Trends in Literature on Cerebral Bypass Surgery: A Systematic Review

Grüter, Basil E ; Tosic, Lazar ; Voglis, Stefanos ; Vasella, Flavio ; Mutschler, Valentino ; Bichsel, Oliver ; Scherrer, Natalie ; Regli, Luca ; Esposito, Giuseppe

Abstract: INTRODUCTION Ever since the beginning of cerebral bypass surgery, the role of the bypass has been debated and indications have changed over the last 5 decades. This systematic literature research analysed all clinical studies on cerebral bypass that have been published from January 1959 to January 2020 for their year of publication, country of origin, citation index, role of and indication for bypass, bypass technique, revascularized territory, flow capacity, and title (for word cloud analysis per decade). METHODS A systematic literature research was conducted using PubMed, Web of Science, EMBASE, and SCOPUS databases. All studies that have been published until January 1, 2020, were included. RESULTS Of 6,013 identified studies, 2,585 were included in the analysis. Of these, n = 1,734 (67%) studies addressed flow-augmentation bypass and n = 701 (27%) addressed flow-preservation bypass. The most common indication reported for flow augmentation is moyamoya (n = 877, 51%), followed by atherosclerotic steno-occlusive disease (n = 753, 43%). For flow preservation, the most common indication is studies reporting on cerebral aneurysm surgery (n = 659, 94%). The increasing popularity of reporting on these bypass operations almost came to an end with the FDA approval of flow diverters for aneurysm treatment in 2011. Japan is the country with the most bypass studies (cumulatively published 933 articles), followed by the USA (630 articles) and China (232 articles). DISCUSSION/CONCLUSION Clinical studies on cerebral bypass surgery have become increasingly popular in the past decades. Since the introduction of moyamoya as a distinct pathologic entity, Asian countries in particular have a very active community regarding this disease, with an increasing number of articles published every year. Studies on bypass for chronic steno-occlusive disease peaked in the 1980s but have remained the main focus of bypass research, particularly in many European departments. The number of reports published on these bypass operations significantly decreased after the FDA approval of flow diverters for aneurysm treatment in 2011.

DOI: https://doi.org/10.1159/000517415

Grüter, Basil E; Tosic, Lazar; Voglis, Stefanos; Vasella, Flavio; Mutschler, Valentino; Bichsel, Oliver; Scherrer, Natalie; Regli, Luca; Esposito, Giuseppe (2021). Trends in Literature on Cerebral Bypass Surgery: A Systematic Review. Cerebrovascular Diseases:1-12.
DOI: https://doi.org/10.1159/000517415

Cerebrovascular Diseases

Stroke Spectrum

Cerebrovasc Dis
DOI: 10.1159/000517415

Received: February 12, 2021
Accepted: May 14, 2021
Published online: July 21, 2021

Trends in Literature on Cerebral Bypass Surgery: A Systematic Review

Basil E. Grüter[a, b] Lazar Tosic[a, b] Stefanos Voglis[a, b] Flavio Vasella[a, b] Valentino Mutschler[b] Oliver Bichsel[a, b] Natalie Scherrer[b, c] Luca Regli[a, b] Giuseppe Esposito[a, b]

[a]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland; [b]Clinical Neuroscience Center, University Hospital Zurich, Zurich, Switzerland; [c]Neurointensive Care Unit, University Hospital Zurich, Zurich, Switzerland

Keywords
Cerebral bypass · Cerebral revascularization · Extra- to intracranial bypass · Intra- to intracranial bypass · Literature

Abstract
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Both B.E.G. and L.T. contributed equally to the manuscript and should be considered first authors.

karger@karger.com
www.karger.com/ced

Correspondence to:
Basil Erwin Grüter, basil.grueter@ksa.ch

Introduction

Cerebral revascularization surgery can be categorized according to a number of factors. One of the most important distinctions concerns the purpose of the bypass: flow-augmentation versus flow-preservation [1]. Indications for flow-augmentation bypass include moyamoya vasculopathy, chronic steno-occlusive disease, and acute ischaemic stroke. Indications for flow preservation typically include intracranial aneurysm surgery and tumour surgery [2]. Furthermore, bypass surgery is categorized into direct, indirect, and combined procedures. Indirect procedures rely on the overlay of vascularized tissue (i.e., muscle, dura, pericranium, and omentum) onto the cerebral cortex to promote neoangiogenesis over time and achieve a delayed revascularization. By contrast, a direct bypass instantly stimulates blood flow to the brain by direct microvascular anastomosis between a donor artery (or graft interposition, i.e., connected to a donor artery) and an intracranial recipient artery. Combined procedures consist of applying both direct and indirect techniques in the same surgical session. Depending on the choice of the donor artery (extracranial vs. intracranial donor), a direct bypass is further classified into extra- to intracranial (EC-IC) versus intra- to intracranial (IC-IC). As mentioned above, the donor and the recipient artery can be anastomosed with or without graft interposition, depending on the interposition of a vascular graft (arterial or venous). The bypass is generally named after the donor and recipient vessel (i.e., STA-MCA bypass). Lastly, direct bypass procedures are categorized according to the rate of flow (capacity) the bypass can carry: low capacity (<50 mL/min), intermediate (50–100 mL/min), or high capacity (>100 mL/min) [2–4].

On October 30, 1967, Professor Yasargil famously performed the first microsurgical direct flow-augmentation bypass by anastomosing the superficial temporal artery to the middle cerebral artery (STA-MCA) of a 20-year-old man suffering from Marfan's syndrome with left M1 segment occlusion [5–7]. This microsurgical flow-augmentation bypass technique is considered a surgical breakthrough and has remained the most frequently used bypass technique in the treatment of cerebrovascular disease to this day.

Over the past 50 years of intensive bypass research, certain questions have been answered, while others remain open. Different aspects of the bypass procedure have been the focus of publications, and authors have claimed diverse issues to play a leading role at different points in time. This systemic review aims to provide an overview of the entire clinical bypass literature, showing: (1) how the number of new articles increased or decreased according to the evidence-based medicine and the corresponding grade of recommendation on indication, (2) how different countries and continents contributed to the subject, and (3) how the role of and the indication for bypass has differed over time and among countries.

