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MORFOLOGIA DESCRITIVA E HEMODINÂMICA DOS ANEURISMAS DO SIFÃO CAROTÍDEO

PATRICIA BOZZETTO AMBROSI

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Tese de doutorado apresentada à Coordenação do Programa de Pós-Graduação em Ciências Biológicas da Universidade Federal de Pernambuco, como parte dos requisitos à obtenção do grau de Doutor em Ciências Biológicas, área de concentração: Biologia Química para a Saúde

Orientação: Prof. Dr. Marcelo Moraes Valença

Co-orientação: Prof. Dr. Laurent Spelle
Prof. Dr. Jacques Moret

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Não há palavra no mundo capaz de expressar o amor e a gratidão que sinto por todos vocês.

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“*Le succès ne se mesure pas là* où *vous êtes arrivé, mais le nombre des difficultés que vous avez surmonté ”.*

“***O exito da vida não se mede pelo caminho que você conquistou, mas sim pelas dificuldades que superou no caminho”.***

Abraham Lincoln

(1809-1865)

RESUMO

Bozzetto-Ambrosi P. *Morfologia Descritiva e Hemodinâmica dos Aneurismas do Sifão Carotídeo* [Tese de Doutorado] Recife, 2016.

Os novos stents modificadores de fluxo apresentam elevadas taxas de sucesso obtidas no tratamento dos aneurismas que se desenvolvem na circunferência do sifão carotídeo. Esses aneurismas são bastante diversificados e apesar de dinâmicos muitas vezes são silenciosos. Além disso, sua história natural e seu comportamento biológico ainda são bastante desafiadores e incertos. Estudos experimentais tem recentemente demonstrado que a morfologia (remodelamento vascular) e as variações na hemodinâmica cerebral estariam envolvidos tanto na gênese bem como no desenvolvimento e na eventual ruptura dos aneurismas intracranianos. Outrossim, estudos populacionais tem evidenciado uma correlação entre a assimetria das artérias do polígono de Willis e o aparecimento de aneurismas em várias localizações dentro do polígono de Willis. Contudo, estudos específicos voltados para aos aneurismas localizados na circunferência do sifão carotídeo ainda não foram abordados. A presente tese teve como principal objetivo caracterizar o papel das variantes arteriais do círculo de Willis particularmente implicadas na gênese dos aneurismas da circunferência do sifão da carótida. Ao mesmo tempo, foi realizada uma análise de regressão para superar o desequilíbrio significativo entre homens e mulheres em relação a ambos: local do aneurisma e a presença de variantes arteriais do polígono. As duas variantes anatômicas do polígono de Willis consideradas no presente estudo foram a presença do segmento A1 dominante (Hipoplasia A1 contralateral) e a presença de artéria cerebral posterior (PCA) fetal. Realizamos um estudo caso-controle em um dos centros franceses de referência, e que também é um centro de classe mundial contendo cinco principais amostras: (1) Grupo 1, agrupando os aneurismas que se originam em algum ponto da circunferência do sifão carotídeo unilateralmente (n = 178); (2) Grupo 2, contendo aneurismas em algum ponto bilateralmente nos dois sifões carotídeos (n = 99); (3) Grupo 3, composto de sifões sem aneurismas contralaterais do grupo A1 (n = 178); (4) Grupo 4, contendo sifões de pacientes sem aneurismas (n = 210) e Grupo 5, controles combinados contendo os Grupos 3 e 4 (n=388). Em grupos equilibrados, a configuração tipo A1 do polígono de Willis parece ter um efeito protetor na gênese dos aneurismas. A configuração do tipo A1 foi significativamente mais encontrada no Grupo 3 (55/178) versus Grupo 1 (12/178) denotando provalvemente um efeito protetor no aparecimento dos aneurismas na região do sifão carotídeo ($p<0.0001$, OR 0.1617). A presença da A1 dominante foi significantemente maior no grupo 3 do que no grupo 1, tanto no grupo de homens (1/24 versus 11/24, $p=0.0070$, OR 0.0514) quanto de mulheres (44/154 versus 1/154, $p<0.001$, OR 0.1923). A associação incluindo ambas A1 dominante/ Fetal PCA foi encontrada apenas em 3/178 (1.6%) pacientes do grupo 1 (3/178) e um total de 13/178 dos sifões do grupo 3 ($p = 0.0189$, OR 0.2176). O novo conceito poderá ajudar na melhoria do *screening* e abrindo as portas para novas estratégias no tratamento dos aneurismas do sifão carotídeo. Nesta análise, também evidenciou-se que um grupo controle equilibrado pode reduzir o viés multivariado e, assim, melhorar as estimativas. Por conseguinte, são necessárias mais investigações com dados multicêntricos com abordagens analíticas melhoradas. Além disso, nessa tese discutimos sobre as biotecnologias aplicadas aos aneurismas intracranianos, apresentamos uma abordagem clínica e uma revisão histórica sobre as técnicas de tratamento dos aneurismas do sifão carotídeo, apresentamos as novas perspectivas sobre as variantes anatômicas aplicadas aos aneurismas intracranianos e propusemos uma nova classificação morfológica baseada nas áreas de susceptibilidade dos aneurismas do sifão carotídeo. Concluindo, o efeito protetor da presença das variantes anatômicas arteriais com hiperfluxo suporta a hipótese do uso da hemodinâmica cerebral como fator preditivo no desenvolvimento dos aneurismas intracranianos. Estudos adicionais são necessários com a inclusão dessas novas ferramentas tecnológicas que proporcionem acurácia nas medições de fluxo da circulação cerebral e dos aneurismas intracranianos permitindo a utilização na prática clínica.

Palavras-chave: Aneurismas. Artérias. Biotecnologias.

ABSTRACT

Bozzetto-Ambrosi P. *Carotid Siphon Aneurysm: Its Hemodynamic and Descriptive Morphology.* [PhD Thesis] Recife, 2016.

Despite the high success rates obtained with the new modifier flow stents in the treatment of intracranial aneurysms that develop on the circumference of the carotid siphon. These aneurysms are very diversified and despite being dynamic, often silent. Therefore, their natural history and biological behavior remain controversial and little understood. Recent experimental studies have widely shown the morphology (vascular remodeling) and variation in the cerebral hemodynamics would be involved both in the genesis as well as in the development and eventual rupture of intracranial aneurysms. In addition, population studies have shown a correlation between the asymmetry of arteries of the circle of Willis and the genesis of aneurysms in several locations within the circle of Willis. However, specific studies applied to the carotid siphon location has not yet been addressed. This thesis aimed to examine the association of arterial variants of Circle of Willis particularly implicated in the genesis of aneurysms within the circumference of the carotid siphon. At the same time, a regression analysis was performed to overcome the significant imbalance between men and women as compared to both the aneurysm site and the presence of arterial polygon variants. The two anatomical variants of the circle of Willis studied were the presence of dominant A1 segment (contralateral hypoplasia A1) and the presence of fetal-PCA. A case-control study was conducted derived from World-Class and French University referral Center with five different samples: (1) Group 1, composed by aneurysms that originate somewhere along the circumference of the carotid siphon unilaterally (n = 178); (2) Group 2, containing aneurysms at some point bilaterally in the two carotid siphons (n= 99); (3) Group 3, composed by contralateral healthy siphons of the group 1 (n = 178); (4) Group 4, containing siphons from healthy patients (n = 210) and Group 5, containing the combined control groups 3 and 4 (n = 388). In balanced groups, Circle of Willis with A1 dominance appears to have a protective effect in the genesis of carotid siphon aneurysms. The Willis polygon configuration with A1 dominance had a significantly higher frequency in Group 3 (55/178) vs. Group 1 (12/178) denoting a protective effect on the genesis of aneurysms in the carotid siphon region ($p < 0.0001$, OR 0.1617). The presence of the dominant A1 had a significantly increased protection of an aneurysm development compared with the group of men (1/24 versus 11/24, $p=0.0070$, OR 0.0514) versus women (44/154 versus 1/154, $p<0.001$, OR 0.1923). Both A1/Fetal PCA dominance were founded in 3/178 (1.6%) patients of the group with a unilateral aneurysm (3/178) and 13/178 of the contralateral healthy siphons ($p = 0.0189$, OR 0.2176). The Willis polygon configuration with A1 dominance and PCA fetal variant may prevent the carotid siphon aneurysm development. The new concept might help in improvement f the screening and open the door for new strategies in the treatment of carotid siphon aneurysms. This analysis also showed that a balanced control group multivariate can reduce the bias, and thus improving the estimates. Therefore, more investigations are needed multicenter data with improved analytical approaches. In addition, this thesis contains chapters about the biotechnology applied to the intracranial aneurysms, the current approach and a historical review of endovascular techniques for the carotid siphon aneurysms, the new perspectives of use of cerebral hemodynamic applied to intracranial aneurysms and the proposal of a new morphological classification based on the areas susceptibility to carotid siphon aneurysms. Briefly, the protective effect of the presence of arterial anatomical variants supports the hypothesis of the use of cerebral hemodynamics as a predicting factor in the development of intracranial aneurysms. Additional experimental studies with the further accurate flow measurements of cerebral circulation with and without intracranial aneurysms then allowing the application of this new concept used in the clinical practice.

Keywords: Aneurysms. Arteries. Biotechnology.

LISTA DE FIGURAS

LISTA DE ABREVIATURAS E SIGLAS

A1= Segmento A1

AAA= Aneurismas da Aorta Abdominal

ACA= Artéria Cerebral Anterior

ACha= Artéria Choroidal Anterior

AcomA= Artéria Comunicante Anterior

AAT = Aneurismas da Aorta Torácica

BA=Artéria Basilar

CFD= *Computational Dynamics Flow*

DOPHA= Artéria Dorsal Oftálmica

ICA Cd= Artéria Carótida Interna

MCA= Artéria Cerebral Média

PCA= Artéria Cerebral Posterior

P1= Segmento P1

P2= Segmento P2

TOF= *Time of flight*

VA= Artéria Vertebral

VOPHA= Artéria Ventral Oftálmica

WWS=*Wall Shear Stress*

SUMÁRIO

Ce travail a été réalisé dans le Service de Neuroradiologie Interventionnelle – Neuri Beaujon, Brain Vascular Center – Université Paris Diderot, en coopération avec l'Université Fédérale de Pernambouc- UFPE/Brésil

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CAPÍTULO I

Introdução

1 INTRODUÇÃO

A presente tese de doutorado é o resultado das atividades de pesquisa que foram desenvolvidas a partir de uma parceria científica entre o Centro de Biociências da Universidade Federal de Pernambuco, Brasil, e o Centro Neuri Beaujon, Departamento de Neurorradiologia Intervencionista, Universidade Paris Diderot, França. Discorre sobre a morfologia descritiva e a hemodinâmica dos aneurismas do sifão carotídeo enfatizando a aplicação da hemodinâmica cerebral na gênese e desenvolvimento dos aneurismas intracranianos. Também, inclui capítulos em forma de artigos relacionados as novas biotecnologias aplicadas aos aneurismas intracranianos, as técnicas de tratamento endovascular dos aneurismas do sifão e os seus aspectos desafiantes, uma nova classificação morfológica dos aneurismas do sifão carotídeo é apresentada, além de dois capítulos em especial dedicados à aplicabilidade das variantes anatômicas das artérias na gênese dos aneurismas intracranianos e do sifão carotídeo.

Os trabalhos de pesquisa tiveram início em janeiro de 2011 sob a co-orientação dos professores Jacques Moret e Laurent Spelle, no Departamento de Neurorradiologia Intervencionista do Hospital Beaujon em Paris, o qual é um dos pioneiros e referenciados serviços da Neurointervenção Endovascular tendo uma parceria com o Centro de Pesquisas Medicen, localizada em Suresnes, na região metropolitana de Paris.

O tema proposto deve-se ao fato de que os aneurismas do sifão carotídeo correspondem aos mais frequentemente tratados por via neuroendovascular pela acessibilidade e pelos excelentes resultados obtidos com os novos stents modificadores de fluxo. Por outro lado, a idéia de rever essa temática trata-se de um "renascimento" na Neurorradiologia sob a forma de idéias evolutivas e agora fazendo referência à hemodinâmica e à morfologia vascular.

O objetivo foi analisar se existem fatores relacionados com a morfologia vascular como certos subtipos de configurações do polígono de Willis que estariam relacionadas com os aneurismas do sifão carotídeo e possivelmente envolvidas na gênese desses aneurismas.

Em 1927, Egaz Moniz (Moniz, 1933; Moniz 1934) descreveu o sifão carotídeo que ainda permanece pouco desvendado (Sanders-Taylor et al., 2014). É considerado um marco anatômico e radiológico importante durante a realização de exames angiográficos, além de ser um local comumente acometido pelos processos patolológicos degenerativos, ateroscleróticos e de dissecção vascular (Platzer et al ., 1956; Routsonis et al., 1973; Goldsmith et al., 1991; Algra et al., 1998; Nixon et al., 2010). Também são frequentemente identificados aneurismas

ao longo de sua circunferência arterial (Day, 1990; Larson et al., 1995; Barami et al., 2003; Jin et al., 2009; Colby et al., 2012; Wang et al., 2013; Ahn et al., 2014; D'Urso et al., 2014).

Estudos recentes têm indicado que a tortuosidade do sifão, a sua complexa geometria de curvas e a sua variabilidade são características que o fazem uma estrutura relevante para o estudo da gênese dos aneurismas intracranianos (Jou et al., 2008; Valen-Sendstad et al., 2014). Principalmente o formato sinuoso pode gerar instabilidades no fluxo dinâmico com significante correlação nos processos de iniciação e ruptura aneurismática (Cebral et al., 2005; Piccinelli et al., 2011; Valen-Sendstad et al., 2014; Lauric et al., 2014).

Poucos estudos foram encontrados na literatura investigando o sifão carotídeo e seus aneurismas com essa proposta de entender a fisiopatogênese. Os estudos existentes são essencialmente pequenas amostras baseadas em estudos de fluxo aneurismático *in vitro* dedicados à análise da hemodinâmica vascular e outros analisando a angulação do sifão propriamente dito (Piccinelli et al., 2011, Valen-Sendstad et al., 2014; Lauric et al., 2014). Sobretudo, quanto a estes estudos *in vitro,* na maioria eles utilizam modelos experimentais hemodinâmicos tridimensionais com custos bem elevados, além de serem pacientes-específicos e difíceis de se obter.

Estudos morfológicos e de fluxo aplicados aos aneurismas intracranianos mais viáveis são esperados, porque os poucos estudos existentes além de serem *in vitro* são específicos para cada paciente (Cebral et al., 2005; Sun et al., 2012; Valen-Sendstad et al., 2014). Análises de fluxo dinâmico através de softwares do tipo "*computational flow dynamics*" ainda com pouca acurácia clínica, laboriosos e de alto custo. Esses estudos permanecem a nível de pesquisa, e ainda pouco disponíveis no cenário clínico. Portanto, são necessários mais estudos de baixo custo, embasados na aplicabilidade clínica que possam ser utilizados dentro do cenário operatório.

De uma forma geral, o estudo da morfologia e da hemodinâmica vem se destacando particularmente com os vários trabalhos correlacionando os novos tratamentos endovasculares e as novas tecnologias de estudo dos aneurismas (Chong et al., 1994; Aenis et al, 1997; Lieber et al., 1997; Liou et al., 1997; Liou et al., 2004; Rhee et al., 2002; Cebral et al., 2005; Bor et al., 2008; Ausburger et al., 2009; Tateshima et al., 2010; Levit et al., 2014; Sorkin et al., 2014; Xiang et al., 2015) dentre outros.

As novas opções de tratamento não-invasivas tem sido cada vez mais utilizadas no tratamento dos aneurismas intracranianos sendo feita a partir de stents chamados de modificadores de fluxo com propriedades específicas (Wong et al., 2011; Alderazi et al., 2014). Esses novos stents também podem ser utilizados como marcadores biológicos

durante os estudos de fluxo por permitirem a análise antes e depois de sua colocação (Lieber et al., 1997; Barath et al., 2005).

Para um bom desempenho como stents propriamente ditos e também como marcadores, a indústria tem aperfeiçoado suas propriedades e buscado oferecer mais segurança em primeiro lugar para o paciente e aos médicos neurointervencionistas durante os procedimentos (Girard, 2014). No entanto, por ser uma técnica relativamente recente pode ser considerada um desafio, e fatores preditivos quanto a morfologia e a hemodinâmica vascular ainda são esperados.

Nosso assunto, os aneurismas do sifão carotídeo, além de desafiador e sobretudo seu comportamento é algo não previsível, pois os aneurismas intracranianos são dinâmicos e agem em silêncio (Brainin, 2006; Vernooij et al., 2007; Valenca, 2012; Turjman et al., 2014). Altas taxas de sucesso tem se mostrado com os novos tratamentos, porém antes disso sua verdadeira prevalência não é conhecida e o consenso de tratamento dos aneurismas é baseado na sua primeira manifestação que pode ser catastrófica. Logo como ainda temos poucos dados sobre o comportamento dos aneurismas, normalmente a escolha do tratamento é baseada em balançar os riscos tentando evitar a probabilidade da hemorragia subaracnóide. Mas, é imperativo compreender e encontrar explicações para a origem e a história natural dos aneurismas intracranianos, em particular a interação das forças mecânicas da parede com o fluxo e a circulação cerebral.

Assim sendo, neste trabalho, estudamos a morfologia do sifão carotídeo e seus aneurismas e fizemos uma correlação com as variantes anatômicas arteriais utilizando estudos angiográficos convencionais e estudos morfológicos tridimensionais.

Este presente trabalho se concentra nos seguintes tópicos já descritos: os aneurismas da circunferência do sifão carotídeo e sua morfologia e hemodinâmica fazendo parte de uma nova abordagem que poderá proporcionar nova visão para o diagnóstico e tratamento desses aneurismas.

CAPÍTULO II

Referencial Teórico

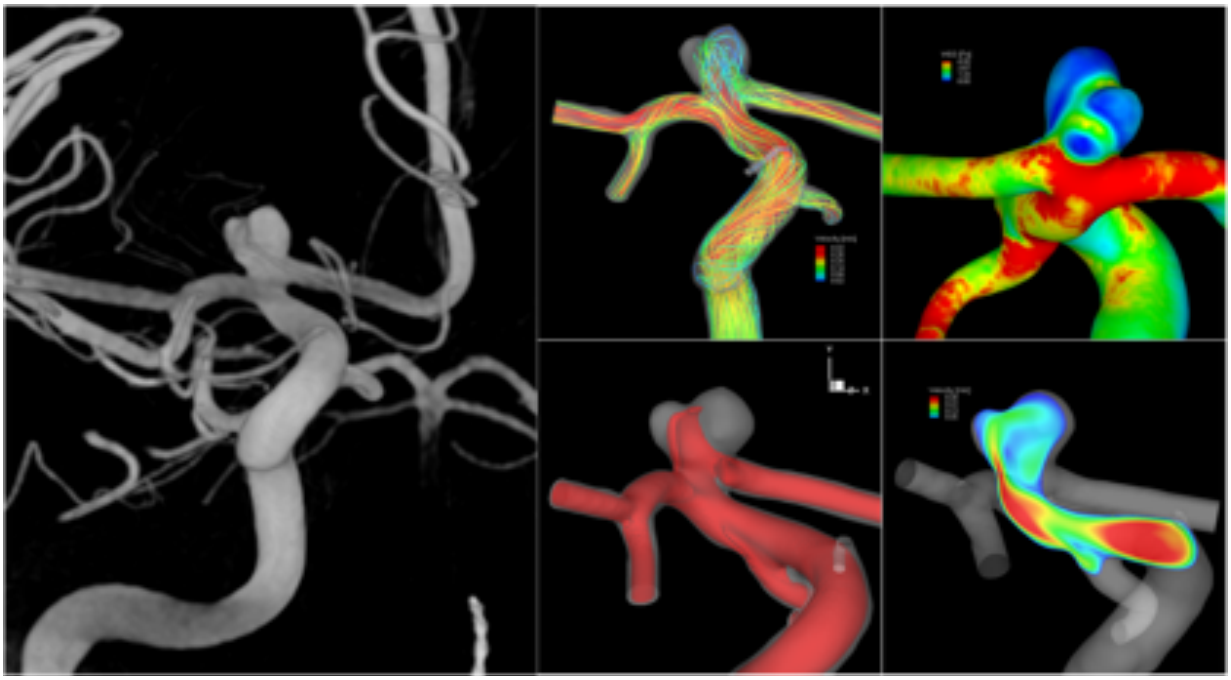
2 REFERENCIAL TEÓRICO

2.1 INTRODUÇÃO

O estudo dos fatores morfológicos e hemodinâmicos que contribuem para a formação e desenvolvimento dos aneurismas intracranianos é uma nova estratégia destinada a melhorar a sua investigação e trazendo um melhor entendimento da sua fisiopatogênese conforme ilustramos na **Figura 1**.

Ao mesmo tempo, o estudo morfológico e hemodinâmico vem abrindo novas perpectivas em melhorias no seu manejo clínico e tratamento. Paralelamente, com o crescente aprimoramento das técnicas terapêuticas em Neurorradiologia intervencionista/Neurocirurgia endovascular, cada dia mais existe a necessidade de ter um estudo morfológico e angioarquitetônico mais bem detalhado que possa ser rapidamente acessado dentro da sala operatória.

(A) (B) (C)



(D) (E)

Figura 1 – Imagem tridimensional da artéria carótida direita ilustrando um aneurisma na bifurcação da carótida interna (A) Padrões de fluxo intra-aneurismático ilustrado em forma de vetores (B) Aneurismas com áreas de afluxo e regiões com aumento da força de cisalhamento na artéria parente (C) Áreas de estudo selecionadas do estudo tridimensional (D) Áreas com aumento da tensão de cisalhamento aumentada na artéria parente e demontrada em porções do colo do aneurisma (E). Fonte: Extraída do arquivo do Serviço de Neurorradiologia, Neuri-Beaujon.

Na **Figura 2**, ilustramos um aneurisma complexo que se origina dentro do sifão carotídeo que foi estudado através de imagens morfológicas tridimensionais. Particularmente com relação aos aneurismas que se desenvolvem dentro do sifão carotídeo, a patogênese dos aneurismas do sifão carotídeo parece muito mais complexa e multivariada comparada aos aneurismas intracranianos em geral. O sifão carotídeo tem uma estrutura arquitetônica com uma série de curvas e voltas, sendo um padrão peculiar, ímpar e relevante dentro da circulação cerebral.

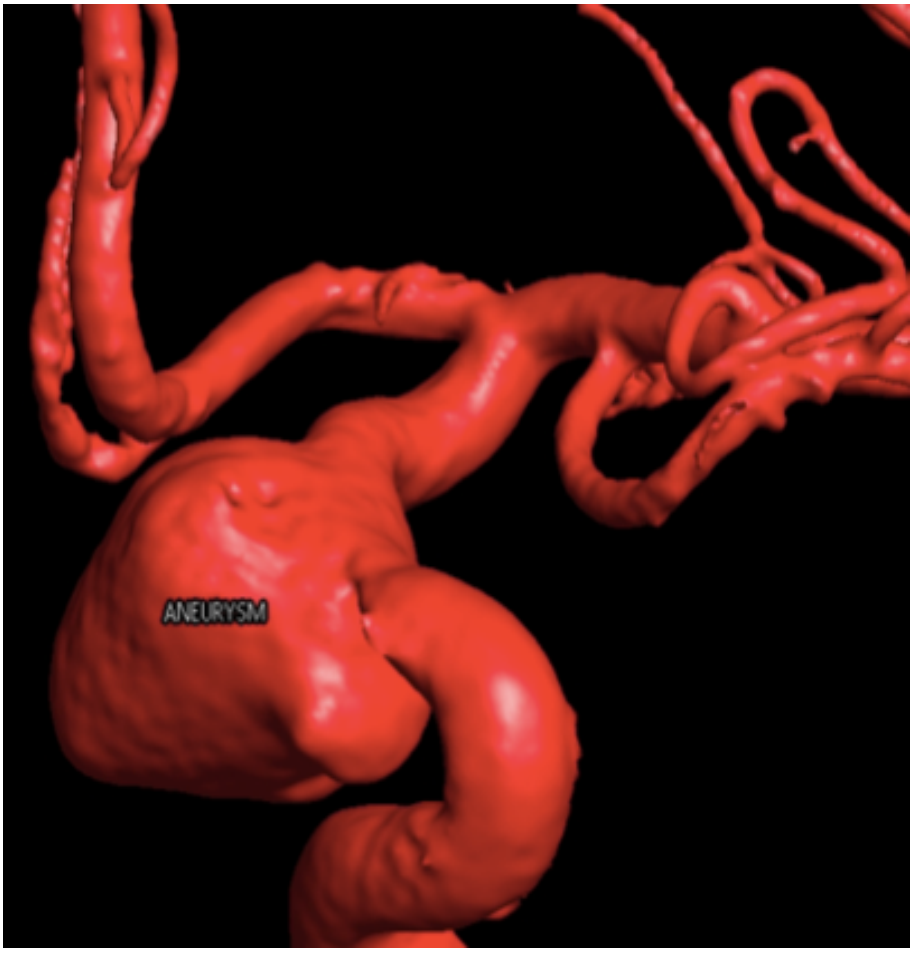


Figura 2 –Imagem tridimensional do sifão carotídeo e um aneurisma sacular. Fonte: Extraída do arquivo do Serviço de Neurorradiologia, Neuri-Beaujon.

Apresentamos uma pequena revisão da literatura em forma tradicional com reiteração. Correlacionamos as opiniões da literatura com as pessoais incluindo algumas ilustrações e imagens radiológicas.

2.2 HEMODINÂMICA CEREBRAL

2.2.1 Artérias Cerebrais, o Polígono de Willis e suas Artérias Relacionadas

Nos seres humanos, a estrutura das artérias intracranianas difere consideravelmente das artérias sistêmicas, pois têm ausência da lâmina elástica externa; uma túnica média com menos tecido fibroelástico, porém tem uma desenvolvida lâmina elástica interna. A sua camada de músculo liso é geralmente reduzida ou desorganizada nas áreas de bifurcações vasculares (Lee, 1995; Ku, 1997). Além disso, existem significantes diferenças na configuração da estrutura vascular cerebral dos humanos (Morris, 1997). Provavelmente, resultado de um complexo processo com influência genética. Inicia com o embrião com a vasculogênese e continua com a angiogênese. A formação e persistência do segmento vascular implica na manutenção biológica que inclue ajustes e remodelamento de seus componentes (Berenstein et al, 2004).

Na **Figura 3**, apresentamos uma representação esquemática da vascularização encefálica e do polígono de Willis. Genericamente, o encefálo é irrigado por dois pares de grandes artérias: as duas artérias carótidas internas que se originam a partir das artérias carótidas comuns (Lee, 1995) que surgem do arco aórtico, do lado esquerdo e do tronco braquiocefálico no lado direito constituindo a circulação anterior. E as duas artérias vertebrais que surgem das artérias subclávias e constituem a circulação posterior (Makowicz et al., 2013). Ambas, circulação anterior e posterior estão conectadas entre si através das artérias comunicantes posteriores formando um anel vascular conhecido como círculo arterial de Willis (*circulus arteriosus cerebri*) ou simplesmente círculo/polígono de Willis (Blood Vessels of the Brain, 2013).

A circulação anterior se origina a partir das duas carótidas internas, as quais tem as duas curvas em forma de “S” ou também conhecida como "sifão carotídeo". Logo após o sifão carotídeo emergem as duas artérias cerebrais anteriores ligadas por uma única artéria comunicante anterior que se estende anteriormente. Lateralmente, temos as artérias cerebrais médias que consistem de extensões morfológicas das artérias carótidas internas (Makowicz et al., 2013). A circulação posterior é constituída a partir das artérias vertebrais que se fusionam formando a artéria basilar e originam dois ramos distais, as chamadas artérias cerebrais posteriores.

Thomas Willis, um médico inglês foi o primeiro a descrever a capacidade da circulação cerebral de garantir fluxo sanguíneo de uma área para outra através de uma rede colateral em sua famosa publicação chamada de *Cerebri Anatome* em 1664. O círculo de Willis é oficialmente nomeado como o *cerebri circulus arterial* (Symonds, 1955). Sua função depende da continuidade da sua configuração anelar (referido como integridade morfológica e funcional) que é conhecida por variar e apresentar constantes assimetrias (Krabbe-Hartkamp, et al., 1998).

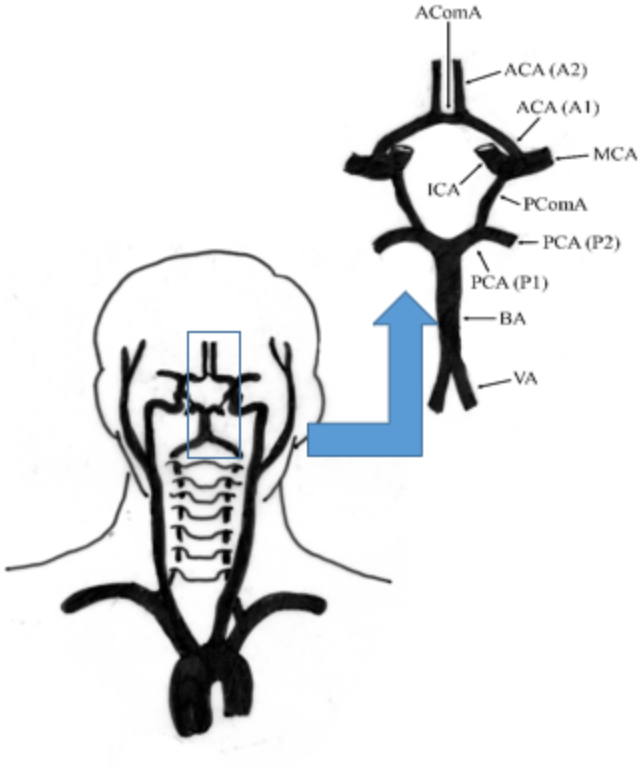


Figura 3 – Representação esquemática da circulação encefálica e do Polígono de Willis. Legenda: AcomA= artéria comunicante anterior, ACA= artéria cerebral anterior, MCA= artéria cerebral média, PCA= artéria cerebral posterior, P1= segmento P1, P2= segmento P2, BA=artéria basilar, VA= artéria vertebral.

O círculo de Willis circunda a haste pituitária e serve com importante via no sistema de colaterabilidade da circulação cerebral, proporcionando trocas entre o suprimento de sangue do cérebro anterior e o rombencéfalo, ou seja, entre a carótida interna e os sistemas vertebrobasilares, após a obliteração de conexões embrionárias primitivas (Lie et al, 1968; Saki et al., 1977; Baptista, 1964; Krabbe-Hartkamp et al., 1998, Kapoor et al., 2008; Liebeskind, 2013).

2.2.2 Variantes Anatômicas

O estudo da filogênese da vascularização encefálica arterial tem sido intensamente debatido e grande quantidade de informação é vista na literatura. Os princípios do funcionamento da hemodinâmica cerebral foram descritos por Guyot, em seguida por Duret e serviram de base para a maioria dos clássicos estudos descritos na literatura. A maioria desses estudos citam as variantes anatômicas do polígono de Willis dentro da circulação cerebral e são baseadas em dissecções anatômicas ou estudos de autópsias (Adachi, 1928; Padget, 1945; Daniel et al., 1953; Alpers et al., 1959; Batista et al., 1964; Fisher, 1965; Lazorthes et al., 1977; Efethkar et al., 2006; Ashwini et al., 2008; Ansari, 2011; De Silva et al., 2011). No entanto, um dos problemas que se observa na maioria dos estudos seria a existência de vieses operador-dependentes levando muitas vezes a resultados com uma certa perda de acurácia.

Um dos primeiros anatomistas a estudar e ilustrar a circulação cerebral foi o antropologista japonês Buntaro Adachi no final do século 19. Naquela época, no Japão um dos principais focos da antropologia teria sido a comparação entre as raças. Adachi acreditava que existiam diferenças morfológicas além dos ossos que eram comumente estudados em sua época e, portanto, investigou os outros tecidos moles do organismo humano. Ele estudou intensamente as variações do sistema arterial e venoso dos japoneses, e seus livros além de terem sido bastante prestigiados na época são de valor inestimável como referência para a variação anatômica humana (Watanabe et al., 2012).

Ilustramos o clássico trabalho de Adachi na **Figura 4** mostrando as diferentes variações no polígono de Willis com 83 dissecções anatômicas cerebrais (59 homens e 24 mulheres). Ele descreveu separadamente vaso a vaso, as possíveis variações hipoplásicas e as combinações entre elas.

Outro autor bastante citado é uma celebre ilustradora, artista e neuroembriologista do Hospital Johns Hopkins que trabalhou com Walter Dandy, a Dorcas Hager Padget. Ela publicou um dos primeiros trabalhos sobre anatomia vascular, embriologia e desenvolvimento das artérias e das veias e ainda sobre a variabilidade das artérias intracranianas (Komiyama, 2009).

Vários trabalhos que se destacam na literatura foram realizados por Riggs e Rupp, 1963, Fisher, 1965; Lazorthes et al., 1979, Milenkovic et al., 1985; El Khamlichi et al., 1985; Kapoor et al., 2008.

Relativo a Lazorthes et al. realizaram um dos mais extensos e minuciosos trabalhos sobre variantes anatômicas e identificaram mais de 22 subtipos de variantes do polígono de

Willis. Efekhar et al. compararam 102 pacientes apenas do sexo masculino detectaram apenas 11 subtipos de variações anatômicas do polígono de Willis similares a Lazorthes (Efekhar et al., 2006).

