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Global research trends in the medical therapy of pulmonary arterial hypertension 2000–2014

Catharina Schreiber [a, d, *], Christoph Edlinger [b], Sarah Eder [b], Mathias Ausserwinkler [b], Bernhard Wernly [b], Ingrid Pretsch [b], Christian Jung [c], Uta C. Hoppe [b], Michael Lichtenauer [b]

[a] Clinic for Cardiac Surgery, Paracelsus Medical University of Salzburg, Austria
[b] Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Austria
[c] Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Duesseldorf, Germany
[d] Clinic for Internal Medicine II, Department of Cardiology, Medical University Vienna, Austria

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ABSTRACT

Background: Pulmonary arterial hypertension is a progressive disease of the pulmonary vasculature that affects more than 200.000 patients worldwide. Without medical treatment it leads to right heart failure and death. Extensive fundamental and clinical research has been performed throughout the globe to modify the disease and improve survival.
Methods: We performed a bibliometric study on medical treatment for pulmonary arterial hypertension to identify study characteristics, impact factors and the countries of origin of basic and clinical studies that were published between 2000 and 2014. For visualization of the obtained data density equalizing maps were prepared.
Results: A total of 681 studies were eligible, of these 56% were clinical studies that have included a total of 30960 patients. Most studies were performed on endothelin receptor antagonists, followed by prostacyclins and phosphodiesterase type 5 inhibitors. Impact factors did not differ between clinical and basic science studies. The United States for clinical studies, and China for basic science studies were identified as main contributors to the global scientific output.
Conclusions: This first bibliometric study in the field of pulmonary arterial hypertension shows that a significant amount of scientific research was performed within the last 14 years mainly in North America, Asia and Europe. As current trends in this field of research we identified combination therapies and Asian countries being a new hatchery for emerging experimental and clinical studies.

1. Background

Pulmonary Hypertension (PH) is a rare heterogenic disease entity accumulating significant morbidity and mortality among approximately 200.000 patients around the world [1–3]. Among the five WHO classes of PH, class I comprises patients with idiopathic, hereditary, drug induced or associated (connective tissue disease, HIV, congenital heart disease and schistosomiasis) pulmonary *arterial* hypertension (PAH) [4–7]. Whereas in WHO classes II to V therapy of the underlying organ or systemic disease is crucial, for PAH patients the therapeutic options are limited. Since the first pathologic description of PH by Ernst von Romberg in 1891, an enormous knowledge has been gathered [8].

The non-specific medical therapy consists of diuretics, anticoagulants and in a minor subset of patients, if vaso-reactive, calcium channel blockers [9]. The majority of patients needs a specific PAH therapy that interacts with one of the three selective pathways [5,10–12]. The first pathway is the prostacyclin pathway. Epoprostenol, given intravenously in 1984, was the first substance of this group [13]. Subsequent development gave birth to further

Abbreviations: BORG, Rating of Perceived Exertion Scale; DBF, DataBase File, file format used by database software; ERA, Endothelin Receptor Antagonist; EU, European Union; HIV, Human Immunodeficiency Virus; PAH, Pulmonary Arterial Hypertension; PDE5, Phosphodiesterase type 5; PH, Pulmonary Hypertension; U.S./USA, United States of America; WHO, World Health Organization.

* Corresponding author. Paracelsus Medical University Salzburg, Department of Cardiac Surgery, Muellner Hauptstraße 48, 5020 Salzburg, Austria.
E-mail addresses: catharina.schreiber@gmx.net, c.schreiber@salk.at (C. Schreiber).

