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Late atrial arrhythmias after lung transplantation: a meta-analysis.

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Abbreviations: AA = atrial arrhythmia; AFib = atrial fibrillation; DLT = double lung transplant; HR = hazard ratio; IQR = interquartile range; IR = incidence rate; LT = lung transplantat; SLT = single lung transplant;

Abstract

Background: Atrial arrhythmias (AA) are common following non-cardiac thoracic surgery. In particular, early postoperative AA after lung transplantation (LT) are very frequent, especially atrial fibrillation (AFib). Late AA occurrence following LT, instead, has been less commonly reported.

Methods: Aim of the present systematic review and meta-analysis is to analyze the incidence rate of late AA and AFib in LT patients, with a special focus on double lung transplant (DLT), also to assess potential predictors of AFib occurrence. After bibliographic search (PUBMED/Medline and Embase databases), a random-effect model meta-analysis was performed: 7 studies were finally included, including 2,068 LT patients.

Results: Pooled incidence rate (IR) of late AA was 4.3%/year (95% CI 2.8-6.1 %/year, I^2 = 69%), while late AFib IR was 1.5%/year (95% CI 0.7-2.6 %/year, I^2 = 87%). In patients undergoing DLT, pooled IR of late AA was 4.1%/year (95% CI 2.5-6.0 %/year, I^2 = 67%), while AFib IR was 0.9%/year (95% CI 0.1-2.4 %/year, I^2 = 92%). A longer follow-up duration significantly related to reduced IR of AFib (p = 0.02). History of AFib (HR 11.2, 95% CI 5.9-21.3) and early postoperative AFib (HR 10.3, 95% CI 5.9-18.0) emerged, instead, as relevant predictors of AFib occurrence.

Conclusion: Late AA occurence is not infrequent in LT patients; however, late Afib incidence was rare and showed a time-dependent decrease, particularly in double lung transplant patients, suggesting that a transmural PV isolation, the mainstay of transcatheter ablation, is effective in decreasing the likelihood of experiencing AFib.

Introduction

In recent years, the rate of lung transplantation (LT) has considerably increased, reaching worldwide more than 4,000 per year. The main indications for LT are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF) [1].

Atrial arrhythmias (AA) are common following non-cardiac thoracic surgery. In particular, early postoperative AA after LT are very frequent, with an estimated incidence of 26.6% [2], with atrial fibrillation (AFib) being the most prevalent arrhythmia [3]. In fact, also post-LT, the early phase is characterized by a pro-arrhythmogenic milieu due to surgical trauma, atrial and systemic inflammatory response, electrolyte disturbances, hemodynamic overload, sympathetic stimulation and use of vasopressors or other pro-arrhythmic drugs that all together favour AA, particularly AFib. Late AA occurrence following LT, instead, has been less commonly reported. Moreover, after the progressive disappearance of the pro-arrhythmogenic context of the early postoperative phase, LT, and especially double lung transplantation (DLT) in which the four donor pulmonary veins (PV) are anastomized to the recipient's left's atrium, constitutes an *in-vivo* model mimicking long-term effects of transmural PV isolation, the milestone lesion set to suppress AFib by transcatheter ablation.

Aim of the present systematic review and meta-analysis is, therefore, to analyse the incidence rate of late AA and AFib in LT patients, with a special focus on DLT, also to assess potential predictors of AFib occurrence.

Methods

The present systematic review and meta-analysis were performed in accordance to PRISMA [4] and MOOSE guidelines [5].

Search strategy

We screened PubMed/MEDLINE and Embase databases from their inceptions to 9th July 2019, using the following search terms: (atrial fibrillation OR atrial arrhythmia) AND (lung transplantation OR lung transplant).

Study selection and quality assessment

Two investigators (AS, MA) independently reviewed the titles/abstracts and studies to determine their eligibility based on the inclusion criteria and extracted all the relevant outcomes of interest. Observational studies were eligible for inclusion if they (a) reported late atrial arrhythmias incidence (late onset was defined as arrhythmia occurrence at least after hospital discharge) and (b) reported the median follow-up duration.

Risk of bias was assessed at the study-level using the Cochrane bias risk assessment tool for RCT and the Newcastle-Ottawa Scale (NOS) for observational studies (Appendix).

Endpoints

Primary endpoints of the study were:

- Incidence rate of late AA in LT patients;
- Incidence rate of late AFib in LT patients.

Subgroup analysis of the primary endpoints focusing on DLT patients were also conducted.

The secondary endpoint of the study was the meta-analysis of the risk estimates of the most significant predictors of late AFib occurrence in lung transplant patients (statistically significant at least in two different studies).

Statistical analysis

Baseline characteristics of pooled study populations were reported as median values between the included studies, along with their interquartile range.