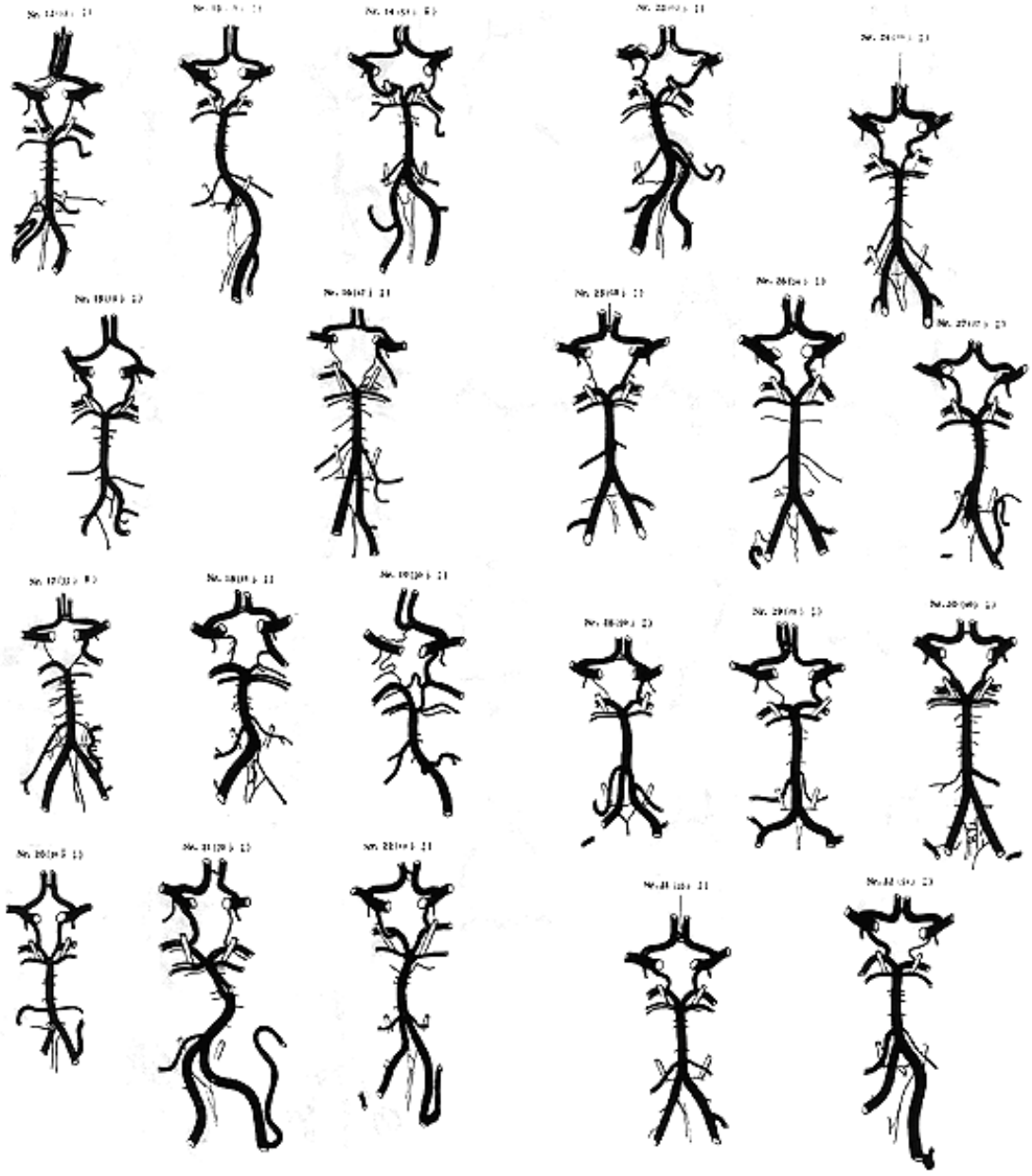


Figura 4 – Variabilidade do Polígono de Willis. Fonte: Extraída de Adachi,1928.

Um polígono considerado completo é visto apenas em 20-25% dos pacientes (Harnsberger et al., 2006; Osborn, 1999, Norton et al. 2012). Porém, funcionalmente o polígono de Willis parece estar presente na maioria dos indivíduos. Em torno de 50% das pessoas, pode-se ligar uma carótida sem repercussão (Matas, 1914) denotando uma boa funcionabilidade do polígono de Willis e uma comunicação bem desenvolvida entre a

circulação anterior e posterior. Estudos têm mostrado que existem diferenças entre homens e mulheres no que tange a configuração do polígono de Willis e quanto a presença de variantes anatômicas (krabbe-Hartkamp et al., 1998; Horikoshi et al., 2002; Silva Neto et al., 2011). Outras evidências tem mostrado diferenças raciais e étnicas relacionadas com a circulação cerebral. Os resultados com populações ainda são conflitantes, mais estudos são necessários (Efekhar et al., 2006). Horikoshi et al., 2002; Bor et al., 2008; Silva Neto et al., 2012 estudando os aneurismas intracranianos e as variantes anatômicas detectaram uma possível correlação entre a localização dos aneurismas e a variante anatômica correspondente. Diferenças quanto a lateralidade também tem sido vistas, aparentemente as variações anatômicas associadas com aneurismas intracranianos seriam mais comumente encontradas no lado direito comparado com o lado esquerdo (Stojanovic et al., 2009).

Com relação a localização, apesar de que na circulação anterior tem se observado um certo grau de assimetria entre as artérias cerebrais anteriores presentes em cerca de 80% dos pacientes. As variantes anatômicas parecem ser mais frequentemente observadas na parte posterior do círculo de Willis (80%) do que na parte anterior (50%) (Pedroza et al., 1987; Hoksbergen et al., 2003).

Na circulação anterior, as anomalias mais comumente observadas são a hipoplasia (10%) e /ou a ausência completa ou aplasia (1-2%) do segmento A1 (10%). Variantes menos frequentes são a artéria mediana do corpo caloso (2-13%), a artéria cerebral anterior ázigos (0,3-2%) e as fenestrações. Quanto as fenestrações, elas parecem ser cada vez mais observadas, onde estudos tem mostrado uma prevalência de até 40% dos pacientes (De Gast, 2008). Outras variantes mais raras seriam a artéria cerebral anterior infra-óptica e as variantes da artéria oftálmica como a persistência da artéria oftálmica dorsal e a artéria oftálmica cavernosa (Dilenge, 1980; Komiyama, 2009).

Quanto as variantes da circulação posterior, elas correspondem a uma frequência entre 10% a 46% dos indíviduos estudados por Merkkola et al., 2006 e Efekhar et al., 2006 sendo a presença de hipoplasia dos segmentos P1 (isto é, o diâmetro externo menor do que 1mm) observada em 12% a 60% dos casos estudados por Efekhar et al., 2006 e Stopford, 1916.

Outra variante bastante comum é a presença de artéria cerebral posterior do tipo fetal, a qual pode ser completa ou incompleta (Shaban et al., 2013). A variante completa é definida como a artéria cerebral posterior que se origina completamente da artéria carótida interna sem conexão com a artéria basilar. Por outro lado, a variante parcial é definida como artéria cerebral posterior proveniente de artéria carótida interna com uma pequena ou estreita ligação com o sistema vertebrobasilar. Ambas tem sido demonstradas em indivíduos saudáveis (15-

40%) (Alpers et al., 1959; Padget, 1945; Shaban et al., 2013). A variante parcial parece mais frequente vista unilateralmente (11-29%) comparada com bilateralmente (1-9%). Outras variações observadas são a duplicação da segmento P1, a fusão da artéria cerebelar superior e as fenestrações (Shaban et al., 2013).

2.3 MECANISMOS DA BIOGÊNESE DOS ANEURISMAS INTRACRANIANOS

Com base em evidências atuais, a fisiogênese dos aneurismas intracranianos apesar do constante surgimento de novas teorias, ainda não foi completamente compreendido (Lasheras, 2007). O processo de gênese dos aneurismas intracranianos é considerado como uma interação entre forças hemodinâmicas levando a uma deformação plástica estrutural com um abaulamento permanente, e subsequente ruptura pelo efeito de uma pressão interna oscilatória e fadiga estrutural (Lasheras, 2007).

O consenso atual parece envolver um complexo processo evolutivo onde vários fatores biológicos estariam envolvidos, fundamentalmente levando ao remodelamento destrutivo da parede arterial. Além de fatores biológicos potencialmente envolvidos e fatores funcionais dentre eles, a própria morfologia e a geometria vascular, forças hemodinâmicas e/ou estado de hipervelocidade em conjunto com os fatores endógenos inerentes à própria parede vascular estariam envolvidos. A fragilidade e a vulnerabilidade são possíveis co-fatores desse processo (Goldsmith et al., 1991; Krex et al., 2001; Gasparotti e Liserre, 2005; Brisman et al., 2006; Lasheras 2007; Bor et al.,2008; Rinkel et al., 2008; Meng et al., 2011; Cebral, 2010; Frosen et al., 2012).

As áreas de bifurcações das artérias aparentam ser mais vulneráveis e mais suscetíveis a danos com mudanças na pressão, força de cisalhamento e outras forças hemodinâmicas. Portanto, sofreriam um processo de remodelamento vascular como um resultado de processos inflamatórios, infecções, processos degenerativos, e mesmo devido ao envelhecimento. Por isso acredita-se que o estresse hemodinâmico ocorreria mais a nível das bifurcações, curvas e próximo ao ângulo dos vasos (Bruno et al, 1998; Wermer et al., 2007; Lasheras, 2007; Krex et al, 2001; Bor et al., 2008).

No entanto, um dos grandes desafios desta doença é desventar os mecanismos biológicos envolvidos em todo o processo da história natural dos aneurismas que aparentemente se interligam. Na **Figura 5** resumimos a interação desses fatores entre si. Desde sua iniciação, seu crescimento, sua ruptura, sobre os processos inflamatórios e degenerativos envolvidos e durante a recanalização que dependendo do caso pode ter altas

taxas. Além disso, saber porque os aneurismas na maioria dos casos permanecem silenciosos até que incidentalmente sejam detectados ou no rastreio de doenças neurológicas ou por ocasião de uma expansão em seu tamanho ou ainda decorrente de uma ruptura (Pokrovskii et al., 2003, Szilagyi, 1982).

Uma vez que o aneurisma se forma, as mesmas forças hemodinâmicas causariam muitas vezes a expansão do saco aneurismático, bem como a geometria vascular e a continuidade do processo degenerativo na parede vascular poderiam levar a ruptura aneurismática que poderia ser a primeira manifestação da existência do aneurisma que é muitas vezes catastrófica. No entanto, o mecanismo exato mantém muitas incógnitas (Stehbens, 1989; Schiewink, 1997; Krex et al., 2001; Krishchek e Inoue, 2006; Weir, 2002; Zhang et al., 2003; Nahed et al., 2007; Ruigrok et al., 2005; Brisman et al., 2006; Sadasivan et al., 2013).

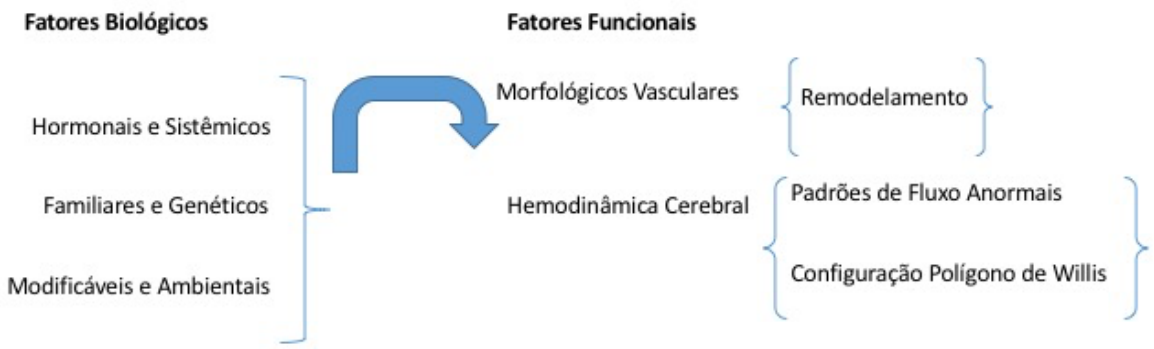


Figura 5 - Interação entre os fatores biológicos e funcionais entre si. Fonte: Elaborada pela autora.

A interação de todos esses fatores gerariam forças hemodinâmicas persistentes que em conjunto com a remodelação da parede vascular envolvendo pelo menos quatro processos celulares (crescimento celular, apoptose e migração, com a produção ou degradação da matriz extracelular) levariam a interações dinâmicas entre os fatores de crescimento gerados localmente, substâncias vasoativas, e esses fenômenos hemodinâmicos.

Entre estas mudanças, podemos citar:

1) Aumento do nível de elastase plasmática (Baker et al., 1995) e expressão alterada ou atividade das metaloproteinases e seus inibidores teciduais (Bruno et al., 1998);

2) Alteração de moléculas nucleares envolvidas na reparação da remodelação vascular dos tecidos;

3) Modificação da manutenção da matriz extracelular (devido a um desequilíbrio entre a degradação e a síntese de colágeno) (Krebs et al., 2000);

4) A depleção de oxigênio levando à liberação de fatores de crescimento;

5) Alterações nas moléculas de adesão celular, a seguir da ativação de células na zona de penumbra (por exemplo, por estímulos oxidativos);

6) A presença de aberrações genéticas (genes/ou regiões genéticas que codificam colágenos, elastina, óxido nítrico, alfa-1 antitripsina, metaloproteinase da matriz);

7) Outros fatores nutricionais, como a fibronectina (uma proteína ácida e rica em cisteína), policistina, endoglina (um fator de crescimento transformador dos beta-receptores), versicano, perlecano, serpina e fibrilina envolvidas na formação de trombo intraluminal e não nutricionais como a fibrina que está relacionada com a turbulência do fluxo de sangue.

2.3.1 Fatores Biológicos

2.3.1.1 Fatores Sistêmicos e Hormonais

O sexo feminino e a idade são um dos mais conhecidos fatores de risco dos aneurismas intracranianos. Na mulher, é bem frequente o aparecimento de aneurismas intracranianos, e particularmente aneurismas múltiplos e em espelho. As estatísticas variam entre 54 a 61% dos aneurismas intracranianos em geral. O risco aumenta significantemente com aneurismas múltiplos (Sarti et al., 1991) e em certas localizações como o sifão carotídeo podem atingir até 90% dos casos conforme nossa series descrita nos capitulos a seguir. Outro achado foi de que no sexo feminino existe tanto um risco maior de desenvolver aneurismas, como também um aumento do risco de ruptura sendo 3 vezes maior em homens e cinco vezes maior em mulheres (Rinkel et al.,1998).

Estudos mostram que as mulheres tem um efeito protetor na pré-menopausa. Acredita-se que a deficiência de estrogênio na menopausa provoca uma redução no teor de colágeno de tecidos (Neil-Dwyer et al.,1983; Jamous et al., 2005). Esta perda de massa de colágeno pode contribuir para o desenvolvimento do aneurisma em mulheres pós-menopáusicas, análoga à

situação em pacientes com doenças do tecido conjuntivo onde a frequência de aneurismas intracranianos é mais elevada do que na população normal. Essa influência hormonal também tem se observado nos acidentes vasculares isquêmicos e na doença coronariana (Samai et al., 2015). Longstret et al., realizou um estudo caso-controle e verificaram que mulheres pré-menopausa sem história de tabagismo ou hipertensão estavam em risco reduzido de hemorragia subaracnóide em comparação com as mulheres da mesma idade pós-menopausa (Odds Ratio 0.24) (Longstret et al., 1994).

Os hormônios sexuais agem na reatividade da vasculatura cerebral. *In vivo*, testosterona e estrogênio parecem ter efeitos opostos na reatividade vascular sendo que o estrogênio tende a causar efeito de vasodilatação contrapondo o efeito de vasoconstritores (Miller e Duckles, 2008) Outros estudos mostraram que as artérias femininas são menos constrictas devido ao efeito que o estrogênio tem sobre o óxido nítrico no endotélio (Li et al., 2004). Outras hipóteses seriam que os diametros arteriais seriam menor em mulheres com excecao do diametro da arteria comunicante posterior (Valenca, 2012).

Quanto a presença de outros aneurismas em outras localizações. Recentemente se c-onstatou que aneurismas da aorta torácica (AAT) e aneurismas intracranianos podem coexistir. Um estudo estudando 212 pacientes com AAT detectou aneurismas intracranianos em 9% dos pacientes, sendo mais frequente naqueles com aneurismas na aorta descendente *versus* ascendente. Inclusive pacientes com válvula aórtica bicúspide tem fator de risco conhecido para ATT com maior risco de desenvolver aneurismas intracranianos (Kuzmik et al., 2010). Um estudo analisando a prevalência de ATT em pacientes com aneurisma abdominal e comparando os sexos mostrou que 2% dos homens tinham aneurisma da aorta ascendente comparado com 25.8% das mulheres ($p < 0.0001$), and 6.6% dos homens tinham aneurisma do arco aórtico comparado com 10.5% das mulheres ($p < 0.4$) (Agricola et al., 2013).

2.3.1.2 Fatores Genéticos e Familiares

Alg et al. recentemente realizaram uma meta-análise abrangente envolvendo sessenta e um estudos, incluindo 32.887 casos de aneurismas e 83.683 pacientes saudáveis e identificaram 19 polimorfismos de nucleotídeo único associados aos aneurismas intracranianos. Os polimorfismos de nucleotídeo único foram encontrados dentro do cromossomo 9 e dentro do inibidor da quinase do gene inibidor 2B antisense dependente da ciclina (OR 1.29; 95 Cl 1.21-1.38) ; (OR 1.24; Cl 95% 1.20-1.29) no cromossomo 8, perto do

gene regulador de transcrição (OR 1.21; CI 95% 1.15-1.27;: OR 1.19; IC 95% 1.13-1.26), e no cromossomo 4, perto da endotelina receptor (OR 1.22; IC 95% 1.14-1.31) confirmando uma contribuição genética substancial para os aneurismas intracranianos esporádicos, implicando múltiplas vias fisiopatológicas, principalmente em matéria de manutenção vascular endotelial. No entanto, outras doenças complexas requerem estudos de replicação em larga escala em um espectro completo de populações, com investigação de como variantes genéticas relacionadas com fenótipo e.g o tamanho do aneurisma, a localização e o *status* de ruptura (Alg et al., 2013).

Existe também uma maior predisposição aos aneurismas intracranianos entre os familiares de pacientes com aneurisma (Ter Berg et al., 1987). Ronkainen et al., mostrou que a prevalência de aneurismas em pacientes com familiares de primeiro grau tende a ser 9% maior que a população em geral (Ronkainen et al., 2000).

Outros estudos mostraram que a história familiar de hemorragia subaracnóide e de aneurismas aumentou em 3.6 o risco de aneurismas. Contudo, embora pareça que exista alguma síndrome genética envolvida, ainda não tem sido associado com nenhuma síndrome hereditária em particular. O modo de herança é variável, com transmissão autossômica dominante, recessiva e multifatorial evidente em famílias diferentes (Foroud, 2012). Aneurismas familiares têm sido associados a vários *loci* cromossômicos e tendem a romper-se com tamanho menor e em pacientes mais jovens do que os aneurismas esporádicos. Irmãos muitas vezes experimentam ruptura na mesma década de vida (Broderick, 2009).

A síndrome de Moya-Moya também está associada com um aumento da frequência de aneurismas intracranianos. Embora a maioria dos casos de Moya-moya é esporádica, provavelmente há uma suscetibilidade genética subjacente à doença e a ocorrência familiar é conhecida. Existem evidências demonstrando uma ligação com outras doenças de ordem hereditária como a doença renal policística, síndrome de Ehlers-Danlos, síndrome de Marfan, deficiência de alfa-1-antitripsina, neurofibromatose, lúpus eritematoso, artrite de Takayasu, arterite de células gigantes e aneurismas intracranianos (Weir et al., 1998; Lietchfield et al., 1998; Conway, 1999; Chaulhod et al., 2013). Certamente mais estudos são necessários a esse nível. Ainda está incerto, se seria ligado a uma influência genética ou populacional. Existem poucos estudos populacionais a esse respeito. Os estudos populacionais sobre aneurismas intracranianos estudando os fatores genéticos e familiares descritos na literatura foram realizados basicamente na Escandinávia e parecem que os aneurismas não tem claramente uma influência genética ainda bem conhecida.

2.3.1.3 Fatores Modificáveis, Nutricionais e Outros

Os fatores modificáveis ligados a formação de aneurismas intracranianos que se destacam são: a hipertensão arterial, o tabagismo, o uso abusivo de substâncias, os fatores nutricionais e emocionais (St Jean et al, 1986; Rinkel et al., 1998). Maioria desses fatores modificáveis se sobrepõem com os fatores associados com a ruptura e a presença de hemorragia subaracnóide.

Pacientes tabagistas têm um risco maior não somente de desenvolver aneurismas, mas também de ruptura, que também aumenta consideravelmente com o sexo sendo três vezes maior em homens e cinco vezes maior em mulheres (Rinkel et al., 1998). Vlak et al., 2011 identificaram que os fumantes de cigarro apresentaram um risco significativamente aumentado de hemorragia subaracnóide em comparação com uma população controle; o risco relativo para os homens e mulheres foi de 3.0 e 4.7, respectivamente, e o risco aumenta com o número de cigarros fumados. Além disso, existiria um efeito aditivo entre hipertensão e tabagismo, onde aqueles hipertensos fumantes tiveram um risco de quase quinze vezes maior em comparação com não-fumantes normotensos (Bonita et al., 1986; Vlak et al., 2011). O mecanismo pelo qual o tabagismo predispõe à formação de aneurisma pode estar relacionado com a baixa da antitripsina alfa-1, um inibidor de proteases importantes, tais como a elastase. O suporte para esta hipótese deriva de estudos que sugerem que os pacientes com deficiência de alfa-1-antitripsina estão em maior risco de formação de aneurisma (St Jean, 1996).

A ingestão de moderada a elevada de álcool aumenta o risco de hipertensão arterial e consequemente aumenta o risco de formação de aneurismas intracranianos. Em uma revisão sistemática, o consumo elevado de álcool foi um fator de risco significativo para hipertensao arterial, tanto na longitudinal (RR 2.1, IC 95% 1.5-2.8) e estudos de caso-controle (OR 1.5, IC 95% 1.3-1.8) (Feigin et al., 2005). Por outro lado, quanto ao uso de drogas ilícitas e álcool, existem uma prevalência maior entre homens jovens (menor que 45 anos). Embora o uso de drogas e álcool é mais prevalente entre os homens, estudos recentes demonstram que uso de álcool entre as mulheres tem se aproximado dos homens (Samai et al., 2015).

Dentre os fatores nutricionais, a obesidade paradoxal ainda está em estudos (apresentamos um capítulo exclusivo sobre esse novo achado). A hipercolesterolemia e o exercício físico regular parecem diminuir o risco de formação de aneurisma; há alguma especulação de que esse efeito é mediado através da terapia com estatinas. Os fatores emocionais embora estejam ligados com a ruptura ainda não está claro se estão relacionados

como fatores de risco que atuariam cronicamente na formação dos aneurismas (Schuie et al., 2010).

2.3.2 Fatores Funcionais

Segundo Adair baseado principalmente em artigos das "Research Publications of the Association for Research in Nervous and Mental Diseases", vol. 18, 1938 os três principais conceitos funcionais da circulação arterial são consistência, economia de distribuição e conveniência de suprimento. Em relação a circulação cerebral, a mesma é estabelecida e garantida por uma organização anatômica e mecanismos fisiológicos particulares. Dentre as suas características anatômicas especiais situam-se: (1) proteção oferecida pela caixa craniana, (2) sinuosidades, angulações e ramificações de grandes artérias, (3) diversos sistemas anastomóticos das artérias cerebrais (Adair, 1947).

As artérias cerebrais são um constante processo de adaptação com mudanças na forma, tamanho conforme as necessidades nutricionais. As forças hemodinâmicas seriam responsáveis pelas modificações na morfologia vascular e consequentemente estimulariam mudanças na angioarquitetura local e regional e.g formação de aneurismas relacionados com o fluxo e o desenvolvimento de circulação colateral cerebral (Lasjaunias, 2002).

2.3.2.1 Fatores Morfológicos

Ainda não foram elucidados a anatomia funcional de formação dos aneurismas ou também chamado de processo de remodelamento vascular (Loschley et al, 1966; Lasheras, 2007; Sforza et al. 2009). Até o momento, acredita-se que o conhecido estresse hemodinâmico parece incitar mudanças murais e resultaria na angiogênese focal, regional e mudanças hipertróficas que resultariam em constrição do lumen arterial ou através de ajustes na morfologia arterial levando ao surgimento do remodelamento vascular. Embora acredita-se que o aneurisma seja uma doença da parede vascular (Tulamo et al., 2010; Krings, 2011) Dependendo do subtipo morfológico, a literatura hipotetiza que exista um processo patológico diferente.

Quanto a sua morfologia, normalmente os aneurismas intracranianos são divididos em oito principais grupos: saculares, dissecantes, fusiformes, ectasias arteriais, relacionados com fluxo e micoticos. Subtipos mais raros são os tipos: *blood blister like* e os pseudoaneurismas. (Krings et al, 2011).

Quanto aos aneurismas saculares tendem a crescer perto de bifurcações, onde a artéria faz um ângulo reto entre a artéria principal e suas ramificações, foram bastante estudados por Rothon através de estudos microcirúrgicos (Wang et al., 2009) e são entre os mais frequentes, estimativas variam entre 66-98% dos aneurismas intracranianos. Os mecanismos ainda sao esclarecidos. O consenso atual é de que a morfologia vascular principalmente nas bifurcações vasculares geraria o estresse hemodinâmico com significante alterações nos parâmetros hemodinâmicos como a força de cisalhamento. Não existem evidências suficientes mas acredita-se que um aumento na força de fricção sobre o endotélio da parede do sangue parece relacionado com o aparecimento desses aneurismas (Gao et al., 2008). Outros fatores envolvidos seria o ângulo do vasos (Perktold et al., 1989; Meng et al., 2007; Bor et al 2008), a morfologia multilobulada dos aneurimas, certas localizações dentro do polígono de Willis, o ambiente perianeurismático como e.g o contato ósseo com o vaso (Sforza et al., 2009).

Os aneurismas não-saculares parecem ser exceções a estes princípios. Eles são geralmente dissecantes e alguns são chamados aneurismas fusiformes. Ao contrário dos saculares são mais frequentes no sistema vertebrobasilar, e mais comumente encontrados nos homens que na mulheres (Yamaura et al., 2000). Os aneurismas fusiformes são normalmente dilatados, tortuosos e dolicoectásicos. Normalmente não possuem um colo definido, com envolvimento circunferencial de toda artéria e frequentemente trombosados. Podem ocorrer em qualquer ponto da circulação cerebral, são comumente vistos na região do sifão carotídeo na porção cavernosa (Mawad e Klucznik, 1995).

Os aneurismas *blood blister like* ou da parede, as ectasias arteriais, os pseudoaneurismas e os aneurismas micoticos parecem ter similar patogênese que bastante difere dos aneurismas saculares, esses aneurismas são derivados de lesão na parede como dissecção, infecção ou origem neoplásica (Hara et al., 2000).

Quanto aos aneurismas relacionados com o fluxo são frequentemente associados com malformações arteriovenosas ou nos casos de aneurisma de novo apos a oclusao de vasos parentes. São causados pelo estado de hiperfluxo com consequente dilatação e mudanças patológicas nas artérias nutridoras (Redekop et al.,1998; Arambepola et al., 2010; Tutino et al., 2014).

Outros estudos também sobre a possibilidade de mudanças na morfologia em grandes como o tronco principal e artérias carótidas internas também poderiam ser responsável pela formação de aneurismas cerebrais (Sekhar et al., 1981). Estudos experimentais têm encontrado, no interior do um aneurisma onde o estresse hemodinâmico poderia ser causado por um fluxo turbulento sequencial e repetitivo. Este tipo de anormalidade é foi evidenciado

na cavidade de um aneurisma durante a sístole. Este fluxo torna-se anormal invertido durante a diástole, de modo que essas mudanças rápidas na direcção do fluxo continuam a causar fricção na parede interna do vaso e contribuem para a formação e progressão de um aneurisma (Gonzalez et al., 1992).

2.3.2.2 Fatores Hemodinâmicos

Os fatores hemodinâmicos tem sido implicado não somente na iniciação, mas em todo o processo de desenvolvimento, ruptura, inflamação, degeneração e recurrência ou recanalização dos aneurismas (Mantha et al. 2006; Jeong et al., 2012) Dentre os fatores hemodinâmicos implicados estariam os padrões de fluxo anormais (Castro et al., 2009; Chatziprodromou et al., 2010; Raschi et al, 2012) e as configurações do Poligono de Willis (Kayembe et al., 1984; Milenkovic et al., 1981, Merkkola et al, 2006; Eldawody et al., 2009).

Anormalidades do fluxo aneurismático e padrões anormais de fluxo vascular tem sido associados com a presença de aneurismas não só intracranianos, mas em outras localizações como coronária ou aorta ascendente (Koller et al, 1993; Stepp et al., 1999). Anormalidades na força de cisalhamento ou no gradiente da força de cisalhamento parecem estar envolvidos na história natural dos aneurismas intracranianos sendo um processo dinâmico em conjunto com a degeneração e inflamação da parede vascular (Bluestein et al., 1996) e tem sido abordados com os novos stents flow diverters (Fiorella et al, 2011).

A força de cisalhamento seria responsável pela regulação do fluxo sanguíneo e do calibre e também a estrutura histológica das paredes arteriais (Stepp, 1999, Meng et al. 2014; Dolan et al., 2013). Um aumento na velocidade do fluxo microvascular produz aumento da tensão de cisalhamento quando a viscosidade e diâmetro são constantes. O aumento da tensão de cisalhamento estimula a liberação de fatores que causem dilatação endotélio-dependente, aumentando assim diâmetro e diminuindo a tensão de cisalhamento. Inibição de dilatadores dependentes do endotélio, portanto, iria prejudicar a regulação da tensão de cisalhamento e levar a níveis mais elevados de cisalhamento intravascular durante aumentos no fluxo sanguíneo, ou seja, tensão de cisalhamento não seria regulada pelo seu valor de linha de base. Esta variação morfológica das camadas de endotélio vascular resulta em diferentes níveis de produção de substâncias vasoactivas, como o óxido nítrico (Guzman et al., 1997, Kamiya et al., 1988, Luscher & Tanner 1993, Tanweer et al., 2010; Dolan et al., 2011).

Em resumo, o calibre e também a estrutura histológica das paredes arteriais são reguladas pelo fluxo de sangue, particularmente pela força de cisalhamento. Na presença de células endoteliais e células do músculo liso, um aumento crônico da forca de cisalhamento devido ao aumento do fluxo sanguíneo arterial provoca uma resposta adaptativa da histologia da parede arterial, conduzindo a um alargamento e uma redução da forca de cisalhamento para valores da linha de base fisiológicas. No entanto, se a forca de cisalhamento é aumentada focalmente, que pode potencialmente causar um aumento focal de danos e para a parede arterial, denominado remodelação destrutivo, que é induzida pela produção excessiva de moléculas, tais como oxido nítrico.

As forças hemodinâmicas são responsáveis pelas modificações na morfologia vascular e consequentemente estimulariam mudanças na angioarquitetura local e regional e.g formação de aneurismas relacionados com o fluxo e o desenvolvimento de circulação colateral cerebral. As artérias cerebrais são um constante processo de adaptação com mudanças na forma, tamanho conforme as necessidades nutricionais. Contudo somente essas anormalidades isoladas não são suficientes para explicar a história natural dos aneurismas intracranianos

Ao analisar a hemodinâmica cerebral, verificou-se que o círculo arterial de Willis tem grande variabilidade, com assimetrias frequentes conforme descrevemos no capitulo dedicado a hemodinâmica cerebral. Além disso, existem grupos anastomóticos podem entrar em ação para reestabelecer uma circulação interrompida em casos especiais. Literalmente, os territórios destes dois sistemas superpõem-se parcialmente pois como se sabe, a circulação da região craniana depende do sistema carótida externa, desde a superficie até o nível da dura-máter e nesses territórios distribuem-se também vasos do sistema da carótida interna, como artéria meníngea anterior, a supra-orbitária e a frontal, ramos da artéria oftálmica (Adair, 1947).

Há evidências de que as variações anatômicas observadas no círculo arterial cerebral e os vasos de Willis relacionados possam desempenhar um papel na gênese de aneurismas intracranianos (Kayembe et al., 1984). Padget foi um dos primeiros a comparar o número de casos de anormalidades embriológicas com aneurismas e sem aneurismas (Padget, 1945). Acredita-se que um círculo assimétrico de Willis, seja congênita ou adquirida, é um fator de risco para o desenvolvimento de aneurismas, onde o estresse hemodinâmico produz alterações degenerativas que levam ao fluxo hiperdinâmico (Milenkovic, 1981).