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prostacyclin receptor agonists that can be given either per inhalation (iloprost), subcutaneous (treprostinil), or oral (beraprost, selexipag) [14–19]. The second pathway is the nitric oxide pathway. The first successful use of a selective phosphodiesterase 5 inhibitor was reported in a rat model of monocrotaline-induced pulmonary hypertension in 1996 by a japanese group [20,21]. Since the approval of sildenafil for human PAH in 2005 many studies have shown a significant benefit for the PAH patient [22–24]. New drug formulations (tadalafil, vardenafil) promise less adverse effect and longer half time [25,26]. Recently, a new substance (riociguat) that acts downstream in the nitric oxide pathway was approved [27]. The third pathway is inhibition of endothelin-mediated vasoconstriction. First *in vivo* use of a non selective endothelin receptor blocker (ERA) is documented in a hypoxia rat model by a group in France in 1995 [28]. At the beginning given intravenously, today bosentan, macitentan and the receptor-type A selective successor (ambrisentan) are orally administered and have a leading role in PAH therapy [29–32]. Prior therapeutic concepts considered monotherapy of one of the above mentioned drugs, recent clinical trials focus on combination therapies [33–36]. Experimental and clinical research efforts of the last 30 years have improved the median survival of PAH patients, from 2.8 to 5 years [3,37,38]. With the actual therapy concepts the disease progression is significantly decelerated, but survival rates for PAH patients still remain poor.

In our work we sought to dissect research efforts in the field of PAH during the last 14 years and to identify countries that mainly contributed to the development of major therapy concepts and trends for treatment of PAH.

2. Methods

Bibliometric studies focus on the analysis of research productivity, quality and progress of science in a specific field by using publicly available bibliographic databases (e.g., PubMed or Web of Science).

2.1. Data sources

We extracted all data on published studies for medical therapy for PAH from PubMed maintained by the U.S. National Library of Medicine. Information obtained was collected in a Microsoft Excel database with a spreadsheet file for each year including the time period between 2000 and 2014.

2.2. Search strategy

For our systemic search with used the terms *"therapy OR treatment"* which was combined with the Boolean operator *"AND"* with the terms *"pulmonary arterial hypertension*". Data were acquired between June 1st and November 30th 2015.

2.3. Inclusion criteria

Based on the search term *"therapy OR treatment" AND "pulmonary arterial hypertension*" the title and abstract of 4181 retrieved publications were further screened by hand by six experienced researchers in the field of clinical cardiovascular medicine whether the study addressed the effects of a medical therapy on pulmonary arterial hypertension. Basic science studies, studies investigating animal models as well as human trials were incorporated. Reviews, case reports, diagnostic and epidemiological studies, studies that included a surgical intervention (e.g. ECMO support, atrioseptostomy, pacemaker-implantation) or studies that were conducted in pediatric cohorts were excluded from the study. As accessible via the library data base of the Medical University Vienna or the Paracelsus Medical University Salzburg the original manuscript of selected studies was downloaded and the relevant data extracted. For studies that were not fully accessible title and the abstract were used to excerpt data as far as at hand.

2.4. Statistical analysis

Statistical analysis was performed using Microsoft Excel (Version 2010, Redmond, Washington, USA) and GraphPad Prism (GraphPad Software, USA). Impact factors for publications from 2000 to 2014 were obtained from the year of publication of the respective paper from the Isi Web of Knowledge database (Thomson Reuters, New York, USA). Descriptive statistical methods were used and the Mann-Whitney *U*-test was performed calculating significances. Logistic regression analysis was used to calculate r-values. P-values <0.05 were considered statistically significant.

2.5. Density equalizing mapping

The technique of density-equalizing mapping was applied to illustrate the focus of research activity by using a method for territorial resizing. The method is based on the algorithm by Gastner and Newman for density equalizing mapping and has been used by our group in a prior publication [39,40]. In brief, countries are resized with an area according to a particular variable, in our study the number of publications or the impact factor.

To this purpose a DBF-spreadsheet file from the cumulated data was generated using DBF Viewer 2000 (DBF Viewer 2000, HiBase Group, Vancouver, Canada) and transferred to our database. The World Borders Dataset was obtained from http://thematicmapping.org/ under a creative commons license. For the calculation procedure and illustration of the maps ScapeToad Software (Jacques Lévy, Lausanne, Switzerland, http://scapetoad.choros.ch/) was used [41].

3. Results

Our search term revealed 4181 publications as total. After hand expert selection 685 were suitable according to the predefined inclusion criteria (Fig. 1). Of these we had full access to 551 publications (80.4%). In 19.6% of included studies data was extracted from the title and abstract only.