Methods

Search Strategy

A systematic literature research was conducted using PubMed, Web of Science, EMBASE, and SCOPUS databases. All studies available on the corresponding platforms and published before January 1, 2020, were included. Search terms included: "intracranial bypass," "cerebral bypass," "cerebral revascularization," "brain revascularization," "extracranial-intracranial bypass," "extra-to-intracranial bypass," "extracranial intracranial bypass," "ec-ic bypass," "intracranial-intracranial bypass," "intracranial intracranial bypass," "ic-ic bypass," "synangiosis," "superficial temporal artery to middle cerebral artery bypass," "sta-mca bypass," and "sta mca bypass."

Eligibility Criteria

All articles or video articles reporting original research including prospective studies, randomized control trials (RCTs), case series and case reports, and others with an abstract in English on the topic of cerebral bypass were included. Non-original research (such as reviews, opinions, letters to the editor, correspondence, conference papers, and similar articles) and research articles written in a language other than English and without a translated abstract were excluded. Studies on intestinal bypasses ("duodenal," "jejunal," "gastric," or combinations thereof), cardiac bypasses ("cardio" or "coronary"), peripheral vascular bypasses ("femoral," "axillofemoral"), purely extracranial bypasses for revascularization of the subclavian or vertebral arteries (i.e., in the context of aortic arch surgery), and studies on venous bypass were also excluded. Purely educational articles (and video articles) that only illustrate preexisting techniques without an original research component were also excluded. Furthermore, all non-clinical articles such as ex vivo experiments, cadaver studies, and animal experiments were excluded.

Analysed Features

Studies were screened for publication year and country of origin. In case of international collaborations, the country of origin of the last author was considered decisive. The citation index was determined for every article as given by the Web of Science. Publications were dichotomized between flow augmentation and flow preservation. Indications for flow augmentation included moyamoya vasculopathy, chronic steno-occlusive disease, or acute stroke. For chronic steno-occlusive disease, further differentiation was made between chronic ICA stenosis/occlusion, chronic MCA stenosis/occlusion, chronic combined ICA and MCA stenosis/occlusion, vertebrobasilar stenosis/occlusion, and other diseases. Furthermore, low-flow (<50 mL/min, typically superficial temporal artery or occipital artery donor), intermediate-flow (50–100 mL/min, typically arterial grafts), and high-flow (>100 mL/min, typically venous grafts) bypasses were distinguished. In addition, articles were categorized according to direct and indirect bypasses and a combination of both.

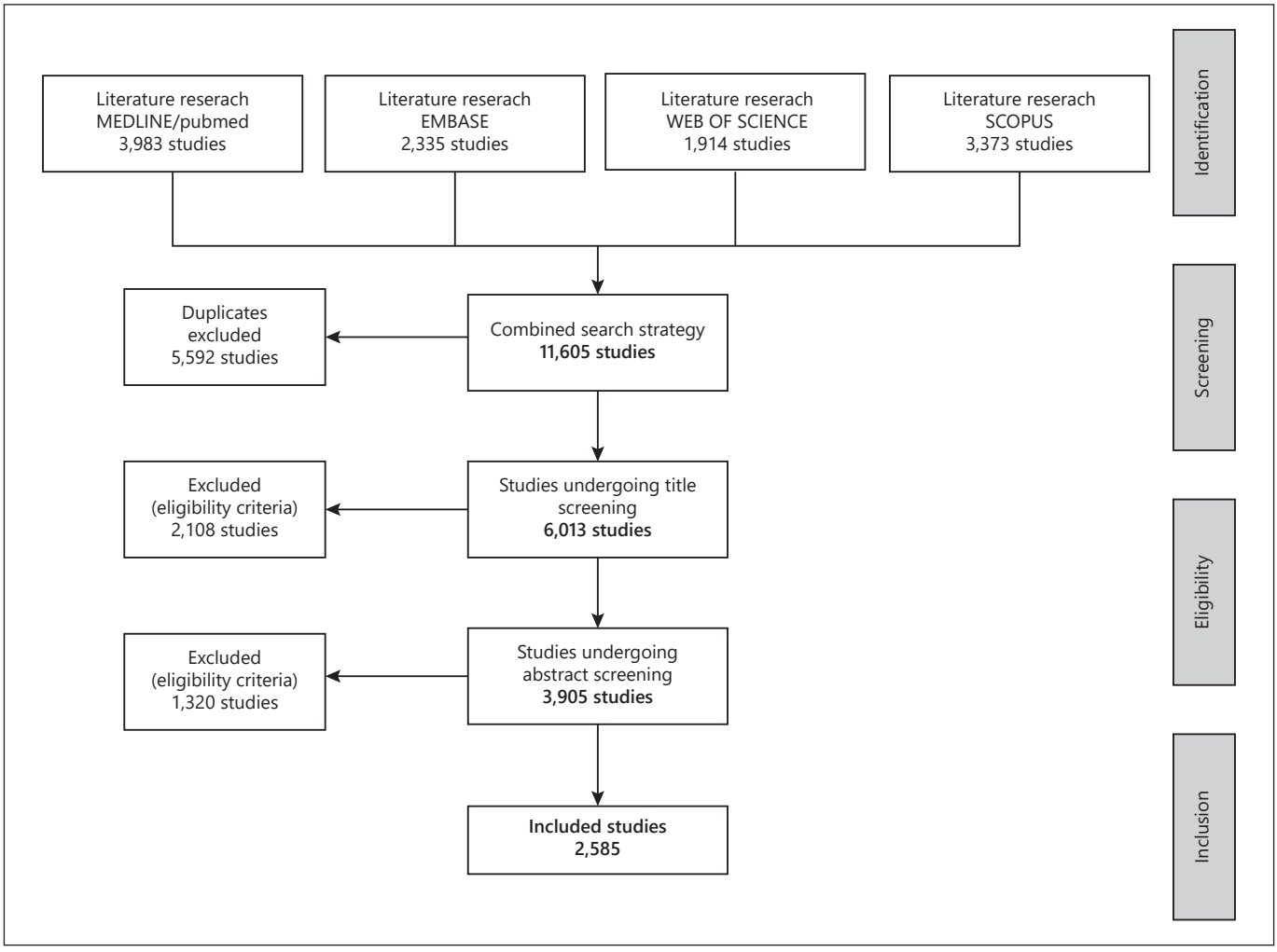

Fig. 1. PRISMA flow chart outlining the screening, exclusion, and inclusion process of studies. After removal of 5,592 duplicates, 6,013 studies were screened. Of these, 2,108 were excluded during title screening and 1,319 during abstract screening. Finally, 2,586 studies were included and analysed. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Lastly, a distinction was made between anterior and vertebrobasilar circulation with regard to the revascularized territory.