Por outro lado, estudos recentes têm proposto que uma ausência congênita da capacidade anastomose do círculo de Willis é correlacionada com outras doenças cerebrovasculares como doenca microangiopática, referindo-se assim para o mecanismo

hipoperfusão no desenvolvimento de patologia isquêmica crênica ou doença cerebrovascular pequeno vaso (Ryan et al., 2015). Outra doença conhecida relacionada com o fluxo tem sido demonstrada com após a ligação da artéria carótida conforme já comentamos acima. Este procedimento foi realizado longo tempo para o tratamento de aneurismas gigantes do sifão carótideo como a técnica de escolha antes do desenvolvimento de terapia neuroendovascular. No entanto, este tipo de procedimento tem sido associada com a formação de aneurismas intracranianos de novo e em remodelação vascular induzida pelo fluxo (Gao et al., 1981). Estudos experimentais sobre a ligadura da carótida demonstraram que existiria um fluxo sanguíneo compensatório após a oclusão da carótida com remodelamento patológico secundário. O desenvolvimento adaptativo de fluxo ao longo do círculo de Willis resultaria na formação de um aneurisma da artéria carótida contralateral (Tutino et al., 2014).

É provável que o mesmo princípio pode ser aplicado aos aneurismas do sifão carotídeo e aos aneurismas da bifurcação da artéria carótida e os seus ramos, que pode ser explicado devido a uma alteração nos parâmetros hemodinâmicos a este nível. Estudos de fluxo têm evidenciado que o ponto de origem de um aneurisma intracraniana é distal em relação à bifurcação onde os gradientes seriam mais elevados (Alnaes et al., 2007). Portanto, é provável que o estresse hemodinâmico e o fluxo sanguíneo turbulento associado com os padrões de fluxo hiperdinâmicas poderiam causar um desgaste excessivo e vibrações, resultando em fadiga estrutural e a ruptura da lâmina elástica interna e, por conseguinte, a formação de aneurisma cerebral. Pacientes com padrões de fluxo hiperdinâmicas como resultado de condições de alto fluxo anormais ou outras vias colaterais são, portanto, predispostos a alterações degenerativas acelerados na parede do vaso e conseqüente crescimento de um aneurisma (Wiebers et al., 2003).

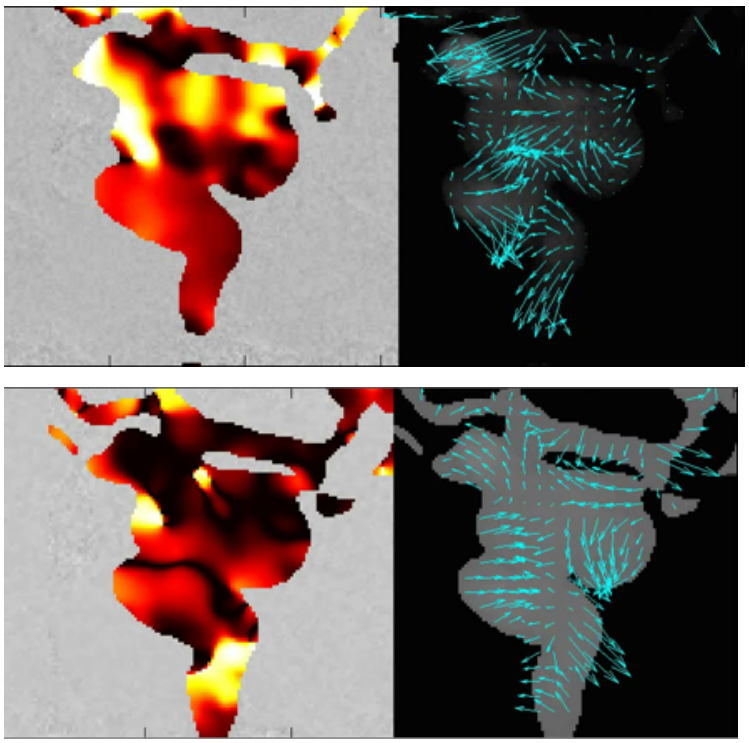
2.4 O SIFÃO CAROTÍDEO E ANEURISMAS RELACIONADOS

Os aneurismas do sifão carotídeo sempre foram um desafio para os neurocirurgiões e neuroradiologistas intervencionistas devido à complexidade anatômica da área onde eles estão localizados (Amacher et al., 1979; Sundt & Gelber, 1980; Dolenc, 1985; Hidashida, 1990; Drake et al., 1994; Roy et al.,1997; Hoh et al., 2001, Xu et al., 2011).

Uma nova abordagem dos aneurismas intracranianos, parte do tratamento endovascular tem sido idealizada para corrigir os distúrbios decorrentes dos distúrbios hemodinâmicos e morfológicos envolvidos na biogênese dos aneurismas intracranianos. Algumas ferramentas que têm sido incorporadas na sala de intervenção para ajudar o operador

na estratégica dos tratamentos como podemos visualizar na **Figura 6** abaixo, onde as alterações hemodinâmicas decorrentes da colocação do stent flow diverters são analisadas antes e depois do procedimento. Observa-se nítida alteração na disposição dos vetores que mudam de orientação, além disso também a cartografia de fluxo demonstra uma redistribuição de fluxo (áreas escuras) após a colocação do stent dentro da circulação cerebral.

(A)



(B)

Figura 6 – Estudos de fluxo óptico realizado antes (A) e depois (B) da colocação do stent em um aneurisma do sifão carotídeo. Fonte: Extraída do arquivo do Serviço de Neurorradiologia, Neuri-Beaujon/ Suresnes.

Em se tratando dos aneurismas do sifão carotídeo, a problemática dos distúrbios hemodinâmicos e morfológicos parece ainda mais complexa e peculiar. De fato, os aneurismas que se desenvolvem na circunferência do sifão da carótida são bastante diversificados e por vezes lesões quase que aberrantes (Day, 1990; Larson, 1995; Roy, 1997; Hoh et al., 2001; Barami, 2003; Jin 2009; Ogilvy et al., 2011; Colby et al., 2012; Wang et al., 2013; kim et al., 2014; Ahn, 2014; D'Urso 2014; Alba et al., 2014).

Até o momento, não existem estatísticas sobre sua real frequência, porque esses aneurismas são na maioria clinicamente silenciosos e assintomáticos. Detectamos através de

estudo realizado em Paris que a maioria dos pacientes com aneurismas do sifão carotídeo eram encontrados de maneira incidental durante investigação por neuroimagem de sintomatologia banal. Apenas 20% desses pacientes tinham apresentado algum evento hemorrágico recente, enquanto mais de 90% do restante dos aneurismas intracranianos são descobertos na ocasião de ruptura, descrevemos melhor sobre isso no capítulo relativo a sintomatologia clínica dos aneurismas do sifão carotídeo ou artigo Editorial.

Outro fato curioso, revisando na literatura é que não existe uma terminologia precisa para os aneurismas do sifão carotídeo (kim et al., 2000; Sherif et al., 2009). Logo, possivelmente muitos dos aneurismas do sifão carotídeo tendem a ser subestimados estatisticamente, talvez devido a falta de marcos anatômicos e radiológicos precisos de delimitação. Esses aneurismas tem uma significante complexidade anatômica devido a área onde se localizam, que é relativamente de mais difícil acesso contida por um envoltório ósseo e uma série de estruturas anatomicamente complexas situadas próximo a base do crânio, sendo assim foram considerados inoperáveis por muito tempo. Até que técnicas endovasculares foram desenvolvidas e vem revolucionando a sua terapêutica (Debrun et al., 1981; Fox et al, 1987; Moret et al, 1991; Van del Schaaf et al., 2002; Jin et al., 2009; Know et al, 2010; Nelson et al., 2011; Colby et al., 2012; Lanzino et al., 2012; Sato et al., 2012, Wang et al., 2013; Tanweer et al, 2014). Dedicamos um capítulo exclusivo discutindo sobre as técnicas de tratamento endovasculares existentes até o momento. Além disso, apresentamos outro capítulo apresentando uma nova classificação proposta aos aneurismas do sifão carotídeo. Na **Figura 7**, ilustramos os diferentes tipos morfológicos de aneurismas do sifão que detectamos durante estudo de nossa séries.

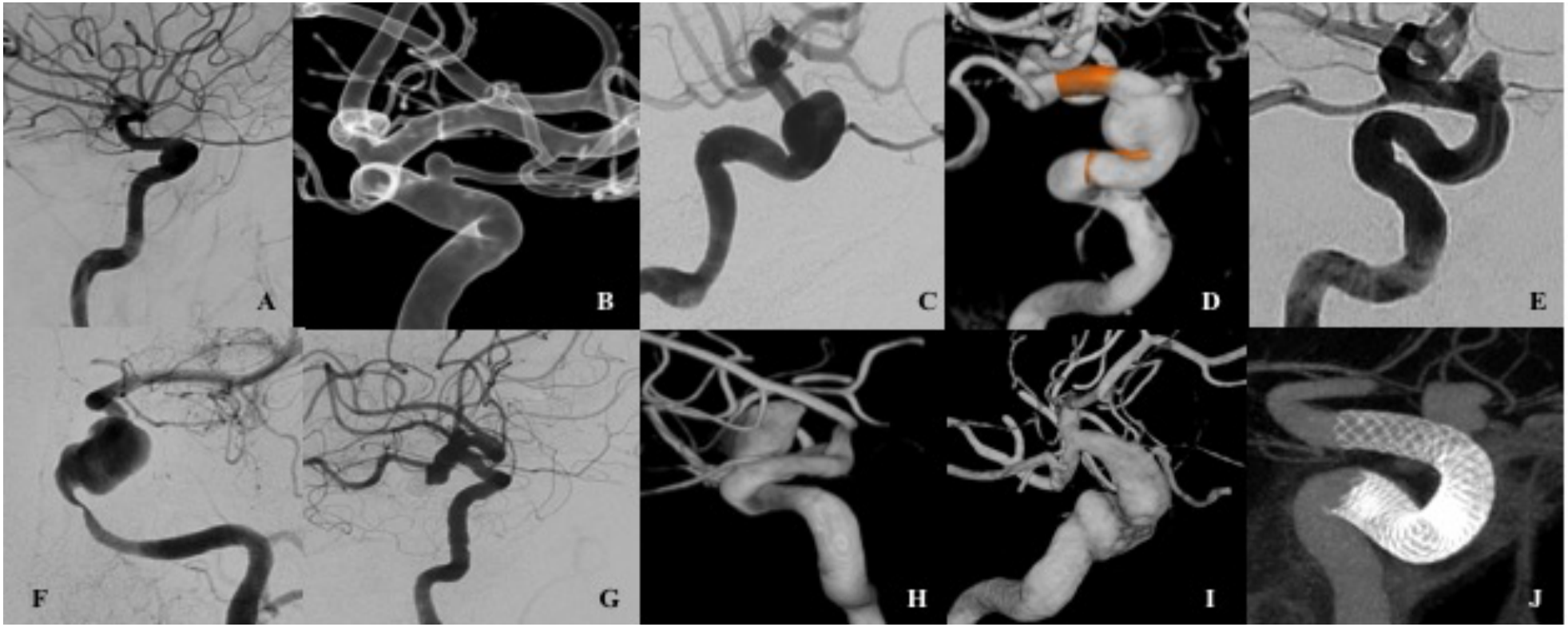
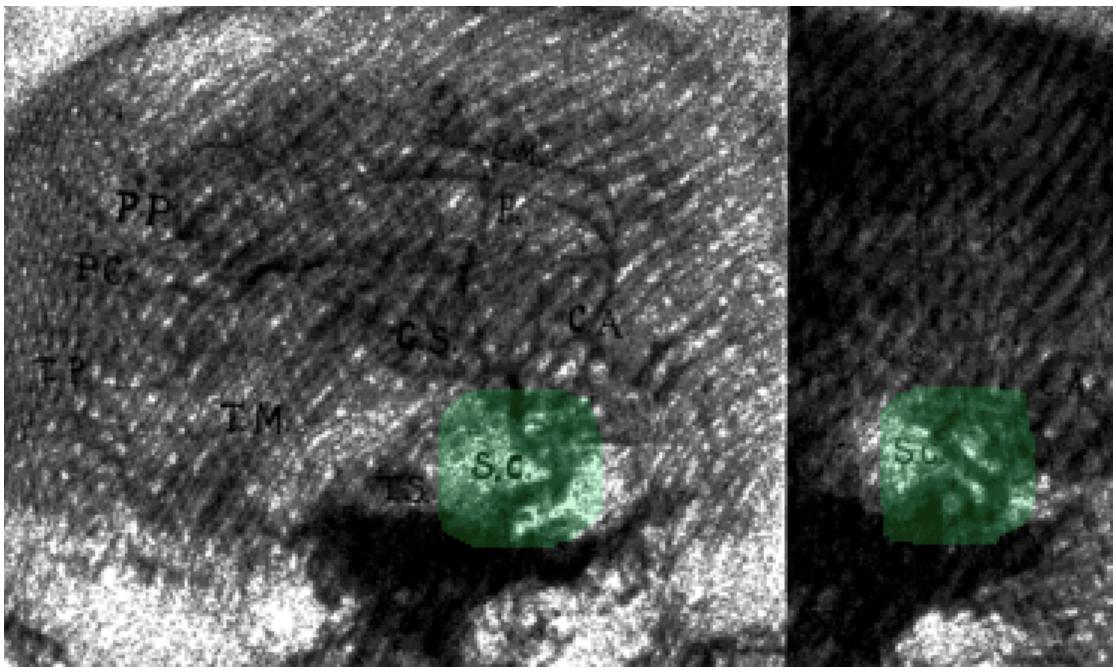


Figura 7 – Diferentes aneurismas localizados na artéria carótida interna e no sifão carotídeo. Imagem angiográfica ilustrando aneurisma cavernoso (A). Reconstrução tridimensional ilustrando um aneurisma saindo da artéria oftálmica (B), Imagem angiográfica de um aneurisma do segmento cavernoso com uma porção supra-clinóidea (C), Reconstrução tridimensional ilustrando aneurisma da porção cavernosa do sifão carotídeo (D), Imagem angiográfica ilustrando duplo sifão com aneurisma no segmento horizontal do sifão carotídeo (E), Imagem angiográfica ilustrando artéria carótida displásica com aneurisma gigante do sifão carotídeo (F), Imagem angiográfica ilustrando aneurisma do segmento comunicante posterior do sifão carotídeo (G), Imagem tridimensional ilustrando aneurisma do segmento oftálmico (H), Imagem tridimensional ilustrando aneurisma fusiforme do sifão carotídeo (I), Imagem tridimensional ilustrando aneurisma do segmento oftálmico tratado com stent Pipeline.
Fonte: Extraída do arquivo do Serviço de Neurorradiologia, Neuri-Beaujon. Fonte: Imagens originais elaboradas pela autora.

2.4.1 Estudos Anatômicos

A angiografia cerebral foi descoberta pelo neurologista Português Antonio Caetano de Abreu Freire de Resende, ou também conhecido como Egaz Moniz, através da realização das primeiras radiografias contrastadas para estudar a angioarquitetura dos vasos cerebrais em 1927 (Almeida, 1950; Lima, 1951; Schierhorn, 1981; Dagi et al., 2001, Harrigan, 2009).



(A) (B)

Figura 8 – (A) Primeira imagem radiográfica do sifão carotídeo e da artéria carótida interna com os seus ramos intracranianos, (B) Imagem radiográfica mostrando o duplo sifão. Fonte: Extraído de Moniz, 1933.

Cinco anos mais tarde, Moniz demonstrou um aneurisma no ramo da artéria carótida interna na base do crânio descrevendo o sifão carotídeo (Moniz, 1933) conforme ilustramos na **Figura 8**, baseada em imagens originais da publicação de Moniz no Lancet.

Essa porção da carótida ficou conhecida como sifão carotídeo ou, também, como sifão de Egaz Moniz. Essa última denominação foi dada em homenagem ao seu descobridor que introduziu essa nova terminologia anatômica que a partir de então passou a ser amplamente utilizada (Moniz, 1934; Pimenta, 1954).

Conforme descrição do próprio Egaz Moniz seria complexo de aplicar o termo “sifão carotídeo” e relacionar com a anatomia. Quanto aos limites anatômicos e radiológicos do sifão carotídeo como estrutura anatômica ainda continua confuso na literatura. Do ponto de vista imaginológico, o sifão carotídeo refere-se a aparência radiográfica da artéria carótida interna como uma série de voltas e curvas que caracterizam esta região anatômica (Moniz, 1933).

Anatomicamente não existem estudos específicos sobre o sifão carotídeo. Os estudos anatômicos descritos até então parecem ser mais atrelados as certas regiões e estruturas anatômicas vizinhas ao sifão carotídeo, e.g seio cavernoso, artéria oftálmica, etc.., Muitos desses estudos foram desenvolvidos por neuroanatomistas e por neurocirurgiões da base do crânio. Parkinson, Dolenc e kawase descreveram vários importantes marcos anatômicos em forma de triângulos nessa região (Parkinson, 1965; Parkinson, 1967; Dolenc, 1989, Watanabe et al., 2003).

Tentando situar melhor a anatomia da artéria carótida interna foram criadas classificações subdivididas em segmentos. Ilustramos as classificações mais conhecidas na **Figura 9.**

A primeira classificação foi desenvolvida por Fischer em 1938, onde ele dividiu elegantemente a artéria carótida interna em 5 segmentos: (C1) o cervical, (C2) o petroso, (C3) o cavernoso, (C4) segmento cerebral e (C5) que são classificadas de maneira retrógrada oposta à direção do fluxo de sangue. Essa classificação ainda é bastante utilizada em vários centros de neurointervenção endovascular e bastante citada na literatura.

Posteriormente, outras classificações foram sendo descritas na literatura através da análise angiográfica. Gibo et al. Desenvolveram uma classificacao dando mais atenção a artéria carótida supraclinóidea descreveu uma classificação mais direcionada especificamente aos aneurismas intracranianos e introduziu um sistema alfanumérico anterógrado, de C1 até C4: C1 - cervical, C2 - petroso, C3 - cavernoso, C4 - supraclinóide, sendo o segmento subdividido em oftálmico, comunicante posterior e coroidal (Gibo et al., 1981).

Bouthilier et al. baseou-se na classificação de Fischer, embora estruturamente diferente. Utilizou a designação alfanumérica de C1 a C6 sendo C1- cervical, C2- petroso, C3- lacerado, C4-cavernoso, C5-clinóide, C6-oftálmico, C7-comunicante posterior que foi basicamente dirigida para as técnicas neurocirúrgicas permitindo acessar os aneurismas da região paraoftálmica (Bouthilier et al, 1996).

Antes disso, Ziyal et al. descreveram uma classificação simplificada removendo o segmento lacerado de Bouthilier, e, ao invés do segmento oftálmico, delimitação do segmento

cisternal e em 5 subtipos (C1- cervical, C2- petroso, C3- cavernoso, C4- clinóideo, C5- cisternal) (Ziyal et al., 1995).

Lasjaunias e Santoyo-Vasquez, 1984 desenvolveram uma classificação baseada nos fatores morfológicos e embriológicos e dividira em oito partes: 1. cervical (até o forame lacerado) 2. petroso ascendente 3. petroso horizontal 4. cavernoso ascendente 5. cavernoso horizontal 6. clinóide 7. oftálmico 8. terminal.

Shapiro et al. sugerem que a maior parte desses sistemas de classificação baseados em sistemas de numeração parece confusa, e portanto desenvolveram uma classificação segundo eles baseada em fatores endovasculares, sem correspondência alfanumérica, dividindo desde a porção cervical da artéria carótida interna até a bifurcação intracraniana em nove segmentos respectivamente: A-Cervical, B-Petroso, C-Cavernoso, D-Transicional, E-Oftálmico, F-Hipofisiária, G-Comunicante Posterior e T-Terminal (Shapiro et al., 2013).

Revisando rapidamente a anatomia dessa região do sifão carotídeo, situada logo após a bifurcação das artérias carótidas comuns, geralmente ao nível da quarta vértebra cervical, onde a artéria carótida interna aparece ser mais alargada (Bendorf, 2010).

O primeiro segmento de Fisher se estende quase verticalmente à base do crânio para chegar a abertura externa do canal carotídeo e entrar no osso petroso. Situa-se medialmente à veia jugular interna e o nervo vago geralmente entra em ambos os vasos (Bendorf, 2010).

Essa porção corre verticalmente e se transforma em medial e anterior para formar um joelho da carótida e torna-se a parte horizontal que emerge anteriormente e acima do forame lacerado para, eventualmente, deixar o canal ósseo próximo ao ápice petroso. O segmento petroso pode dar origem a dois pequenos ramos arteriais em 38% dos casos. A artéria vidiana usualmente emerge a partir da artéria maxilar interna que pode também surgir a partir da carótida interna petrosa (30%). A seguir, o segmento cavernoso começa na margem superior do ligamento petrolingual na porção posterior do seio cavernoso e termina no processo clinóide. Este segmento está dentro do seio cavernoso cercado de seus espaços venosos e por algum tecido conjuntivo trabecular (Rothon, 2002; Bendorf, 2010).

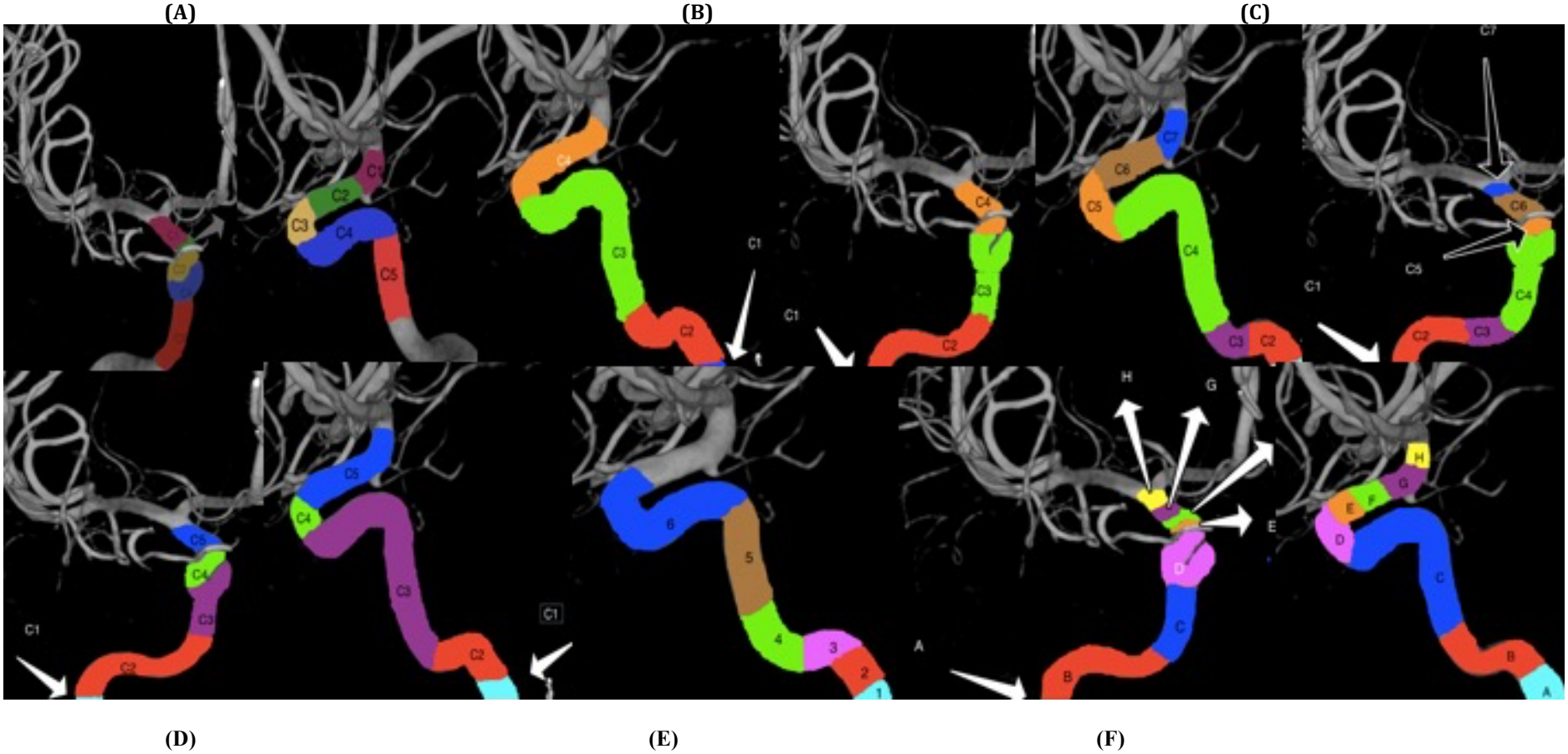


Figura 9 –Representação esquemática das classificações mais conhecidas da artéria carótida interna: **1-**Fisher em incidência AP (A) e Lateral (B), **2-** Gibo em incidência AP (A) e Lateral (B), **3**- Boutillier em incidência AP (1) e lateral (2), **4 -** Ziyal em incidência AP (A) e Lateral (B), **5-** Lasjaunias**, 6-** Shapiro em AP (A) e Lateral (B). Fonte: Imagem de base foi extraída do arquivo do Serviço de Neurorradiologia, Neuri-Beaujon, ilustrações originais criadas pela autora.

2.4.2 Estudos Embriológicos

A embriogênese das artérias carótidas internas começa a partir de 5 semanas de gestação. Normalmente, há também anastomoses embrionárias entre estes dois troncos principais: as artérias trigeminais; artérias óticas; artérias hipoglossos; e artérias proatlantais. A artéria comunicante anterior se origina a partir da artéria carótida interna. Durante o mesmo período de tempo, a artéria carótida interna se bifurca nas duas divisões craniais e caudais que posteriormente dará origem a artéria comunicante posterior. A divisão craniana dará origem ao complexo anterior, a artéria coróide anterior e a artéria cerebral média (Lasjaunias, 2002).

De acordo com Padget, a embriogênese é o resultado de duas fases importantes: em primeiro lugar, o desenvolvimento, a partir da divisão cranial da artéria carótida interna, de numerosas artérias que irrigam a parte anterior do cérebro; e, em seguida, a regressão de determinados segmentos arteriais no útero e, em alguns casos, durante o desenvolvimento do útero na idade adulta.

Na **Figura 10**, ilustramos a idéia do célebre neuradiologista Pierre Lasjaunias sobre o processo de segmentação ligado ao desenvolvimento da carótida interna e do sifão carotídeo, onde acreditava que a artéria carótida interna deriva de uma série de sucessivos segmentos distintos embriologicamente de cada uma das artérias embrionárias.

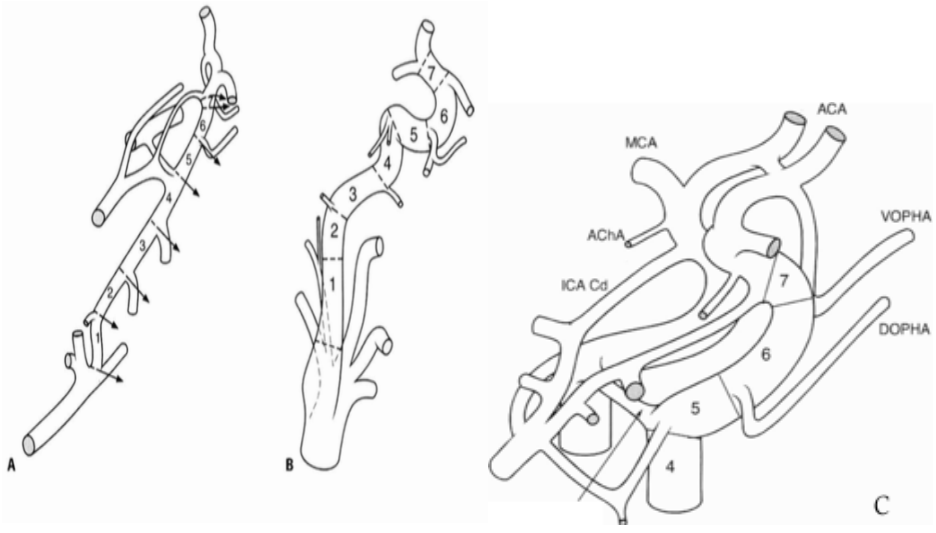


Figura 10 – (A) Segmentação embrionária da artéria carótida (B) Segmentação embrionária da artéria embrionária interna do sifão carotídeo e da artéria carótida interna com os seus ramos intracranianos, (C) Imagem centrada no sifão carotídeo Fonte: Extraído de Laujasnias, 2002. (Legenda: 1, 2,3,4, 5,6,7 DOPHA= artéria dorsal oftálmica, VOPHA= artéria ventral oftálmica, ACA= artéria cerebral anterior, MCA= artéria cerebral média, ACha= artéria choroidal anterior, ICA Cd= artéria carótida interna). Extraído de Lasjaunais, 2002.

Em 1984, Lasjaunias tentando aprimorar seu conceito, lançou o desafio de que a artéria carótida interna termina com a bifurcação originando um ramo rostral e um ramo caudal. Essa nova perspectiva se baseou na observação da agenesia segmentar da carótida interna distal ao segmento comunicante posterior. A partir desta perspectiva, um novo segmento (o oitavo segmento) distal a artéria carótida e a artéria comunicante posterior foi descrito que terminaria com a bifurcação em artéria cerebral média e artéria cerebral anterior(Lasjaunias e Santoyo-Vasques, 1984).

De acordo com Egas Moniz, o sifão carotídeo em 70% dos casos mostrava outra curvatura para a região frontal dando a impressão de duplo sifão (Moniz 1933; Moniz, 1934) conforme ilustramos na **Figura 11**. Posteriormente, os estudos anatômicos sobre o sifão carotídeo mostraram que 84% dos adultos têm artéria carótida interna com forma de duplo sifão característica (Platzer, 1957), mas curiosamente em recém-nascidos aparentemente a artéria toma um rumo muito mais retificado.

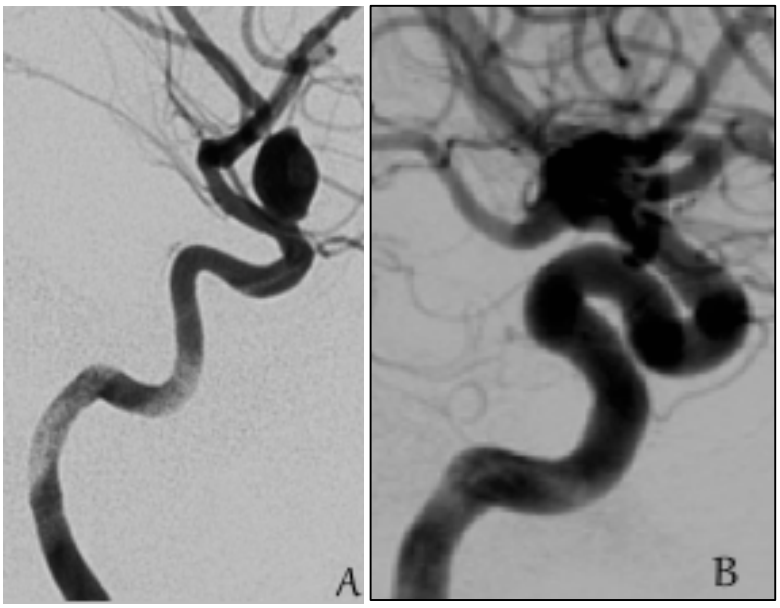


Figura 11 – Morfologia do sifão (A) Imagem angiográfica bidimensional da artéria carótida interna esquerda de uma paciente jovem (B) Imagem angiográfica bidimensional da artéria carótida interna direita. Fonte: Imagens elaboradoras pela autora a partir do arquivo do próprio Serviço de Neurorradiologia- Neuri-Beaujon.

Estudos particularmente da investigação de Weninger e Muller demonstraram que a anatomia da porção paraselar nas crianças difere distintamente do adulto, e particularmente a

porção paraselar da carótida dos recém-nascidos não forma um sifão (Weninger e Muller, 1999) indicando que a forma de artéria carótida interna é fortemente transformada durante a primeira infância. Além disso, em crianças, também são observados que em mais da metade dos casos, a bifurcação da artéria carótida primitiva ou origem da artéria carótida interna está normalmente localizada mais superiormente, quando comparada à origem dessa artéria no adulto, na altura da segunda e terceira vértebras cervicais (Dilenge, 1962).

2.4.3 Estudos Morfológicos e Hemodinâmicos

A importância clínica do estudo da morfologia e da hemodinâmica da vasculatura cerebral tem cada dia se salientado mais (Menshawi et al., 2015). Consequentemente, observa-se um significante aumento na quantidade de estudos e publicações sobretudo nos últimos 10 anos (Algra et al., 1998; Cebral et al., 2005; Chatziprodromou et al., 2007; Alnaes et al., 2007; Ansari et al., 2011).

Essa tendência não é apenas evidenciada na investigação e no tratamento dos aneurismas intracranianos (Gao et al., 2008; Jeong et al., 2012, Silva Neto et al, 2012, Cucchiara et al., 2013), mas nas patologias neurovasculares em geral: no acidente vascular encefálico isquêmico (Hoksbergen et al., 2013, Shaban et al., 2013; Ryan et al., 2015) e hemorrágico e nas cefaléias migranosas (Cucchiara et al., 2013).

Ambos tanto o aumento no número de publicações como a importância clínica desses estudos estão diretamente implicados como a impressiva evolução das ciências das imagens e dos materiais de cirurgia endovascular. A revolução tecnológica experimentada nos últimos tempos está diretamente correlacionada e cada dia envolve a necessidade de uma equipe multidisciplinar composta de engenheiros, técnicos especializados não apenas o cirurgião ou neurorradiologista (Djindjian et al., 1978; Wang et al., 2005; Bey et al, 2011; Sorkin et al., 2014; Girard, 2014).