Over the observation period the mean output was 48.9 publications per year with a mean impact factor of 4.7 (±5.9). The graphic presentation shows a logistic increase with minor fluctuations with an r-value of = 0.93 for total publications per year and 0.86 for total impact factor (Fig. 2). 56% of all publications were

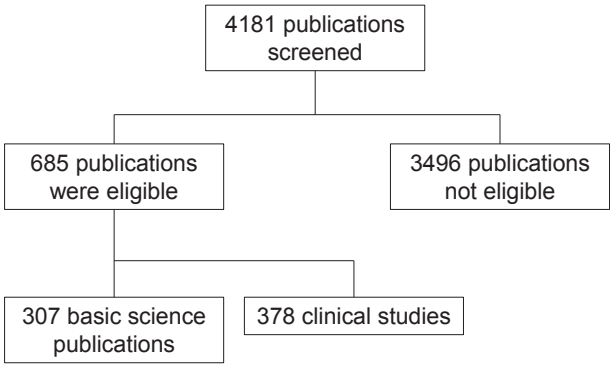

Fig. 1. Flow chart of the study design. 4181 publications were screened, 685 met the inclusion criteria. Basic science and clinical studies were rather equally distributed with a slight advantage for clinical trials (307 vs. 378 publications).

clinical studies with a mean sample size of 84.1 (±139) patients. In total 30960 patients were included into clinical studies and received a medical or placebo therapy for PAH. In 67.1% the route of administration was orally, followed by 13.2% intravenous, 12.9% inhalative and 4.7% for subcutaneous drug delivery. In the majority of publications patients received an ERA (32.1%). Prostacyclin and PDE5 inhibitor therapies were given in 22.6 and 20.0% of publications, respectively. The remaining therapies varied and consisted of calcium channel-blockers, rho-kinase inhibitors, statins, or antihypertensive agents. 47 studies (13.5%) investigated combination therapies in human. Most combined therapies consisted of an ERA and a prostacyclin or PDE5 inhibitor as add-on (n = 26). Triple therapy as add-on or upfront therapy scheme was studied in 5 patient cohorts (1.3%).

Basic science publications had a mean impact factor of 4.7 (±3.6) and were stratified into *in vitro* (21.3%) and *in vivo* experiments. Within these, the rat is the most frequently used animal model (83.2%) followed by mouse models (10.7%) and large animal models such as dogs and pigs that were under investigation in 6.2%. A mean rat cohort for medical intervention therapies in PAH comprises 41.1 (±49.0) rats whereas large animal cohorts were of smaller size (20.0 ± 15.7). Data on included subjects was incomplete in 37.8% of the animal studies. This was not correlated with the corresponding impact factors. As expected, the therapeutic schemes differed broadly between studies. Established specific PAH therapies account for only 12.8% of given medications in animal studies. In contrast to human studies, cell and gene therapies are of encouraging interest in basic science and also anti-hypertensive and anti-proliferative drugs that are often given parenteral are of common use. The analyzed data showed positive study results in 94.8%. This was more pronounced in basic than in clinical science studies (p = 0.014). The population-normalized ratio of patients included into clinical studies was calculated for each continent and reached 35.9 patients per million in North America, 32.6 for the Europe and significantly lower in Asia with 5.1 patients per million.

Regarding topographic diversification, Europe (36.3%), Asia (33.2%) and North America (33.2%) contribute each with nearly one third to the total scientific output on PAH therapy (Fig. 3). The US published a cumulative load of 158 papers during the observation period, followed by China (n = 123) and Germany (n = 59; Fig. 4a). The ranking for cumulative impact factors is in line with the above given publication numbers (Fig. 4b). We found a significant difference in the publication pattern. In clinical studies the US published 85 papers with a mean impact factor of 5.4 (±4.5) (Fig. 4c). China reported 41 clinical studies with a mean impact factor of 3.8 (±4.2)

