Internal and Emergency Medicine (2019) 14:11–15
https://doi.org/10.1007/s11739-018-1985-9

IM - COMMENTARY

Atrial fibrillation in organ transplant recipients: only a marker of the underlying disease?

Francesca Innocenti[1] · Riccardo Pini[1]

Received: 18 October 2018 / Accepted: 13 November 2018 / Published online: 29 November 2018

Despite good progress in the management of patients with atrial fibrillation (AF), this dysrhythmia remains one of the major causes of cardiovascular morbidity and mortality in the world [1–5]. In the general population, the number of patients with AF is predicted to rise steeply in the coming years: the increase in AF prevalence can be attributed both to better detection of silent AF alongside increasing age and conditions predisposing to it [6–8]. But AF is not just a problem of the general population: in the critically ill, this dysrhythmia is gaining increasing attention, because it represents a frequent complication (reported incidence from 5 to 15% in different studies), and its presence is associated with an increased mortality, as well as with a longer stay in the Intensive Care Unit [9]. Risk factors include advanced age, white race, high severity scores, presence of organ failures and sepsis. This situation underlines the need to prevent and treat patients with AF in an effective and timely manner: however, while available guidelines give us clear information for AF management in the general population, we do not have specific indications in the critically ill.

In the present issue of Internal and Emergency Medicine, Hu et al. [10] address an important topic, which is the risk factors and prognostic effect of new-onset AF among heart, kidney and liver transplant (OT) recipients. These patients presented the risk factors related to their end-stage organ failure, as well as those present in the critically ill. In this large-scale, retrospective analysis, based on the catastrophic illnesses patient database in Taiwan, the authors find that these patients show a higher AF incidence, compared with critical patients who did not receive a transplantation. Risk factors for new-onset AF were partially surprising, as they include female gender, but also younger age and absence of comorbidity; the patients who underwent liver transplantation show the highest incidence of AF among the whole population of OT recipients. Mean follow-up length is 2 years for non-OT patients and 4 years for OT patients: the mortality rate is similar for OT and non-OT patients with atrial fibrillation. As AF onset is an end point, the authors do not report any mortality rate comparison between patients with and without AF. They conclude that the relevant incidence of AF after OT deserves high clinician vigilance to facilitate an early diagnosis and a better outcome.

The AF predisposing factors reported by this study are surprising: in the general population, the age-adjusted incidence and prevalence of AF are lower in women than in men; anyway, in women with AF, the risk of death is similar to or higher than that in men with AF [11, 12]. An advanced age and presence of comorbidities, such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease, are reportedly associated with increased AF prevalence [13, 14]. This study population has a disproportionally lower mean age, compared with that of all the other studies on this topic, with an insignificant 5% of patients aged > 65 years. The comorbidities' distribution is unusual, as prevalence of arterial hypertension is low (about 50%, compared with 70% in other study populations), probably because only patients with end-stage renal disease showed a high prevalence of arterial hypertension, while cardiac and liver transplant candidates did not. Valvular and hypertensive heart diseases, alongside congestive heart failure, are not considered among comorbidities: as these are the most common cardiac predisposing factors, their exclusion could have altered the comorbidities' prognostic weight. Moreover, all patients with pre-existing AF were excluded from the study, which further modified the pattern of previous medical conditions, compared with other studies. To the best of our knowledge, this is the first study, which accounted for the competing risk of death when comparing AF incidence in OT and non-OT

✉ Francesca Innocenti
innocenti.fra66@gmail.com

[1] High-Dependency Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria Careggi, Lg. Brambilla 3, 50134 Florence, Italy

Table 1 Overview of the previous papers, which investigated epidemiology and predisposing factors to AF development in transplant recipients

