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Short communication

The association between pulmonary hypertension and stroke: A systematic review and meta-analysis

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ABSTRACT

Background: Pulmonary hypertension is associated with atrial fibrillation and paradoxical embolism. Yet, the association between pulmonary hypertension and stroke has not been well studied.
Methods: We reviewed Medline and Embase from inception to December 1, 2018, to identify observational studies reporting prevalence of stroke in adult patients with pulmonary hypertension. We sought studies that included patients with pulmonary hypertension secondary to any etiology except left heart failure, and excluded studies that reported rates of perioperative stroke. We conducted random effects meta-analyses to obtain pooled prevalence of stroke in patients with pulmonary hypertension, and pooled unadjusted odds ratio of stroke in patients with pulmonary hypertension compared to those without.
Results: We included 14 studies including 32,523 participants of which 2976 (9.2%) had pulmonary hypertension, and 727 (2.2%) had a stroke. The pooled prevalence of stroke in patients with pulmonary hypertension was 8.0% [95% confidence interval (CI), 5.1%–10.9%, I^2 91.9]. The pooled unadjusted odds ratio of stroke in patients with pulmonary hypertension compared to those without was 1.46 (95% CI, 1.07–1.99, I^2 55.6, $n = 7$ studies).
Conclusion: Stroke is a major non-cardiac morbidity in patients with pulmonary hypertension, requiring further evaluation to determine its etiology, and measures to reduce its risk.

1. Introduction

Pulmonary hypertension is associated with up to 15,000 deaths annually in the United States, though the true prevalence of this condition is unclear [1]. A recent systematic review found that even mild pulmonary hypertension, defined as mean pulmonary artery pressure between 19 and 24 mmHg, has been associated with an increased risk of mortality [risk ratio, 1.52; 95% confidence interval (CI), 1.32–1.74; $I^2 = 47$] [2]. Recent advances in the treatment and management of pulmonary hypertension has led to increased survival of these individuals putting them at risk of developing age- and disease-related comorbidities, the latter leading to lower quality of life [3,4].

Pulmonary hypertension can result from primary pulmonary arterial pathology or due to a variety of secondary causes. Regardless of the underlying etiology, pulmonary hypertension leads to high pulmonary pressures that is associated with a higher risk of paradoxical embolism, atrial fibrillation, and cerebral venous congestion – each of which are independent risk factors of stroke [5,6]. Case reports of stroke due to paradoxical embolus in patients with pulmonary hypertension have been previously published [7]; however, to our knowledge, the burden of stroke in this population has not been well studied. Stroke is considered one of the leading causes of disability world-wide, and is associated with both higher health care needs and health care costs [8]. Therefore, understanding the burden of stroke in patients with pulmonary hypertension, a patient population known to have high health care needs, is imperative. We systematically appraised the literature and planned a meta-analysis in accordance with MOOSE (meta-analyses and systematic review of observational studies) guidelines to determine the association between pulmonary hypertension and stroke [9].

2. Methods

We searched Medline and Embase from inception to December 1, 2018 for articles of interest using both indexed and free-text search terms. Our population of interest were adult patients with a known diagnosis of pulmonary hypertension due to any etiology except systolic or diastolic heart failure or perioperative patients. The outcome of interest was stroke of any etiology. We included studies published in English language that were either cohort or case-control designs, and excluded case reports.

Two independent reviewers selected articles that met study eligibility criteria after full-text review. We abstracted the following data: study characteristics (year of publication, study design and location), and patient characteristics (number of patients with

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pulmonary hypertension, number of patients with stroke, average age of patients with pulmonary hypertension and stroke).

We evaluated the quality of included studies based on pre-specified factors: well-conducted study design and sampling; exclusion of patients with prior stroke; appropriate method of stroke assessment (neuroimaging or clinical evaluation); reporting of the type of stroke (ischemic or hemorrhagic); accounting for other risk factors that can lead to stroke (matching or regression methods); and appropriate method for pulmonary hypertension assessment (measurement of mean pulmonary artery pressure). We used this information to create a risk of bias chart similar to the Cochrane Handbook risk of bias tool [10].