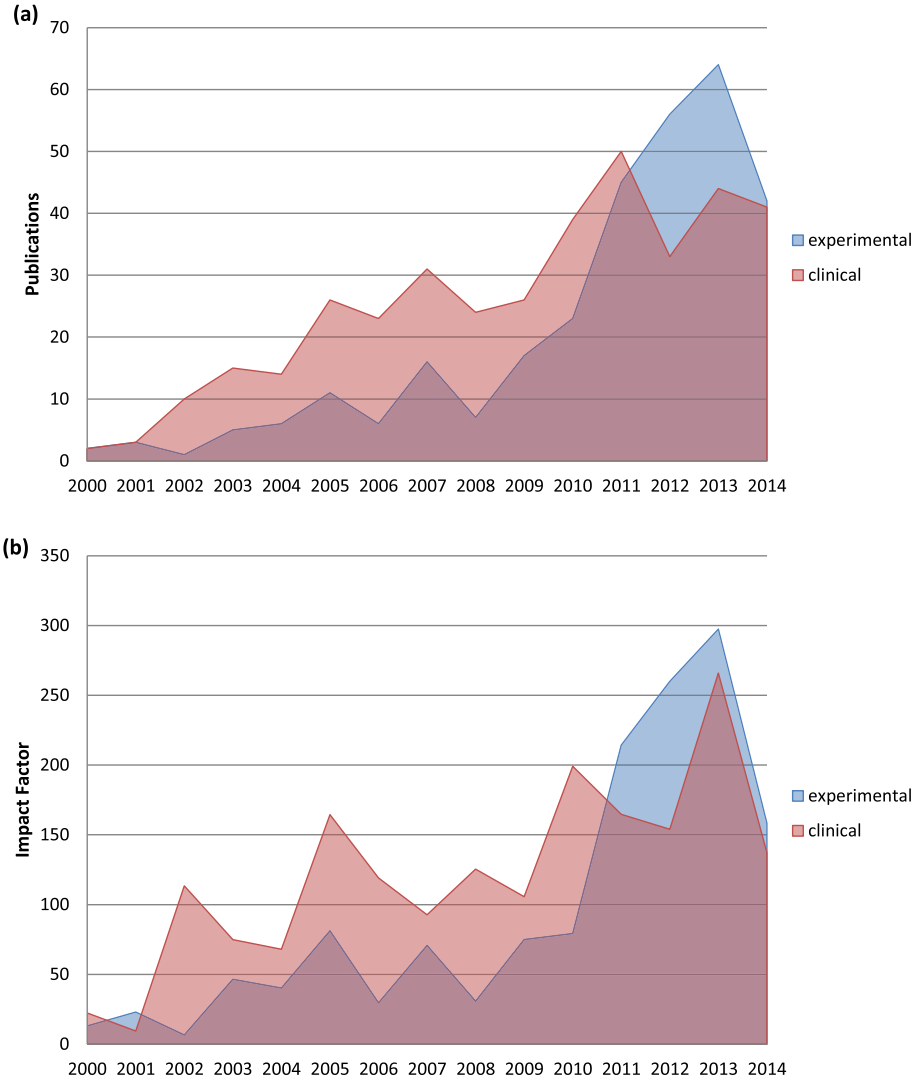

Fig. 2. The number and the impact of publications tended to increase over the years (a,b). The mean impact of clinical publications peaked in 2013.