Por outro lado, hoje é possível, graças a novas sequências de imagens e softwares avançados acessar a circulação cerebral mesmo por meio de estudos de imagens não invasivos como a angiotomografia, a angioressonância magnética ou o doppler transcraniano (Zwiebel et al., 1985Algra et al 1998; krabbe et al., 1998; Van Gelder et al., 2003; Hendrikse et al., 2005; Alnaes et al., 2007; Ansari et al., 2011; Makowicz et al., 2013). O screening vascular cerebral até recentemente só seria possível através de métodos invasivos como angiografia convencional, ou a céu aberto durante avaliação intra-operatória ou por meio de

autópsias (Fischer, 1965; Alpers et al., 1959; Lazorthes et al., 1979, Ter Berg et al., 1987; Hacen-Bey et al., 2011).

Consequentemente, esses recentes e fascinantes avanços na precisão do estudo da circulação cerebral tem permitido detectar cada vez com mais freqüência diferentes configurações, variantes da normalidade, anomalias e irregularidades na vasculatura cerebral.

Após a introdução dos métodos digitais e da técnica de Seldinger, a angiografia cerebral passou a ser considerada o padrão-ouro no diagnóstico por imagem para a doença neurovascular (Dagi et al, 2001). As novas técnicas de pós-processamento modernas tem transformado a angiografia cada vez mais informativa para os neurocirurgiões ou aos neurorradiologistas intervencionistas. O estudo aprofundado da anatomia da patologia vascular antes e após a cirurgia, muitas vezes através de angiografia cerebral seletiva, é um componente crítico do planejamento cirúrgico (Li et al., 2009).

A imagem tridimensional é crucial para a compreensão da anatomia vascular e ajudado na tomada de decisão cirúrgica. Esta é uma nova estratégia de combinar a angiografia cerebral seletiva adquirida de forma independente para criar uma representação mais precisa da anatomia vascular. Dada a crescente disponibilidade das tecnologias de aquisição e processamento de imagem relevantes, tem se tornado uma estratégia preciosa e auxiliar em procedimentos vasculares cerebrais (Hope et al., 2010).

Importantes avanços tem sido registrados nas técnicas de imagem morfológicas *in vivo* permitindo a visualização com alta precisão do sistema vascular cerebral e também consequentemente do sifão carotídeo.

No que concerne as técnicas não invasivas iniciou com o desenvolvimento da angiografia computadorizada com contraste ou ressonância magnética sem administração de contraste mediante a técnica "*time of flight"* ou "TOF" com reconstrução tridimensional, essa última considerada uma técnica de eleição por ser simples, com boa resolução temporal e permitir uma boa identificação das anormalidades e variantes normais das artérias cerebrais incluindo as artérias carótidas intra e extracranianas e seus ramos (Stock et al., 1996; Takano et al., 1990).

No caso do sifão carotídeo tanto a imagem bidimensional convencional angiográfica quanto as técnicas não-invasivas supracitadas fornecem uma imagem anatômica incompleta (Tamakloe et al., 2011). Graças aos novos estudos tridimensionais hemodinâmicos uma melhor avaliação para a morfologia do sifão carotídeo, particularmente devido à sua forma sinuosa (Kim et al., 2015) e do envoltório ósseo tem sido possível. Outra modalidade de imagem que permite estudo dinâmico e que tem ganhado espaço o doppler intracraniano,

porém devido ao pobre impacto na visualização tem sido mais utilizado a nível das pesquisas.

Ainda não existem estudos refinados para a artéria carótida interna e o sifão carotídeo permitindo o estudo anatômico e funcional ao mesmo tempo. Até então sobretudo a superficie óssea do sifão dificultava os estudos não invasivos. Acredita-se que num futuro bem próximo com a fusão das técnicas de imagem isso será possível.

Ainda na década de 70 com poucos recursos, e apenas mediante os estudos angiográficos bidimensionais, Krayenbuel e Yasargil perceberam que existiam diferentes tipos morfológicos de sifão carótideo. Eles subdiviram em sete subtipos segundo a sua tortuosidade baseando-se na incidência angiográfica lateral e particularmente na porção cavernosa do sifão carotídeo: uma forma de U, uma forma em V, forma de Arco e forma de Omega, forma de duplo sifão, megasifão ou dolicosifão. Os diversos subtipos estão ilustrados na **Figura 12** esquematicamente, e na **Figura 13** baseada em exemplos de casos com aneurismas do sifão carotídeo.

Os três primeiros tipos são vistos com mais freqüência, enquanto que em pacientes mais velhos (51-74 anos) do tipo omega ocorre com mais frequência (Yasargil e Krayenbuel et al., 1968).

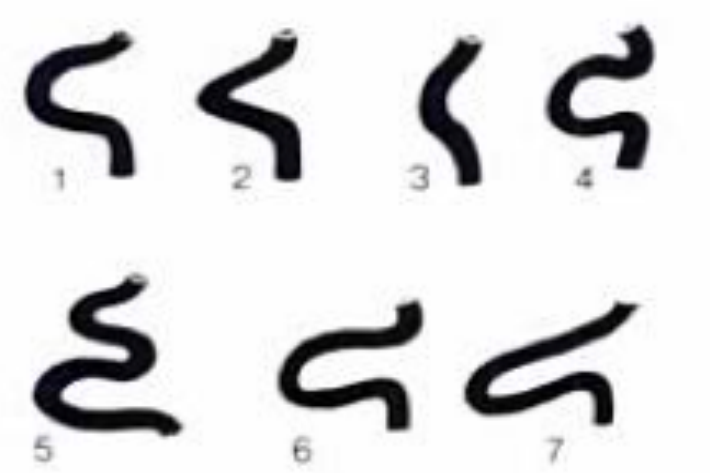
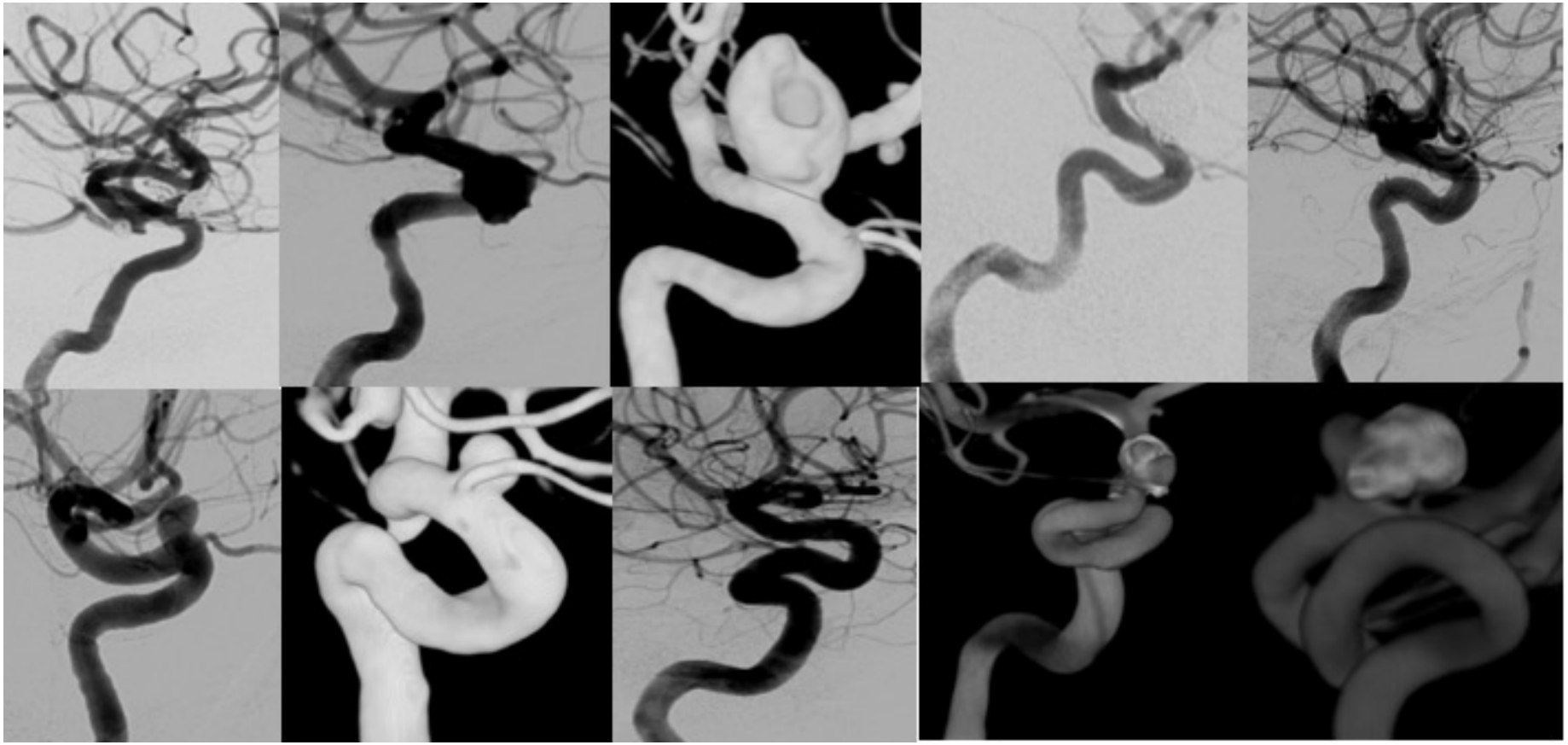


Figura 12 – Representação esquemática da classificação de Yasargil e Krayenbuel **Tipo 1:** formato de C, **Tipo 2:** formato de V, **Tipo 3:** formato de arco, **Tipo 4:** Tipo de Ômega, **Tipo 5:** Tipo Duplo, **Tipo 6:** Tipo Dólico, **Tipo 7:** Megasifão. Fonte: Adaptado de Yasargil e Krayenbuel, et al. 1968.

(A) (B) (C) (D) (E)

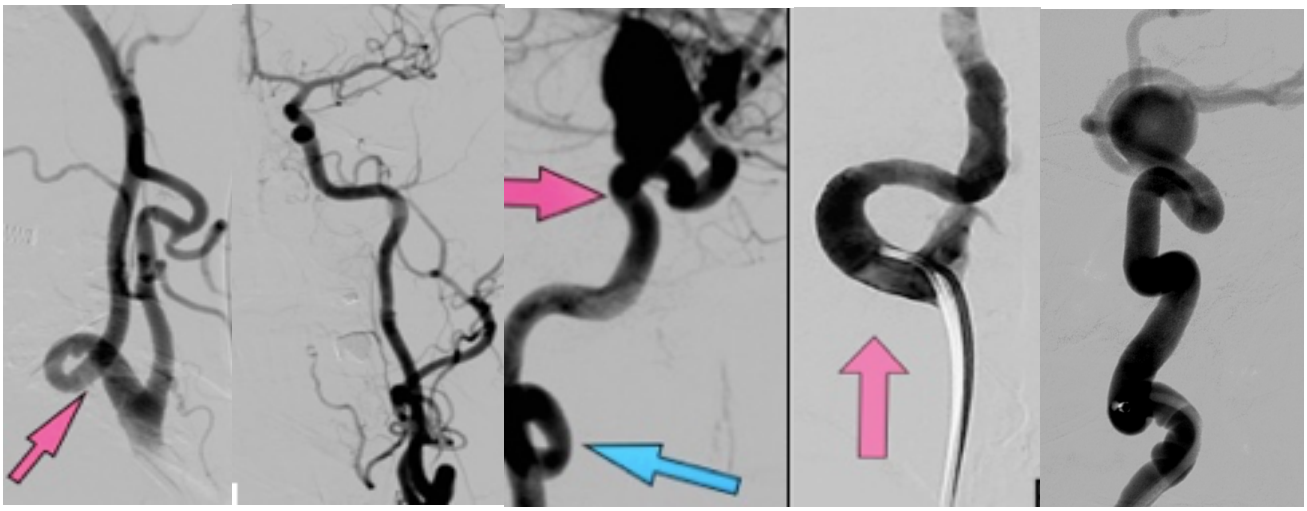


(F) (G) (H) (I) (J)

Figura 13 – Imagem angiográfica demonstrando sifão tipo C (A), Imagem angiográfica demonstrando sifão tipo V (B), Imagem angiográfica demonstrando sifão tipo U (C), Imagem angiográfica demonstrando sifão tipo Omega (D), Imagem do sifão tipo Omega (E), Imagem angiográfica do sifão carotídeo demonstrando subtipo dólico (F), Imagem angiográfica demonstrando duplo sifão (G), Imagem angiográfico demonstrando duplo sifão (H), Imagem angiográfica demonstrando sifão sinuoso (I), Imagem I em outra incidência (J). Fonte: Imagens elaboradoras pela autora a partir do arquivo do próprio Serviço Neuri-Beaujon.

Novas técnicas de telenavegação e telereconstrução associadas a arteriografia convencional (com sequências tridimensionais) que tem se desenvolvido nos últimos anos para uso na sala operatória para estudo do sifão carotídeo e estruturas vizinhas durante colocação de stents. Ilustramos na Figura 15. Elas tem permitido a obtenção de um estudo mais preciso e ao mesmo tempo diminuindo o risco de radiação ionizante. Uma dessas técnicas é chamada VasoCT® e compreende novas técnicas fusionadas que começaram a se desenvolver a partir da tomografia computadorizada, mais atualmente já conta com programas informatizados bem mais performantes que tem permitido inclusive acessar a medida de fluxo vascular e tentando conquistar o espaço do *Computational Flow Dynamic* (ilustrado na **Figura 5**).

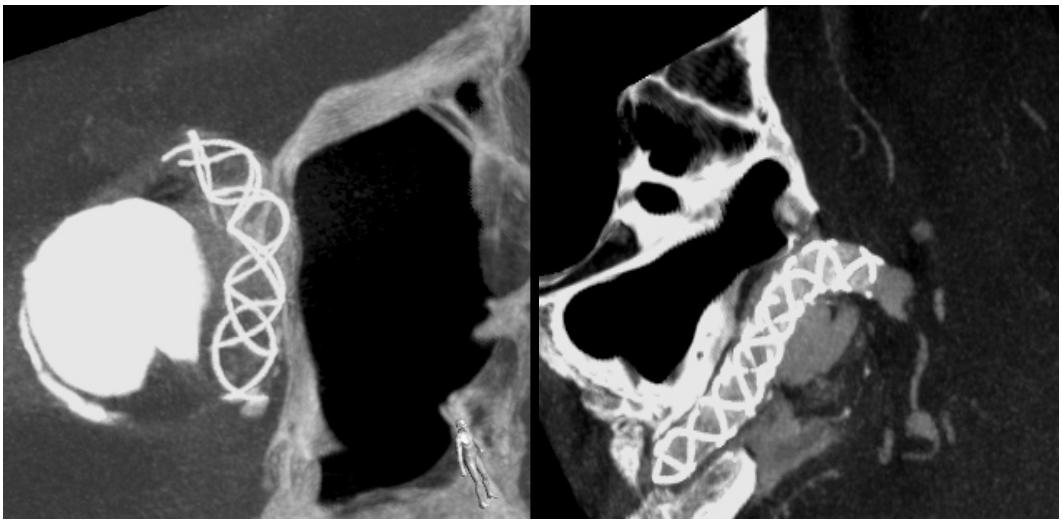
Os sifões carótideos são locais comuns onde encontramos aterosclerose. Provavelmente devido à sua natureza, um segmento de vaso tortuoso com curvas acentuadas e grandes variações da área e que também tem relevância para o estudo de iniciação dos aneurismas e da ruptura (Sendstad, 2014) conforme observamos na **Figura 14** abaixo.



(A) (B) (C) (D) (E)

Figura 14 – Imagem angiográfica das artérias carótidas comum, interna e externa esquerda em projeção de perfil (A) Imagem angiográfica da artéria carótida comum e seus ramos em uma projeção anteroposterior (B) Imagem angiográfica da artéria carótida direita (C) Imagem angiográfica da bifurcação carotideana direita (D) Imagem angiográfica mostrando a sinuosidade da carótida interna (E). Fonte: Imagens elaboradoras pela autora a partir do arquivo do próprio Serviço de Neurorradiologia- Neuri-Beaujon.

A tortuosidade do sifão da carótida em pacientes idosos está particularmente relacionada à aterosclerose. Estas curvas podem ser vistas até mesmo em crianças, e descrita como tipo de variante anatômica. Em crianças, no entanto, observa-se que, em mais da metade dos casos a bifurcação da artéria carótida comum, a origem da artéria carótida interna está tipicamente localizada mais superior em comparação com a origem da artéria no adulto, no momento da segunda e terceira vértebras cervicais (Dilenge, 1962; Al-Rafiah et al., 2011).



(A) (B)

Figura 15 – Imagem tridimensional mostrando o sifão nas proximidades do seio esfenóide, controle após colocação de stent flow diverters (A), Imagem tridimensional mostrando o sifão nas proximidades do seio esfenóide, controle após colocação de stent flow diverters (B). Fonte: Imagens elaboradoras pela autora a partir do arquivo do próprio Serviço de Neurorradiologia- Neuri-Beaujon.

Mais atualmente a tortuosidade do sifão tem sido importante como estratégia durante os procedimentos endovasculares pode ajudar a prever as complexidades processuais e levar ao sucesso técnico.

Lin et al, 2014 propuseram uma classificação de quatro níveis para a tortuosidade baseada na geometria do joelho anterior e posterior (**Figura 16**). O grau de tortuosidade em seguida, foi categorizado em mínima (tipo I, n = 28), moderada (tipo II-III, n = 29), e severos ou 'Simmons-tipo' (tipo IV, n = 26). Os três grupos foram comparáveis para a idade do paciente (média ± anos, Tipo I: 55.6 ± 10.4, II-III: 56.4 ± 14.4, IV: 55 ± 12.8), o tamanho do aneurisma (média mm, Tipo I: 6.25 ± 3,5 mm, Tipo II-III: 7.6 ± 4.9 mm, Tipo IV: 9.11 ± 4.9 mm), o arco aórtico (p = 0.635), e a presença de tortuosidade cervical (p = 0,578). Os grupos foram significativamente diferentes na sua grau de tortuosidade (D/ AP) com o tipo IV tendo a

maior valor de 0,482 ± 0,365 em comparação com 0,141 ± 0,07 e a média 0,008 ± 0,0008 para o tipo II-III e tipo I, respectivamente (p <0,0001).

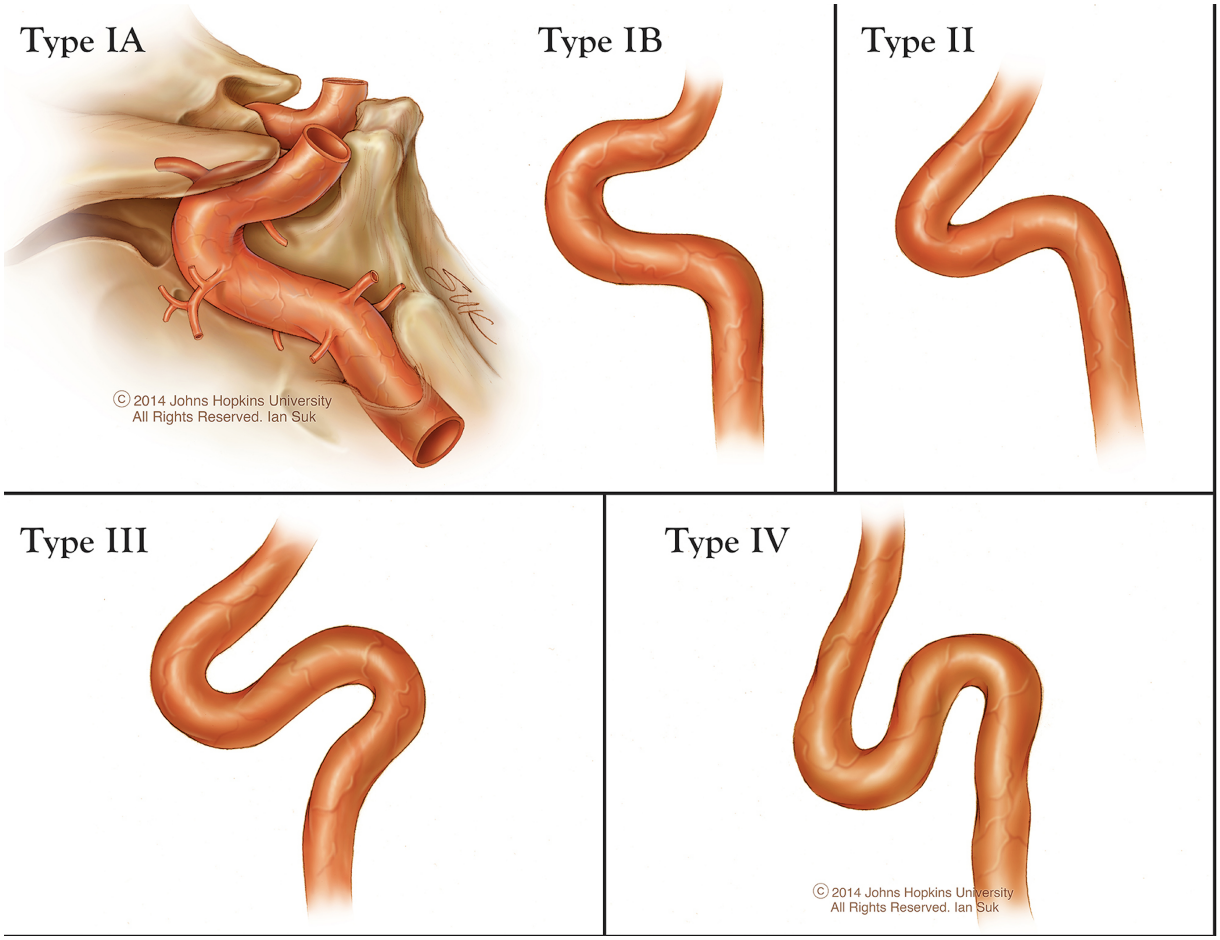
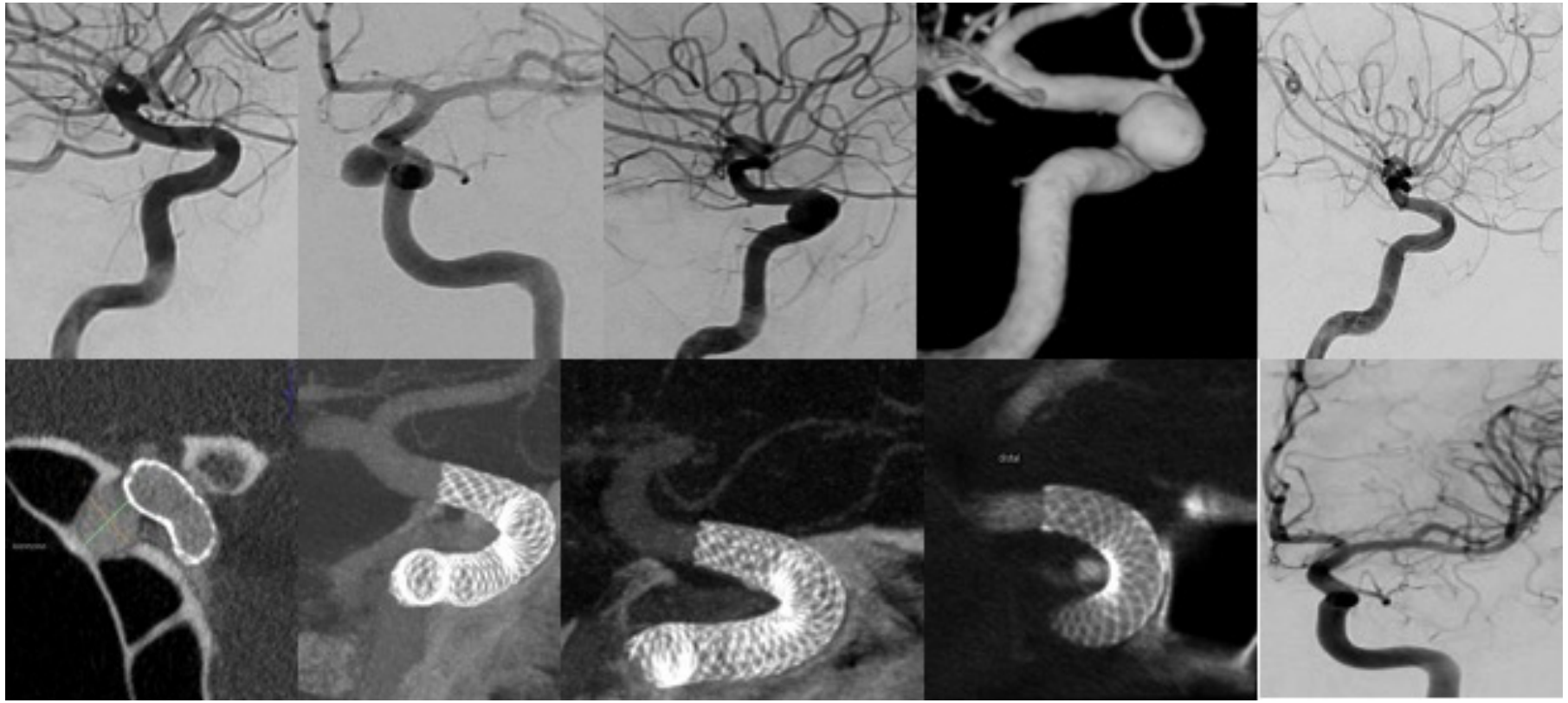


Figura 16 – Classificação da tortuosidade da artéria carótida interna cavernosa. Tipo I tem configurações aberta / ângulo do gênero com subcategoria determinada pelo ângulo do joelho posterior sendo IA é maior do que 90 e IB é igual a 90 °. Tipo II é caracterizado pela configuração fechada do joelho anterior com um ângulo mais agudo dos joelhos em comparação com o tipo I. Tipo III é definido pela deformação posterior do joelho posterior dando-lhe aparência afivelada. Tipo IV é mais tortuoso com característica em forma de cateter Simmons, onde o joelho posterior é afivelado superiormenteem comparação com o joelho anterior.

Fonte: Extraído de Li et al. 2014.

(A) (B) (C) (D) (E)



(F) (G) (H) (I) (J)

Figura 17– Imagem angiográfica mostrando o sifão normal (A), Imagem angiográfica mostrando o sifão com aneurisma medialmente situado (B), Imagem angiográfica em incidência lateral (C), Imagem tridimensional do sifão carotídeo (D), Imagem angiográfica de controle após colocação do stent (E e J), Imagem tridimensional mostrando o aneurisma nas proximidades do seio esfenóide (F), controle após colocação de stent flow diverters (G), Imagem tridimensional mostrando o sifão nas proximidades do seio esfenóide, controle após colocação de stent flow diverters (H e I).
Fonte: Imagens elaboradoras pela autora a partir do arquivo do próprio Serviço de Neurorradiologia- Neuri-Beaujon.

Com o intuito de estudar melhor a hemodinâmica, modelos experimentais e computacionais dos aneurismas intracranianos tem sido obtidos (Rhee et al, 2002; Steinman et al., 2003; Rayz et al., 2008; Jiang et al., 2011). O estudo do fluxo dinâmico a partir das imagens dos aneurismas intracranianos com base, teoricamente poderia fornecer informações sobre os eventos hemodinâmicos e auxiliar na estrategia do tratamento (Wong et al, 2011; Damiano et al., 2015, Xiang et al, 2015). A mesma tecnologia já é amplamente utilizada em outras áreas, como engenharia mecânica e da indústria automotiva.

Um dos métodos para estudar mais objetivamente o fluxo é medindo as alterações no fluxo sanguíneo induzidos pelos stents modificadores de fluxo em aneurismas cerebrais *in vitro*, o que pode ser produzido por um stent implantado na artéria principal. A avaliação do efeito sobre o fluxo *in vitro* é feita para estimar os efeitos do fluxo *in vivo*. Estes testes podem permitir a avaliação dos efeitos hemodinâmicos sobre o fluxo na artéria principal e seus ramos, tais como valores de velocidade, pressão e seus parâmetros, que inclui vorticidade (circulação), helicidade (rotação), força de cisalhamento e oscilação no cisalhamento e outros índices (Ausburger et al., 2009).

Com a melhoria do poder de computação da dinâmica dos fluidos do computador, simulações numéricas tem ganhado em velocidade e precisão. A combinação de técnicas de processamento de imagem avançadas e modelagem geométrica permitem a avaliação hemodinâmica detalhada dos aneurismas em geometrias específicas do paciente.

Hoje, as aquisições através do CFD tem poder suficiente para calcular o fluxo em uma geometria específica do aneurisma de um paciente em poucas horas. A qualidade das imagens médicas para a reprodução da geometria vascular ganharam com muita precisão, e também simulam o fluxo do aneurisma com eficácia (Cebral et al., 2007; Steinman et al., 2003). Cebral et al. desenvolveu CFD usando stent Pipeline® que permite o cálculo do fluxo da artéria e aneurisma com base na angiotomografia e imagens tridimensionais a partir da angiografia rotacional. Os limites morfológicos do lúmen do vaso são obtidos através da segmentação e da reconstrução 3D. Os limites do fluxo fisiológico foram estabelecidas com base em medições de ultra-som (Cebral et al., 2005; Cebral et al., 2007; Cebral et al., 2010).

Antes disso, os primeiros estudos iniciaram com técnicas angiográficas com injeção de produtos de contraste permitindo a visualização direta do fluxo. Kim et al. foi um dos pioneiros a visualizar os padrões de fluxo das bifurcações carótidas cervicais humanas. Kim et al. concluíram que as forças hemodinâmicas causariam alterações degenerativas na camada

endotelial e iniciar a formação dos aneurismas (Ausburger, 2009).

Um ano mais tarde, Natakani et al. analisando artérias de ratos realizou a injecção de partículas fluorescentes na corrente sanguínea e o mesmo conseguiu visualizar o sangue fluindo em forma de espiral *in vivo*, a nível das bifurcações arteriais proximais e distais na base do cérebro do rato (Nakatani et al.,1999). Chong comparou os padrões de fluxo em um modelo de artéria vertebrobasilar usando medições de fluxo com base na ressonância magnética (Chong et al., 1994).

Lieber et al. 1997 realizaram estudos através de medições de velocidade utilizando a técnica "Particle Immage Velocity" que permite a reconstrução dos vetores de velocidade dentro de um campo de fluídos (Lieber et al., 1997) conforme ilustramos na **Figura 18**. Validação e comparação com simulações numéricas e dados clínicos sem stent foram feitas por Liou et al. em relação aos campos de fluxo tridimensionais com as simulações de dinâmicas de fluidos computacionais nos modelos de aneurismas. Verificaram-se que o ângulo de entrada para dentro da parede lateral do aneurisma e as forças de cisalhamento máxima que atuam sobre o lado da extremidade distal do aneurisma e no interior do aneurisma. aumentavam com a diminuição do tamanho do aneurisma, com destaque para a geometria do aneurisma (Liou et al., 1997).

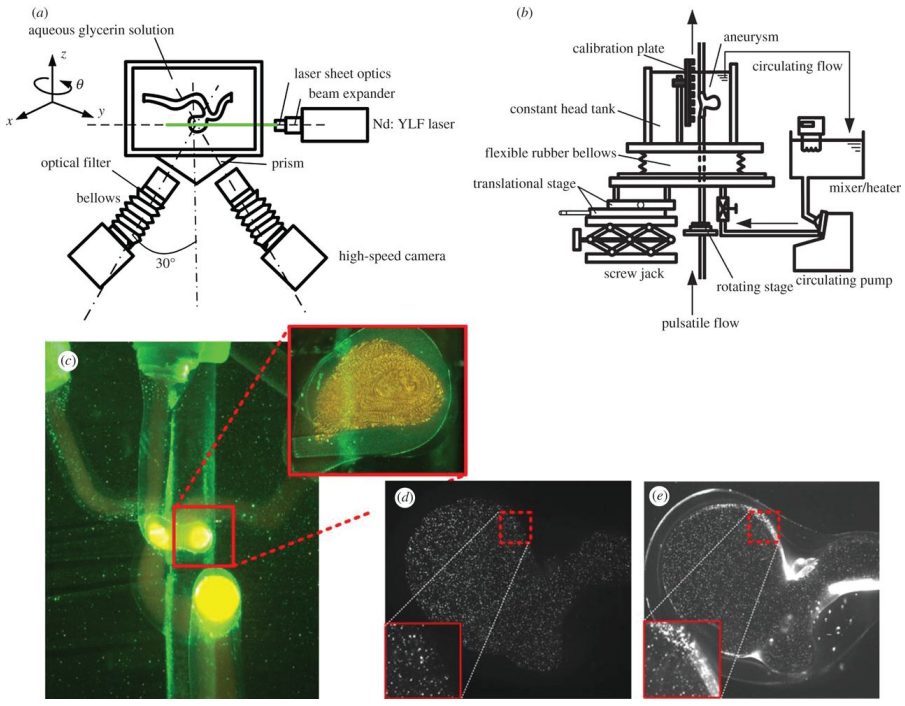


Figura 18 – Imagem demonstrando o processo de análise através da técnica "Laser Doppler Velocity". Extraída da Royal Society, 2014.

Anos mais tarde utilizando um novo metodo baseado na fotografia de partícula de

luz, Barath et al. estudou 20 stents diferentes, com diferentes faixas de permeabilidade e porosidade. Visualizaram os diferentes padrões de fluxo utilizando partículas de vidro e de laser e o efeito do posicionamento dos stents. Em seguida, investigaram as mudanças nos fluxos intrassaculares induzidos pelos stents dentro de um modelo experimental de artéria carótida que foi extraída a partir da vasculatura humana (Ausburger et al., 2009; Barath et al., 2004; Barath et al.,2005).