2.1. Statistical analysis

We performed random effects meta-analyses using the '*metaprop*' routine in STATA to obtain overall pooled prevalence of stroke in patients with pulmonary hypertension, and reported it by disease specific subgroups [11]. We performed meta-regression to asses if the prevalence of stroke in patients with pulmonary hypertension changed over the years. We also calculated a pooled unadjusted odds ratio of stroke in patients with pulmonary hypertension compared to those without using data from the studies that reported number of stroke patients in both groups. To look for publication bias, we created a funnel plot [12]. All data analysis was performed using StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

3. Results

We reviewed 9750 unique titles, and selected 14 articles in the final review that included 32,523 patients, 2976 (9.2%) patients with pulmonary hypertension, and 727 (2.2%) with stroke. Most of these were retrospective cohort studies, had patients with various disease groups, and were conducted in various countries (Table 1). The weighted average age of patients with pulmonary hypertension and stroke was 52.2 years (standard deviation = 11.5). The included studies had high risk of bias for not excluding patients with prior stroke or accounting for vascular risk factors associated with stroke and thus were considered of overall low quality (risk of bias graph – e-Fig. 1).

The overall pooled prevalence of stroke in patients with pulmonary hypertension was 8.0% [95% CI, 5.1%–10.9%, $I^2 = 91.9$], and this did not change over time ($P = 0.19$). The prevalence of stroke was higher in patients with pulmonary hypertension with co-existent chronic obstructive pulmonary disease, chronic kidney disease, or sickle cell disease (Fig. 1). The pooled unadjusted odds ratio of stroke in patients with pulmonary hypertension compared to those without pulmonary hypertension was 1.46 (95% CI, 1.07–1.99, I^2 55.6, $n = 7$ studies). However, disease specific subgroup analyses could not be performed due to small numbers in each subgroup. We found no evidence of publication bias based on our analysis (funnel plot – e-Fig. 2).

4. Discussion

We found that up to 1 in 13 patients with pulmonary hypertension had a stroke, and that pulmonary hypertension was independently associated with 1.5 times higher odds of stroke, suggesting it to be a major non-cardiac comorbidity in these patients. To put this context, prevalence of stroke in patients with infective endocarditis – a well-established risk factor for stroke – has been estimated to be between 10 and 20% [13,14]. The higher prevalence of stroke in patients with pulmonary hypertension with co-existent chronic kidney disease, sickle cell disease, or COPD suggests a possible additive role of pulmonary hypertension to increase the risk of stroke in these patient populations already at a higher risk of stroke.

As per the American Heart Association (AHA) guidelines, primary prevention of stroke with antiplatelets drugs should be considered in patients who are at a high risk of stroke (10-year risk >10%) (class IIa; Level of evidence A) [15]. Our findings raise the question whether primary prevention with antiplatelet drugs should be considered in all patients with pulmonary hypertension. Furthermore, guidelines on secondary prevention of stroke in patients with pulmonary hypertension are unclear. New guidelines on surgical closure of patent foramen ovale for stroke prevention raise challenges for secondary stroke prevention in patients with pulmonary hypertension who are young and often dependent on offloading the right ventricle by these functioning shunts in whom surgical closure may not be advisable [16].

Our study has limitations because stroke was not a primary outcome of interest in the included studies, the etiology of stroke was not described, and these studies did not exclude patients with prior stroke, nor did they adjust for vascular risk factors such as atrial fibrillation. Furthermore, varying disease groups were included in the final studies, and all of them have been independently associated with higher risk of stroke [17]. Yet, the pooled unadjusted odds ratio suggests that pulmonary hypertension may additionally increase the risk of stroke, even in patients already at risk of stroke due to the underlying disease.

The burden of stroke in patients with pulmonary hypertension will continue to rise as their life expectancy improves with the advent of new therapies [1]. Our results suggest the need for well-designed

Table 1
Characteristics of the included studies by the disease group of interest.

Study	Year	Design	Setting	Country	Total sample size	Mean age in years	PH patients with stroke, n/N	non-PH patients with stroke, n/N
Sickle cell disease								
Akgül et al. (e-1)	2007	Cohort	Single center	Turkey	87	21.1	4/33	4/54
De Castro et al. (e-2)	2008	Cohort	Single center	US	125	46.5	4/42	13/83
Congenital heart disease								
Daliento et al. (e-3)	1998	Cohort	Multicenter	Italy & England	188	33.0	15/188	n.r.
Niwa et al. (e-4)	1999	Cohort	Single center	US	77	n.r.	0/77	n.r.
Giannakoulas et al. (e-5)	2017	Cohort	Multicenter	Greece	2086	41.8	3/52	n.r.
Nir et al. (e-7)	2017	Cohort	Single center	Israel	32	42.6	5/32	n.r.
Hoffmann et al. (e-8)	2010	Cohort	Multicenter	Europe & Canada	23,153	n.r.	24/467	434/22,686
Primary pulmonary hypertension								
Okada et al. (e-9)	1998	Cohort	Multicenter	Japan	223	28.4	2/223	n.r.
Galo de Moraes et al. (e-10)	2016	Cohort	Single center	US	155	53.9	2/155	n.r.
Rådegran et al. (e-11)	2016	Cohort	Multicenter	Sweden	457	67.0	28/457	n.r.
Chronic obstructive pulmonary disease								
Orea-Tejeda et al. (e-12)	2017	Case control	Single center	Mexico	162	n.r.	25/91	10/71
Chronic kidney disease								
Li et al. (e-13)	2014	Cohort	Single center	China	2351	59.6	56/426	209/1925
Navaneethan et al. (e-14)	2014	Cohort	Multicenter	US	2959	63.2	84/625	240/2334
Bolignano et al. (e-15)	2015	Cohort	Multicenter	Italy & Germany	468	71.0	10/108	31/360