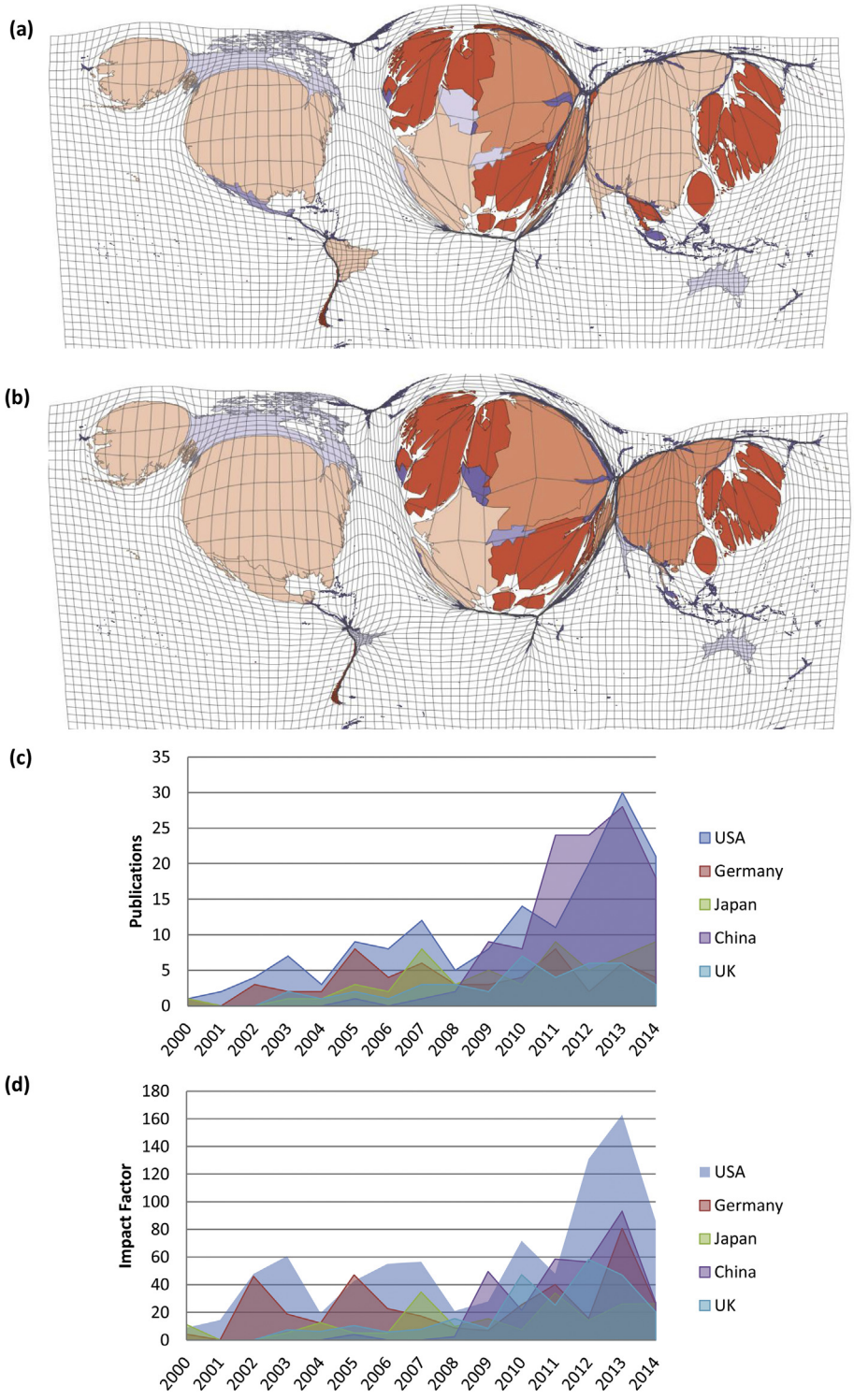

Fig. 3. Density equalizing map of total publications (a) and summarized impact factors (b) from 2000 to 2014. The research output was rather equally distributed between continents except for Africa. China showed a massive increase in publication numbers over the last few years (c,d), however, the US is still the leading country in the field.

points, which was significantly lower compared to the US ($p = 0.003$). Germany, in terms of number of publications was ranked third worldwide and first in Europe with 36 clinical studies that yielded a mean impact factor of 5.0 (±5.4). In Europe, a significant amount of clinical studies also came from Italy ($n = 28$) and France ($n = 21$) that globally seen reached the highest impact factors for their clinical studies (7.2 (±9.0) and 6.3 (±3.2)). In basic science publications China was ranked first with 82 publications with a mean impact factor of 2.4 (±2.0). The US followed closely with 73 studies, but with a better mean impact factor of 5.8 (±3.8) ($p = 0.001$). In the third place was Japan with a total of 36 articles and a mean impact factor of 3.6 (±2.8). The UK published 19 studies in the observation time with a remarkable impact factor of 10.1 (±11.5) that was significantly better than the US ($p = 0.04$).

