2837 patients with AF enrolled in the Olmsted County Study (mean age: 71 years), it was found that the rate of dementia was 2.7% over the first year of follow-up and approximately 2.0% per year thereafter, with a cumulative event-rate that reached 10.5% at 5 years [12]. Moreover, the difference in the incidence of dementia between AF patients and normal subjects was particularly evident at advanced age (i.e., 80–84 years of age; AF patients: 58.3 and 55.8 per 1000 person/year event-rate for men and women, respectively vs normal subjects: 28.1 and 24.7 per 1000 person/year event-rate for men and women, respectively) [12]. The association between AF and dementia could be explained by the observation that the presence of a microvascular disease and the activation of the metabolic cascade leading to inflammation are typical features of both conditions [13–15].

Finally, some conclusions can be drawn from the study regarding the clinical setting in which the arrhythmia develops. In fact, AF often represents a comorbid condition; in this case, the main diagnosis is almost always a common geriatric

Executive summary

- The prevalence of atrial fibrillation (AF) increases with age; for this reason, the arrhythmia is often considered a clinical signature of the aging process.
- The presence of an atrial arrhythmia (usually AF) in a hospitalized frail elderly population is an independent predictor of all-cause mortality during follow-up.
- AF is linked with inflammation.
- AF is correlated with stroke and heart failure.
- New findings associate AF with worsening health-related quality of life, depression and dementia.
- The increased incidence of AF complications in the elderly may explain the different clinical course of arrhythmia in older compared with younger individuals.
- AF might represent a marker of frailty in older subjects.
- New, specifically age-oriented guidelines are necessary in order to effectively manage AF in elderly patients.

clinical problem, such as chronic heart failure, pneumonia, non-ST segment elevation myocardial infarction, chronic obstructive pulmonary disease, stroke or urinary incontinence [5]. Accordingly, the results obtained in the 23,174 hospitalized patients enrolled in the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA) study demonstrated that the prevalence of AF as a comorbid condition underwent a sharp age-related increase [16]. AF patients were older, more frequently disabled and characterized by a greater comorbidity and a longer in-hospital length of stay. Moreover, their urea nitrogen concentration was higher, while total cholesterol was lower. Finally, in-hospital mortality was slightly but significantly greater in subjects with AF (7.1 vs 6.0% in sinus rhythm patients, $p < 0.001$) [16]. Therefore, it is not surprising that patients who died during follow-up in the study by Vesin and colleagues displayed not only an increased prevalence of arrhythmias at baseline, but also lower body weight and diastolic blood pressure and a higher left atrial diameter [1].

Future perspective

Previous evidence linking AF with stroke or worsening heart failure, and new findings linking AF with HRQL, dementia and mortality, appear to indicate that the clinical burden of AF is greater in the elderly, in whom arrhythmia may represent a marker of frailty [16]. Based on this, in the near future, geriatricians should draw their own guidelines for the management of AF in older patients. Do we practice geriatric cardiology? At least for AF, this 13 year-old question is still legitimate [17].

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