Data Analysis and Graphs

Search results from all 4 platforms were merged together and duplicates were excluded with the endnote function (Endnote X9 software for Windows, Clarivate Analytics, Philadelphia, PA, USA). Two authors (B.E.G. and L.T.) independently screened all titles, followed by abstract screening and data extraction (B.E.G., L.T., F.V., S.V., V.M., O.B., and N.S.). Disagreements were discussed to find consensus and the final decision was made by the last author (G.E.). Guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses [8] were strictly followed. Extracted data were analysed in a descriptive way and summarized in graphs. Graphs were drawn with GraphPad Prism, version 8.4.0 for Windows (GraphPad Software, Inc., San Diego, CA, USA). To generate word clouds, words were extracted from all included manuscript titles by excluding common English stop and linking words as well as unspecific terms (e.g., bypass, surgery, surgical, articles, report, disease, and cerebral), and by harmonizing different spellings of the same terms. Tokenization functions were used to find linked terms. For clarity reasons, only the most common 45 key words (which appeared at least 5 times) were plotted. Building and plotting were performed using R version 4.0.2 (R Core Team [2020], R Foundation for Statistical Computing, Vienna, Austria).

Results

Our combined literature research revealed 11,605 studies, of which 5,592 articles were identified as duplicates. Of the remaining 6,013 studies, 2,108 were exclud-

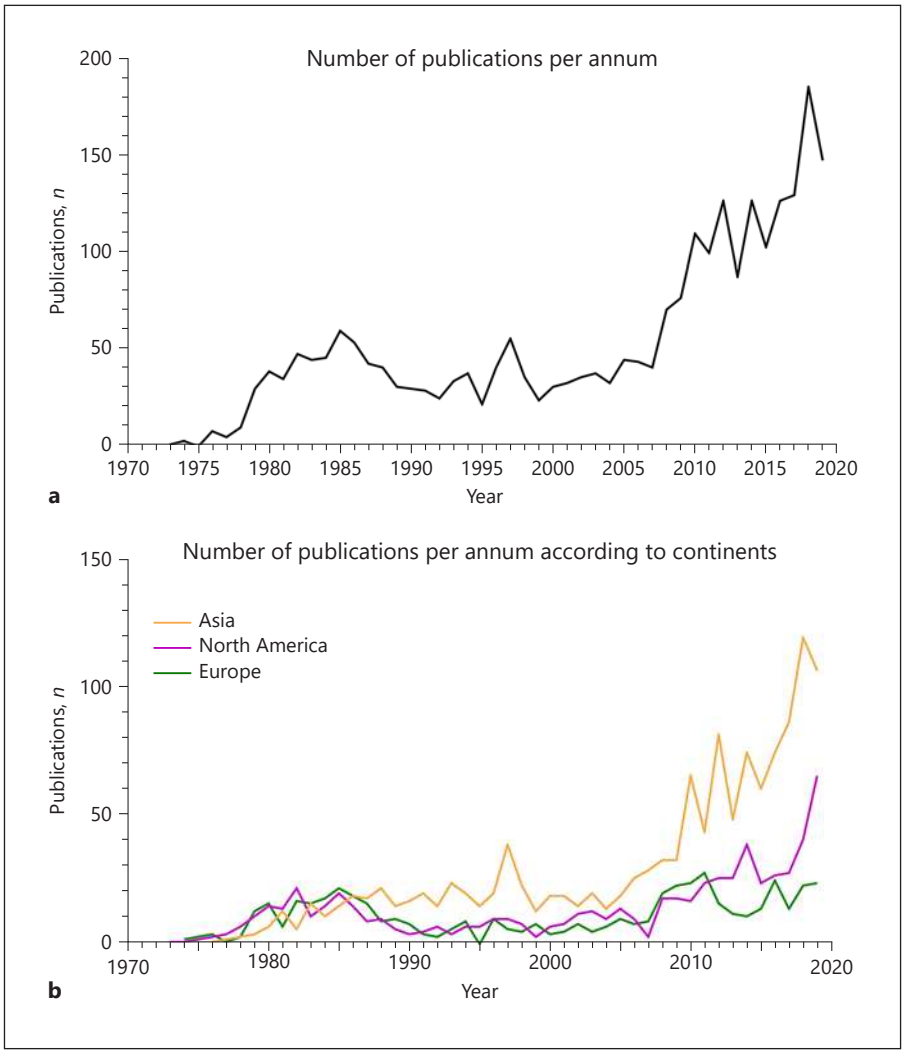

Fig. 2. Number of publications per year and continent. Annual number of publications (**a**) and annual number of publications per continent (**b**).

ed after title screening and 1,320 studies after abstract screening, because they did not meet the eligibility criteria. Finally, 2,585 studies were included for data extraction. The flow chart in Figure 1 shows the numbers of all included and excluded studies.

Since the first studies on bypass procedures were published in 1973, the number of publications has steadily increased until 1985, when it peaked at 60 studies/year for the first time (Fig. 2a). Overall, Europe was the biggest contributor during these years, closely followed by North America (Fig. 2b). After that, the global number of publications decreased to as little as 22 studies/year in 1995. The number of articles originating from Europe and North America in particular decreased drastically between 1985 and 1995. In contrast, research from Asian countries increased, surpassing the other continents for the first time in 1987 and every year since. A second short publication peak was reached in 1997, with 56 publications/year released, predominantly originating from Asia (n = 39, 70%). In the early 2000s, the publication level dropped back to its height a decade earlier. Since 2008 however, there has been an increase of publications every year. Despite increased activity in Europe and North America, Asia has clearly remained the most active region. In 2018 for instance, of n = 186 bypass articles published, n = 23 (12.4%) originated from European institutions, n = 41 (22.0%) from American institutions, and n = 120 studies (64.5%) were written in Asian departments (Fig. 2, 3).

Regarding the contribution of other continents over the entire 50 years that have been investigated, n = 18 studies were released from a South American institute, n = 17 studies originate in Australia, and n = 7 studies came from Africa.