Abbreviations: n.r. – not reported; PH - pulmonary hypertension; US – United States.

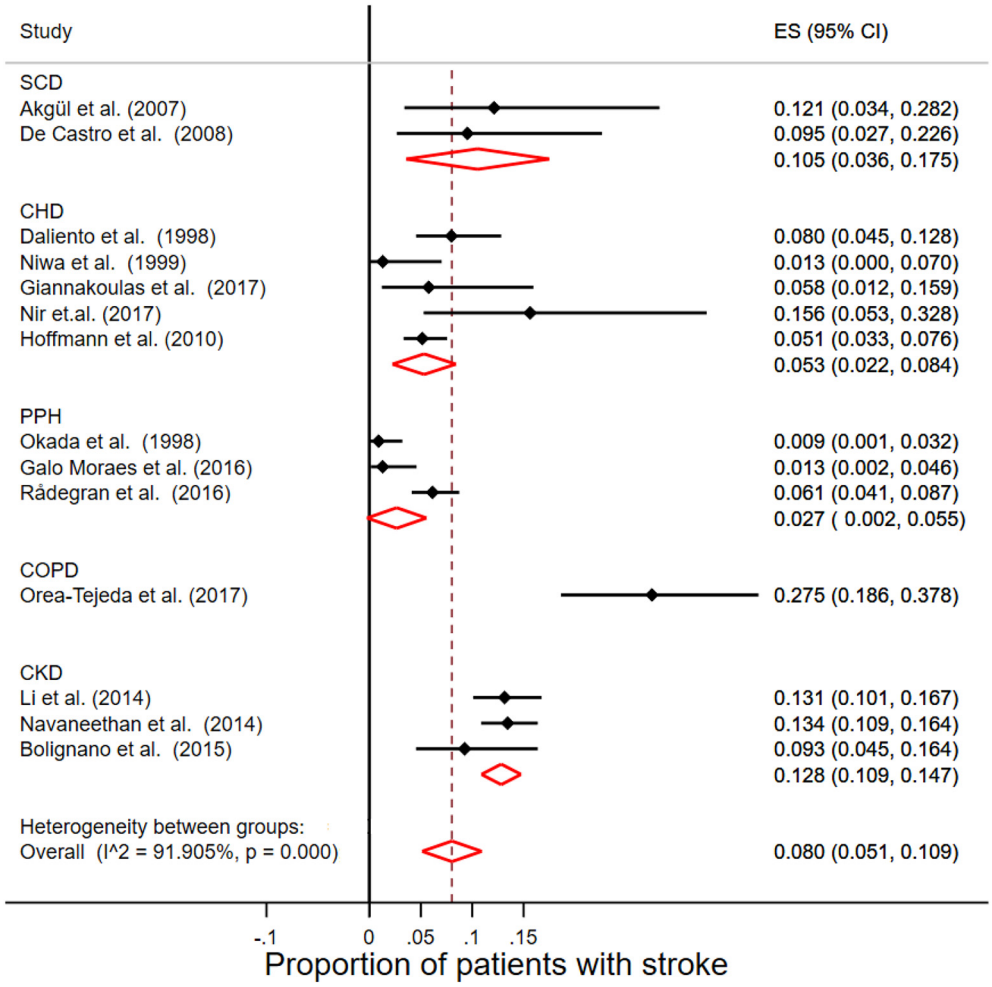

Fig. 1. Results of meta-analysis of observational studies on the association between pulmonary hypertension and stroke. Abbreviations: CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CHD – congenital heart disease; PPH – primary pulmonary hypertension; ES, effect size, refers to the prevalence of stroke in patients with pulmonary hypertension.

prospective studies to ascertain the incidence and etiology of stroke in patients with pulmonary hypertension, and measures to prevent it.

Author contributions

TGS and MVV were responsible for study conception, design of the study, data acquisition, and analysis and interpretation of results. JMS was responsible for data acquisition and interpretation of results. TGS wrote the manuscript that was reviewed and revised by JMS and MVV.

Author disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.085.

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