References; transplanted organ	Patients (n); AF incidence (%). Age (years)	Study design; clinical setting Follow-up length for NOAF (years)	Previous history of AF	Mortality rate (%)	Graft failure rate (%)	Risk factors for AF
Xia [15]; Liver	$n=1387$; 102 (7.4%) 54 ± 11 years in pts without NOAF and 59 ± 9 years in pts with NOAF	Retrospective, single-center, cohort study; medical center; 30 days	28% in patients with NOAF and 4% in patients without	11, 20 and 24% at 1, 3, 6 months in pts with NOAF; 4, 8, 12% in pts without	17, 25 and 28% at 1, 3, 6 months in pts with NOAF; 7, 11, 15% in pts without	Age > 56 years MELD score > 32 The highest BW group PADP > 20 mmHg at end of surgery, History of AF prior to LT Requirement of pretransplant vasopressor
Lentine [18]; Kidney	$n=31.136$; 2.6, 3.6, 7.3% at 6, 12 and 36 months 0–30 years: 32% 30–49 years: 36% 50–60 years: 24% > 60 years: 8%	Retrospective study; cohort of recent kidney transplant recipients recorded in the United States Renal Data System (USRDS), 1995–2001; 3 years	Excluded	18 and 24% at 1 and 2 years in pts with AF; not reported for pts without	10 and 14% at 1 and 2 years in pts with AF; not reported for pts without	Advanced age (> 60 years) Male gender White race ESRD caused by hypertension, Extended pretransplantation dialysis duration. Among the baseline comorbidities: Pretransplantation angina/coronary disease
Abbott [19]; Kidney	$n=39.628$; 43 ± 15 years	Retrospective; data from the United States renal data system, 1994–1998; 3 years	Not mentioned	AF independently associated with increased risk of mortality after renal transplantation in cox regression analysis	Not mentioned	Graft lossB Cadaveric donor Age > 33 years BMI earlier year of first ESRD treatment Dialysis in the first week post transplant Rejection Diabetes and hypertension as cause of ESRD (vs. all others) Maintenance medications cyclosporine (vs. tacrolimus)
La Manna [16]; Kidney	304 pts; 25 (8%) POAF 60 ± 7 years in pts without POAF and 50 ± 13 years in pts with POAF	Retrospective; Kidney Transplant Centre of St. Orsola University Hospital (Bologna, Italy); period January 2005–December 2008; 20 days	16 (5%)	Not mentioned	Not mentioned	Age Acute myocardial infarction history Transplant type (increased incidence in combined liver–kidney transplant)

Table 1 (continued)

References; transplanted organ	Patients (n); AF incidence (%). Age (years)	Study design; clinical setting Follow-up length for NOAF (years)	Previous history of AF	Mortality rate (%)	Graft failure rate (%)	Risk factors for AF
Ahmari S [21]; Heart	167 pts; 16 (10%) with NOAF 50 ± 12 years in pts without NOAF and 49 ± 14 years in pts with NOAF	Retrospective; patients who received an orthotopic heart transplant at the Mayo Clinic from 1988 to 2000; 6 ± 3 years	Excluded	5-year mortality rate 25% in pts with NOAF and 12% in pts without ($p < 0.05$)	59% in pts with NOAF	No significant clinical or echocardiographic predictor
Dasari [22]; Heart	228 pts; 45 pts (20%) with NOAF or atrial flutter 52 ± 11 years	Retrospective, Medical Center Cardiology/Heart Failure and Heart Transplant Program, Loyola University Medical Center, Maywood; period from March 1996 to July 2007; 11 years	Not mentioned	All cause mortality rate 43% in the AF/AFL group and 23% in the sinus rhythm group	Not mentioned	Not mentioned

NOAF new-onset atrial fibrillation, *POAF* peri-operative onset atrial fibrillation

