Journal of Cardiology 74 (2019) 483–487

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Editorial

Innocent bystander or criminal? Influence of respiratory dysfunction on risk of atrial fibrillation☆

Atrial fibrillation (AF) is a cardiac arrhythmia commonly encountered in clinical practice, and it is strongly associated with an increased risk of stroke, cardiovascular events, and death. Epidemiologic studies have shown risk factors for AF to be advancing age, male sex, hypertension, obesity, diabetes, myocardial infarction, congestive heart failure, and valvular heart disease [1]. Lung disease and/or habitual smoking sometimes coexist with these risk factors. Several epidemiologic studies have identified an association between AF and respiratory dysfunction, shown by reduced forced expiratory volume in 1 s (FEV1) or FEV1/forced vital capacity (FVC). However, whether a true relation exists between respiratory dysfunction and AF remains open to question.

In this issue, Kim et al. [2] describe a large population-based Korean cohort study in which they examined the association between decreased lung function and AF. Their study, which included 9631 individuals who were followed up for approximately 12 years, revealed the following: The prevalence of AF upon enrollment was 0.6% (59 enrollees), and the FEV1% and FVC% predicted values were relatively low in these individuals. New-onset AF occurred in 162 (1.7%) of the enrollees during the follow-up period, and the incidence of new-onset AF was shown, by multivariable analysis, to be significantly associated with relatively low FEV1% predicted values even [adjusted hazard ratio (HR) 1.59; 95% confidence interval (CI) 1.02–2.50]. However, the incidence did not differ significantly between individuals in the lowest FVC% predicted quartile (adjusted HR 1.34; 95% CI 0.86–2.09) and those in the highest FVC% predicted quartile. Moreover, a significant association between FEV1/FVC <0.7 and new-onset AF was not found.

An association between respiratory dysfunction and AF has been investigated in several large cohort studies (Table 1). The oldest study, the Framingham Heart Study ($n = 4731$) [1] showed no association between FEV1 and incident AF over a 38-year follow-up period. The Renfrew/Paisley Study [3] included 15,406 individuals who were followed for a short period (4 years), and although AF patients' baseline FEV1% predicted values were relatively low, FEV1% predicted was not an independent risk factor for incident AF. Patients in the Framingham Heart Study were relatively older (mean age 65 years), the prevalence of myocardial infarction was 13.0% among men and 4.6% among women, and that of valvular heart disease, which differs pathophysiologically from nonvalvular AF, was 7% among men and 9% among women. Among patients in the Renfrew/Paisley study, the prevalence of angina was 31.6% for men and 24.5% for women. It is possible that the strong association between overt cardiac disease-related factors and AF seen in these two early studies obscured the relation between indicators of lung dysfunction and AF. In addition, the Renfrew/Paisley cohort included middle-aged patients (mean age 54 years) who thus might have been at low risk for AF within the short 4-year follow-up period, accounting for the low number of incident AF cases ($n = 19$).

Results of the Kim et al. study [2] agree with those of the more recent cohort studies. In the Cardiovascular Health Study [4] which included 5201 adults $\geq$65 years of age, an independent inverse relation was found between FEV1 and AF during a relatively short follow-up period of 4 years. More recently, among 13,430 Copenhagen City Heart Study [5] participants, who were followed up for 5 years, and the incidence of AF among those with a relatively low FEV1% predicted value was significantly higher than among those with a normal FEV1% predicted value. The relative risk of hospital admission for AF was significantly associated with the degree of FEV1% predicted. The Malmö Preventive Project cohort [6] ($n = 28,744$) comprised equal proportions of smokers and non-smokers, making it well suited for stratified analysis. According to this analysis, reduced FEV1 and FVC were associated with an increased AF risk in both smokers and non-smokers of both sexes. This suggests that the effect of impaired lung function on AF risk is independent of smoking. Advantages of that study were the large cohort, long follow-up of a relatively young population, and control for inflammation as measured by the erythrocyte sedimentation rate. In the Atherosclerosis Risk in Communities (ARIC) study ($n = 15,004$ enrollees) conducted by Li et al. [7], after multivariable adjustment for traditional cardiovascular disease risk factors, increased HRs for AF were seen among persons in the lowest vs. highest FEV1 quartile across the cohort, regardless of sex, race (white vs. black), or smoking status. These large cohort studies covered only Western populations, however. Data pertaining to Asians are scarce. Shibata et al. [8] conducted a cross-sectional study of Japanese patients and reported an association between reduced pulmonary function and AF. A multiethnic study conducted by Chahal et al. [9] revealed an association between relatively low FEV1 values and an increased risk for AF, but only 16.4% of their participants were Asian. Their findings corroborate those of recent cohort studies, and there is strong evidence that impaired lung function independently predicts AF across races,

DOI of original article: https://doi.org/10.1016/j.jjcc.2019.05.014.

https://doi.org/10.1016/j.jjcc.2019.06.009

Table 1
Cohort studies of the relation between respiratory dysfunction and risk of atrial fibrillation: variables and results.