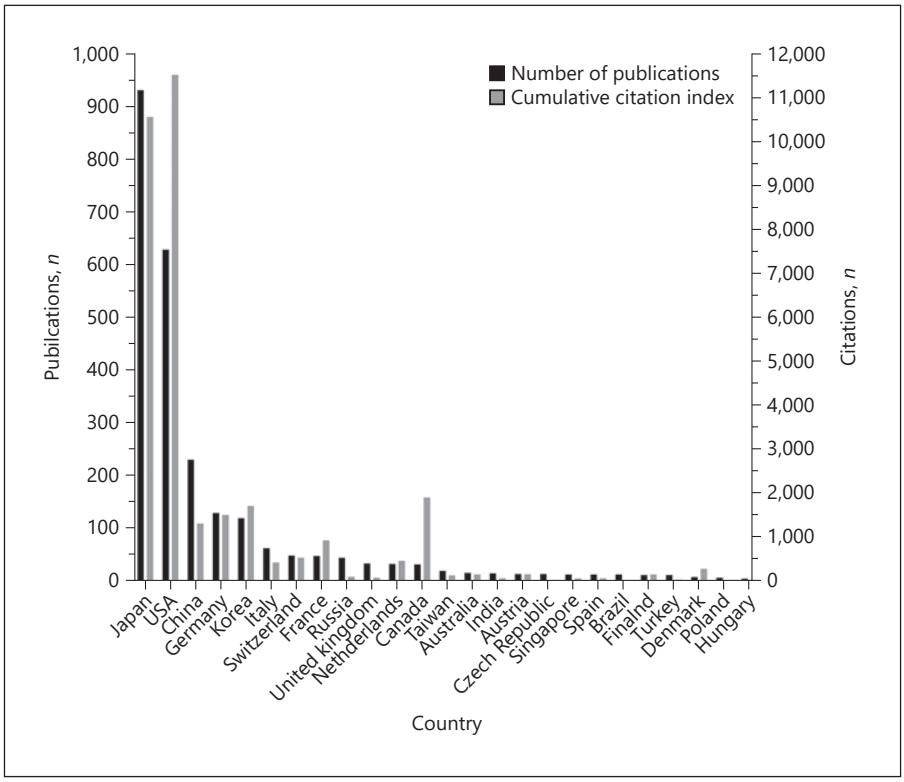

Fig. 3. Number of publications and cumulative citation index according to the country of origin. The black bar in histogram shows the absolute number of publications according to the country on the left axis. Countries with a contribution of 5 or less bypass articles were omitted for better readability. The grey bar relates to the right axis and shows the absolute number of the total cumulative citation index for all articles originating in these nations.

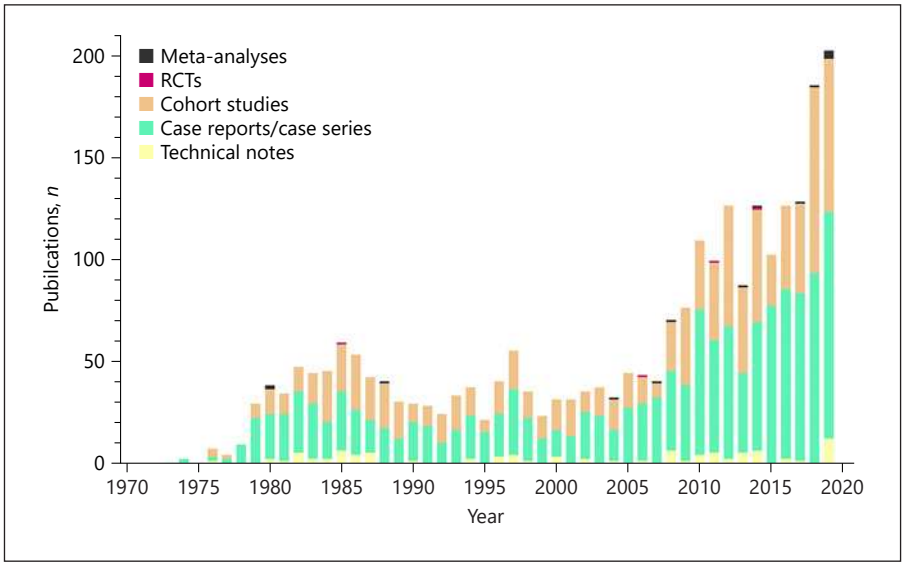

Fig. 4. Types of articles over time. The bar diagram shows the types of studies published over time (per annum). Bypass literature consists predominantly of case reports/case series and to a lesser extend of cohort studies, whereas RCTs and meta-analyses are few and far between. RCTs, randomized control trials.

On a national level, Japan was found to be the country with the most active bypass research community. Japanese institutions have cumulatively published 933 articles, followed by the USA with 630 articles and China with 232 articles. Figure 3 shows the number of publications for all countries with >5 contributions. When looking at the 7 countries with the numerically highest contributions (those with >50 articles), 5 countries (Germany, Italy, Japan, Switzerland, and USA) recorded activity in bypass research in the 1970s already and have remained active ever since. By contrast, China and Korea started to contribute to the field later, and both countries showed distinctively increased activity during the past 10 years. China released 210/232 articles after 2009 (91% of the total amount of na-