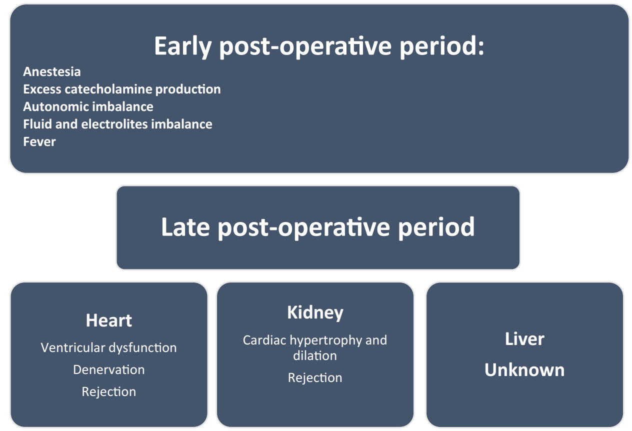

Fig. 1 Pathogenetic mechanism of atrial fibrillation in transplant recipients: differences between early and late post-operative period

patients: anyway, we cannot take for granted that this kind of analysis is adequate enough to explain this peculiar pathogenetic picture.

In Table 1, we present an overview of all the previous papers, which investigate AF prevalence and determinants among OT recipients: each study includes a single kind of transplantation. Heterogeneity between the studies is very high, in terms of study sample dimensions, inclusion criteria and follow-up length. Patients with AF show an increased mortality rate and a higher rejection rate, compared with those who did not develop the dysrhythmia.

Looking at this overview, the first observation is that several papers restrict their observation to the early post-operative period [15, 16]: in this phase of the disease, all transplant recipients, regardless of the specific transplanted organ, probably share some predisposing factors to AF development, including surgical stress, anesthesia, excess catecholamine production and autonomic imbalances [17] (Fig. 1). In a population of liver transplant recipients followed for 30 days, Xia et al. [15] show that the overall incidence of AF approximates that in the eldest population segment in the Framingham Heart Study, a data that demonstrate that dysrhythmic risk are more elevated among transplant recipients than in the general population.

Things become more complicated, when the period of observation is longer than the first post-operative month: the end-stage organ failure creates some modifications, which do not reverse immediately after the operation, and are different, according to the kind of organ failure.

Patients with end-stage renal disease have a high prevalence of diabetes, hypertension, coronary and peripheral arterial disease; the chronic kidney disease is by itself a known risk factor for AF development. Consequent cardiac hypertrophy and left ventricular systolic dysfunction persist for at least 2 years after transplantation and continue to exert their negative effect on dysrhythmogenesis [16, 18, 19].

Patients with end-stage liver disease are probably more critically ill than other transplant recipients; in the pretransplant period, transaminase levels show a U-shaped association with AF risk, which is weakened after adjustment for potential confounders. By contrast, gamma glutamyl transpeptidase (GGT) levels are linearly associated with AF risk after multivariable adjustment: a doubling of GGT levels is associated with a 20% increased risk of AF [20]. In the long term, we do not have any data about predisposing factors to AF development in liver transplant recipients.

For patients who receive a cardiac transplant, the situation is different [21, 22]: the severe cardiac dysfunction, which determined the need for transplantation, is removed by the operation, but new pro- and anti-dysrhythmic mechanisms appear after the transplant. The isolation of the pulmonary vein foci, coupled with vagal denervation and consequent loss of both sympathetic and parasympathetic input to the intrinsic cardiac nervous system, might lead to a decreased incidence of AF after OT. On the other hand, several other pro-dysrhythmic mechanisms develop: postoperative atrial remodeling, with frequent atrial dilatation and presence of surgical scars; electrolyte imbalance, resulting from pharmacologic treatment of rejection; possible thyroid dysfunction after transplantation; the nearly constant features of some myocarditis and fibrosis, altogether with acute or subclinical rejection and immunosuppressive drug side effects.

It is, therefore, clear that AF pathogenesis in transplant recipients of different organs have different causative mechanisms: to evaluate all these patients as a single group might represent an oversimplification. Hu and coll have the merit to have called the attention of the scientific community on the prognostic value of atrial fibrillation in a peculiar group of critically ill: further studies are warranted to elucidate better pathogenetic mechanisms and to find effective measures for prevention and treatment.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Statement of human and animal rights The study protocol was approved by the local Ethics Committee.