Authors	Journal (year)	Study name Population (country)	Cohort size (enrollment period)	Follow-up time[a]	Mean age	Sex, smoking status, comorbidities (%)	AF documentation	Prevalence of AF (% of total subjects) and risk factors	New-onset AF (approximate %/year) Factors associated with AF after multivariate adjustment
Benjamin et al. [1]	*JAMA* (1994)	Framingham Heart Study Western (USA)	*n* = 4731 (1948)	38 years	65 years (men) 66 years (women)	44.2% males Current smoking 33.7% (men) 23.4% (women) Hypertension 30.9% (men) 40.7% (women) Myocardial infarction 13% (men) 4.6% (women) Valvular disease 6.7% (men) 8.7% (women) Heart failure 3.2% (men) 2.9% (women)	ECGs from biennial clinical visits, hospital records, or outside physician records	N.A.	*n* = 562 (11.9%) (0.31%/year) Age >60 years, diabetes, hypertension, congestive heart failure, and valve disease in both sexes. Myocardial infarction in men. No association between FEV1 and AF risk.
Stewart et al. [3]	*Heart* (2001)	Renfrew/ Paisley Study Western (Scotland)	*n* = 15,406 (1972–1976)	4 years for new-onset AF 20 years for those discharged with a diagnosis of AF	54.1 years (men) 54.5 years (women)	45.8% males Current smoking 81.2% (men) 54.1% (women) Angina 31.6% (men) 24.5% (women) Stroke 1.3% (men) 1.2% (women) TIA 9.8% (men) 9.7% (women) Diabetes 1.3% (men) 1.2% (women)	ECGs from baseline and 4-year follow-up visits AF coded upon hospital discharge or AF listed as cause of death	*n* = 100 (0.65%) Male sex, age, and relatively low adjusted FEV1% predicted	19 (0.2%) of 8532 subjects at 4 years (0.05%/year) Male sex, age, and radiologically determined cardiomegaly No association between adjusted FEV1 and AF risk *n* = 537 (3.5%) discharged from hospital with a diagnosis of AF within 20-year follow-up period (0.19%/year) Radiologically determined cardiomegaly and high systolic blood pressure
Psatey et al. [4]	*Circulation* (1997)	Cardiovascular Health Study Western (USA)	*n* = 5201 (1989–1993)	3.28 years	≥65 years 72.2 years (no CVD) 73.6 years (CVD)	42.3% males Current smoking 11.9% (no CVD) 11.2% (CVD) Hypertension 39.2% (no CVD) 54.5% (CVD) Diabetes 19% (no CVD) 29.6% (CVD) Valvular disease 3.8% (no CVD) 8.0% (CVD)	Annual self-reports, annual ECGs, or hospital discharge diagnoses	N.A.	*n* = 304 (6.3% of 4844 subjects) (1.92%/year) Diuretic use, valvular heart disease, coronary disease, age, high systolic blood pressure, height, glucose, and left atrial dimension β-blocker use, high alcohol intake, cholesterol, and FEV1 were associated with a reduced risk for AF

Table1 (*Continued*)