To account for the anticipated heterogeneity across studies, a random effect model (inverse-variance weighting) was adopted. Incidence rates (IRs) for the different studies were obtained by dividing the cumulative incidence over the median follow-up period by the total person-time at risk (estimated as the number of patients multiplied by the median follow-up duration). Meta-analysis of IRs was performed by a Freeman–Tukey double arcsine stabilizing transformation, using a random-effect model. Meta-analysis of the hazard ratio (HR) for the significant predictors of late AFib occurrence was performed after logarithmic transformation, using a random-effect model. The results with the corresponding 95% confidence interval (CI) were back-transformed and forest plots for the different outcomes were generated. To investigate potential publication bias, Egger test was used to identify asymmetry of funnel plot. Heterogeneity across studies was assessed using the Cochran Q test. Higgins I^2 statistics was used to determine the degree of between-study heterogeneity ($I^2 < 25\%$—low, 25–50%—moderate, and >50%—high). In case of high degree of heterogeneity, meta-regression analysis was performed to assess potential source of heterogeneity. P values < 0.05 were considered statistically significant. Statistical analyses were performed with R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The initial search identified 353 potential studies: among these, 24 were screened for possible inclusion, and full texts were carefully reviewed. 11 studies were excluded since they focused on early AFib occurrence after LT, while 6 studies were excluded since they were case reports (Figure 1).

Finally, 7 studies were included in the present systematic review and meta-analysis [6-12] encompassing 2,068 patients (Table 1). Time cut-offs for defining arrhythmia occurrence as "late" are also reported in Table 1. The median follow-up was 2.9 (IQR 2.2-2.9) years. Table 2 summarises the pooled baseline features of the meta-analytic population. The majority of patients were males (58%, IQR 48%-61%), while median age was 53 years (IQR 49-56 years). Median left ventricular ejection fraction was 60% (IQR 60%-60%). A median of 6.8% (IQR 5.5%-7%) of the patients had previous history of AFib. The most prevalent aetiology prompting LT was idiopathic pulmonary fibrosis/interstitial lung disease (median 28%, IQR 20%-50%).

Pooled IR of late AA in the overall meta-analytic population was 4.3%/year (95% CI 2.8-6.1 %/year, $I^2 = 69\%$), while late AFib IR was 1.5%/year (95% CI 0.7-2.6 %/year, $I^2 = 87\%$). Within DLT patients, pooled IR of late AA was 4.1%/year (95% CI 2.5-6.0 %/year, $I^2 = 67\%$), while late AFib was 0.9%/year (95% CI 0.1-2.4 %/year, $I^2 = 92\%$). Forest plots of incidence rates are reported in Figure 2. Egger test analysis did not reveal any potential publication bias in the meta-analytic outcomes.

All the estimates presented high heterogeneity as indicated by I^2 values > 50%. Meta-regression analysis (Supplementary Table 1) indicates potential source of heterogeneity in the subgroup of DLT patients, with a longer follow-up duration significantly associated with a reduced IR of AFib ($p = 0.02$; Supplementary Figure 1), and increased male percentage associated with an increased IR of both AA ($p = 0.01$) and AFib ($p = 0.03$).

Concerning predictors of late AFib occurrence, eventually, history of (HR 11.2, 95% CI 5.9-21.3) and early postoperative AFib (HR 10.3, 95% CI 5.9-18.0) emerged as the two most relevant predictors (Figure 3). Additional significant single-study late AFib predictors are reported in Supplementary Table 2.

Discussion

The main findings of the present systemic review and meta-analysis are:

- AA occurrence is not infrequent following LT (IR 4.3%/year);
- AFib is not common and it is not the most prevalent AA (IR 1.5%/year);
- Following DLT, late AA occurrence is similar to that reported in the general group (IR 4.1%/year), while AFib definitely occurs less frequently (IR 0.9%/year).

AA are common following noncardiac thoracic surgery. In the setting of LT, a recent meta-analysis [2] suggests that they occur early in the postoperative period, within 6.7 days, in 26.6% of the cases, and AFib emerges as the main postoperative arrhythmia [3]. Given the high circulating levels of inflammatory mediators [13], the amplified sympathetic activity [14,15] and the common hemodynamic overload this is not surprising. What instead is astonishing is, after the early post-transplantation phase, the decrease in late AFib occurrence.

The likely explanation relates to the LT procedure itself. In fact, differently from other noncardiac thoracic surgery, during LT the recipient's heart is indirectly involved. The standard surgical LT technique requires amputation of the PV from the recipient's heart at the antral side of the PV–left atrium junction, and subsequent anastomosis to the donor's PV attached to the donated lung or lungs. This suture leads to a complete electrical isolation (monolateral in case of single LT, bilateral in case of DLT,) of the PV from the heart, the mainstay lesion set targeted by AFib ablation. By transcatheter approach, either with radiofrequency or cryoenergy, ablation has, in recent years, achieved good results in preventing AFib recurrences [16,17]; however there are still patients in which the arrhythmia relapses. In some of these cases, as shown by Lin [18], the PV appear still electrically connected to the left atrium despite three ablation procedures or more. The question weather the arrhythmia is due to the persistent PV-left atrium connection or to non-PV triggers for AF remains open, however an *in-vivo* model of truly transmural PV isolation surely provides suggestive data.