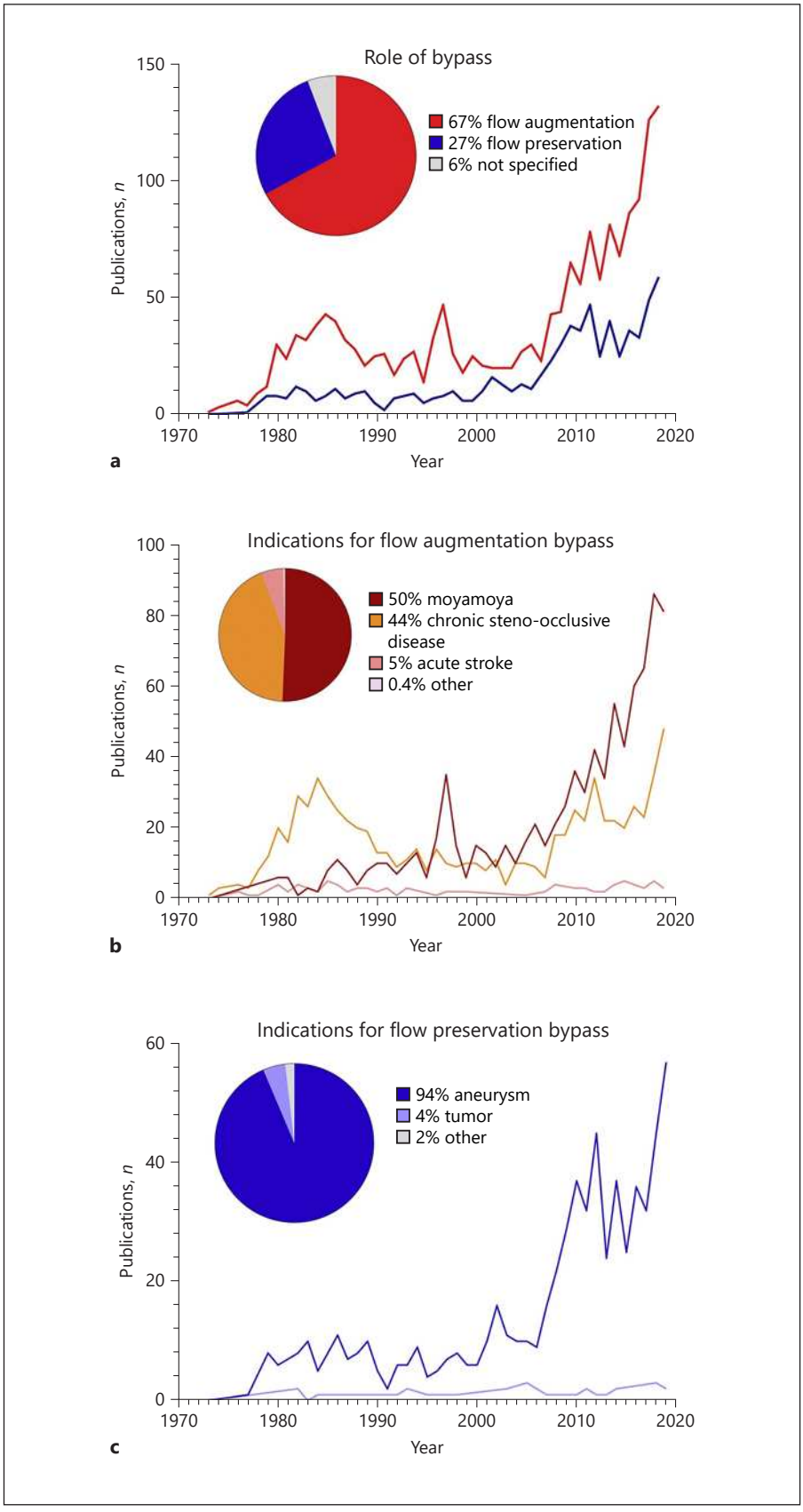

Fig. 5. a Role of and indication for bypass. Relative distribution of publications according to the role of bypass (flow augmentation vs. preservation), as well as its distribution over time. **b** Within publications pertaining to flow-augmentation bypass, 50% of publications were on moyamoya vasculopathy. This indication peaked in 1997 and is constantly increasing since 2007. Regarding flow-preservation bypass (**c**), aneurysm is by far the most common indication (94%), whereas tumour (4%) and others (2%) have remained on a consistently low level.

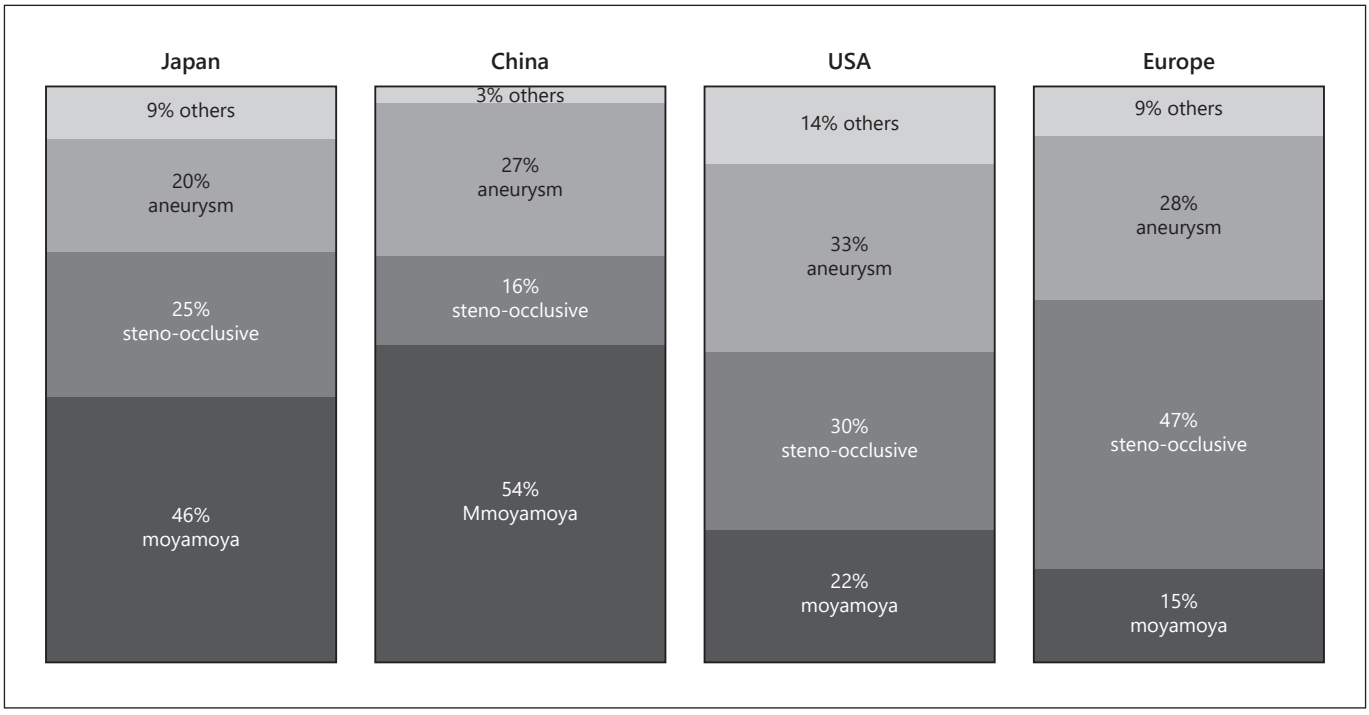

Fig. 6. Trends of bypass indication according to the country. The main indication for the Asian countries of Japan (46%) and China (54%) directed towards moyamoya. In contrast, only 22% of all publications originating in the USA and 15% of those originating in European countries were published on this indication. Instead, chronic steno-occlusive disease is the most commonly investigated indication in Europe (47%), and aneurysm (33%) in the USA. "Europe" integrates studies from Germany, Switzerland, France, UK, Italy, the Netherlands, Austria, Czech Republic, Spain, Finland, Denmark, Poland, Hungary, Belgium, and Croatia.

tional articles), and Korea 88/121 articles (73% of the total amount of national articles). However, the cumulative citation index of all published articles is highest for the USA (11,528 citations), followed by Japan (10,571) and Canada (1,921). The citation index for China (1,330) is lower than that of Korea (1,729) and Germany (1,528) (Fig. 3).