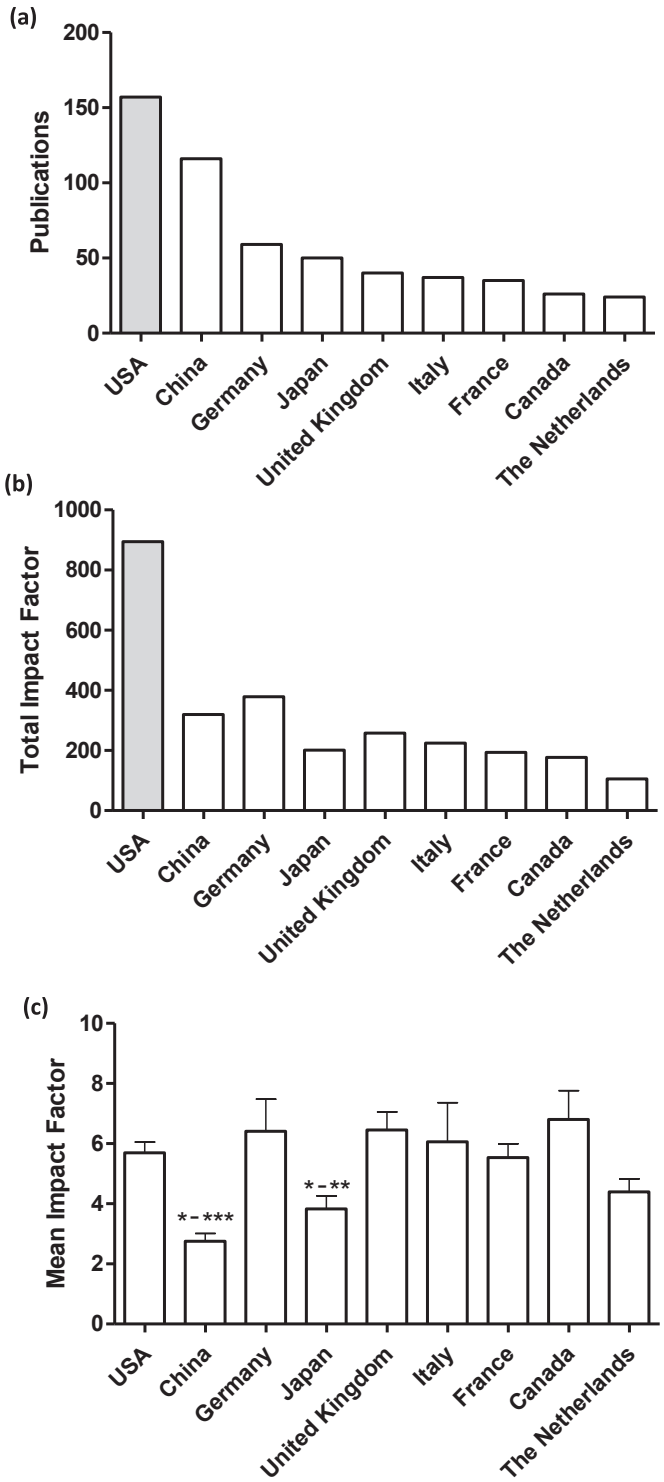

Fig. 4. Total number of publications, summarized and mean impact factor for the leading nations in PAH research. The US was the leading country in terms of publication numbers and impact factor. Chinese and Japanese publications were published in journals with less impact.

3.1. Conclusion

On first sight the number of publications has mushroomed since the turn of the millennium and shows an undulating time line with strong ascent over the last years. This correlates with publication of multi-center randomized controlled trials and approval of respective drugs and the world meetings on PH (2003, 2008 and 2013). The ratio between experimental and clinical studies was slightly in favor of clinical studies. A possible explanation is that only medical interventional studies were included, though a huge number of basic research studies, investigating genetic or enzymatic interactions or pathways were excluded. Surprisingly, the mean impact factor for experimental publications was not lower than that for clinical papers. This emphasizes the attempt of understanding pathophysiologic concepts to develop a curative treatment for a disease that has a rather short medical history.