Authors	Journal (year)	Study name Population (country)	Cohort size (enrollment period)	Follow-up time[a]	Mean age	Sex, smoking status, comorbidities (%)	AF documentation	Prevalence of AF (% of total subjects) and risk factors	New-onset AF (approximate %/year) Factors associated with AF after multivariate adjustment
Buch et al. [5]	*Eur Respir J* (2003)	Copenhagen City Heart Study Western (Denmark)	*n* = 13,430 (1976–1978)	5 for new-onset AF 13 years for AF diagnosis upon hospital admission.	56.5 years (<60% FEV1 predicted) 52.6 years (60–80% FEV1 predicted) 51.4 years (>80% FEV1 predicted)	45.3% males Current smoking 73.0% (<60%FEV1 predicted) 72.8% (60–80% FEV1 predicted) 50.0% (>80% FEV1 predicted) Diabetes 5.3% (<60% FEV1 predicted) 3.6% (60–80% FEV1 predicted) 2.0% (>80% FEV1 predicted)	ECGs from 5-year follow-up visits or AF coded upon hospital admission (by 1990)		62 (0.58%) new-onset AF within 5 years (0.12%/year) FEV1 predicted 60–80% (vs. FEV1 ≥80%) No association between FEV1/FVC and AF risk *n* = 290 (2.20%) diagnosed upon hospitalization within 13 years (0.17%/year) FEV1 predicted 60–80% and FEV1 <60% (vs. FEV1 >80%)
Johnson et al. [6]	*Europace* (2013)	Malmö Preventive Project Western (Sweden)	*n* = 28,744 (1974–1992)	24.8 years	44.6 years (total) 43.5 years (men) 47.7 years (women)	73.3% males Current smoking 49% (men) 45% (women) Systolic blood pressure 127 mmHg (men) 123 mmHg (women)	Swedish Hospital Discharge Register	N.A.	*n* = 2669 hospitalized for AF (9.3%) (0.37%/year) FEV1 inversely related to incidence of AF for both sexes
Li et al. [7]	*Circulation* (2014)	Atherosclerosis Risk in Communities (ARIC) Study Western (USA)	*n* = 15,004 (1987–1989)	17.5 years	54 years	44.9% males Current smoking 25.8% Heart failure 4.7% Coronary heart disease 4.7%	AF coded upon hospital discharge or death certificate or ECGs from triennial follow-up visits	N.A.	*n* = 691 (11.3%) (0.65%/year) Lowest FEV1 quartile of (vs. highest FEV1 quartile) for both white and black women and men FEV1/FVC <0.70 (vs. FEV1/FVC ≥70) FEV1 <80% predicted (vs. FEV1 ≥80%)
Shibata et al. [8]	*Int J Med Sci* (2011)	Community-based annual health check study Asian (Japan)	*n* = 2917 (2004–2005)	N.A.	62.7 years	45.4% males HT medication 33.7%	Baseline ECGs	*n* = 43 (1.5%) FEV1 predicted FVC % predicted	
Chahal et al. [9]	*Am J Cardiol* (2015)	Multi-Ethnic Study of Atherosclerosis (MESA) Western (6.4% Chinese)	*n* = 3811 (2004–2006)	4.1 years	64.5 years	49.4% males Ever-smoking 54.7% Use of anti-hypertensive drugs 34.4% Diabetes 15.0%	Hospital admission for AF or atrial flutter		149 subjects (3.8%) admission due to AF (0.93%/year). Relatively low FEV1 and FVC

Table1 (*Continued*)

Authors	Journal (year)	Study name Population (country)	Cohort size (enrollment period)	Follow-up time[a]	Mean age	Sex, smoking status, comorbidities (%)	AF documentation	Prevalence of AF (% of total subjects) and risk factors	New-onset AF (approximate %/year) Factors associated with AF after multivariate adjustment
Kim et al. [2]	*J Cardiol* (2019)	Ansung-Ansan cohort Asian (Korea)	*n* = 9631 (2001–2002)	12 years	50 years (median)	48.1% males Current smoking 26% Hypertension 15.4% Diabetes 6.7% Heat failure 0.2% CAD 0.8% MI 1.0% CVD 1.1% COPD 0.6%	Baseline ECGs, ECGs from biennial follow-up visits, and/or self-reported history of outside physician-determined diagnosis	*n* = 59 (0.6%) FEV1% predicted FVC% predicted	*n* = 162 (1.7%) with new-onset AF 0.14%/year Lowest FEV1% predicted quartiles (vs. highest quartiles).

AF, atrial fibrillation; CAD, coronary artery disease; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HT, hypertension; MI, myocardial infarction; N.A., not available.
[a] Mean follow-up time is shown unless otherwise indicated.

despite a lower incidence of AF in Asian cohorts than that in Western cohorts.