Overall (and for every single year) published bypass literature is numerically led by case reports/case series (n = 1,433) and cohort studies (n = 1,003). Technical notes (n = 131) are by far less common, and RCTs (n = 4) and meta-analyses (n = 14) are particularly sparse (Fig. 4).

A majority of n = 1,734 (67%) studies were written on the topic of flow augmentation, n = 701 (27%) on flow preservation, and n = 149 (6%) studies reported on either function of the bypass (Fig. 5a). The last category comprises studies on surgical techniques, pre- and intraoperative imaging techniques, methods for flow measurement, bypass-specific anaesthesiologic considerations, and outcomes of bypass series (including surgical complication, long-term patency, or studies on psychological changes in bypass patients).

Indications for flow augmentation included moyamoya vasculopathy in n = 877 (50%) studies, steno-occlusive disease in n = 753 (44%) studies, acute stroke in n = 95 (5%) studies, and other indications in n = 7 (0.4%) studies (Fig. 5b). In steno-occlusive disease, the stenosed or occluded vessel was the ICA in n = 250 (47%) studies, the MCA in n = 92 (17%) studies, combined ICA and MCA occlusion in n = 116 (22%) studies, vertebrobasilar occlusion in n = 56 (11%) studies, and other vessels (i.e., anterior cerebral artery) in n = 5 (3%) studies. The category "other" indications for flow-augmentation bypasses comprises studies on refractory vasospasms, encephaloduroarteriosynangiosis in patients with cerebrovascular complications of sickle cell disease, tuberculosis-induced vasculopathy, isolated cerebral pan-angiitis, and omental transposition for Alzheimer's disease. Studies reporting on flow-augmentation bypass for acute stroke are relatively sparse. Their annual release rate fluctuated between 0 and 5 publications, without any specific pattern or change over time.

Concerning flow-preservation bypass, the most common indication by far are studies reporting on cerebral

aneurysm surgery (n = 659, 94%), followed by tumour surgery (n = 32, 4%) and others (n = 13, 2%) (Fig. 5c). The last category ("others") includes trauma (penetrating trauma of the MCA, vertebral artery, ECA, or ICA), post-traumatic carotid-cavernous fistulae, and thromboembolic or haemorrhagic complications of ICA, MCA, or ACA dissection, respectively.

Overall, moyamoya vasculopathy is the most common subject for studies originating in Asian countries, that is, Japan (46%) and China (54%). By contrast, aneurysm is the most common (33%) topic of articles originating in the USA, followed by chronic steno-occlusive disease (30%). In Europe, the latter is the most frequently reported topic (47%), followed by aneurysm (28%). Figure 6 shows the distribution of research articles of the top 5 contributing countries.

With regard to the categorization of "direct versus indirect versus combined," of all articles, the vast majority of n = 2,009 (78%) studies reported on direct bypass surgery. In n = 334 (13%) studies, an indirect bypass was performed, and n = 198 (8%) studies reported on combined direct/indirect procedures. In the specific setting of moyamoya vasculopathy, indirect bypass and combined procedures were used to be more popular than direct bypass in the second half of the 1990s. However, with the ongoing boost of bypass articles from 2009 onwards, direct bypass has clearly emerged as the most frequently reported procedure, followed by indirect and combined bypass (see online suppl. Fig 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517415).

Concerning the categorization "low versus intermediate versus high flow" instead, most of the analysed studies on direct bypass, that is, n = 1,546 (69%), reported on low-flow bypasses. Publications on high-flow bypasses (n = 215, 10%) or on intermediate flow (n = 141, 6%) were considerably less frequent. Furthermore, n = 58 (3%) studies evaluated multiple flow constellations, and in n = 290 (13%) studies, the authors did not specify flow dynamics. More specifically, in the setting of aneurysm surgery, low-flow bypasses dominate the literature, but after 2008, reports on intermediate- and high-flow bypass have become increasingly popular (online suppl. Fig. 2).

With regard to revascularized territory, for flow-augmentation, n = 1,527 (88%) studies investigated revascularization of the anterior circulation, and n = 61 (4%) of the posterior circulation. For flow preservation, n = 544 (78%) studies investigated revascularization of the anterior circulation and n = 114 (16%) of the posterior circulation. N = 134 publications reported series or techniques with bypasses in both locations (online suppl. Fig. 3).

The focus of bypass research has changed over time. In 1970–1979, articles were generally addressed indication and technique of bypass surgery, and often written in the form of a single-centre personal experience, such as Yasargil reporting his series. In the 1980s, studies on bypass for chronic steno-occlusive disease peaked, but the results of the international multicentre RCT by the EC/IC Bypass Study Group showed a failure of EC-IC arterial bypass to reduce the risk of ischaemic stroke. About 10 years later, moyamoya disease had become an established entity and claimed the main attention in bypass research. With endovascular aneurysm therapy becoming more popular in 2000, bypass in aneurysm surgery was increasingly investigated until 2011, when the flow diverter was finally approved by the FDA. In the last decade, moyamoya vasculopathy and stroke prevention in chronic steno-occlusive disease have remained the backbone of bypass research with a few studies on flow preservation for aneurysm treatment. Online suppl. Table. 1 shows the most frequent words used in titles of bypass articles per decade, as well as the most frequently cited studies per decade.

Discussion

Our systematic review identified 2,585 clinical publications on the topic of cerebral bypass surgery. Japan is the country where most articles come from, followed by the USA and China. However, articles originating in the USA are most often cited, followed by Japanese and Canadian articles. Two-thirds of articles address flow-augmentation bypass and one-third addresses flow-preservation bypass. The most common indication reported for flow augmentation is moyamoya vasculopathy, followed by chronic steno-occlusive disease; the most common indication reported for flow preservation is aneurysm surgery. The majority of all publications addressed direct, low-flow bypass procedures in the anterior circulation.