Outro metodo utilizado foi a velocimetria por imagem de particulas que foi utilizado por Canton et al.. Neuroform stents em modelos de aneurismas intracranianos de bifurcações foram utilizados. Eles demonstraram que uma redução na amplitude do escoamento giratório ou vorticidades nas bifurcações logo após seguida a introdução de dois a três stents (Canton et al., 2005).

Yu et al. também utilizou modelos experimentais de aneurisma em condições de fluxo constante, onde o número de Reynolds variou de 200 a 1600. Eles descobriram que, para um número de Reynolds superior a 700, uma grande turbulência seria formada na inserção de stents com duas diferentes zonas de amortecimento do fluxo e de velocidade média, o que consequentemente reduz a força de cisalhamento (Yu et al., 1999).

Ohta estudou padrões de fluxo descrito nos modelos hemodinâmicos de aneurismas da bifurcação antes e depois do stent num ciclo cardíaco. Como o sangue foi modelado para ser um fluido não-newtoniano, valores de velocidade e a força de cisalhamento, devido à colocação de stent foram menores com o aumento da viscosidade dinâmica. Simulações numéricas também foram realizadas para avaliar a forma como os stents podem ser otimizados para melhorar a sua capacidade para desviar o fluxo e, por conseguinte, reduzir o risco de ruptura. Efeitos do stent endovascular no fluxo do aneurisma, a força de atrito sobre a pressão e o valor do cisalhamento oscilatório foram quantificados.

Aenis et al. estudaram os padrões de fluxo dentro de um aneurisma em condições de fluxo fisiológico e pressão. O stent mudou a hemodinâmica local e diferenças significativas nos padrões de valores do fluxo e da pressão foram observados e quantificados (Otha et al., 2005). Stunhe tentou criar ferramentas para gerenciar as dificuldades com a colocação do stent e a geometria vascular do aneurisma.

Outros métodos consistem do uso da ressonância magnética (Isoda et al,. 2010). Hollnagel et al. usaram a angiorressonância magnética para analisar um modelo de aneurisma específico em condições de fluxo constante. Descobriram que pequenas diferenças na distribuição do campo de velocidade e dos valores médios de velocidade entre as duas técnicas, a precisão, dependia do tamanho da artéria e do posicionamento do plano de

medição (Hollnagel et al., 2007). A vantagem da ressonância magnética avaliando as características hemodinâmicas é por ser de alta resolução. Na simulação numérica do fluxo dinâmico, um perfil de velocidade espacial e temporal é medido em três direções através da sequências tridimensionais (Van Ooij et al., 2012). A resolução da imagem é limitada a determinados vasos de muito pequeno calibre como a artéria oftálmica ou artéria comunicante posterior, que não podem ser bem visualizadas na ressonância magnética. No entanto, a resolução espacial e temporal das imagens da ressonância magnética podem ser melhoradas aumentando o tempo de aquisição.

Com relação aos aneurismas do sifão carotídeo foram identificados apenas poucos estudos detectados na literatura estudando a sua hemodinâmica através de modelos experimentais ou computacionais (Jou et al., 2008; Wang et al., 2009; Zhu et al., 2010; Takeuchi et al., 2010, Xiang et al 2014). Takeuchi et al., estudaram cinco sifões analisando as várias curvas agudas e sua hemodinâmica. Como resultado, notaram que a velocidade foi menor na bifurcação terminal da artéria carótida interna, mas foi maior na primeira bifurcação da MCA. Assim, neste última bifurcação, existiria uma colisão maior com a parede do vaso com uma velocidade muito maior do que na bifurcação do terminal anterior da artéria carótida interna. Ao longo da artéria carótida interna, as lesões ateroscleróticas foram encontrados quase exclusivamente em regiões de baixa tensão de cisalhamento (Takeuchi et al, 2010).

Lauric et al. estudaram 35 sifões carotídeos sendo 10 aneurismas e 25 controles utilizando o CFD. Sugerem que a curvatura focal da porção horizontal do sifão carotídeo está correlacionada com a presença do aneurisma. Os aneurismas nestas regiões parecem se formar distalmente do local da curvatura máxima, em áreas de fluxo estagnado e apresentam elevados picos de estresse hemodinâmico que foram significantemente comparados com os controles conforme ilustrado na **Figura 19**. Além disso, áreas de aumentada força de cisalhamento foram encontradas na região do colo desses aneurismas (Lauric et al., 2014).

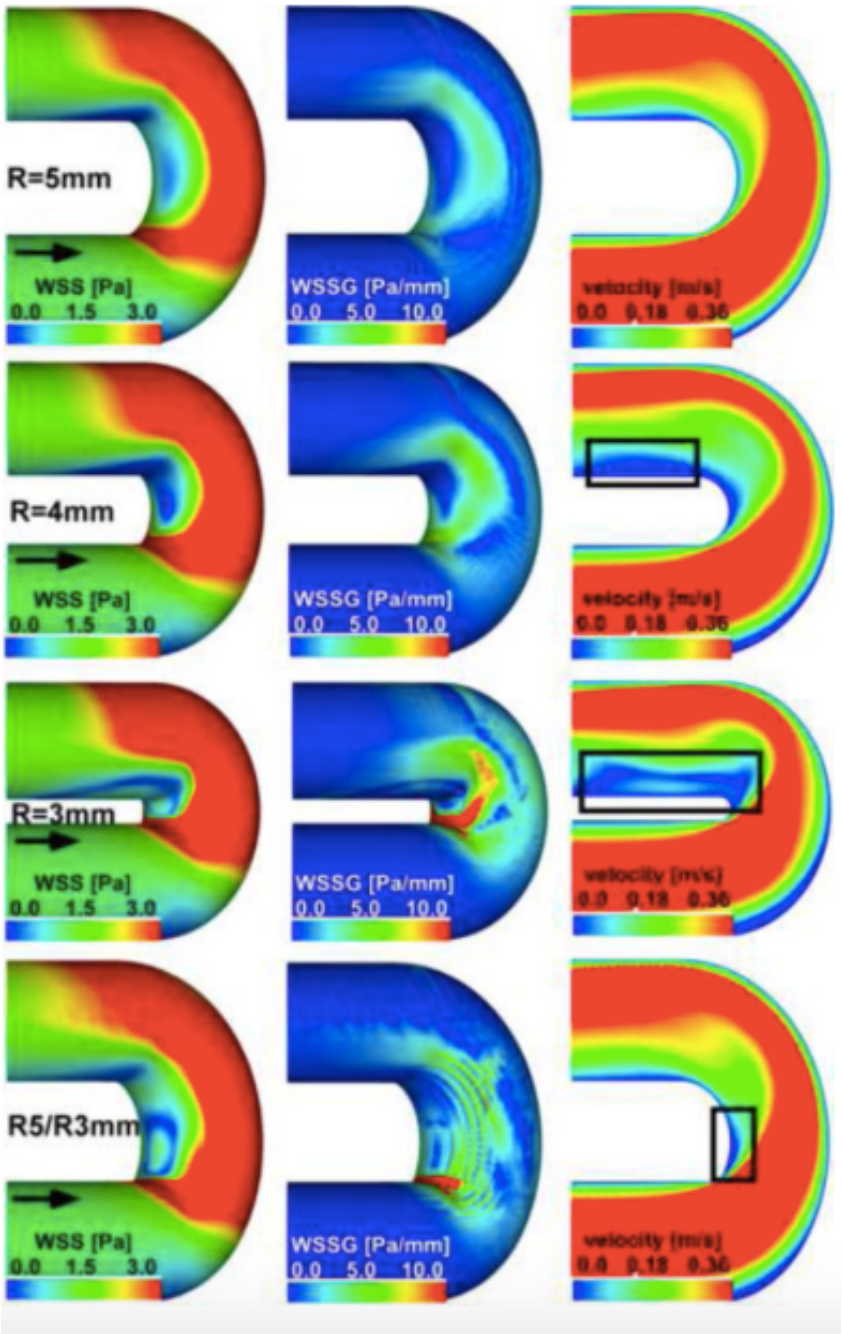


Figura 19 – Resultados hemodinâmicos a partir de estudos de CFD. As setas pretas apontam para o influxo aneurismátco. Na primeira coluna, observa-se as medidas de força de atrito ou Wall Shear Stress (WSS). Na segunda coluna, observa-se a magnitudade do WSS. Na terceira coluna, a velocidade através de corte no modelo na linha média.

Fonte: Extraído de Lauric et al., 2014.

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CAPÍTULO III

Objetivos

3 OBJETIVOS

Dentro do contexto apresentado, a presente tese tem os seguintes objetivos:

3.1 OBJETIVO GERAL

✓ Estudar a correlação entre o segmento A1 dominante (Hipoplasia A1 contralateral) e a presença de PCA Fetal com o desenvolvimento de aneurismas na circunferência do sifão carotídeo. Ao mesmo tempo, realizar uma análise de regressão para superar o desequilíbrio significativo entre homens e mulheres, tanto no que tange aos aneurismas quanto a presença de variantes anatômicas do polígono de Willis;

3.2 OBJETIVOS ESPECÍFICOS

✓Revisar sistematicamente a literatura e apresentar as recentes aplicações das biotecnologias utilizadas para o tratamento de aneurismas intracranianos;

✓Apresentar uma curta discussão sobre os aneurismas do sifão carotídeo, uma patologia silenciosa e desafiante;

✓Apresentar um histórico do resultado dos mais de 10 anos de experiência do Departamento de Neuroradiologia Intervencionista, Hospital Beaujon, Paris, França com as descrições das técnicas mais usadas, os desafios e as evoluções das últimas décadas que têm feito da terapia endovascular (através de *coiling*, técnica de remodelamento do colo, *stents* modificadores de fluxo e mais recentemente *stents* disruptores de fluxo) e o tratamento de escolha relacionado aos aneurismas do sifão carotídeo;

✓Estudar a morfologia tridimensional de uma série de aneurismas do sifão carotídeo tratadas no Departamento de Neuroradiologia Intervencionista, Hospital Beaujon, Paris, França e identificar os subtipos mais prevalentes com base em áreas de susceptibilidade usando marcos microcirúrgicos e radiológicos e correlacionar com a morfologia do sifão.

✓Apresentar uma breve discussão sobre as nossas futuras direções na patogênese, hemodinâmica e o desenvolvimento de aneurismas intracranianos;

✓ Revisar sistematicamente a literatura dos últimos 35 anos e apresentar as perspectivas atuais sobre as variantes arteriais do polígono de Willis e suas ramificações envolvidas na patogênese dos aneurismas intracranianos;

✓ Apresentar uma mini *review* sobre os aneurismas intracranianos e a obesidade paradoxal;

CAPÍTULO IV

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Biotechnologies Applied to Intracranial Aneurysms

REVIEW

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Abstract

Background: Despite several ongoing studies about new biotechnologies applied to intracranial aneurysms, particularly its genesis, its haemodynamic and its endovascular management; there are few studies with clinical validation until now.

Objective: To systematically review studies about biotechnologies used for the treatment of intracranial aneurysms.

Method: The authors searched the following databases: MEDLINE via PubMed (May 2014), EMBASE (May 2014), Science Citation Index Expanded (May 2014), AMED Allied Medicine (May 2014). It was considered for inclusion all studies when the role of biotechnologies and intracranial aneurysms were analysed using correlational or experimental researches.

Results: Three hundred fifty seven articles met the inclusion criteria. Most of the studies were about devices, flow studies, focused on bioinformatics, or computer science. The number of such investigations have proliferated considerably during the past five years.

Conclusion: Use of biotechnologies has raised expectations for both understanding of genesis and development of intracranial aneurysms and their strategical management. Based on current evidences, mostly small pilot trials, there are too few validated data. Refinements have dramatically improved flow studies in clinical settings.

Keywords
Intracranial Aneurysms; Flow; Bioinformatics; Biotechnology; Biotechnologies; Medical Devices.

Introduction

In the last years, biotechnologies –particularly intravascular flow modifiers– have been incorporated into the clinical management of intracranial aneurysm as a viable alternative to classical neurosurgery.

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[1-5] In the interim, many other biotechnological tools have been created to support and assist in interventional neuroradiology strategies. [6-8] These advances have been the subject of several studies, mostly clinical or experimental researches of intracranial aneurysms. [5-19] Biotechnologies applied to intracranial aneurysms encompass a number of tools and elements, including new techniques of treatment, computational flow dynamics (CFD) software programs to study flow, and updated strategies that may be used during the management of intracranial aneurysms. Unfortunately, however, many might not be routinely available in all catheterization laboratories. [7-12, 15-17]

Since measuring haemodynamic values directly in patients entails risk, models of patient-specific conditions have been used. The ultimate focus of these techniques is to mathematically describe and project the haemodynamic milieu of a diseased arterial wall. In turn, such models may be used to create automated algorithms, collectively surrogates, that predict focal weakening. Such analyses enable discrimination of aneurysmal risk, thereby guiding treatment decisions.

Enthusiasm generated by these studies should be tempered by the paucity of compelling data demonstrating tangible clinical benefits this new biotechnological arsenal. [5-19] Systematic reviews on the role of biotechnologies and intracranial aneurysms are expected. The aim of this study was to systematically review biotechnology studies concerning including new devices, flow investigations, and/or bioinformatics as applied to the management of intracranial aneurysms. [6-7]

Methods

Eligibility Criteria

The review was based upon data from clinical and research studies about biotechnologies and intracranial aneurysms. Studies in children and those in conventional MR imaging were excluded. Additional search about carotid aneurysm, carotid siphon and aneurysms classification was included but it were not considered in the final analysis.

Search Strategy

The authors searched MEDLINE via PubMed (May 2014), EMBASE (May 2014), Science Citation Index Expanded (May 2014) and AMED Allied Medicine (May 2014). A set of specific terms were used to devise the search strategy described in **Table 1**. The initial strategy was to match single words, then combine terms, their derivatives, and related terms. Thesaurus, MeSH and systematization of bibliographic searches were added in order to improve the search. Only articles written in English were included.

Table 1. Search strategy.

	Results
Medline	
1. (intracranial and aneurysm).ti,ab,af;	24026
2. biotechnologies.ti,ab,af	3847
3. biotechnology.ti,ab,af	212594
4. flow.ti,ab,af	601190
5. exp biotechnology/	49069
6. exp *biotechnology/	29366
7. exp biotechnology/	49069
8. 1 and 3 and 4	0
9. 1 and 4	2506
10. (intracranial and aneurysm).ti,ab	6888
11. (intracranial and aneurysm).ti,ab,af	24026
12. flow.ti,ab,af	601190
13. biotechnology.ti,ab,af	212594
14. bioinformatics.ti,ab,af	47648
15. biorobotics.ti,ab,af	186
16. (computer and science).ti,ab,af	60145
17. devices.ti,ab	110299
18. 2 and 3	2506

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	Results
19. 2 and 4	3
20. 2 and 5	9
12. 2 and 7	40
13.2 and 8	303
14. 13 [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	22
15. 2 and 3 and 7 and 8	3
16. 4 and 5 and 6 and 7 and 8	0
17. 7 and 8	1383
18. 2 and 17	3
19. model.ti,ab [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	33546
20. 2 and 3 and 19 [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	6
21. 20 [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	6
22. (optic and flow).ti,ab,af	3527
23. 2 and 22	13
24. 9 [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	128
Embase	
25. (intracranial and aneurysms).ti,ab,af	10990
26. flow.ti,ab,af	768434
25 and 26	1527
26. (carotid and aneurysm).ti,ab	6549
27. classification.ti,ab,af	501997
28. 25 and 29	318
Medline	
29. (carotid and siphon).ti,ab,af [limit to: (publication types clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial)]	15

Data analysis

The data extracted were (a) year of publication; (b) number of subjects; (c) the type of methods used to assess flow as experimental, computational or others; (d) whether it was a clinical or research study; (e) whether it concerned genesis of aneurysms; (f) treatment; (g) prevention; (h) the clinical impact of the study in routine clinical practice; and/or (i) whether the study employed vascular ultrasound.

Results

Search Results

A total of 24026 publications about intracranial aneurysms, 212594 publications about biotechnology, 601190 publications about flow, and 2056 publications about both intracranial aneurysms and flow were found.

There were 357 artides identified that focused upon biotechnologies (flow, biotechnology, bioinformatics, biorobotics, computer and science, devices) as described in **Figure 1**. Using the strategy of inclusion of Publication Types Clinical Trial, a relative lack of validated studies about devices and intracranial aneurysms became apparent. Flow, biotechnology, bioinformatics, biorobotics, computer and science were added to improve our search. The majority of studies were limited to case reports and small pilot series.

In seeking to broaden the spectrum analysis, we added the words model and optic flow, by referring to the experimental models, respectively only 6 and 13 studies were identified, following the words flow and intracranial aneurysms were matched and 128 results were founded.

All told, 22 studies met the basic inclusion criteria –biotechnologies versus intracranial aneurysms– and were subsequently filtered by reading, and were clinical trials, Phase I or Phase II identified **(Figure 1)**.

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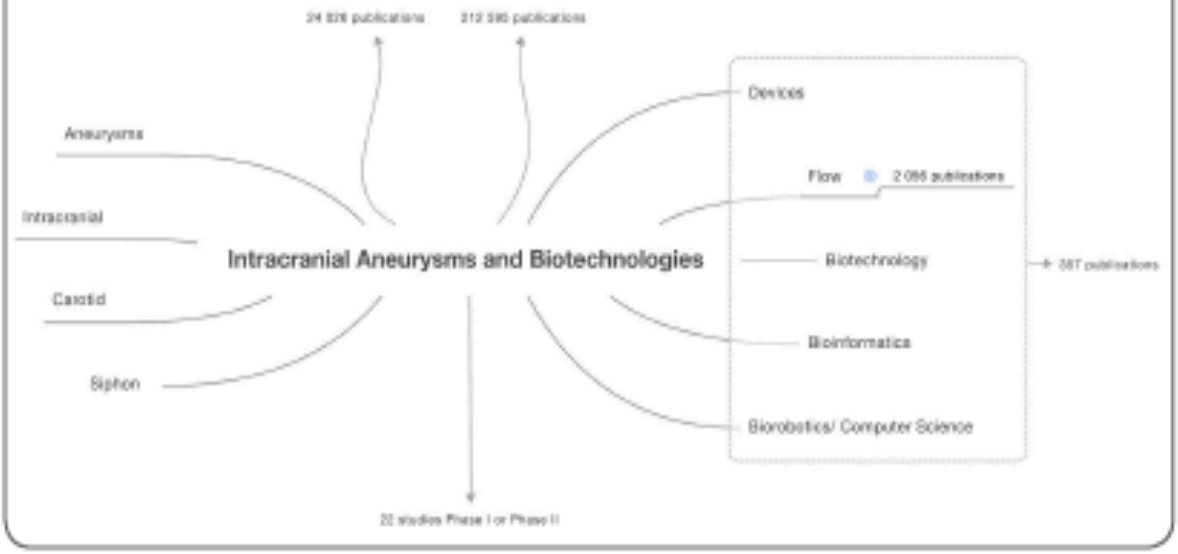
Figure 1: Flow of elements and filters used to retrieve final studies included..



Subgroup Analyses and Clinical Applications

Experimental studies described were *in vitro* vascular models and *in vivo* vascular models developed in animals which were used to analyze the dynamic flow within intracranial aneurysms induced by flow diverters studying flow effects, thrombosis and endothelialization after flow diversion. Computational methods has been an improvement over the conventional angiographical studies. Additional technologies have been added using angiography and/or other dynamic methods.

Other clinical applications include the identification and stratification of rupture risk in aneurysms, which might lead to detect possible future preventive treatment.

Discussion

This brief review found that new biotechnologies have been incorporated into the management of intracranial aneurysms in proportion to the volume of published research. However, the validity of these tools in clinical management, ie, outcomes, remains to be shown. [1-5, 6-9]

Flow is believed to be a major factor involved in many steps during the natural history of intracranial aneurysms, including initiation, growth, degeneration, rupture, and recurrence recanalization. Due to the complex modeling of patient-specific aneurysms, it has been important to validate new technologies to better understand the pattern of aneurysmal flow. [6-9, 14-20]

With the improvement of computer power and evolution in CFD, numerical simulations gained in speed and precision. Numerical simulations may include assessment of effects upon flow within the aneurysm and flow within the parent artery and its branches. [9, 16-17] Quantifiable flow values of velocities and pressure within the virtual aneurysm are compared with their related virtual parent artery parameters including velocity, helicity (rotation), wall shear stress and oscillatory shear index, among others. Many haemodynamic variables, including flow pattern and wall shear stress, are hypothesized to be the causes of growth and development of intracranial aneurysms. [9, 15, 16]

Blood flow simulation of intracranial aneurysms in patient-specific aneurysms according to specific

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Disclosures

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CAPÍTULO V

Artigo Publicado na Revista Neurobiologia

Artigo Publicado na Revista Neurobiologia

Editorial

ANEURISMAS DO SIFÃO CAROTÍDEO: UMA DOENÇA SILENCIOSA E DESAFIANTE

Patrícia Bozzetto Ambrosi[1,2], Marcelo Moraes Valença[3,2]

Em 1927, historicamente surgia a Neurorradiologia Intervencionista, com a realização das primeiras radiografias contrastadas (atualmente mais conhecida como angiografia ou arteriografia cerebral) pelo neurologista português Egaz Moniz (1874-1955)[1], com o intuito de diagnosticar tumores cerebrais. Cinco anos mais tarde, Egaz Moniz descreve o "sifão carotídeo", uma característica radiológica de um segmento da artéria carótida interna, por apresentar uma série de voltas e curvas, tornando-se assim um marco anatômico.[1,2]

A técnica desenvolvida por Egaz Moniz apenas veio a torna-se um método importante para detecção de anormalias vasculares entre os anos 1950 e 1960. Mas, a arteriografia cerebral, ainda hoje é considerado padrão-ouro no diagnóstico de aneurismas intracranianos e de malformações arteriovenosas.[2]

Na década de 70, o neurorradiologista James Ambrose e o engenheiro Godfrey Hounsfield desenvolveram a primeira imagem axial diagnóstica do cérebro em Londres; e a partir daí surgia a tomografia computadorizada que não parou de evoluir com aparelhos cada vez mais refinados e mais rápidos.[4] Na mesma época, o neurocirurgião russo Fedor Serbinenko introduzia o balão intra-arterial para o tratamento das fístulas carótido-cavernosas traumáticas e para os aneurismas inoperáveis da carótida cavernosa.[5] Os trabalhos de Serbinenko inspiraram vários centros no mundo inteiro, porém principalmente na França, o que levou ao desenvolvimento em poucos anos da especialidade de Neurointervenção Endovascular.[6]

Após esse período, as técnicas de diagnóstico, e principalmente de tratamento dos aneurismas cerebrais começaram a se aprimorar cada vez mais. Novos aparelhos e materiais foram se desenvolvendo, o que tem culminado como um elevado nível tecnológico e com vários estudos multicêntricos mostrando a eficácia do método endovascular.[7] Além disso, existe a possibilidade de se identificar eficazmente os aneurismas através da simples realização de angioressonância (que identifica aneurismas pequenos entre 3 mm a 5 mm de tamanho) com até 95% de sensibilidade ou acurácia quando realizados sequências especiais como volume-rendering e 3D-time-of-flight, ou de angiotomografia que tem boa sensibilidade para aneurismas maiores de 3 mm.[8,9]

Quanto aos aneurismas do sifão carotídeo, sempre foram considerados um desafio para o neurocirurgião, sobretudo os aneurismas fusiformes da artéria carótida interna cavernosa. Consequentemente esses aneurismas foram inicialmente abordados com balões de silicone por oclusão intra-aneurismática.[2] Atualmente, os aneurismas do sifão carotídeo são os aneurismas cerebrais que mais frequentemente são tratados por via neuroendovascular, pela fácil acessibilidade angiográfica. A morfologia variável do sifão e o fenômenos hemodinâmicos podem dificultar as vias de acesso endovasculares e a colocação dos stents intravasculares ou endossaculares.

Um breve histórico está sendo demonstrado, descrições das técnicas mais usadas, os desafios e as evoluções das últimas décadas que têm feito da terapia endovascular (através de coiling, técnica de remodelamento do

colo, stents modificadores de fluxo e mais recentemente stents disruptores de fluxo) e o tratamento de escolha relacionado aos aneurismas do sifão carotídeo. Por ser de menor risco e menos invasivo o procedimento endovascular, este fato abriu, sem dúvida alguma, uma porta que permitiu lesões antes inoperáveis pudessem ser tratadas com segurança e eficácia.

Apesar de todos esses avanços tecnológicos, ainda muitos desafios precisam ser superados, os quais, de uma forma ou de outra, dificultam de sobremaneira o diagnóstico e tratamento eficaz dessa afecção vascular. O diagnóstico clínico-radiológico do aneurisma ainda persiste como desafio.

Detectamos em estudo prévio em Paris que a maioria dos pacientes com aneurismas do sifão carotídeo eram encontrados de maneira incidental, durante a investigação por neuroimagem de sintomatologia banal.

O fato curioso é que a maioria desses pacientes com aneurismas ditos incidentais apresentou cefaléia como sintoma principal, a qual tinha motivado a realização do screening imaginográfico. O fato mais intrigante é que a cefaléia é geralmente relacionada com a ocorrência de hemorragia subaracnóide pela ruptura aneurismática, e não com a presença de aneurismas cerebrais. Apenas 20% desses pacientes tinham apresentado algum evento hemorrágico recente. A pergunta seria: o que estaria ocasionando a cefaléia? Será que não existiria uma relação entre o aneurisma e sua expansão e isso poderia levar a compressão de alguma estrutura adjacente?

Tendo como base, as diretivas da American Association of Stroke, [10] o screening de aneurismas apenas seria justificado em algumas populações com alto risco de formação de aneurismas cerebrais. Por exemplo, estaria indicado quando (1) há uma história familiar de parentes do primeiro grau com aneurisma, quando dois ou mais seriam acometidos, ou (2) em pacientes com doença hereditária associada com a presença de aneurismas intracranianos, tais como doença policística renal dominante, hiperaldosteronismo sensível aos glucocorticóides, válvula aórtica bicúspide, ou ainda doenças do colágeno (síndrome de Ehlers-Danlos e pseudoxantoma elástico).

Embora muitos médicos já indiquem, ainda não existem protocolos incluindo a cefaléia e suas nuances como parte do screening dos aneurismas cerebrais, incluindo os aneurismas do sifão carotídeo. **Infelizmente, os nossos dados para esta situação são ainda demasiados escassos para permitir conclusões sólidas a respeito.** Mas, tudo indica que definitivamente deveríamos monitorizar e estudar mais em detalhes os nossos pacientes com cefaléia, pois a doença poderia estar ocorrendo em silêncio e passar desapercebida. Provavelmente, existem subgrupos e graus diferentes de cefaléia para cada tipo de aneurismas, ou vice-versa, o que ainda requer rigoroso e minucioso estudo.

Nesse sentido encerramos citando uma reflexão do célebre Albert Einstein (1879-1955): "Somos todos muito ignorantes, mas nem todos ignoramos as mesmas coisas".

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CAPÍTULO VI

Artigo Publicado na Revista Neurobiologia

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Original Article

BALOON REMODELING TECHNIQUE AND FLOW DIVERTERS DEVICES: HISTORICAL REVIEW AND PRESENT PERSPECTIVES FOR MANAGEMENT OF CAROTID SIPHON ANEURYSMS

Patricia Bozzetto Ambrosi[1,2], *Laurent Spelle*[1], *Jacques Moret*[1], *Marcelo Valença*[2,3].

ABSTRACT

INTRODUCTION - Innovative and breakthrough technologies have emerged in the endovascular management of brain aneurysms. Nevertheless, until recently, there has been a dearth of established techniques and studies pertaining aneurysms arising within the carotid siphon of the internal carotid artery. The authors review their clinical experience and outline the current perspectives on the present state of the art in the management of carotid siphon aneurysms. **METHODS** - Three hundred and eight internal carotid artery siphon aneurysms were reviewed, encountered in 232 patients treated at two centers of Interventional Neuroradiology in France (Rothschild and Beaujon), between February 2002 and May 2014. Aneurysms were divided into two groups, namely I (those managed until 2010), and II (those managed after 2010). **RESULTS** - The rate of endovascular aneurysm repair has significantly increased during the past 5 years since new medical devices were introduced. There was a predominance of the balloon-remodeling technique in group I versus that of flow diverting devices in group II. **CONCLUSIONS** - The management of carotid siphon aneurysms has become notably safer using new endovascular techniques. More studies are required to compare different endovascular aneurysm repair techniques.

KEY WORDS: intracranial aneurysm, carotid siphon, carotid artery, carotid artery stenting, endovascular repair, interventional neuroradiology.

Técnica de remodelamento do colo com balão e stents modificadores do fluxo: reconstrução histórica e perspectivas presentes para o tratamento endovascular dos aneurismas do sifão carotídeo

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RESUMO

INTRODUÇÃO - Tecnologias avançadas e inovadoras têm surgido para o tratamento dos aneurismas intracranianos. Contudo, até o presente momento, existe uma escassez de técnicas e de estudos estabelecidos com relação aos aneurismas do sifão carotídeo. Os autores revisam sua experiência clínica e apresentam as perspectivas presentes no atual estado da arte do tratamento dos aneurismas do sifão carotídeo. MÉTODOS - Trezentos e oito aneurismas do sifão carotídeo diagnosticados em 217 pacientes tratados em dois centros de Neuroradiologia Intervencionista franceses (Rothschild e Beaujon) entre fevereiro de 2002 e maio de 2014 foram revisados. Os aneurismas foram agrupados em dois grupos, nomeados em grupo I (os tratados até 2010) e grupo II (tratados após 2010). RESULTADOS - A taxa de reparo endovascular tem aumentado significativamente nos últimos cinco anos desde que novos stents têm sido introduzidos. Observou-se uma predominância do uso da técnica de remodelamento do colo com balão no grupo I versus uma predominância do uso de novos stents modificadores de fluxo no grupo II. CONCLUSÕES - O tratamento dos aneurismas do sifão carotídeo parece ser notavelmente mais seguro com o uso dessas novas técnicas endovasculares. Mais estudos são necessários para comparar as diferentes técnicas de reparo endovascular.

ABBREVIATIONS - conventional coiling, CC; D, Dimensional; EAR, endovascular aneurysm repair; endovascular trapping, ET; FB, flow breaking; FD, flow diversion; FB; stent-assisted coiling, ICA, Internal Carotid Artery; SAH; subarachnoid hemorrhage, SAH; remodeling technique, RT.

PALAVRAS-CHAVE: aneurisma intracraniano, sifão carotídeo, artéria carótida, stenting carotídeo, reparo endovascular, neuroradiologia intervencionista.

INTRODUCTION

Brain aneurysms are well known public health concern worldwide at all ages, accounting for over 50 million of world's population would be suffering from this vascular pathology[1,2]. Given to their risk of bleeding, when more frequently intracranial aneurysm became apparent, particularly during an episode of subarachnoid hemorrhage, which will carry high mortality, a risk of rebleeding and chronic neurological impairment[2,3]. Many challenges are expected as primary preventive treatment, and as well early detection and improvements in strategies of effective management[1-3].

However, the aneurysms arising either within the ICA siphon aneurysms, these aneurysms are more preponderant in women under age of 50 years (ranging from 70- 80 percent) and sometimes can reach a significant size without major bleeding. Their clinical manifestation is more frequently incidental, headache or other compressive symptoms of adjacent neighbors structures resulting in visual or other neurological impairments[2,4,5,6,7].

The major challenge, therefore, is related with carotid siphon management due to the complexity of anatomical region where these aneurysms are located and their morphologic aneurysmal features (eg. Usually with large volume and wide neck, intraluminal thrombus and calcification) which make their treatment more difficult and with some peculiarities[4,5,8-10].

Over the last years, there have been several techniques namely: i) Endovascular Trapping (ET) or ligation of ICA, [11-15,17] ii) Conventional Coiling (CC), 9,16-19 iii) Remodeling Technique (RT), 20 iv) Single Stenting (SS), 10- v) Stent-assisted Coiling (SAS), 19-20 vi) Onyx® Embolization, 28 vii) Flow-Diverting (FD) occlusion, viii) FD-assisted coiling and ix) Flow-Breaking (FB) techniques to challenge conventional

techniques and overcome treatment limitations induced by endovascular therapy which has been used to date[24]. This paper presents a brief review of strategies of treatment based on a large number of selected case studies from a state of art French reference university center for intracranial aneurysms.

METHODS

Study Population

After reviewing our database of 1932 aneurysms treated by Endovascular Aneurysm Repair (EAR) techniques since 2002, we identified a total of 232 patients (with 308 carotid siphon aneurysms) who were treated at two of six neuroradiological centers in Paris (population of approximately 10 million).

The population analyzed were divided in two groups: Group I that included 1288 patients (432 men and 856 women) with 1552 intracranial aneurysms (IAs) which was treated between 1st of February 2002 and 25th of May 2010 at Foundation Adolphe Rothschild, Paris, France. Additionally, it contained 176 patients (21 men and 155 women; 1:7) with 238 saccular aneurysms within the ICA carotid siphon, which were analyzed retrospectively. Group II included 532 patients (295 IAs) treated between 1st November 2010 and 25th of May 2014 at the Beaujon University Hospital, Clichy, France. This group contained 56 patients (5 men and 51 women; 1:10) with 70 saccular aneurysms within the ICA carotid siphon, which were analyzed prospectively.