Informed consent All subjects provided oral and written informed consent.

References

1. Andersson T, Magnuson A, Bryngelsson IL et al (2013) All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case–control study. Eur Heart J 34:1061–1067
2. Stewart S, Hart CL, Hole DJ, McMurray JJ (2002) A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the renfrew/paisley study. Am J Med 113:359–364
3. Prisco D, Cenci C, Silvestri E, Emmi G, Barnini T, Tamburini C (2012) The risk stratification in atrial fibrillation. Intern Emerg Med 7:S233–S240
4. Raparelli V, Pastori D, Pignataro SF et al (2018) Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study. Intern Emerg Med 13:651–660
5. Pastori D, Farcomeni A, Poli D et al (2016) Cardiovascular risk stratification in patients with non-valvular atrial fibrillation: the 2MACE score. Intern Emerg Med 11:199–204
6. Sanna T, Diener HC, Passman RS et al (2014) Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 370:2478–2486
7. Wang TJ, Larson MG, Levy D et al (2003) Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the framingham heart study. Circulation 107:2920–2925
8. Salvatori V, Becattini C, Laureti S et al (2015) Holter monitoring to detect silent atrial fibrillation in high-risk subjects: the perugia general practitioner study. Intern Emerg Med 10:595–601
9. Yoshida T, Fujii T, Uchino S, Takinami M (2015) Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. J Intensive Care 3:19
10. Hu WS, Lin CL (2018) Risk of new-onset atrial fibrillation among heart, kidney and liver transplant recipients: insights from a national cohort study. Intern Emerg Med. https://doi.org/10.1007/s11739-018-1950-7
11. Andersson T, Magnuson A, Bryngelsson IL et al (2014) Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: a nationwide cohort study of 9519 patients. Int J Cardiol 177:91–99
12. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE (2016) Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol 13:321–332
13. Nguyen TN, Hilmer SN, Cumming RG (2013) Review of epidemiology and management of atrial fibrillation in developing countries. Int J Cardiol 167:2412–2420
14. Oldgren J, Healey JS, Ezekowitz M et al (2014) Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY atrial fibrillation registry. Circulation 129:1568–1576
15. Xia VW, Worapot A, Huang S et al (2015) Postoperative atrial fibrillation in liver transplantation. Am J Transplant 15:687–694
16. La Manna G, Boriani G, Capelli I et al (2013) Incidence and predictors of postoperative atrial fibrillation in kidney transplant recipients. Transplantation 96:981–986
17. Amar D (2004) Strategies for perioperative arrhythmias. Best Pract Res Clin Anaesthesiol 18:565–577
18. Lentine KL, Schnitzler MA, Abbott KC et al (2006) Incidence, predictors, and associated outcomes of atrial fibrillation after kidney transplantation. Clin J Am Soc Nephrol 1:288–296

19. Abbott KC, Reynolds JC, Taylor AJ, Agodoa LY (2003) Hospitalized atrial fibrillation after renal transplantation in the United States. Am J Transplant 3:471–476
20. Alonso A, Misialek JR, Amiin MA et al (2014) Circulating levels of liver enzymes and incidence of atrial fibrillation: the Atherosclerosis risk in communities cohort. Heart 100:1511–1516
21. Ahmari SA, Bunch TJ, Chandra A et al (2006) Prevalence, pathophysiology, and clinical significance of post-heart transplant atrial fibrillation and atrial flutter. J Heart Lung Transplant 25:53–60
22. Dasari TW, Pavlovic-Surjancev B, Patel N et al (2010) Incidence, risk factors, and clinical outcomes of atrial fibrillation and atrial flutter after heart transplantation. Am J Cardiol 106:737–741