Bypass Research over Time

From the first reports in 1971 until 1980, bypass research had a marginal existence. This niche research was originally conducted in few European and North American neurosurgical departments and mainly directed towards anatomical and technical aspects of bypass feasibility. In the decade 1980–1989, publications on flow-augmentation bypass, more specifically on steno-occlusive disease, steadily increased, and peaked for the first time in 1985. Probably due to the disillusioning results of the EC-IC bypass trial published in that year [9], research de-

creased afterwards. The decrease continued in European and American departments over the second half of the 1980s, and from 1987 on, Asian departments took over in the numeric lead of bypass articles, focusing predominantly on the new entity of moyamoya disease. In the decade 1990–1999, bypass research nearly sank into oblivion in Western countries, but remained at a relatively stable level in Asian departments. In 1997, another peak was reached, due to a short-lasting increase of Asian studies on indirect and combined bypasses for moyamoya vasculopathy. With the overall number of publications in the year 2000 back on the level it used to be 10 years before, articles studying bypass in the setting of aneurysm surgery started to be published with increasing popularity. The total global research remained more or less stable until 2007, followed by a steep increase which can be explained by 2 reasons: firstly, studies on flow preservation increased because complex open aneurysm surgeries were probably increasingly challenged by the more widespread availability of endovascular treatments. That effect lasted until 2011 when the FDA finally approved flow diverters for aneurysm treatment. Secondly, studies on flow augmentation have drastically risen from 2007 to 2020, with a short drop in 2012, most likely as a result of the publication of the COSS study in 2011 [10]. The steep increase in publications parallels an increased activity in Asian countries previously not active in bypass research. For instance, China and Korea are amongst the most productive countries worldwide during the last decade (2010–2019), and both countries have substantially contributed to the total global number of bypass literature. However, only a minor amount of these articles were released before 2007 (27% for Korea and 9% for China). Because of the second-mentioned reason, clinical bypass research has remained a steadily growing field during the last decade. The major contributions continue to originate in Japan, China, and the USA.

Citation Index of Countries and Particular Studies

The young but very active research community in China is probably at least partially reflected by the substantial differences in the cumulative citation index between nations. American articles reach a higher number of citations relative to the national cumulative number of publications (on average 18 citations/article) than a third of that (on average 6 citations/article) for research originating in China. The scientific community had less time to discuss and potentially cite the high volume of the relatively recent publications in the latter group. The conspicuously high relative citation index of Canada is explained by the 1985 article of the EC/IC bypass study group [9], which was an international multicentre study based in Canada and has been cited more than a thousand times since. Likewise, exceptionally popular single articles originating in France [11] (564 citations) and Denmark [12] (245 citations) explain the high relative citation index in light of a moderate cumulative number of publications from these countries.

From a qualitative point of view, the numerical increase of bypass literature is predominantly generated by a proportional increase of case reports/case series and to a lesser extend of cohort studies. A distinctively increased pool of published data from these 2 types of studies may have led to a subsequent, slight increase of meta-analyses in recent years. Divergently, there was no increase in RCTs observed.

Flow-Augmentation Bypass

Moyamoya represents the bypass indication with the most literature available. The disease "of spontaneous occlusion of the circle of Willis and development of an abnormal vascular network at the base of the brain" was first recognized as a single clinical entity in 1965, in Japan, followed by an international echo in the English literature in the years 1968–1970 [13]. However, it started to be a frequent topic of scientific publications only in the early 1980s, and parallels the increasing number of studies originating in Japan and more recently in China. In these countries, moyamoya is more common than in Western countries [14]. Currently, observational studies provide level-4 evidence for indication of bypass surgeries in ischaemic moyamoya vasculopathy, for children and adults with symptomatic moyamoya and compromised haemodynamics [2]. Observational studies have shown unfavourable clinical outcomes and annual ischaemic stroke rate to be as high as 13.3% with untreated patients (those not undergoing bypass surgery) [15, 16]. Therefore, randomization of patients would be unethical, and it seems highly unlikely that it would be possible to conduct an RCT for this indication in the future, to raise the evidence to a higher level [4]. However, the value of bypass surgery for prevention of recurrence of haemorrhagic stroke in patients with moyamoya vasculopathy has been proven in an RCT, the "Japanese Adult moyamoya (JAM) Trial" [17]. Although statistically marginal, the Japanese Adult moyamoya Trial revealed that direct or combined bypass surgery on adult patients with haemorrhagic moyamoya reduces the rebleeding rate and improves the patient's prognosis during the 5 years after enrolment (level of evidence 1 – grade of recommendation A) [2]. However,

despite the number of studies available, the preferred type of bypass in these patients remains debated and studies continue to report beneficial outcomes with direct, indirect, and combined procedures [4, 18, 19]. These controversies may explain the ongoing research and publication activity in this field.

For chronic steno-occlusive (non-moyamoya) disease, the situation is different. This has remained a main focus of bypass research from the early 1970s until today. The aim of these early studies was to report on successful bypass surgeries for stroke prevention. Indirect cerebral revascularization methods are and were considered ineffective for non-moyamoya vasculopathy [4, 20]. Two large multicentre prospective RCTs (the EC-IC bypass trial in 1985 and the COSS study in 2011) investigated if a direct STA-MCA bypass (in addition to the best medical treatment) could prevent new ischaemic events. Results of these studies showed that bypass surgery did not make a significant difference in the incidence of fatal and nonfatal ischaemic strokes compared to patients under the best medical treatment [9, 10]. This may explain the drop of bypass articles published after 1985. In contrast, the Japanese EC-IC Bypass Trial was a multicentre RCT including patients with recent symptomatic haemodynamic cerebral ischaemia from chronic ICA or MCA occlusion. In this trial, a significant reduction of major stroke and death in patients receiving bypass plus the best medical therapy was achieved in comparison to best medical therapy alone (5.1 vs. 14.3%) [21]. However, findings of that study are controversial and publication of the final results in a peer-reviewed English-written journal is pending [21, 22]. Therefore, it is difficult to include the Japanese EC-IC Bypass Trial study results into the general evidence base regarding bypass in atherosclerotic disease [4]. The findings of the still ongoing Chinese Middle Cerebral Artery Occlusion Surgery Study [23] are expected to provide further insights into the role of bypass surgery for steno-occlusive disease. Furthermore, the recently published American Encephaloduroarteriosynangiosis Revascularization for Symptomatic Intracranial Arterial Stenosis phase II trial provided the evidence of safety and strong signals of efficacy of indirect bypass in addition to the best medical management [24], supporting advancement to a consecutive phase IIb/III trial.