Data Collection

The Institution's Research Ethics Committee of University of Pernambuco, Brazil, analysed and approved this study under ethical rules for research involving human being and according the resolution number 196/96 of Health National Council which was labeled under the following protocol: CAAE-0196.0.172.000-10. Statistical analysis was applied using Statistical Analysis Software (SAS)® version 22 (SAS Institute Inc., Cary, NC 27513-2414, USA). The mean and median were calculated using the standard error and 95% confidence interval. For categorical variables, data were presented in terms of numbers and percentages. Written informed consent was obtained from each patient or legally representative prior to being treated and to use clinical and radiological data.

The patient demographical data (age and gender), and clinical data (history of subarachnoid hemorrhage) and other clinical features as incidental presentation, headache, visual and other neurological symptoms were reviewed and described in Table 1.

TABLE 1- Our experience about endovascular techniques for management of siphon carotid aneurysms between 2002-2014.

Total of patients	**232**	
Gender	**216 Females (93,1%)** **16 Males (6,9%)**	
Total of aneurysms	**308**	
Ruptured	**40 patients**	
Type of treatment	**Group I**	**Group II**
Demographics features	n (%)	n (%)
Age (yr)	50,02 ± 12,98	50,71 ± 14,41

Gender		
Male	21/176 (11,9)	5/56 (8,9)
Female	155/176 (88,1)	51/56 (91,1)
Multiple aneurysms	80/176 (45,9)	17/56 (30,35)
Mirror	39/176 (22,2)	10/56 (17,9)
SHA	31/176 (22,9)	9/56 (16,0)
Total of aneurysms treated	238 (100)	70 (100)
Total of cases	176 (100)	56 (100)

Further data from pre-treatment angiograms, including 2- and 3-dimensional (D) rotations were reviewed to characterize the aneurysms within the carotid siphon. Aneurysms were considered within carotid siphon when they were located at segments C4-6 by Bouthiller (C2-C4 in the Fischer's classification)[31,32], including literature spectrum referred as several denominations as carotid-ophthalmic, cavernous, cervical, petrous, parasellar, paraclinoid, paraophthalmic. Siphon nomenclature were used referred to the modern method of classifying endovascular aneurysm treatment, which is closely referenced to the vessel curvature, while comparable neurosurgery such as ophthalmic aneurysms or paraophthalmic, make closer reference to regional microanatomy.

Aneurysm angioarchitecture measurements were performed using a Philips® 3D workstation, and included aneurysm size, neck size, dome-to-neck ratio and parent-vessel measurements (stenting) during pre-operative planning. The aneurysms were also sub-classified in two groups: a) giant, including true giant (> 2.5 mm) and large (>1.5 cm) and b) non-giant (<1.5 cm). All patients were categorized for treatment as either: 1) undergoing initial treatment or 2) failure of previous treatment, recanalization/ recurrence, or 3) multiples aneurysms.

Of a total of 308 aneurysms, only 48 patients (15.7%) were treated in acute setting of subarachnoid haemorrhage episode. Once admitted, patients underwent Digital Subtracted Angiography (DSA) of the cervical or intracranial vasculature, depending on the location of the aneurysm. Subsequently, additional routine imaging relevant to the clinical scenario and treatment plan, such as 3D-reconstruction, intra-arterial vasoCT®, arterial perfusion and 2D flow acquisitions, were performed. All angiographies were obtained via the percutaneous trans-femoral approach, with patients under either local and/or general anaesthesia. Neuro-interventional acts were performed using a mono- or bi-plane angiography system (Philips®, Netherlands). Images were stored using the Easy Web® system.

Patients whose aneurysms supposed were managed by stenting; they followed the antiplatelet protocol of our institution in accordance with guidelines established by Hematology team of Bichat-Claude Bernard Hospital. [35] The EAR technique rate for 308 carotid siphon aneurysms, treated by using the endovascular approach or by single or combined treatment modalities. The assessment of balloon techniques and stenting commenced in our department in 2002 (Rothschild). This is followed by the introduction of flow-diverting stents in 2009.

RESULTS

Characteristics of patients with carotid siphon aneurysms are shown in Table 1 above illustrated. Patients were 93% female (216/232), with a mean admission age of years 50.19 ± 13.1(range 16-84). When comparing ruptured and un-ruptured aneurysms, the median age of patients was 50 ± 13.07 years (range 23-81) and 50.22 ± 13.4 years (range 16-84) respectively. The most common age group was between 41-60 years (59.3% of the total sample),

followed by 21-40 years (22.2%). Mirror aneurysms were present in 21.1% (49/232) of patients. The most frequently ruptured aneurysms were encountered in left siphon (177/308); 57.5% as compared to ones on the right siphon (146/259); 56.4%. The mean dome average of the carotid siphon aneurysms analyzed was between 5.1 and 8.0 mm. and the mean dome-to-neck ratio was >1:2 in (165/308); 53.4%.

Group I (Balloons Remodelling Technique)

Two hundred and fourteen aneurysms (214/238, 90%) of group I were managed by coiling which was the predominant primary technique. (Case 1 illustrated) The balloon-remodeling technique was required in 81% (192/238) of aneurysms treated, not only to assist coiling, it was also used routinely to protect the neck aneurysm from rupture at the time of the procedure. The use of balloon was observed in 94% (29/31) of ruptured aneurysms subgroup. The use of balloon Hyperglide® was observed in 188 patients and Hyperform® in only four patients. Remaining cases were treated by other techniques.

Ten giant aneurysms were treated by ET with detachable balloons or coils which were deployed inside the parent vessel. Two aneurysms were treated by aneurysm occlusion with Onyx® Embolic System. Thirty-five percent (85/238) of aneurysms (including 13 recanalized aneurysms) were managed additionally by stenting techniques subdivided into three groups:

I. Group treated by Balloon-Expandable Stents: [Cerebrence ® (Medtronic - Santa Rosa, CA, USA)]; which included three aneurysms.

II. Group treated by Self-Expandable Stents [Enterprise ® (Cordis , Miami, Florida, USA); Leo ® (Balt Extrusion, Montmorency, France); Leo plus ® (Balt Extrusion, Montmorency, France); Solo EV3 ® (ev3, Irvine, CA, USA); Neuroform ® and Neuroform 3TM (Stryker, Irvine, USA) and Solitaire ® (EV3, Irvine, CA, USA)];which included 64 aneurysms. Additional balloon remodeling was used to decrease the risk of coil loop protrusions through the self-expandable stent in many cases.

III. Flow-Diverters Stents [Silk (Balt Extrusion, Montmorency, France); Pipeline ® (Chestnut Medical Technologies, Inc., Menlo Park, CA, USA); Fred ® (Microvention, Tustin, CA)]; This group included 18 aneurysms.

Group II (Flow Divertion)

Ninety-two percent (64/70) of the aneurysms of this group were managed with flow diverters stents. Seventeen percent of aneurysms were treated with additional coiling (Case 2 illustrated) as well 7 % of aneurysms were treated with coiling alone.

One patient had carotid siphon aneurysm with a 4.0 mm width, a 4.3 dome and 5.1 mm neck. The Silk stent was tried but the device was not stable within the parent vessel. A different sized was tried with no success. The aneurysm was subsequently treated with Leo® stent. Two aneurysms were treated by aneurysm occlusion with Onyx® Embolic System. Two aneurysms were treated by FB, but were excluded from further analyzes.

DISCUSSION

We present a historical review of carotid siphon aneurysms management which is based on series of cases treated in a French reference center for intracranial aneurysms. To our knowledge, this is the largest series about endovascular management of carotid siphon aneurysms described until now[8,11,16,21,22,23,31].

Since the key role of endovascular repair is to eliminate blood flow into an aneurysm whilst also preventing the aneurysm sac re-bleeding[16,20,27]. Posteriorly, the approach was gradually changed after the introduction of flow diverters in 2009 and has been directed to correct the hemodynamic disturbance[22,24].

Nevertheless, the several techniques were developed in order to overcome morphological characteristics of these aneurysms with wide neck and large volume, intraluminal thrombus and calcifications have made their treatment difficult when compared with aneurysms in other locations (i.e. using either endovascular or microsurgery)[10-11, 15-19].

Table 2 shows that largest endovascular series described in the literature until now. An important remark regarding our experience showed that is frequently needed more than one technique to completely treated the aneurysm.

TABLE 2 – Brief summary of endovascular series about carotid siphon aneurysms

	Aneurysms/Patients	Ruptured/Unruptured	Location
Larson, 1995	58/58	-/-	Cavernous Petrous Cervical Ophthalmic
Roy, 1997	28/26	8/18	Ophthalmic Parasellar Paraclinoid
Nelson, 2001	64/64	-/-	Paraclinoid
Jin, 2009	65/67	9/58	Ophthalmic Paraclinoid Carotid Clinoid Suprasellar
Colby, 2012	90/90	14/76	Paraophthalmic
D'Urso, 2014	136/140	136/0	Paraclinoid
Ahn, 2014	43/43	1/42	Ophthalmic
Group I	238/176	33/143	Siphon
Group II	70/56	7/49	Siphon

Endovascular advances has given credibility to the endovascular management allowing that giant aneurysms within the carotid siphon of the ICA that before without treatment 80 % of people die or became handicap two years after the diagnosis. 38 However, the main advantage of this type of treatment is to prevent microsurgery, with the opening of the skull, which has less discomfort for the patient and the surgical risks seem to decrease[4-7,12,43,46].

We emphasize two most frequent techniques used for carotid siphon aneurysms management whilst shows endovascular advances has revolutionized their endovascular treatment[9,20,23]. This refinement and sophistication of endovascular techniques appear to allow all aneurysms within the carotid siphon of the ICA could be treated with excellent results[1,8-10,15,16,20,23]. Therefore, further sophistication of materials and catheters and tools to help in the clinical setting has evolved with appearing with proper technologies in order to increase its safety and effective[45].

The first endovascular repair of carotid siphon aneurysm were developed by Serbinenko. He repaired an cavernous aneurysm using detachable latex balloons either by depositing the balloon directly into the aneurysm and occluding the artery lumen from which the aneurysm arose[45]. Following, the electrolytic detachable platinum coils, called Guglielmi detachable coils (GDCs) started to be used

during coiling techniques to occluding the aneurysm, thus excluding it from the circulation[47].

Conventional coiling which was then addressed to treat ruptured aneurysms, come the choice treatment for unruptured aneurysms as well[8;9;18;24]. In order to treat complex and wide-neck aneurysms, remodeling technique (RT) was introduced by the senior author (J.M)[12;20]. His RT technique helped considerably in the development of interventional neuroradiology to address the limitations of single coiling compared with open surgery[2;12]. Recanalization has remained still an inconvenient and main limitation of conventional coiling with frequent reassessment needed[48].

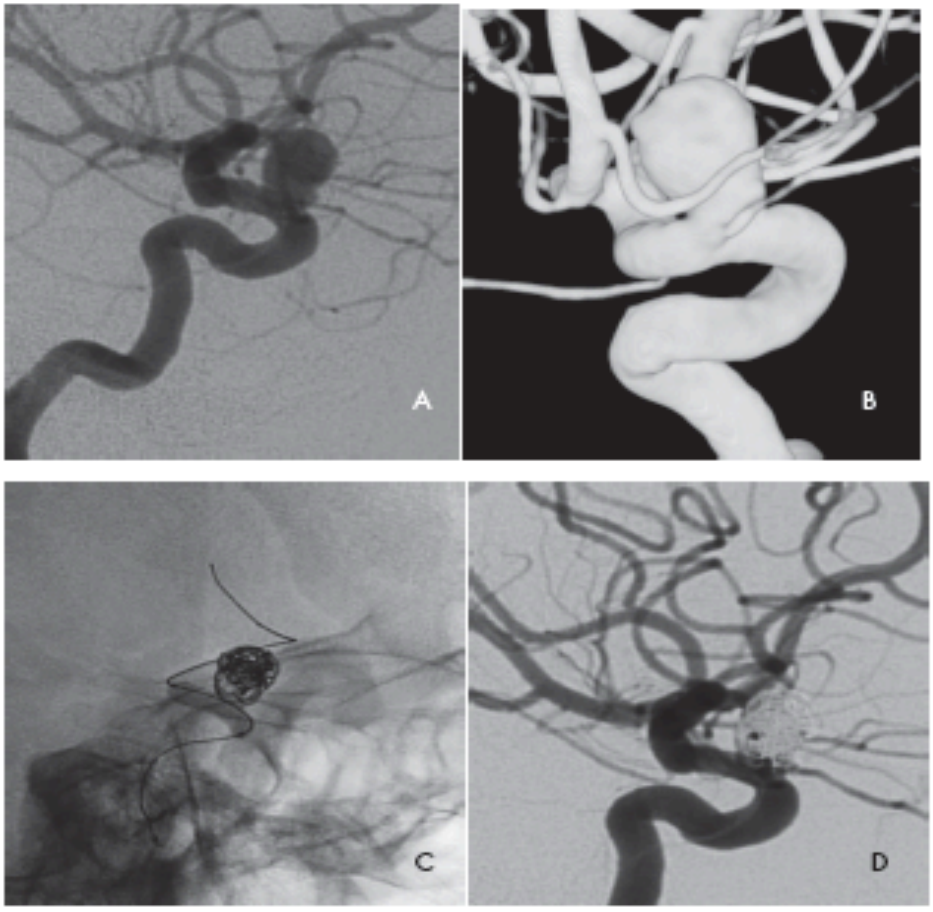
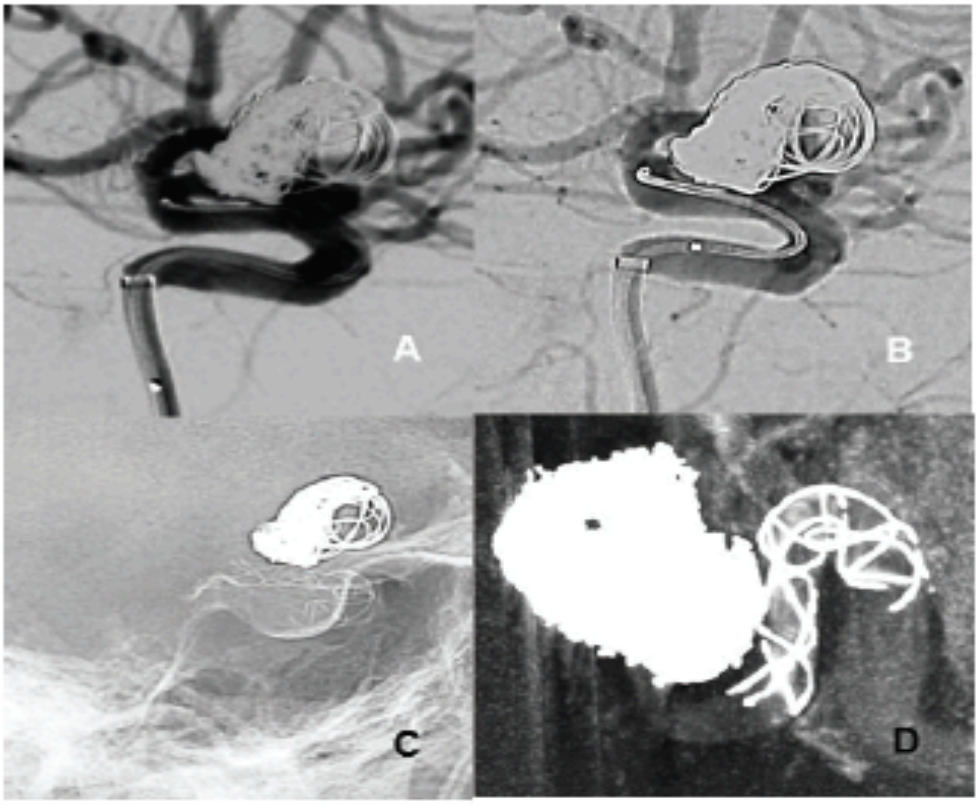


Figure 1 - Images obtained from a 53yo, female with history of dizziness, strong familiar maternal and paternal history of ruptured intracranial aneurysm and incidentally left carotid siphon aneurysm which was treated by remodeling balloon technique. Figures 1A and 1B illustrated respectively working position and 3D reconstruction of left carotid angiogram. Figures 1C and 1D show remodeling balloon of neck of ophthalmic aneurysm and final DSA control showing the total occlusion of the aneurysm(ophthalmic segment of carotid siphon aneurysm).

Consequently, a more effective EAR method that can reduce the need for controls and can work in the pathophysiology of an intracranial aneurysm has been desirable[49]. In this point, stenting was developed to permanently protect the parent vessel, by containing the coil mass alone or inside the aneurysm sac. The first stents balloon-expandable had poor flexibility and maneuverability and the authors had encountered significant complications using these devices, e.g. mostly dissection or rupture of the parent vessel[50].

The most important factor to be considered when choosing EAR techniques is angioarchitecture of the aneurysm and particularly in the carotid siphon aneurysm, the siphon geometry is also another factor important[20,50]. When the aneurysm had an enlarged neck (or size and neck ratio > 1), the decision was taken promptly and required remodeling technique or more than stenting assisted coiling. When the aneurysm was considered large or giant, then it was more suitable for stenting to avoid mass effect of coiling. Our department had traditionally deployed coils to pack the aneurysm to fill dead space even if stenting was employed.

Moreover, stent placement always poses a risk of acute in-stent thrombosis, necessitating sufficient premedication with antiplatelet drugs[25]. As a result, stent placement has been avoided in the treatment of acutely ruptured broad-necked aneurysms, unless there is no other solution.



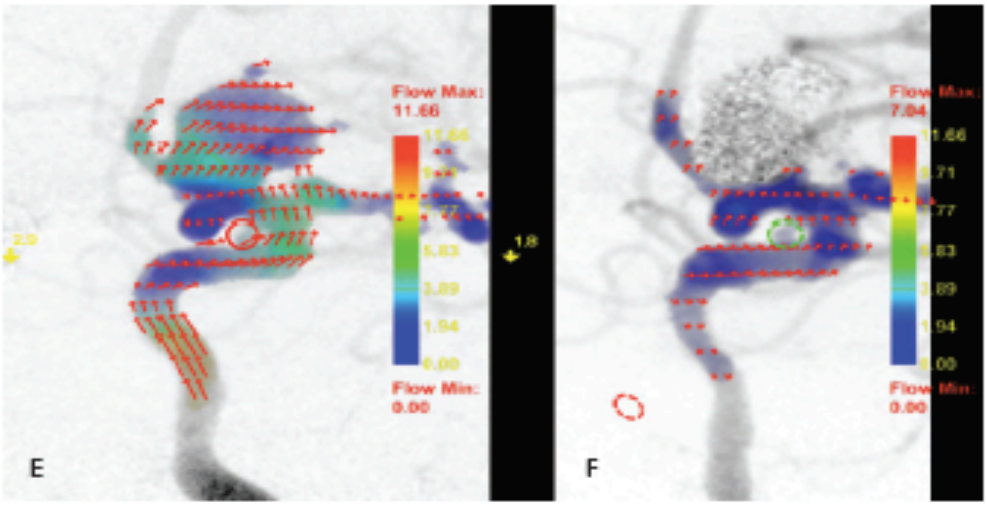


Figure 2 – Images obtained from a 57yo, female with a history of a migraine, familiar history ofa ruptured aneurysm and incidental left multiple carotid siphon aneurysms. The large ophthalmic aneurysm was treated with remodeling balloon technique and following flow diverterstenting, which also had covered the two other small aneurysms within the left carotid siphon. Figure **2A** and **2B** show DSA control of remodeling balloon of the large aneurysm and microcatherization in order to make the placement of the flow diverter stent. Figure **2C** and **2D** - Subtraction image obtained afterstenting and 3D reconstruction of stented area. Figure **2E** and **2F**- Flow study images obtained pre and poststenting showing the flow diversion.

New materials and neurovascular stents which modify the blood flow and thus seek to normalize flow are really very promising. The expected result is thrombosis induced by stent inside the aneurysm, which leads to the formation of a new wall[9,22,24,69].

The geometry of parent vessel, when the carotid artery shown dysplasia, which is a quite frequent event, related to probably remodeling vascular, then it was required additional techniques, such as ballooning to reconstruct the carotid artery for stent placement.

A good assessment of perforator vessel is highly expected in order to protect these vessels. In the specific case of carotid siphon aneurysms, the ophthalmic artery has always been a subject of debate, since treatment decision was microneurosurgery. Then, discuss an important concern regarding ophthalmic artery aneurysms occlusion after FD treatment. In our institution, we have experienced delayed and partial occlusion when the ophthalmic artery originates directly from the sac. For example in our second case illustrated that has showed continuous aneurysm filling after coiling, even if the residual sac patency is very limited. From this, discuss the "endoleak phenomenon" as a possible cause of this observation and further FD was indicated.

The collateral circulation is another important factor to analyze which appears to be particularly important in giant aneurysms with pre-assessment of collateral circulation if the parent vessel will be occluded by balloon pre-occlusion test. Special attention should also be paid to possible anatomical

variations which can change the flow orientation and modify the result of flow diversion treatment.

The presence of vascular loops and atherosclerosis sometimes represent an obstacle to a suitable treatment of the aneurysm. Despite the powerful materials currently in use, carotid loops can sometimes prevent endovascular treatment.

CONCLUSION

Historically, the techniques of EAR were introduced for the intracranial aneurysms management for inoperable aneurysms, EAR has become the choice technique particularly in the carotid siphon aneurysms.

The endovascular technique obviates microneurosurgery with lesser associated surgical complications in the management of aneurysms within carotid siphon. Balloon RT revolutionized the treatment of wide-necked IAs and consequently siphon carotid aneurysms. Flow diversion is a modern and promising technique that has overcome techniques problems, where maneuverability has become easy. Thromboembolic issues has been solved with good knowledge about biological effects of antiplatelet drugs in cerebrovascular stenting.

Using a combination of different techniques has been the key to long-term success for management of ICA siphon aneurysms, and it is important to master all techniques, to be able to use them effectively.

Our increased availability of different technologies and increased the indications for this type of intervention, probably has resulted in new ways to improve the management of carotid siphon aneurysms with safety and efficacy.

Innovative advances are expected in near future, especially in terms of new targeted biomolecular treatments, and also providing preventive and screening measures.

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CAPÍTULO VII

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Aneurysms of Egas Moniz Siphon: A Three-Dimensional Geometric Morphometric Classification Proposed in the Areas of Susceptibility

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ABSTRACT

The aneurysms that develop on the circumference of the carotid siphon are a diverse group of challenging lesions, due to the anatomical complexity of the region in which they are located (i.e. using either endovascular or microsurgery). A new approach of endovascular treatment has been addressed to correct the disturbances involving hemodynamic and vascular morphology. Furthermore, it has been hypothesized that siphon carotid morphology variability might be related to aneurysms development. However, until recently, there has been no consensus yet about morphologic subtypes of carotid siphon aneurysms. Two hundred ninety human aneurysms were analyzed and nine different morphologic subtypes most frequently found were identified. We attempt to identify the most prevalent subtypes based in areas of susceptibility using previous microsurgical and radiological landmarks held and correlating with siphon morphology. Results indicate that Egaz Moniz siphon aneurysms despite the diversity seem to be more frequent in the upward curve of a carotid siphon. More future studies are desired to understanding the morphological and functional patterns of the carotid siphon.

Key words: vascular geometry; morphology; intracranial aneurysms; carotid siphon; bends; genesis

Abbreviations: CTA= computed tomography angiography; DSA= digital substration angiography; ICA= internal carotid artery; ; PSR= parasellar; WSS= wall shear stress; WSSG= wall shear stress gradient

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INTRODUCTION

In 1927, the Portuguese neurologist Egas Moniz introduced the contrasted X-Ray cerebral angiography to study the angioarchitecture of cerebral vasculature (Bozzetto, 2014; Lima, 1951; Schierhorn, 1981). Five years later, Moniz described the carotid siphon and demonstrated an aneurysm arising from the internal carotid artery (ICA) at the skull base (Bozzetto, 2014; Moniz, 1933).

The aneurysms that develop in the circumference of the carotid siphon are quite diversified (Ahn, 2014; Barami, 2003; Colby, 2012; Day, 1990; D'Urso 2014; Jin 2009; Larson, 1995; Wang 2013; Roy, 1997). Beyond anatomical, microsurgical and complex neuroendovascular repair, the natural history of intracranial aneurysms of remains poorly understood. However, several studies showed a correlation between geometric variability of the carotid siphon and the possible aneurysm formation (Bozzetto, 2010; Lee, 2008; Silva Neto, 2012). The areas of turbulent flow are susceptible to weakness and morphological changes of the vascular wall, which may be associated with aneurysm development (Bozzetto, 2010; Valen-Stendstat K et al., 2014).

On reviewing the literature, two main points in the natural history of carotid siphon aneurysms require further investigation. Firstly, there is a need of accurate statistics because an underestimation is observed, as most of the current statistics are based on ruptured aneurysms and less about unruptured aneurysms. Secondly, most of series highlight ruptured aneurysms particularly that appear above clinoidal (described in the literature as carotid-ophthalmic, para ophthalmic, para clinoid among others (Ahn, 2014; Barami, 2003; Colby, 2012; Day, 1990; Larson, 1995; Roy, 1997). In fact, it was observed that there is still no agreement on the morphological subtypes of the different types of carotid siphon aneurysms. As far the other subgroups as the cavernous aneurysms, cave, transitional, dorsal wall carotid, blister-like and others remain largely unexplored. It is stated that carotid siphon aneurysms should represent about 5-10% of intracranial aneurysms. However, it is estimated that more than 30 % of all aneurysms are located in the intracranial segments of ICA usually at or distal to the carotid siphon (Bogunovic et al, 2012).

New biotechnologies have been incorporated into the diagnosis and management of intracranial aneurysms (Bozzetto et al.,2015). Some of these new technologies consist of tools to better understanding the pattern of aneurysmal flow and detect possible morphological or hemodynamic aneurysm-specific features which could be responsible for the formation of cerebral aneurysms (Bozzetto et al., 2015; Sekhar et al., 1981). Through experimental studies and flow inside the dome of an aneurysm seems to be the hemodynamic stress is caused by a sequential and repetitive turbulent flow. This type of abnormality was evidenced in the cavity of an intracranial aneurysm during systole. This abnormal flow becomes reversed during diastole so that these rapid changes in the direction of flow continues to cause friction on the inner wall of the vessel and contributing to the formation and progression of an aneurysm (Gonzalez et al., 1992).

Following to refinement of endovascular treatment which has targeted to correct the disturbances involved in hemodynamics/geometry and vascular morphology, a new morphological classification would be particularly useful to give a new approach linking pathogenesis and treatment of carotid siphon aneurysms. In this paper, we analyze the carotid siphon morphology and discuss the relevance

of classifying in subtypes morphological for the better understanding of pathogenesis and treatment of this peculiar aneurysms.

FUNCTIONAL SHAPE OF CAROTID SIPHON

The carotid siphon or also known as Egas Moniz's siphon refers to the radiographic appearance of the internal carotid artery as a series of twists and curves that characterize this anatomical landmark (Moniz, 1933). The term carotid siphon gained popularity after Egaz Moniz publication based on brain contrasted radiographic studies of ICA (Sander-Taylor et al., 2013), when he also described an aneurysm of internal carotid at the base of the brain and described the siphon carotid using a two-dimensional projection with anatomical documentation and being the most important landmark in the angiogram (Moniz, 1933).

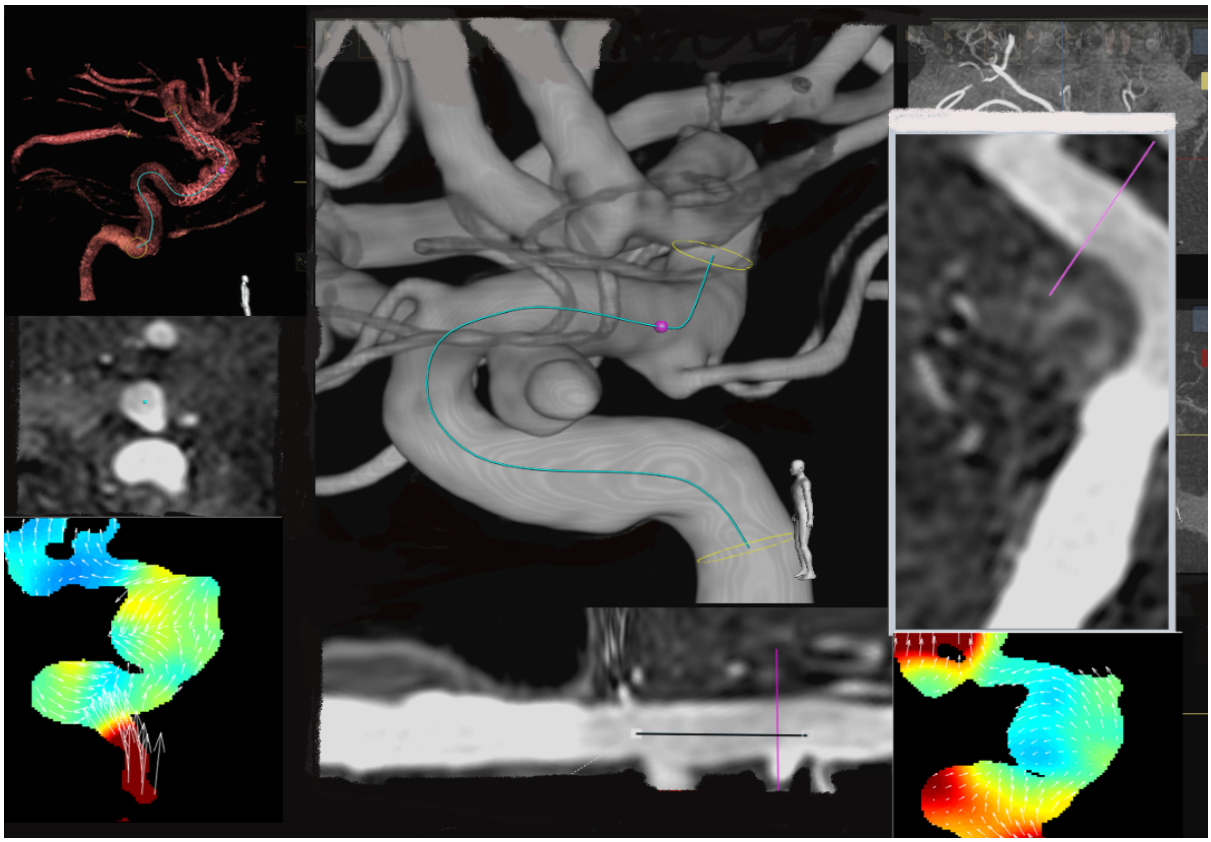
According to Egas Moniz's original description, the carotid siphon in 70 per cent of cases showed another curvature towards the frontal region, giving the impression of the double siphon (Moniz, 1933; Moniz,1934). Posteriorly, anatomical studies about carotid siphon showed 84% of adults have ICA has the characteristic double-bent shape (Platzer, 1957) but curiously in neonates apparently ICA takes a much straighter course. Studies particularly the investigation of Weninger and Muller demonstrated that the anatomy of the infant para sellar portion (PSR) differs distinctly from that of the adult and the PRS of the ICA of the neonates does not form a siphon (Weninger and Muller, 1999) which indicates that the shape of ICA is strongly transformed during early childhood.

Inside the carotid siphon and along the ICA is frequent to find tortuous curves and angles as Moniz described and illustrated in Figure 1 below. Carotid siphons are common sites of intracranial atherosclerosis. Probably due to its nature a tortuous vessel segment with sharp bends and large area variations and which also has relevance to the study of aneurysms initiation and rupture (Sendstad, 2014).Generally carotid siphon tortuosity in elderly patients is particularly related to atherosclerosis. These curves can be seen even in children, and described as anatomical variant type. In children, however, it is observed that in over half the cases, the bifurcation of the common carotid artery, the origin of ACI, is typically located more superior compared to the origin of this artery in the adult at the time of the second and third cervical vertebrae (Dilenge, 1962).

More recently three-dimensional and hemodynamic studies have been helpful providing the better assessment to the carotid siphon morphology, particularly due to its sinuous shape which sometimes difficult to exact positionally and analysis (Kim et al., 2015). Further studies have showed that high peak focal curvature of the carotid siphon is correlated with aneurysm presence. In synthetic and patient-derived models, carotid loops are characterized by high WSS and WSSG, which correspond to the site of peak focal curvature. Aneurysms in these regions seem to form distal from the site of peak curvature, in areas of stagnant flow flanked by dynamically fluctuating high WSS and WSSG peaks. The distance between WSS peaks correlates with the size of the aneurysm neck (Lauric et al., 2014).

The new strategy of endovascular treatment also has been addressed to explore carotid shaping. In **Figure 1**, we also illustrated the flow studies, which are taking part of the endovascular strategic particularly during the treatment of carotid siphon aneurysms with flow diverters. However, this research focused on areas of susceptibility and morphology but did not consider the influence of flow instabilities and hemodynamic measures.

Fig. 1. Three-Dimensional geometric morphometric reconstruction (a) and curve reformatted view (b) of an female adult and its left carotid siphon The distal tip of the blue linel in this geometric configuration is within the carotid siphon (c) blue line in the lumen of siphon (d) optic flow study before (e) and after flow diverters treatment (f) linear reconstruction of same siphon (g)



GEOMETRIC MORPHOLOGICS OF CAROTID SIPHON

Although the understanding that local geometrical and hemodynamics factors are still contradictory.