This expectancy is also mirrored in the striking high number of studies reporting a positive study result. More than 90% of included studies reported efficacy of the investigated agent. In clinical studies only 7.2% failed to show an improvement for the patient. Naturally, the threshold for translation and further investigation into human is high and the respective medication has to have shown efficacy in many animal studies before, so one would expect a higher success rate for clinical than in basic science studies. Beyond, the high success rate of clinical studies also shows our current medications potency and the psycho-physical benefit for patients that are included in studies and regularly seen on a study schedule. However, published data for the treatment of cardiovascular disease reports a success rate of 8% for randomized controlled trials and therefore substantially differs from data on PAH treatment [42]. In contrast to other cardiovascular diseases the therapeutic options for PAH are limited and it is possible that as empathetic clinicians we define the outcome parameters (e.g. 6 min walking distance, BORG-scale) for our clinical studies not as ambitious as they should be. But also in the laboratory only 3% of the study results were negative. This might reflect a publication bias because a high number of negative studies is kept behind lab doors or rejected by journal reviewers upon submission. In addition, some research fields with a strong commercial interest are driven by selected researchers with proven records. Accordingly, we suspect an existing potential for publication of studies with negative results. Researchers should be encouraged to submit their experimental work with negative study results to renowned journals if they are well conducted and scientifically sound. Publishing negative study results will promote the research efforts and save scientific resources that on long-term benefit the patients.

Independent of full text access, a surprisingly high number of animal studies (38%) did not report at all or did not clearly point out how many study objects were included in different study arms. A correlation with the impact factor was not found, therefore many journals seem to accept experimental work with non-comprehensible data on quantity of study objects. This disagrees with the EU Directive 2010/63/EU that was issued for the protection of animals used for scientific purposes and therefore the *Good Scientific Practice* guideline.

Globally the US, as expected, plays a major role and has traditionally a strong reputation in basic science as well as in clinical studies. Although divided into several smaller countries, Europe is for sure at par with the US in the global field of PAH research. Headed by France, Germany and Italy also smaller countries as Austria and the Netherlands contribute a significant volume of scientific output in meetings and multi-center studies. Close communication between the experts of reference centers throughout Europe results in targeted research efforts and conjoint guidelines.

In 2008 China started to publish results of extensive foundational research projects and numerically caught up with the US but still with lower impact factors. Clinical studies from China are mostly internal works but involvement into international multi-center collaborations has begun [43]. Throughout Asia a mean of 5.1 patients, in North America 35.9 patients per million population

were included into clinical studies. These numbers have to be interpreted carefully as double inclusion or international multicenter enrolment may be overlooked, but these numbers match with the existing epidemiologic data on PAH prevalence [2]. According to this there is still a notable potential for further studies in PAH patients in Asia. The same applies for Australia and South America. Both contribute a small, but because of a different etiology (e.g. schistosomiasis) important patient volume to the field of PAH research. From the African continent no studies have been found in the respective observation period.

4. Conclusion

Although first described more than 150 years ago, the field of PH is an upcoming and prosperous topic in cardiovascular and pulmonary research and is of general global interest. Major scientific research was performed on five out of seven continents with differing publication patterns. Major studies led to a fundamental change in clinical therapy guidelines within the last 14 years. The spectrum of PAH medications shifted from rather simple inhalative vasodilators in the beginning to multimodal intracellular active therapies that are orally available. This comes along with an improved survival as well as an increase in quality of life in PAH patients. Despite huge advances in the understanding and modification of the disease development, the pathogenesis is still not entirely understood and PAH cannot be cured yet. Considering the remarkable increase of publications within the last five years, we are confident that the rise keeps on for the next years until a plateau is reached or a curative medication is found.

Contributions

C.S. planned the study, acquisited, analzyed and interpreted data, wrote the manuscript. C.E. planned the study, acquisited and interpreted data and contributed in manuscript preparation. S.E., M.A., B.W. acquisited study data and revised the manuscript. I.P. and C.J. revised the article critically for the content. U.H. has provided final approval of the article. M.L. planned and coordinated the study, acquisited and analyzed data, prepared figures, contributed in manuscript preparation and final submission.

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