In the present analysis AA occurring late after LT are mainly atrial tachycardias and/or flutters, known to relate to iatrogenic scars and specific re-entry circuits, rather than AFib, experienced very rarely, especially in DLT patients. After the progressive resolution of the early post-operative arrhythmogenic milieu, surgical PV isolation likely exerts its effect by eliminating most of PV triggers and preventing AFib recurrences. This hypothesis is strengthened by the evidence that DLT, which implies a complete PV isolation (four PV, on both sides), carries a lower incidence rate of late AFib occurrence (0.9%/year) compared to the overall LT estimate (1.5%/year), including those patients with partial, monolateral PV isolation (only two out of four PVs).

Truly transmural and durable PV isolation, challenging to achieve by transcatether approaches, in addition, emerges as protective also in respect of persistent AF occurrence. In fact, the PV antra are known to harbor several reentrant drivers of this clinical form of the arrhythmia [19], thus complete PV isolation appears effective in preventing not only paroxysmal (trigger-dependent), but also persistent (substrate and driver-dependent) AFib.

Limitations

This systematic review and meta-analysis is, to our knowledge, the largest cohort evaluating late AAs occurrence in LT patients. However, the study has several limitations.

First, the observational design of the included studies carries an inherent risk of unaccounted confounders. In addition, the included studies defined late arrhythmia occurrence using different time cut-offs (in two studies, late occurrence was defined as any arrhythmia occurrence after hospital discharge; Table 1): if we consider a reasonable cut-off of late occurrence set at 1 month after discharge, this heterogeneity may have inflated the estimate of late AFib, since AFib occurrence in the first postoperative month could be seen as part of the early post-transplantation phase, characterized by high incidence of AA and particularly AFib [2].

Moreover, asymptomatic AFib recurrences may have not been detected since patients were mostly followed by periodic clinical assessment and by tracking hospital and emergency department medical records.

In addition, the lack of patient-level data limited establishing the impact of previous AFib subtype (paroxysmal vs. persistent) and medications on the late incidence of AA and AFib in LT patients, as well as distinguishing the specific characteristics of late arrhythmia occurrence (paroxysmal vs. persistent AFib, atrial tachycardia, typical and atypical atrial flutter).

Conclusion

Late AA occurrence is not infrequent in LT patients, over a median follow-up of nearly three years (IR 4.3%/year); however, late AFib incidence was rare (IR 1.5%/year) and showed a time-dependent decrease, particularly in DLT patients (IR 0.9%/year), suggesting that a complete and transmural PV isolation is effective in strongly decreasing AFib episodes.

Acknowledgments

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Figure Legends

Figure 1. Search strategy flow-chart.

Figure 2. Forest plot for late AA and AFib in a) overall LT and b) DLT patients. AA: atrial arrhythmia; AFib: atrial fibrillation; DLT: double lung transplant; LT: lung transplant.

Figure 3. Forest plot displaying the meta-analytic hazard ratio estimates of the significant predictors of late AFib after LT. AFib: atrial fibrillation; LT: lung transplant.

Tables

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Study	Year	Number of patients	Follow-up (years)	Type of LT transplant (D, double; S, single)	Prevalent aetiology	Time cut-off for “late” arrhythmia occurrence
Dizon et al.	2009	122	1.4	100% D	IPF/ILD (33%)	1 month
See et al.	2009	127	4.2	100% D	CF (64%)	3 months
Lee et al.	2010	327	4.6	61% D; 39% S	COPD (46%)	From hospital discharge
Chaikriangkrai et al.	2015	293	2.3	63% D; 37% S	IPF/ILD (65%)	1 month
Magruder et al.	2016	173	3.1	100% D	IPF/ILD (28%)	From hospital discharge
Hussein et al	2017	755	2.2	61% D; 39% S	IPF/ILD (50%)	6 months
Jesel et al.	2017	271	2.9	82% D; 18% S	COPD (30%)	1 month

CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; IPF/ILF: idiopathic pulmonary fibrosis/interstitial lung disease.

Table 2. Pooled baseline clinical features of the included studies (2,068 patients).

Variable	**Median value (interquartile range)**
Male (%)	58 (48-61)
Age (years)	53 (49-56)
HTN (%)	25 (23-29)
CAD (%)	31 (20-41)
Diabetes (%)	21 (12-29)
Previous history of AFib (%)	6.8 (5.5-7.0)
LVEF (%)	60 (60-60)

CAD: coronary artery disease; HTN: hypertension; LVEF: left ventricular ejection fraction.