Lastly, acute ischaemic stroke as an indication for flow-augmentation bypass only comprises a small percentage of all articles published on bypass surgery. A few older retrospective series reported good outcomes in patients with emergency bypass for reperfusion of brain tissue at risk (penumbra concept) [25–27]. Today, other revascularization techniques (i.e., drug-induced thrombolysis or endovascular procedures) have become a well-established standard. Emergency bypass operations in the setting of acute stroke are limited to very specific cases (with failure of medical/endovascular revascularization and penumbra tissue to save) and performed in highly specialized centres only. Accordingly, contemporary literature primarily comprises only a few case series published on that topic [28–30].

Flow-Preservation Bypass

With the establishment of bypasses in the neurosurgical armamentarium, neurosurgeons realized that this technique could be a helpful tool for the treatment of complex intracranial aneurysms otherwise not amenable to clipping [31, 32]. Angioanatomy of complex aneurysm (size, shape, location, etc.) is highly variable and surgical treatment of such lesions cannot be reduced to some standard procedures. Therefore, if a bypass is needed for the treatment of a complex intracranial aneurysm, revascularization strategies will be tailored depending on the case (aneurysm and angioanatomical characteristics). As such, the corresponding literature primarily consists of case series and case reports. The heterogeneity of the disease and the low number of cases do not allow for proper randomization, which is why it is unlikely that higher evidence derived from an RCT will enlighten the field. Interestingly, the topic is more popular in Europe and North America than in Asia. An increasing popularity of reporting on these bypass operations almost came to an abrupt end with the FDA approval of flow diverters for aneurysm treatment in 2011. Over the subsequent years, the amount of bypass articles published on the topic of aneurysm surgery decreased by more than 50% (i.e., from 45 studies in 2012 to 24 studies in 2013). The effect lasted longer in Europe than in North America, where a rebound effect was observed already in 2014. Nevertheless, neurosurgeons have continued to report their experiences with these fascinating cases, and in more recent years, the number of publications is increasing again. In older days, most of these bypasses were STA-MCA anastomoses, but with the overall rise of publications on bypass for aneurysm surgery in the second half of the 2000s, reports on the use of arterial or venous grafts to establish intermediate- and high-flow bypasses have become increasingly popular, particularly in the USA.

In contrast to revascularization for aneurysm surgeries, bypass in the setting of tumour surgeries is far less common; the literature consists of only a few case reports and case series. With only a handful of studies older than 1990 [33–35], 1 to 2 reports/series on the topic have been

released annually since then, without any observable geographic predominance. With a few exceptions, most of these publications report on direct bypasses in the anterior circulation. Low-flow constructs and interposition grafts (intermediate and high flow) are equally reported. The reports are limited to patients, for whom radical tumour resection (at the price of arterial scarification) leads to improved survival rates with a good quality of life. However, recent advances in oncological treatment modalities nowadays often attest a better risk-benefit ratio for partial tumour resection combined with adjuvant radio-/chemotherapy than complete resection [4]. Therefore, this indication will probably continue to play a negligible role in the bypass literature [36, 37].

Strengths and Limitations

With the current comprehensive review, the intention was to categorize the clinical literature on cerebral bypass procedures in order to analyse trends, for instance on how the number of articles increased or decreased according to the evidence-based medicine and the corresponding grade of recommendation, how different countries and continents contributed to the subject, and lastly, how the role of and the indication for bypass changed over time and differs amongst countries. Despite our systematic approach and the use of 4 different independent databases, we cannot rule out the possibility that we might have not identified other relevant studies. Japan is the country with the highest activity in bypass research, but we were not able to include studies written in Japanese unless they have been published with an English abstract. Furthermore, categorization of studies is not always clear. For instance, certain articles reported surgical series for various indications and using several bypass techniques. Therefore, not all studies could be assigned to 1 single type of bypass or a given indication. Unfortunately, categorization according to key words was not possible, since some studies did not use any key words at all, or they were not meaningful within our specific context (i.e., cerebral revascularization, bypass, etc.). Therefore, we plotted word clouds for words used in the titles of the studies. Lastly, for the purpose of this review, all published articles that met the inclusion criteria were included without weighing the individual studies. Therefore, a simple case report equals the weight of a more meaningful RCT in our descriptive analysis. For this reason, we additionally determined the citation index of all the included articles. With the aim to provide an overview of the past and current trends in bypass research, this is likely more adequate than a critical appraisal of all studies.

Conclusion

This systematic review reported on 2,585 clinical publications on the topic of cerebral bypass surgery. These studies have become increasingly popular in the last decades. Two-thirds of the articles address flow-augmentation bypass, whereas one-third addresses flow-preservation bypass.

Japan is the country with the highest number of published articles, followed by the USA and China. In turn, articles from the USA are cited most frequently, followed by Japan and Canada. The majority of all publications addressed direct, low-flow bypass procedures in the anterior circulation. The most common indication reported for flow augmentation is moyamoya vasculopathy, followed by chronic steno-occlusive disease. Since the introduction of moyamoya as a distinct pathologic entity, Asian countries in particular have a very active community regarding this disease, with an increasing number of articles published every year. Studies on bypass for chronic steno-occlusive disease peaked in the 1980s, but have remained the main focus of bypass research particularly in many European departments.

The most common indication reported for flow preservation is aneurysm surgery. During the past few years, these bypasses are reported more frequently again. In the USA, bypass for complex aneurysm surgery is most frequently investigated. An increasing popularity of reporting on these bypass operations markedly decreased after the FDA approval of flow diverters for aneurysm treatment in 2011. In the subsequent years, the amount of bypass articles published on the topic of aneurysm surgery has slightly increased again.

Statement of Ethics

This study does not involve animal or human subjects. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained for this study.

Author Contributions

Basil E. Grüter and Giuseppe Esposito had had the idea for the article. Lazar Tosic was in charge of data extraction of the studies with further contributions from Basil E. Grüter, Stefanos Voglis, Flavio Vasella, Valentino Mutschler, Oliver Bichsel, and Natalie Scherrer. Basil E. Grüter and Stefanos Voglis analysed the data and plotted graphs and word clouds. Basil E. Grüter took the lead in writing the manuscript with critical feedback from all the authors. Giuseppe Esposito supervised the project and Luca Regli was in charge of the overall direction. All the authors approved the final version to be published and agree to be accountable for all aspects of the work.

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