Recent studies have showed that an association between the presence of aneurysms and intracranial ICA area expansions (Schimansky et al., 2013), curvatures (Lauric et al., 2013), angle (Silva Neto et al., 2012) geometric features know to affect flow stability ICA area expansions. There is no yet specific pattern described of carotid siphon associated with aneurysms or subtypes of aneurysms.

In 1965, Weibel and Field performed anatomical studies and demonstrated that the initial portion tortuous of carotid siphon shape is more frequently observed in individuals older than 50 years old (Weibel and Field, 1965). Three year later, Yasargil and krakenbuel using 2D angiographical projections demonstrated that carotid siphon may differ remarkably due to its tortuosity and described seven important variations noted in the carotid siphon: (1)U-shaped observed in 40,1 % of patients between 0-20 years, 35.0% between 21-50 years and 15,2 % between 51-74 years, which indicates that it type of young siphon. (2) C-shaped also observed in 45,2% between 0-21, 14,6% between 21-50 years and 15,2% between 51-74 years, also denotates a type of young siphon. (3) V-shapes has equilibrated distribution respectively (Yasargil and krakenbuel, 1968). Dilenge and Heon, 1974 simplified the Krayenbuhl and Yasargil's classification and reclassified in four types: U, C, arch and double siphon (Dilenge and Heon, 1974).

Recently Lin et al., reintroduced Yasargil & Kraenbuel's classification based on the tortuosity of the cavernous segment of the internal carotid artery as a predictive factor in the complexity of embolization with Pipeline® (Lin et al., 2014). Lin et al., classified into Class IA and IB, when the siphon showing a configuration with open angle determined by the angle of the posterior knee, where IA is greater than 90 and IB is equal to 90°. The Type II was characterized by the closed configuration of the previous angle with a more acute angle compared to the Type I and Type III when the carotid siphon had the further deflection of the knee. Type IV represents the most tortuous of all with the characteristic feature of Simmons® catheter.

CAROTID SIPHON AND ITS ANEURYSMS IN ANIMALS

Comparing the cerebral vasculature between humans and other animal species, particularly the rat (Rattus norvegicus) one of the most common animal used in scientific experimentation. The cerebral circulation differs between men and animals. Most animals have the rete mirabile (Ashwini, 2008). We found that carotid siphon has a similar confirmation in its proximal trajectory, but the anatomical topography is unique in humans compared with other vertebrates and mammals, as well as other primate species (Ashwini, 2008; Lee, 1995).

Although aneurysms in rats are not common, German and Black, 1954 were the first researchers to produce experimental aneurysms using the surgical construction of saccular aneurysms on the common carotid artery of dogs (German and Black, 1954). Carotid aneurysms experimental models mimicked the ones occurring on the side wall and were frequently used in hemodynamic studies. However, they produced fibrosis at the suture site, which was a disadvantage. Since then, surgical models have evolved with the culmination of the swine model consisting of a graft of the venous pouch onto the common carotid artery of pigs. This method produces lateral wall aneurysms but includes disadvantages such as venous histology, induction of intense fibrosis at the suture site, hemodynamic and low tension.

HYPOTHESES

An attempt to estimate the most prevalent morphological subtypes based in areas of susceptibility. A review of microsurgical landmarks and previous classifications of carotid siphon aneurysm were held. It has been hypothesized that there are specific morphological and shapes configurations related to aneurysms development.

1. What are main susceptible areas of carotid aneurysms development?

2. What are the subtypes of siphon most frequently related to siphon carotid aneurysms, is there differences between males and females siphon?
3. Is there a difference between human age and their carotid siphon and subtype of carotid siphon aneurysm?
4. Can we predict bleeding by carotid siphon morphologic subtype?
5. Perhaps certain aneurysms would justify screening and preventive treatment?

MATERIALS AND METHODS

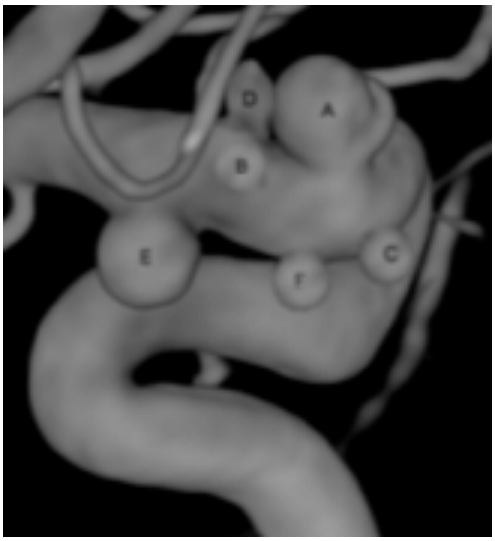
STUDY DESIGN AND ANEURYSM POPULATIONS

After reviewing most known classifications of ICA and carotid siphon aneurysms in the literature which are described in Table 1. Some authors have classified as carotid-ophthalmic, para clinoid, superior hypophyseal and cavernous aneurysms. Most of the classifications were addressed to the horizontal and supraclinoid portion of ICA. Several classifications of carotid siphon on basis of surgical considerations had been addressed in the literature and a established classification system based on the exact point from the carotid artery into ophthalmic, superior hypophyseal, clinoidal, cave, transitional, intracavernous (Al-Rodhan et al., 1993, Barami, 2003; Day, 1990; Roy, 1997; Ogilvy, 1995;Wang et al., 2013).

Aneurysms are considered within the carotid siphon when they were located in segments by C4-6 Bouthilier 5 (C2 -C4 classification of the Fischer) (Fischer, 1938; Bouthilier,1996) or based on the original description of Egas Moniz (Moniz, 1933). Data were collected with institutional and university ethics committee approval (CAAE-0196.0.172-000-10) regarding the group I and (CAAE-4707.5.215.1.0000.5208) regarding group II.

The aneurysms population analyzed were divided into two groups: **Group I** that included 1288 patients (432 men and 856 women) with 1552 intracranial aneurysms (IAs) which were treated between 1st of February 2002 and 25th of May 2010 at Foundation Adolphe Rothschild, Paris, France. We identified a total of 135 patients (with 178 carotid siphon aneurysms). When compared with those patients with aneurysms in another location than siphon segment (414 men and 739 women; 1: 1.8) there was a significantly higher chance of finding females in siphon segment aneurysms of the ICA group (OR 3.641, 2.185 to 6.068 95% CI p <0.0001). Each type of carotid siphon aneurysm were considered based on its specific clinical and angiographical features according to the **Figure 2**. There were five most prevalent groups of siphon carotid aneurysms: (1) ophthalmic, (2) superior hypophyseal (3) clinoidal or cave, (4) suprasellar, (5) others. Four aneurysms were purely located in the intracavernous segment and were not included in the first analysis.

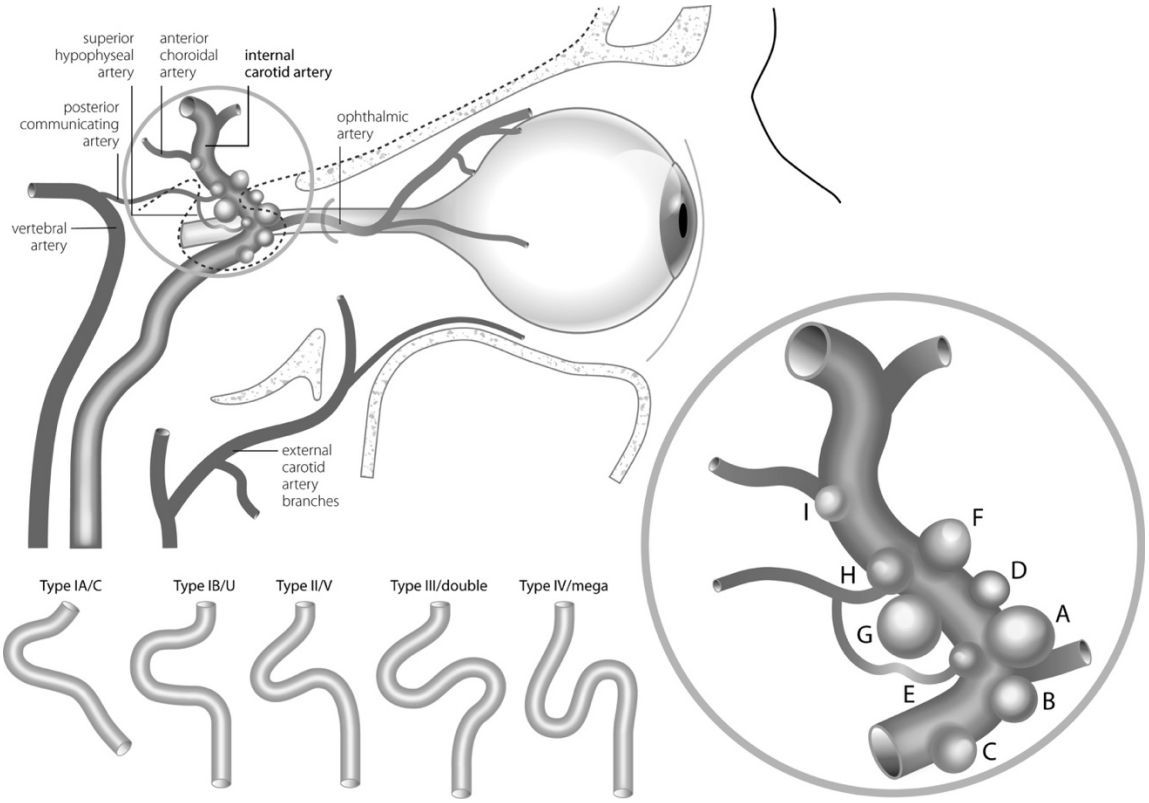
Fig. 2 - Three-Dimensional siphon reconstruction illustration



Group II included 532 patients (295 IAs) treated between 1st November 2010 and 31th of October 2014 at the Beaujon University Hospital, Clichy, France. This group contained 79 patients (5 men and 75 women) with 112 aneurysms within the ICA carotid siphon, which were analyzed prospectively.

After our redefinition about carotid siphon aneurysms, combined analysis of both groups were performed and nine most prevalent groups were considered: (1) ophthalmic linked, (2) ophthalmic related (3)superior hypophyseal, (4) clinoidal or cave, (5) suprasellar, (6) dorsal wall, (7) anterior wall (8) posterior communicant artery related, (9) choroidal anterior or terminal as illustrated in **Figure 3.** There are possible subtypes not covered, for example, some of the aneurysms can be difficult to classify.

Fig. 3- Three-Dimensional geometric siphon schema and neighbour structures (a), siphon shape subtypes (b), magnification of carotid siphon with morphological subtypes most prevalent encountered



RESULTS

DEMOGRAPHICS AND CLINICAL FEATURES

Characteristics of patients with siphon carotid aneurysms analyzed shown in Table 2. Patients were 90.6% female (194/214), with a mean admission age of years 49.24 ± 11.8 (range 16-84) in the group I and 50,23 ± 13,18 in the group II. Thirty-nine patients (18,2 %) had a history of subarachnoid bleeding.

In the group I, when comparing ruptured and un-ruptured aneurysms, the median age of patients was 48.90 ± 14.62 years (range 18-81) and 50.22 ± 13.4 years (range 23-84) respectively. The most common age group was between 41-60 years (59.3% of the total sample), followed by 21-40 years (22.2%). Multiple aneurysms were present in 45.9% (62/135) of patients. Mirror aneurysms were present in 17% (23/178) of patients.

Clinical features were tenaciously studied in the group I, the most common clinical presentation that was founded in the referral was the presence of a headache (observed in 51.1 % (69/135) of patients), only 22.9% of patients had ruptured aneurysms. A group of 24 patients complained of visual disturbances, ie 19.2 % of patients had visual deficits. The incidental finding of an aneurysm detected through studies by MRI or CTA during an investigation in the context of a chronic headache or other neurological symptoms occurred in 61/135 (45 %) patients. Remaining symptoms were other

neurological symptoms (dizziness, seizures, tinnitus, cranial nerves paralysis, following head trauma, hemiparesis) in 27 patients and hyperprolactinemia, renal polyposis screening, in other 4 patients which motivated the search for vascular pathology.

MORPHOLOGICAL FINDINGS

Table 3 describes the baseline distribution of 290 aneurysms. Most frequently aneurysms were encountered in left carotid siphon 55,9 % (162/290). Regarding the group I, 174 siphon carotid aneurysms were analyzed, the most common type of an aneurysm was type A (107/174, 60,1 %) of aneurysms and variant B (30/174, 17,2%] followed by type C involving 10,3% or 18/174 aneurysms. Types D (10/174) and E (including dorsal variant) (9/174) were less frequently observed. The most commonly ipsilateral carotid siphon shapes observed were typed C and V, corresponding 28,7 % of cases each variant and 16,7 % of cases. The other types U and double siphon respectively 48 (27,6%) and 26 (14,9%).

Our final analysis were combining group I and group II, a total of 290 siphon carotid aneurysms were analyzed. The subtype A or ophthalmic artery linked was the most prevalently observed in the total of 104 aneurysms between 290 carotid siphon aneurysms. The second most prevalent was subtype B or Ophthalmic artery-related, observed in 56/290 (19,31%). The subtypes superior hypophyseal and suprasellar represented respectively 6/290 and 23/290 aneurysms. Other subtypes were respectively cave/clinoidal, suprasellar, hypophyseal, anterior wall, posterior wall, choroidal/terminal, PCOM, other, nonclassified which represented respectively 33/290,

Table 4 describes the carotid siphon shapes distribution and analysis per gender. The most frequently demonstrated were subtype U/O observed in 74 patients between 290 patients which were significant more frequently encountered in females compared males. (p=0.0510, 0.0870 to 1.055, OR=0.2958). Between males siphon, the subtype most frequently observed was subtype D ((p=0.04, 1.0349 to 4.9843, OR= 2.2712), followed by subtype M which was demonstrated in 7 siphons between 30 siphons analyzed. Some siphons could not be classified and were in another category. Regarding ruptured and unruptured aneurysms and siphon subtypes: The subtype C was observed in 28/242 (unruptured), 7/48(ruptured). The subtype D, 59/242; 12/48. The subtype M, 35/242(unruptured) and 5/48(ruptured). The subtype O 13/242 and 4/48. The subtype U and V, 46 and 32 (unruptured) followed by 11 and 8 (ruptured).

DISCUSSION

1.What are main susceptible areas of carotid aneurysms development?

We have demonstrated the most recent large series about the three-dimensional geometric study of carotid siphon aneurysms or Egaz Moniz a siphon aneurysm. In the same time, we attempt to classify carotid siphon aneurysm by subtype related to morphology.

Table 1 showed the previous classifications which were held based in surgical and microsurgical analysis with reference to the location of an aneurysm and adjacent structures [proximal ICA para clinoid, supraclinoid, infra clinoid, para ophthalmic, supra ophthalmic, parachiasmatic, subchiasmatic, suprachiasmatic]. (Al-Rodhan et al., 1993, Barami, 2003; Day, 1990; Roy, 1997; Ogilvy, 1995; Wang et al., 2013).

DAY'S CLASSIFICATION

Kothandaram et al., 1971 were the first authors to describe differents subtypes of para clinoid aneurysms. Therefore, Day 1990 draw attention to differents subtypes of carotid siphon aneurysm and established the first classification which was used as a baseline in the future classifications.
Day, 1990 analyzed clinical, radiographic and anatomical features in 80 patients with the ophthalmic aneurysms and categorized into (1) ophthalmic and (2) superior hypophyseal aneurysms, according to a presumed aneurysmatic origin related. The main interest was in the fact to display a difference in the technical challenge and morbidity associated with the treatment of these two groups of aneurysms. The first group represented the true carotid-ophthalmic aneurysms, that is those arising at the junction between the ICA and the origin of the ophthalmic artery, pointed superiorly or superomedially and (when large) deflected the carotid artery posteriorly and inferiorly. The second group, superior hypophyseal artery aneurysms arose just above the dural ring from a medial bend of ICA, at the site of superior hypophyseal artery origin to the superior aspect of the hypophysis, and had no direct association with the ophthalmic artery. These lesions could extend medially beneath the chiasm (suprasellar variant), producing a clinical and computerized tomography picture similar to a pituitary adenoma, or they could extend ventrally to burrow beneath the anterior clinoid process (para clinoid variant) (Day, 1990).

AL-RODHAN & OGILVY'S CLASSIFICATION

Al-Rodhan et al., 1993 described five subgroups:
Group I – when the neck was intradural located and ICA segment that is supra-ophthalmic and infra posterior the posterior communicating. This group is divided into two subgroups: Ia- refers to aneurysms known as hypophyseal superior projecting superiorly Ib- are aneurysms that Yasargil & Fox has called ventral paraclinoidal protruding posteriorly and inferiorly intradural or extradural into the cavernous sinus.
Group II - true aneurysms whose arises at the junction between the ophthalmic artery and ACI, which projects anterior-superior and remain infra-durally.
Group III - are aneurysms that Kobayashi called cave carotid. Are medial, infra-ophthalmic and cavernous (Kobayashi, 1989; Hitotsumatsu, 1997).
Group IV - are so-called transitional, whose lap surge in the cavernous space, but its dome protrudes intradural.
Group V - purely intracavernous.

Posteriorly, Ogilvy et al., applied this classification and reviewed their experience using a combined surgical and endovascular treatment to approach to para clinoid segment aneurysms between 1991 and 1999. They reviewed 238 aneurysms in 216 patients and subdivided into five subgroups: 1) true ophthalmic aneurysm, arise from the of the ophthalmic artery which is equivalent of subgroup 1 of Day. 2) Superior hypophyseal aneurysm arises distal to the ophthalmic artery and project medially, often incorporating perforating branches of the hypophysis also equivalent of subgroup 2 of Day 3) Carotid a cave aneurysm arises at or bellow the dural ring around the ICA as it enters the subarachnoid space which was described by Kobayashi, 1989 4) Posterior carotid wall aneurysms arise just distal to the ophthalmic artery on the posterior wall of the ICA and project posteriorly which were described originally by Dandy. 5)Transitional aneurysms originate within CS and extend superiorly into the subarachnoid space.

ROY & RAYMOND'S CLASSIFICATION

In 1997, Roy and Raymond reviewed their endovascular experience and twenty-eight aneurysms encountered in 26 patients were analyzed and the second group described by Day was subdivided into two variants: para clinoid and suprasellar. The para clinoid variant when an aneurysm had an intracavernous proximal neck and fundus with only the distal neck lying in the subarachnoid space. It was included a para clinoid variant what Kobayashi called carotid cave aneurysms when both involve the proximal and medial parts of an ophthalmic segment (Roy et al, 1997, Beretta et al, 2004). On the

other hand, the aneurysms arising in association with aberrant origin of the ophthalmic artery and superior hypophyseal artery, occurring in 10% of cases. An aneurysm was initially expanding toward the optic strut and may project laterally or medially or superiorly leading to optic nerve compression or rash toward hard dural ring adjacent to the subarachnoid space. Subsequently, this same classification was adapted by Roy describe the endovascular treatment of aneurysms of the ophthalmic segment 28 in 26 patients treated by coiling as the first indication as to the treatment (Roy et al., 1997.

2. What are the subtypes of siphon most frequently related to siphon carotid aneurysms, is there differences between males and females siphon?

We demonstrated that carotid siphon may differ remarkably from normal patients as Yasargil description where

(1)U-shaped observed in 40,1 % of females;

(2) C-shaped which could indicate the denotates a subtype of "young" siphon;

(3) V-shapes has equilibrate distribution respectively 14,6 (0-21y),24,5% (21-50 y), 22,3% (51-74y)

(4) Omega- shaped siphon appear to be normal variant from U-shaped, which respectively 23,7% (21-50 y) and 50,7% (51-74y).

(5) Double siphon, Megasiphon, and Dolicosiphon were the most frequently observed which might denotate a vascular remodeling occurring in the carotid siphon.

Female and males vasculatures appear to have a different configuration. At the same time, our research corroborates the recent speculations where the authors have been investigating the relationship between the circle of Willis (circulation variations) and analyzing the risk of aneurysm formation detected.

The known correlation between the men and women to the anatomical presence variants also appear to be correlated with the difference the distribution of aneurysms. Females also have a predominance of PCOM fetal comparing to males. Evidence shows that the local aneurysmatic distribution could be linked with sex. At the same time, the Willis Circle anatomy has considerable variability with frequent asymmetries So probably the vessel geometry variations can play a role in the genesis of intracranial aneurysms, particularly in this siphon region that is subjected to significant variability. At this point, Padget was among the first to say this for a number of cases compared to embryological abnormalities with aneurysms and without aneurysms (Padget, 1968).

FUTURE DIRECTIONS

To summarize, the results of this present research confirm there are several morphological patterns of siphon related to carotid siphon aneurysms. It appears that the siphon carotid aneurysms development is related to aging process of the vascular wall and accelerated by atherosclerosis. The siphon which is straight in the children appears to suffer remodeling which could be particularly accelerated in patient with hyperdynamic status or asymmetric will polygon.

This study suggests that there is certainly a particular shape morphology modifying that happen and which be related with aneurysms genesis. Besides, there is probably standard pattern with the geometry siphon associated with certain subtypes of aneurysms.This is one the first recent studies related to siphon morphology which are more focused in treatment operative techniques. There is a lack of detailed studies in this matter. The lack of information is also related to a hidden position of carotid siphon which prevents the use of some techniques as doppler for example.

We attempt to incorporate new methods to our routine to better understand the morphology and hemodynamic of carotid siphon aneurysms. However, the understanding of vascular morphology appear to be promising for the understanding of the genesis of aneurysms, and also the response to treatment with new technologies as flow diverters stents.

These new evidence should contribute to the increased of studies in this matter and helping us to better understand the pathophysiology and mainly pointing to a more effective and efficient direction in the detection and prevention of aneurysms.

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TABLE 1. Overview of morphological classifications, types of aneurysms, sample studied, type of treatment performed, carotid segment, type of analysis done, carotid surface analysed.

	Types of aneurysms	Patient, SAH and aneurysms (n, n, n)	Surgical or Endovascular Treatment	Carotid Segments (Fisher, Bouthillier)	Type of Analysis	Surface
Kothandaram, 1971	Subchiasmal, Suprachiasmal, Paraclinoid	19	Surgery	C2, C3	intraoperative	Superior
Day, 1990	True carotid-ophthalmic Superior hypophyseal	80, 28, 41 carotid-ophthalmic 39 hypophyscal	67% (54/80) clipping remaining-not	C2, C3	intraoperative	Superior
Al-Rodhan, 1993	Group I a- superior hypophyseal Group I b- ventral paraclinoid Group II- true ophthalmic Group III- Kobayashi Group IV- transitional Group V- intracavernous	118, 13, 23 transitional	73% (18/23), 17 direct clipping, 1, bypass	C2, C3, C4	Angiographic/ Intraoperative findigns	Superior
Ogilvy, 1995	Transitional Carotid Cave Ophthalmic Superior Hypophyseal Posterior Carotid Wall	216, 59(25%), 238	180/216 (%) clipping, 57/216 endovascular, 1 bypass	C2, C3	Angiographic/ Intraoperativve Findings	Superior
Kato , 1996	Ophthalmic Clinoid Horizontal	48, -, 45	All surgical patients	C2- C4	-	Superior
Roy, 1997	1-ophthalmic	26, 8, 28	26 endovascular	C2, C3	Angiographic	Superior

	2A upper-paraclinoid variant of superior hypophyseal 2A lower-kobayashi cave 2B suprasellar variant of superior hypophyseal		100% treated		findings	
Barami, 2003	Ophthalmic artery (Ia) Dorsal ICA (Ib) Ventral ICA (II) Medial Supradiaphragmatic (IIIa) Infradiaphragmatic (IIIb)	61,-,61	61 surgical	C2, C3	Angiographic findings	Superior, Ventral
Sherif, 2008	Ophthalmic artery Superior Hypophyseal Artery Posterior Wall Carotid Carotid Cave Transitional	64, -, 64	23 surgery, 38 embolization 3 bypass	C2		
Wang, 2013	Type I- distal ophthalmic Type II- ventral, medial or lateral segment Subtype a- proximal Subtype b- distal	56, -, 64	12 coiling and 52 stenting	C2, C3	Angiographic findings	Superior
New classification	9 types		Until 2010, 90% coiling, 81% remodeling balloon After 2010, 90% flow diverters			
	A- linked to the ophthalmic artery ; Superior face of carotid artery B- Superior face of ICA, not linked to ophthalmic artery C- Cave carotid	214,-, 290	Group I- 93% endovascular, 81% remodeling balloon 7% no treatment Group II- 100% endovascular, 90% flow diverters	C3-C5	Group I-2D and 3D Group II-3D	All

TABLE 2. Demographical features of patients analysed.

Total of patients	214	
Gender	194/214 Females (90,6%) 20/214 Males(10,2%)	
Total of aneurysms	290	
Ruptured	39/214 patients (18,22%)	
	Group I	**Group II**
	n/n(%)	n/n (%)
Age (yr)	49,24 ± 11,8	50,23 ± 13,18
Gender		
Male	18/135 (13,3)	5/79 (6,3)
Female	117/135 (86,7)	74/79 (93,7)
Multiple aneurysms	62/135 (45,9)	33/79 (41,7)
Mirror	23/135 (17,0)	10/79 (17,9)
SAH	31/178 (22,9)	8/79 (10,1)
Total of aneurysms	178/135 (1,3)	112/79(1,4)
Total of treated aneurysms	163/178 (91,5)	112/112(100)

TABLE 3. Distribution of carotid siphon aneurysms.

	Arch-shaped Syphon	Double Syphon	Mega/Dolico Syphon	Non Classified	Omega Syphon	U-shaped Syphon	V-shaped Syphon	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ophthalmic-True	11/290(3,7)	31/290(10,7)	15/290(5,2)	3/290(1,0)	6/290 (2,2)	22/290(7,6)	18/290(7,0)	107/290 (36,8)
Opthalmic-Related	6/290(1,8)	18/290(6,5)	10/290(3,6)	4/290(1,5)	3/290 (1,1)	9/290(3,3)	6/290 (2,2)	56/290 (19,3)
Cavernous	3/290(1,0)	5/290(1,8)	7/290(2,5)	11/290(4,0)	3/290(1,1)	10/290(2,5)	7/290 (2,4)	49/290 (15,0)
Cave/Clinoidal	7/290(2,7)	6/290(2,0)	4/290(1,3)	-	1/290 (0,4)	11/290(3,7)	7/290 (2,4)	37/290 (11,3)
Suprasellar	2/290(0,7)	6/290(2,2)	5/290 (1,8)	-	3/290 (1,1)	5/290(1,8)	1/290 (0,4)	23/290 (8,0)
Hypophyseal	2/290(0,7)	1/290(0,4)	-	-	-	3/290(0,7)	-	6/290 (1,8)
Anterior Wall	2/290(0,7)	-	1/290(0,4)	-	-	-	2/290 (0,7)	5/290 (1,8)
Posterior Wall	1/290(0,4)	1/290(0,4)	-	-	-	1/290(0,4)	-	3/290 (1,1)
Choroidal/Terminal	1/290(0,4)	-	-	-	-	1/290(0,4)	2/290 (0,7)	-
PcomA	1/290(0,4)	1/290(0,4)	-	-	-	1/290(0,4)	-	3/290 (1,1)
Others	1/290(0,3)	3/290(0,3)	-	1/290 (0,3)	-	-	-	2/290 (0,7)
Non classified	-	1/290(0,4)	-	-	-	-	1/290(0,4)	2/290(0,7)
Total	37/290(12,7)	71/290(25,0)	40/290(14,0)	18/290(0,0)	17/290(0,0)	57/290(0,2)	40/290(14)	290/290(100)

TABLE 4. Siphons and aneurysms

Gender	**Type C=IA**	**Type U/O= IB**	**Type V=II**	**Type D=III**	**Type M=IV**	**Type R**	Total
Female	34/250(13.6)	71/250(28.4)	35/250(14.0)	59/250(23.6)	33/250(13.2)	18/250(7.2)	250/279(89.6)
Male	1/29(3.4)	3/29(10.3)	5/29(17.2)	12/29(41.3)	7/29(24.1)	1/29(3.4)	29/279(10.3)
Total	35/279(12.5)	74/279(26.5)	39/279(13.9)	62/279(22.2)	40/279(14.3)	19/279(6.8)	279/279(100)

CAPÍTULO VIII

Artigo Submetido para Publicação na Revista Anatomical Record

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Editorial

Pathogenesis, haemodynamic and growth of intracranial aneurysms: our future directions

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Treatments using flow diversion or disrupting stents have increasingly gained attention due to being less invasive, and because they have shown increased levels of safety, as well as being feasible and having high success rates (Tse et al., 2013; Chalouhi et al., 2015). This is especially true of large, dysplastic, and wide neck aneurysms (Brinjikji et al., 2009; Huang et al., 2009; Byrne et al., 2012). In addition, intravascular flow modifier stents are persuasive tools that act directly on the pathogenesis of intracranial aneurysms (McAuliffe and Wenderoth, 2012; Huang et al., 2013).

An intracranial aneurysm is a vascular ectasia arising from the wall of intracranial arteries predominantly in the cerebral arterial circle of Willis, in most cases of saccular form (Keedy, 2006). However, irrespective of its shape and location, an intracranial aneurysm is a disease within the vascular wall particularly at the level of the endothelium of blood vessels, which respond physiologically to blood flow patterns Therefore, flow diverters stents were designed to act by promoting a temporary scaffold for the endothelial proliferation with healing to the formation of a new vessel vascular wall and stimulating aneurysmal thrombosis (Tremmel et al., 2010).

One of our challenges is to understand the interplay of the biological and hemodynamic processes involved in the formation and progression of intracranial aneurysms: its initiation; its growth; the inflammatory and degenerative processes related to the aneurysm's rupture; and the eventual recanalization (Sforza et al., 2009).

Another interesting element regards the behaviour of intracranial aneurysms, which is unpredictable; although they are dynamic, they often remain unnoticed until they are detected incidentally. Also, the true prevalence of intracranial aneurysms is not known, and the current consensus in clinical decisions is often to avoid subarachnoid hemorrhage (Turjman et al., 2014).

Populational studies have shown that 85% of intracranial saccular aneurysms develop in the anterior circulation; more specifically, 35% appear on the complex anterior communicating artery, followed by carotid artery (30%) and middle cerebral artery (22%). They are less common in the posterior circulation at the top of the basilar artery and along its branches. Multiple aneurysms are found in about 30% of patients who already have at least one (Keedy, 2006).

There is a preponderance of intracranial aneurysms in women, which increases with the number of aneurysms (Defillo et al., 2014). In samples of people aged 50 and over, this preponderance can approach a ratio of 1:2, or even greater; this trend seems to be associated with low levels of estrogen (Longstreth et al., 1994).

Regarding the formation of an intracranial aneurysm, the current consensus is that the origins are multifactorial, and there is no completely satisfactory theory. Evidence demonstrates a complex evolutionary process in which many factors may be involved. The possible co-factors involved are: anatomy, vascular geometry, and abnormal flow patterns, with endogenous factors related to the vascular wall (weakness and vulnerability). However, the interplay of biological and hemodynamic factors is not well understood and remains unclear.

Recent experimental studies have shown that arterial vessels' caliber and their histological structure are regulated by blood flow variations (Sforza et al., 2009). Also, variations in the vessels and changes in bifurcation angles are involved in the genesis, development, and eventual rupture of aneurysms. As a result, there is increasing importance placed on cerebral hemodynamic assessment as a predictor of the initiation and development of intracranial aneurysms.

When analysing the cerebral hemodynamic, it was found that the arterial circle of Willis has considerable variability, with frequent asymmetries. A complete circle of Willis was observed only in 20–25% of patients (Puchade-Orts et al., 1975). There is evidence that the anatomical variations observed in the cerebral arterial circle of Willis and related vessels may play a role in the genesis of intracranial aneurysms (Kayembe et al., 1984). Padget was among the first to compare the number of cases of embryological abnormalities with aneurysms and without aneurysms (Padget, 1945). It is believed that an asymmetrical circle of Willis, whether congenital or acquired, is a risk factor for the development of aneurysms, where hemodynamic stress produces degenerative changes leading to hyperdynamic flow (Milenkovic, 1981).

Recent studies have proposed that a congenital absence of the anastomosis capacity of the circle of Willis is correlated with other cerebrovascular diseases thus alluding to the hypoperfusion mechanism in the development of chronic ischemic pathology or small vessel cerebrovascular disease (Ryan et al., 2015). Another known flow-related disease well known is the ligation of the carotid artery. This procedure was performed for the treatment of giant carotid siphon aneurysms as the technique of choice for a long period of time before the development of neuroendovascular therapy. However, this kind of procedure has been associated with *de novo* intracranial aneurysm formation and flow-induced vascular remodelling (Gao et al., 1981).

Carotid ligation experimental models have demonstrated that compensatory cerebral blood flow increases after carotid occlusion with secondary pathologic remodeling. The flow adaptive development throughout the circle of Willis will result in the formation of an aneurysm in the contralateral carotid artery (Tutino et al., 2014). It is probable that the same principle can be applied to the bifurcation of the carotid artery and its branches, which can be explained due to a change in hemodynamic parameters at this level.