Mechanisms underlying the association between reduced lung function and AF have been postulated. Ectopic beats initiating AF often originate in the pulmonary veins, and this can be triggered by hypoxia or pulmonary hypertension [10]. Another possibility is that common risk factors, such as smoking and systemic inflammation, and/or comorbidities, such as hypertension and heart failure, underlie the reduced lung function and coronary heart disease. Reduced lung function has been associated with hypertension, and reportedly, the cardiovascular risk is substantially increased if low FEV1 is combined with hypertension [11]. Reduced lung function in patients with COPD has been shown to be related to adverse cardiac remodeling and an increased prevalence of ischemic heart disease [12]. Kim et al. indicated that smoking, hypertension, ischemic heart disease, and COPD were more prevalent among individuals in the lowest predicted FEV1% quartile than among those in the other quartiles. However, the prevalence of these comorbidities in the cohort reported by Kim et al. was much lower than in the other reported cohorts, and the relation between FEV1 and AF was unchanged after adjustment for several cardiovascular risk factors. Therefore, the effect of the noted comorbidities on AF risk may be small. Kim et al. also discussed the potential influence of smoking on the risk of AF. Although a consistent association between cigarette smoking and the incidence of AF was not found in previous studies, a meta-analysis confirmed an independent association between them [13]. A Malmö Preventive Project sub-analysis identified a significant relation between smoking and the incidence of AF [6]. Kim et al. included smoking status in their multivariate model, and the association between reduced lung function and the risk of AF persisted. This suggests that smoking is a factor that influences the association between reduced lung function and risk of AF without fully accounting for the respiratory dysfunction associated with the risk of AF. The cohort reported by Kim et al. included a large number of never-smokers, and if the authors had performed a sub-analysis that involved only the never-smokers, the influence of smoking on AF risk could have been controlled for. Inflammation is a key pathogenic process, not only with respect to respiratory dysfunction but also with respect to the development (and persistence) of AF. Kim et al. found a modest association between white blood cell counts and C-reactive protein levels and reduced lung function. Unfortunately, those variables were not entered into the multivariate model, so it remains unclear whether those factors weaken the strong association between reduced lung function and AF. The path leading from reduced lung function to AF might be multifactorial, and therefore, further studies are needed to clarify the mechanisms involved in the association between respiratory dysfunction and AF.

Kim et al. [2] should be congratulated for providing us with data from a large population-based cohort study substantiating strong association between reduced lung function and new-onset AF in Asians. Their study on the association between respiratory dysfunction and the incidence of AF has a number of strengths: their cohort comprised healthy middle-aged individuals, which means that the study could be conducted as a simple, straightforward study not requiring the factoring in of mortality, and the possible interactive effects of comorbidities was minimized; enrollees were monitored for AF rather intensively (biennially on the basis of electrocardiograms and/or self-reports of physician-determined diagnosis between follow-up visits); and the cohort represented the largest population of Asians studied thus far over a fairly long follow-up period. Results of the Kim et al. study are important not only because of the epidemiological data produced but also because the authors provide insight into the mechanistic

relation between respiratory dysfunction and AF risk in an Asian population.

References

[1] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840–4.

[2] Kim J, Park JY, Lee Y, Shin JH, Lim YH, Park HC, et al. The relationship between decreased pulmonary function and atrial fibrillation in general population: findings from Ansung-Ansan cohort of the Korean Genome and Epidemiology Study. J Cardiol 2019;74:488–93.

[3] Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001;86:516–21.

[4] Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455–61.

[5] Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003;21:1012–6.

[6] Johnson LS, Juhlin T, Engström G, Nilsson PM. Reduced forced expiratory volume is associated with increased incidence of atrial fibrillation: the Malmö Preventive Project. Europace 2014;16:182–8.

[7] Li J, Agarwal SK, Alonso A, Blecker S, Chamberlain AM, London SJ, et al. Airflow obstruction, lung function, and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2014;129:971–80.

[8] Shibata Y, Watanabe T, Osaka D, Abe S, Inoue S, Tokairin Y, et al. Impairment of pulmonary function is an independent risk factor for atrial fibrillation: the Takahata study. Int J Med Sci 2011;8:514–22.

[9] Chahal H, Heckbert SR, Barr RG, Bluemke DA, Jain A, Habibi M, et al. Ability of reduced lung function to predict development of atrial fibrillation in persons aged 45 to 84 years (from the Multi-Ethnic Study of Atherosclerosis-Lung Study). Am J Cardiol 2015;115:1700–4.

[10] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

[11] Engström G, Hedblad B, Valind S, Janzon L. Increased incidence of myocardial infarction and stroke in hypertensive men with reduced lung function. J Hypertens 2001;19:295–301.

[12] Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, et al. Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2003;158:1171–81.

[13] Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies. Int J Cardiol 2016;218:259–66.

Yasuo Okumura (MD, PhD, FJCC)*
Koichi Nagashima (MD, PhD)
Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

*Corresponding author at: Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Ohyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan
E-mail address: okumura.yasuo@nihon-u.ac.jp (Y. Okumura).

24 June 2019
Available online 26 July 2019