Flow studies have shown that the source point of an intracranial aneurysm is distal to the bifurcation or the gradient fields, which are higher (Alnaes et al., 2007). Therefore, it is likely that the hemodynamic stress and the turbulent blood flow associated with hyperdynamic flow patterns could cause excessive wear and vibrations, resulting in structural fatigue and the rupture of the internal elastic lamina and, therefore, the formation of cerebral aneurysms. Patients with hyperdynamic flow patterns as a result of abnormal high flow conditions or other collateral pathways are therefore predisposed to accelerated degenerative changes in the vessel wall and the subsequent growth of an aneurysm (Wiebers, 2004). In this case, environmental factors such as hypertension, smoking, and connective tissue diseases probably play a contributory role, rather than being the cause.

Studies have also looked into the possibility of changes in morphology in large vessels, as the main trunk and internal carotid arteries could be responsible for the formation of cerebral aneurysms (Sekhar et al., 1981). Experimental studies have found that within the dome of an aneurysm, hemodynamic stress seems to be caused by a sequential and repetitive turbulent flow. This type of abnormality is evidenced in the cavity of an aneurysm during systole. This abnormal flow becomes inverted during diastole, so these quick changes in the direction of flow continue to cause friction in the inner wall of the vessel and contribute to the formation and progression of an aneurysm (Gonzalez et al., 1992).

Given all the facts and ideas that arise when trying to better figure out the local vascular and Willis polygon environment for the understanding of an aneurysm, some key points can help us: is there any correlation between the different pattern of geometries in the circle of Willis and the vessels related to certain subtypes of intracranial aneurysms? Perhaps certain anomalies or circle of Willis patterns justify screening and preventative treatment? Or is it that an aneurysm will not only be a local disease but a disease trigger point in all other hemodynamic spots that develop in the cerebral circulation or are acquired congenitally?

Examining the use of cerebral hemodynamics is not easy because there are some confounding elements as constitutional problems or disease characteristics and blood structure contribution, hemodynamic, mechanical vascular by gender and the formation of aneurysms. As has previously been shown, there is a sex-linked difference in anatomical variations and this is linked to the anatomical distribution of aneurysms (Ghods et al., 2012); we still do not know if these two elements are connected. More controlled studies are needed.

Finally, our current and future directions further elucidate the genesis and natural history of intracranial aneurysms and perhaps predict the response to treatment with stents flow diverters and to have a better understanding of the cerebral hemodynamics. This should also contribute to the understanding of the pathophysiology, in particular, to a more effective direction in the detection and prevention of intracranial aneurysms.

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CAPÍTULO IX

Artigo Submetido para Publicação na Revista Perspectivas Médicas

Artigo Submetido para Publicação na Revista Perspectivas Médicas

The arterial variants of Willis'circle and its associated branches involved in the pathogenesis of intracranial aneurysms: Current perspectives

As variantes arteriais do polígono de Willis e suas ramificações envolvidas na patogênese dos aneurismas intracranianos: perspectivas atuais

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RESUMO

INTRODUÇÃO: Os aneurismas intracranianos são uma das principais causas de morte súbita e incapacidade permanente nos indivíduos adultos, principalmente entre mulheres acima de 50 anos. Dentro de um quadro multifactorial, as conhecidas alterações hemodinâmicas como estresse oxidativo e o fluxo sanguíneo turbulento associados com o polígono de Willis hiperdinâmico e assimétrico levariam a formação do aneurisma intracraniano. Modernos tratamentos utilizando stents modificadores de fluxo tem cada vez ganhado mais espaço, pois além de menos invasivos também atuariam diretamente bloqueando o círculo vicioso da fisiopatogênese dos aneurismas intracranianos. Devido a isso, observa-se um crescimento na importância de avaliar as variantes arteriais embriológicas como fator de risco/preditor dos aneurismas intracranianos.
OBJETIVO: Investigar a aplicabilidade das variantes arteriais embriológicas implicadas na gênese e no tratamento dos aneurismas intracranianos.
METODOLOGIA: Uma revisão sistemática via PubMed e EMBASE foi realizada a partir da combinação de palavras-chaves relacionadas e seus correspondentes. A pesquisa seguiu um protocolo adaptado dos critérios estabelecidos para estudos de medicina baseados em evidências e teve como limite temporal de 1977 a 2015.
RESULTADOS: Foram localizados 2026 artigos, aos quais foram adicionados mais 55 estudos longitudinais publicados nos principais artigos internacionais. A análise dos artigos permitiu dividir em três principais grupos de variantes anatômicas relacionadas com a embriologia arterial com estudos relevantes: Hipoplasia/Dominância de A1, mais evidenciado com 14 estudos, as variantes em geral com 7 estudos, seguido de PCA fetal com dois estudos relevantes apenas. Um total de 12 estudos longitudinais preencheram os critérios de relevância.
CONCLUSÃO: Apesar da escassez de estudos, as variações na própria anatomia vascular do polígono de Willis associadas com a geometria vascular parecem desencadear um processo de desgaste excessivo e vibrações que resultariam em fadiga estrutural e ruptura da lâmina elástica interna das arterias intracranianas levando a formação dos aneurismas intracranianos. A análise das variantes arteriais embriológicas do polígono de Willis e seus ramos poderá se tornar uma técnica potencialmente útil para o entendimento da gênese e na avaliação dos resultados do tratamento dos aneurismas intracranianos.

Palavras-Chave: aneurismas intracranianos, fluxo, gênese, vascularização cerebral

ABSTRACT

INTRODUCTION: Intracranial aneurysms are a major cause of sudden death and permanent disability in adults, especially women over 50 years. In a multifactorial framework, hemodynamic alterations well known as oxidative stress and turbulent blood flow associated with asymmetrical hyperdynamic Willis circle flow might lead to the formation of an intracranial aneurysm. Latest options of treatment using flow modifiers stents have increasingly gained more space, as well as less invasive, would also act directly blocking the vicious cycle of the pathophysiology of intracranial aneurysms. Because of this, there is a needed of assessing the embryological arterial variants as risk factors/ predictor of intracranial aneurysms.

AIM: To investigate the applicability of embryological arterial variants implicated in the genesis and treatment of intracranial aneurysms.

METHODS: A systematic review via PubMed and EMBASE was performed from the combination of related keywords and their corresponding. The research followed a protocol adapted the criteria established for medical studies based on evidence and limited time between 1977-2015.

RESULTS: A total of 2026 articles were identified, of which were added more 55 longitudinal studies published in leading international papers. Analysis of the articles allowed to divide into three main groups relevant studies about anatomical variants related to blood embryology: hypoplasia / Dominance A1, more prominent with 14 studies, variants usually with 7 studies, followed by fetal PCA to two relevant studies only. Twelve studies filled the relevance criteria.

CONCLUSION: Despite the scarcity of studies, variations in the vascular anatomy of the Willis polygon associated with remodeled vascular geometry seem the factor that trigger excessive wear process and vibrations that result in structural fatigue and rupture of the internal elastic lamina of intracranial arteries leading to the formation of aneurysms. The analysis of embryological arterial variants of the circle of Willis and its branches could become a potentially useful tool for understanding the genesis and evaluation of results of treatment of intracranial aneurysms.

Keywords: intracranial aneurysm, flow, genesis, cerebral vasculature.

Abbreviations: P.B.A= Patricia Bozzetto Ambrosi, S.S =Sarah Sutton

INTRODUCTION

The intracranial aneurysms are generally diagnosed, or when rupture occurs, or during the screening of neurological diseases (e.g. a headache)[1,2] and hereditary syndromes associated with high frequency of aneurysms rupture.[3] The Willis of circle (CoW) or circulus arteriosus is a polygonal anastomotic channel vessels surrounding the skull base of the brain which unites both internal carotid arteries and vertebrobasilar system. It maintains the steady and constant supply to the brain. The cerebral vasculature has considerable variability and anatomical variations of CoW are seen often. The CoW appears to be complete only 20-25% of individuals. [4-7]

Since anatomical variations associated with intracranial aneurysms were pictured by Dorcas Padget while she illustrated the neurodevelopment and aneurysm formation [8-9] Few pieces of evidence has been described in the literature correlating congenital variability of Cow and its vessels related and hemodynamic factors. This relationship may be attributable to an increased blood flow and therefore, a significant overload hemodynamic and development of arterial disease which although unsatisfactory proved until now mostly due to methodology difficults, it have possible role in the genesis of intracranial aneurysms. [10-11]

Recent studies have shown the correlation between specific subtypes of anatomical variants e.g A1 dominant hypoplasia or fenestrations and the presence of aneurysms in the anterior communicating artery. Arterial variants of CoW can be congenitally absent or sometimes acquired secondary to clamped vessels. The results of this process induce flow mediated-patterns and could implicate oxidative stress in aneurysmal disease progression. [5-7]

The aim of this study is to briefly to present a systematic review which followed criteria established for medical studies based on evidences of the last 35 years about the applicability of anatomical and embryological variants involved in the genesis of intracranial aneurysms.

METHODS

Eligibility criteria and Search Strategy

A extensive systematic review was performed in the two main databases Medline and EMBASE. The publications before December 21th 2015 were retrieved. The research was performed by author (P.B.A) and a Clinical Librarian (S.S.). After the first selection of articles, the author (P.B.A) reviewed the literature independently. The established limitation criteria were articles published in the last 10 years. The research was firstly performed on 3th September 2015 and updated automatically until 22 th December 2015. New terms (Table - Flow 1) were added in the second time to better tailored the research. The objective relevance criteria were establisedh based on: 1) contends of study longitudinal study or not 2) experience and background: if the study was from reference center or not 3)accuracy/validity: presence of elements of significance statistically or not 3) source of documents: international study or not 4)context: answer to our main question or not

Data Analysis

The following data were extracted from the relevant studies: name of first author, year of publication subtype of anatomical variant, characteristics of arterial variant, distribution of sex, the location of the intracranial aneurysm. Final data analysis were performed by two authors (P.B.A and C.A.V).

RESULTS AND DISCUSSION

Our first systematic review identified 912 publications in EMBASE and 1011 publications in Medline on 3th October, 2015. Following 10 years limitation were applied to Medline final resulting in 508 articles founded between 2004 and 2015. The abstracts were screened and duplications were removed. Other irrelevant papers also were excluded. A total of 1543 were selected for further scrutining. A total of 1517 studies were removed because didn't meet the eligibility criteria. Further update performed on 22 th December 2015 showed 987 publications in the EMBASE and 1039 in the Medline. Fifty-five articles (44 from EMBASE and 11 from Medline) which meet the relevance criteria were added. Twenty-six studies

evaluated the association between intracranial aneurysms and anatomical variations. The table 1summarize our search for eligible studies in our systematic review. From twelve studies eligible, five of them showed a statistically significant association between anatomical variants and intracranial aneurysms. We separated into three main anomalous collateral pathways: (1) hypoplasia / Dominance A1 demonstrated in 14 studies, (2) All variants in 7 studies, followed by (3) persistence of fetal PCA described in two studies only.

In our knowledge, this is the first systematic review to address this matter. It is believed that hyperactive hemodynamic status with endogenous factors related to the vascular wall (weakness and vulnerability) are possible co-factors involved in the intracranial aneurysms genesis. Furthermore, the presence of an asymmetric circle of Willis, whether congenital or acquired, is a risk factor for the development of aneurysms, where the hemodynamic stress produces degenerative changes leading to the hyperdynamic flow.

Studies correlating A1 dominant/ hypoplasia with presence of intracranial aneurysm were performed by Flores et al who studied and correlated the presence of A1 dominance between ruptured and unruptured Acom A aneurysms. In their series comparing 52 patientes with AcomA versus 104 healthy patients. There were no significant demonstrated AComAA rupture (P = .15). However, the A1-2 ratio correlated positively with the presence of ruptured AComAAs (P = .04) . They suggested that this finding may facilitate treatment decision in cases of small, unruptured AComAAs. Another series described by Charbel et al who analysed four significant associations: 1) A1 dominant (filling both A2's) was found in 57% of ACAA patients versus 14% of controls (p less than 0.001). 2) Unilateral hypoplasia of the opposite A1 was present in 24% of ACAA patients versus 6% of controls (p = 0.01). 3) Exclusive filling of the ACAA from one A1 occurred in 78%.. However, no statistically significant relationship was found between the anatomic flow patterns studied and the patients clinical presentation including age, sex, or grade. Their findings conclude that anterior communicating artery aneurysms are significantly related in a majority of patients with the presence of A1 dominant, probably as the result of enhanced haemodynamic stress caused by this anatomic abnormality in the circulation. However, this association is not constant, and a dominant pattern of flow did not correlate with the clinical course. This is probably a reflection of the differences between factors initiating aneurysm formation and those influencing its growth, as well as of the relative limitations of angiography when pathophysiological extrapolations are attempted.

Other studies were described by Chen et al which studied between January 2009 and June 2012, 8,013 patients that underwent MRA examination at 3.0 T. MR using 3D-TOF with volume rendering technique. The presence and location of A1 segment hypoplasia and AcomA aneurysm was reviewed.Among the 8,013 patients examined, 138 patients were identified with AcomA aneurysms. 425 patients were defined with A1 segment hypoplasia, among whom 303 right-sided A1 hypoplasia and 122 left-sided A1 hypoplasia. 60 of these 425 patients were confirmed with AcomA aneurysms, among them were 49 right-sided A1 hypoplasia. The prevalence of AcomA aneurysm with A1 segment hypoplasia was 14.1 %, which was much higher compared with that (1.0 %) of AcomA aneurysm without A1 segment hypoplasia (P\0.001).The incidence of right-sided A1 segment hypoplasia either accompanied with AcomA aneurysm or not was much greater than that of left-sided. The study suggested that intracranial AcomA aneurysm development appeared to be associated with A1 segment hypoplasia. Another study, Tarulli & Fox showed that A1 dominance configuration is strongly associated with the presence of AcomA aneurysms for patients with intracranial aneurysms (odds ratio, 17.8). This association was also present compared with the incidence of A1 dominance in the large sequential control series of patients without aneurysms undergoing CTA for other reasons (odds ratio, 7.5). Outflow dilution of selective angiographic images augments anatomic information. A flow-based assessment of contrast

flowing from the A1 to the A2 segments after injection pressure is superior to an A1 diameter based categorization when A1 vessel diameters are not strikingly different. They concluded that anatomic variant of asymmetric A1 configurations likely facilitates the development of AcomA aneurysms by flow stresses, providing further evidence to support the role of biophysical factors in intracranial aneurysm development.

Xu et al also demonstrated that A1 dysplasia/hypoplasia is a potential risk factor in the formation of ACoA aneurysms. They performed a study using hemodynamic flow measures. The wall shear increase appear to contribute to aneurysm formation. They conclude that wall shear stress decreased and turbulent flow may be responsible for the growth and rupture of ACoA aneurysms.

Studies regarding fetal PCA are more rare. In 2008, Zada et al published a long term series of 15-year period where 271 patients were treated for 273 ICA-PComA aneurysms. Aneurysms occurring at the origin of fetal PCAs were identified in 30 patients (11%). There were 23 women (77%) and seven men (23%) (sex difference, P = 0.0035). The mean aneurysm size was 7 mm. PComA aneurysms originating from fetal PCA vessels posed a more substantial risk for infarction and subsequent neurological sequelae with surgical or endovascular obliteration. Fetal variant circulations were identified at the PComA origin in 11% of ICA-PComA aneurysm patients and were more commonly encountered in women. No group control were included.

Songsaeng et al 2010 studied several anatomical variations including A1 aplais, fetal PCA and assymetrical fusion. Following their analysis, the AcoA, PcoA, and BA tip aneurysms tend to occur more often in anatomically variant parent artery dispositions, some of which are related to aneurysm recurrence following coil embolization. The findigns suggested that a more fragile vessel disposition as it is not fully matured or to altered haemodynamics secondary to the anatomical variations could be responsible for aneurysms formations.

Stojanovic et al published studies about asymmetrical Willis which accounts 64% of in the whole group of patients studied. Within the group of patients suffering from multiple aneurysms, the presence of asymmetrical Willis' circle was 75.7%. The highest incidence of the asymmetrical Circle of Willis was found among patients with aneurysmal rupture detected at the anterior comunicative artery (ACoA) site (72.7% among cases with solitary and 100% among those with multiple aneurysms). Morphological changes on the A1 segment of ACoA were observed in 50 (44%) cases, with higher incidence found on the right side (60%). When comparing location of ruptured aneurysms between genders, a statistically significant prevalence of the ruptured aneurisms on ACoA was present in men, whereas women showed higher incidence of ruptured aneurysms on interior cartid artery (ICA) site ($p < 0.01$). The linkage between aneurysms with hypoplasia of the A1 segment of ACA and decreasing of the angle at which segments A1 and A2 join suggests the relationship between their onset, corresponding configuration type of Willis and subsequent hemodynamic changes. High incidence of asymmetry of Willis circle in the group of patients with ruptured aneurysms imply association of asymmetrical configuration and disorder in haemodynamic relations with forming and rupture of intracranial aneurysms.

Most recently, Van Rooj studied 140 patients where 210 aneurysms were present. In 33 of 140 patients (24%; 95% confidence interval, 17.2%-31.3%), 45 fenestrations were detected with the following locations: anterior communicating artery in 31 (69%), A1 segment of the anterior cerebral artery in 4 (9%), middle cerebral artery in 4 (9%), basilar artery in 4 (9%), vertebral artery in 1 (2%), and anterior inferior cerebellar artery in 1 (2%). Of 56 patients with anterior communicating artery aneurysms, 14 had a fenestration on the anterior communicating artery complex. The remaining 31 fenestrations had no anatomic relation to aneurysms. In 140 patients with 210 aneurysms, 14 aneurysms (7%) were located

on a fenestration and 196 were not. In patients with a suspected ruptured aneurysm, fenestrations of intracranial arteries were detected in 24% (33 of 140). Most fenestrations were located on the anterior communicating artery. Of 45 fenestrations, 14 (31%) were related to an aneurysm.

Other rare associations were described as case reports. No longitudinal studies were published until now. In 2014, Ho Allen studied short MCA. In 2006, Krishnamoorthy descibed callosomarginal variations associatd with intracranial aneurysms Although anatomic variations are well known in the A1 segment of the anterior cerebral artery (ACA), anomalous origin of a cortical artery from the A1 segment is extremely rare. The only reported cortical branch to arise from the A1 segment is the fronto-orbital artery. We report a case of anomalous origin of the callosomarginal artery (CMA) in association with a saccular aneurysm from the A1 segment of the left ACA in a 35-year-old man who presented with intracerebral hemorrhage. Freitas described a high flow association. Most of neurosurgeons and radiologists that work with patients with intracranial aneurysms are familiar with such anatomic variations. Currently, due to the technical improvements, anatomical variations of the small arteries, those were previously reported on cadaveric series, can also be evaluated on CT angiography. (Pekecvik).

The same principle can be applied also to the bifurcation aneurysms of the carotid artery and its branches explained as due to a change in hemodynamic parameters at this level. This could explain the flow changes as a predictor of response to treatment with stents flow diverters well as the induction flow changes in collateral circulation.

CONCLUSION

Although variations of Willis polygon are frequent, the real impact is still unknow. More clinical and hemodynamic detailed studies are expected. Also the development of a predictive model estimating the probability. The analysis of anomalies of the intracranial arteries could become a potentially useful technique for understanding the genesis and treatment of intracranial aneurysms Probably in the near future the understanding of the cerebrovascular anatomy and embryology will became important point for appropriate management of the aneurysm

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Bozzetto Ambrosi Neuronutri

Table 1. Search Strategy

1. EMBASE; exp INTRACRANIAL ANEURYSM/; 27481 results.
2. EMBASE; (brain* adj2 aneurysm*).ti,ab; 480 results.
3. EMBASE; (intracranial* adj2 aneurysm*).ti,ab; 10459 results.
4. EMBASE; ("intra cranial*" adj2 aneurysm*).ti,ab; 54 results.

5. EMBASE; (cerebral* adj2 aneurysm*).ti,ab; 7489 results.
6. EMBASE; 1 OR 2 OR 3 OR 4 OR 5; 29775 results.
7. EMBASE; variance.ti; 4070 results.
8. EMBASE; 6 AND 7; 0 results.
9. EMBASE; "A1 hypoplas*".ti,ab; 13 results.
10. EMBASE; (A1 adj2 hypoplas*).ti,ab; 53 results.
11. EMBASE; a1.ti,ab; 44474 results.
12. EMBASE; 9 OR 10 OR 11; 44474 results.
13. EMBASE; 6 AND 12; 291 results.
14. EMBASE; pcom.ti,ab; 224 results.
15. EMBASE; "posterior* communicating".ti,ab; 1987 results.
16. EMBASE; 14 OR 15; 2142 results.
17. EMBASE; 12 OR 16; 46517 results.
18. EMBASE; 6 AND 17; 1141 results.
19. EMBASE; 18 [Limit to: (Year Published Last 10 Years)]; 695 results.
20. EMBASE; exp POSTERIOR COMMUNICATING ARTERY/ [Limit to: (Year Published Last 10 Years)]; 1341 results.
21. EMBASE; 17 OR 20 [Limit to: (Year Published Last 10 Years)]; 25735 results.
22. EMBASE; 6 AND 21 [Limit to: (Year Published Last 10 Years)]; 987 results.
23. Medline; (brain* adj2 aneurysm*).ti,ab; 594 results.
24. Medline; (intracranial* adj2 aneurysm*).ti,ab; 8802 results.
25. Medline; ("intra cranial*" adj2 aneurysm*).ti,ab; 38 results.
26. Medline; (cerebral* adj2 aneurysm*).ti,ab; 6968 results.
27. Medline; "A1 hypoplas*".ti,ab; 10 results.
28. Medline; (A1 adj2 hypoplas*).ti,ab; 54 results.
29. Medline; a1.ti,ab; 33758 results.
30. Medline; pcom.ti,ab; 131 results.
31. Medline; exp INTRACRANIAL ANEURYSM/; 22737 results.
32. Medline; 23 OR 24 OR 25 OR 26 OR 31; 26345 results.
33. Medline; "posterior* communicating".ti,ab; 1572 results.
34. Medline; 27 OR 28 OR 29 OR 33; 35268 results.
35. Medline; 32 AND 34; 1039 results.
36. EMBASE; NUCLEAR MAGNETIC RESONANCE IMAGING/ OR BRAIN CIRCULUS ARTERIOSUS/ OR THREE DIMENSIONAL IMAGING/ OR RADIOGRAPHY/ OR ANTHROPOMETRY/; 890701 results.
37. EMBASE; (loop AND of AND Willis).ti,ab; 10 results.
38. EMBASE; (cerebral AND arterial AND circle).ti,ab; 569 results.
39. EMBASE; BRAIN CIRCULUS ARTERIOSUS/; 2553 results.
40. EMBASE; 36 OR 37 OR 38 OR 39; 890907 results.
41. EMBASE; ANATOMICAL VARIATION/; 14910 results.
42. EMBASE; (arterial AND variant).ti,ab; 1724 results.
43. EMBASE; 40 AND 41; 2793 results.
44. EMBASE; 41 OR 42; 16540 results.
45. EMBASE; 40 AND 44; 2942 results.
46. EMBASE; 6 AND 45; 44 results.
47. Medline; Willis'circle.ti,ab; 97 results.
48. Medline; (loop AND of AND willis).ti,ab; 7 results.
49. Medline; CIRCLE OF WILLIS/; 1618 results.
50. Medline; (Willis AND polygon).ti,ab; 35 results.
51. Medline; (arterial AND variant).ti,ab; 1140 results.

52. Medline; (anatomical AND variant).ti,ab; 1038 results.
53. Medline; 47 OR 48 OR 49 OR 50; 1707 results.
54. Medline; 51 OR 52; 2115 results.
55. Medline; 53 AND 54; 11 results.

Table 2. Flow diagram

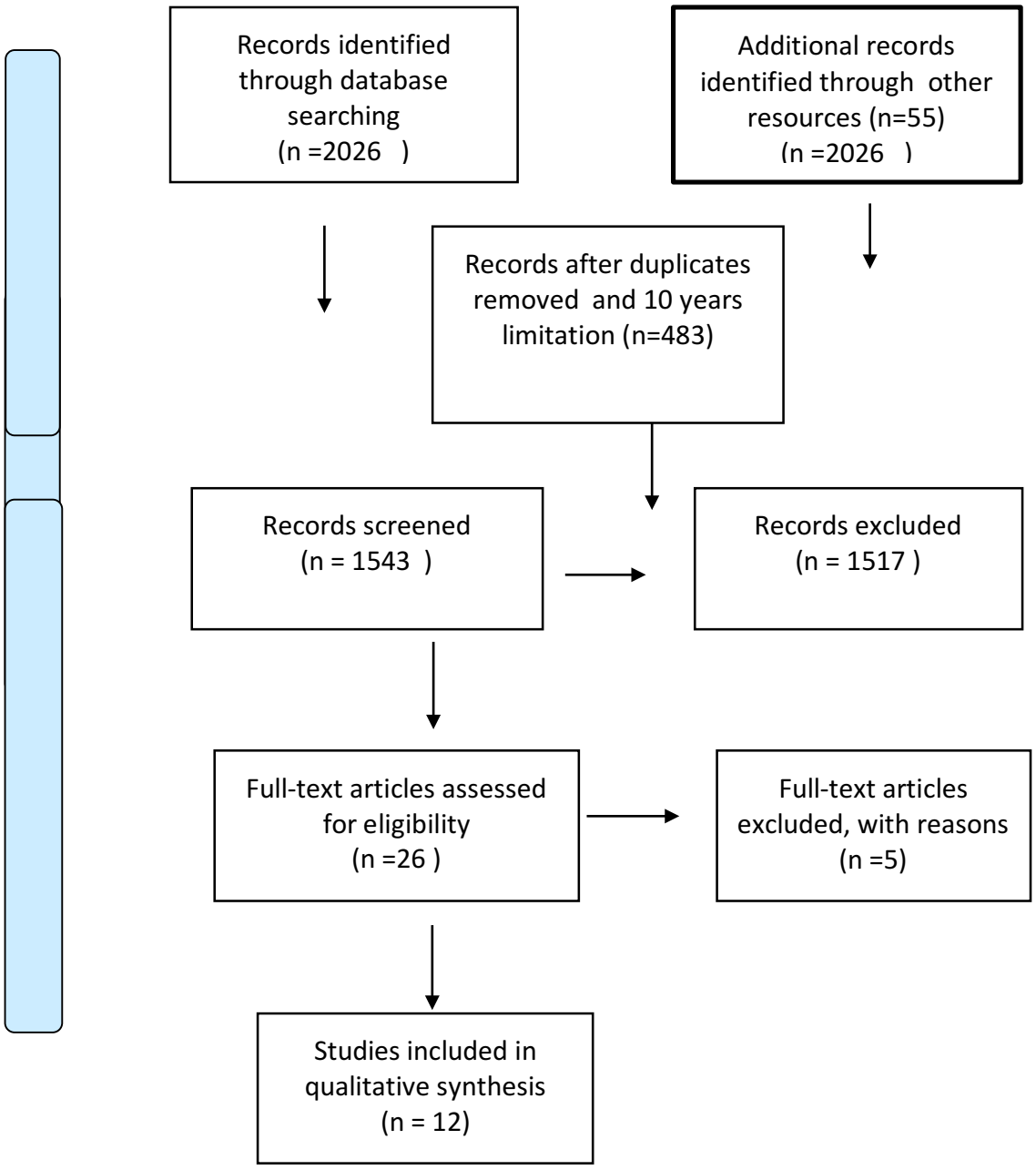

Table 3. Main eligible studies published in the current literature

Author(Year)	Subtype	Location Aneurysm	Sex Patient	Control Group
Van Rooij et. al, (2015)	Fenestrations	Several locations	140 patients/210 aneurysms	No controle group
Chen et. al,(2014)	A1 dominant	AcomaA	138 patients	7875 patients
Flores et. al, (2013)	A1/A2 diameters	AcomA	52 AComA	104 healthy
Xu et al (2012)	A1 dysplasia/ hypoplasia	AcomA	?	?
Songsaeng (2010)	A1 aplasia, foetal PcoA, asymmetrical fusion	AcoA PcoA BA	96 AcoA 67PcoA 29 BA	No control group
Tarulli 2010	A1 dominance	AcomA	105 AcomA 123 other	159 healthy
Stojanović et al (2009)	AcoA	Mutliple aneurysms	114 patients multiple aneuryms	No control group
Zada (2008)	PCA	ICA	271 patients	No control group
Kitami, K (1985)	Dominant A1			
Charbel F (1991)	Dominant A1	AcomA	51 patients	51 healthy and matched controls
Matsumura & Nojiri 1984	Fenestrations	AcomA	12 patients	No control
Kayembe et al (1984)	Multiple	Multiple	44 aneurysms	148 healthy CoW

CAPÍTULO X

Artigo Submetido para Publicação na Revista Clinical Nutrition

Artigo Submetido para Publicação para a Revista" Clinical Nutrition"

Paradoxical obesity and intracranial aneurysms: a mini review

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Abstract

Body mass index above 30 is an independent risk factor for cardiovascular disease and linked to poor prognosis, especially in patients admitted to intensive therapy departments. However, recent reports have indicated that individuals with mild to moderate obesity have favorable outcomes in the survival in coronary heart disease and either in hemorrhagic or ischaemic stroke. The same association has been also encountered in patients who had ruptured intracranial aneurysms. These patients are although obese, they stay metabolically healthy with apparent protection from the disease. More studies are needed to determine its consistent correlation. Obesity, the body mass *index* or Quetelet *index* and its correlation intracranial aneurysms were briefly examined in this article.

Key words intracranial aneurysms, subarachnoid haemorrhage, body mass index, paradoxical obsesity, body weight

Introduction

More than 2500 years, Hippocrates described the association between cerebrovascular or cardiovascular diseases in individuals with obesity and overweight causing sudden death.[1,2] Both obesity and overweight are rapidly advancing in worldwide and has become a socio-political problem due to the fact to be an independent risk factor for cardiovascular disease particularly in developing countries.[3-5]

World obese populations have doubled since 1980.[3,4]According to National US studies, it has been estimated that more than one-third (about 35% or more than 78 million individuals) are obese and more than 70% of American adults [6]are affected by obesity and/or overweight.[6,7] Further studies carried out by World Health Organization (WHO) have found that both obesity and overweight also affects over 50% of the South American populations.[4]

For immediate primary care of the population estimates by the WHO already showed increased mortality from nutritional chronic diseases in Brazil of up to 22% by 2015. [4,5] Although not yet have accurate data in the northeast of Brazil, is known the number of cases of type 2 diabetes is increasing every day as well as childhood obesity, among other associated factors such as physical inactivity and poor diet, excessive consumption of the simple carbohydrates and excess saturated and trans fats. The association of obesity with abdominal aortic aneurysm is also a great indicator and risk factor to worsen the picture of morbidity, because reducing body weight, reduces associated risk as anthropometry measures and other diagnostics. [7]

Obesity, Overweight and Quetelet index

According to National Institutes of Health in Bethesda, overweight is defined as having excess body weight for a particular height from fat, muscle, bone, water, or a combination of these factors.[8] And the obesity is defined as having excess body fat. [8] The term body mass index (BMI) was based in Quetelet's theory of human trait measurement based in normal curve.[9] This term is universally adopted as a screening population measurement.[10,11]Adults with the BMI greater than or equal to 25 are considered overweight and those with BMI greater or equal to 30 are considered obese. [8-10]

Related Risk and Protective Factors

Obesity and overweight are independent risk factors for cardiovascular diseases, cancer, diabetes, hypertension, musculoskeletal disease and stroke. However, since 1999 when the first description about obesity-survival was performed based on survival advantage for overweight and obese patients undergoing hemodialysis, a large studies supporting the paradoxical obesity in several conditions has published.

Several epidemiological studies have showed that obese individuals with coronary heart disease demonstrated a clear survival advantage compared with their nonobsese cohorts. [12,13] Recent studies described the same outcome in patients with mild and moderate obesity who had chronic obstructive pulmonar disease, ischemic and haemorrhagic stroke and subarachnoid haemorrhage (SAH).[13-16]

Cigarette smoking, hypertension, alcohol consumption, estrogen deficiency, collagen diseases, atherosclerosis, ageing and female sex also appear to be involved in the formation, growth and rupture of intracranial aneurysms.[15,17-18] Obesity and other modifiable risk factors, such as hypercholesterolemia, ischemic heart disease, diabetes mellitus are limited and conflicting and controversial. Hypercholesterolemia and regular physical exercise appear to decrease the risk of aneurysm formation; there is some speculation that the former effect is mediated through statin therapy.

We recently reviewed main sources of researches as Embase, Pubmed and Cochrane (CENTRAL), Allied, Amed, BNI, CINAHL, Health Business Elite using key-terms correlated changes in weight, obesity paradox with intracranial aneurysms, hemorrhagic stroke and SAH over the last 30 years. [19] A total of 690 studies were found, 45 were duplicates, 147 showed stroke and "paradox obesity" association.

After reading all relevant articles, only one study from Vlak et al [17], studying 206 patients with unruptured intracranial who never had a SAH and 574 controls who were randomly retrieved from general pratices of area of catchment of Utretch. Unruptured aneurysms and obesity were consistently correlated unruptured, however no significant statistical correlation was founded. [17]

Two main studies correlated obesity and ruptured aneurysms. [17,20] Both studies indicated that obesity reduces mortality to short and long term, although remain controversial with regard to functional recovery. First one was performed by Platz et al. 14 analyzing 741 patients with the history of SAH secondary to intracranial aneurysms: 36.2% or 267 patients were

overweight and 15.2% or 113 patients were obese. Although many physicians anticipated a worse outcome for the obese patient the BMI was not an independent predictor of outcome. [15]

In the Platz'study the multivariate analysis, only age (OR:1.051, 95% Cl: 1.04-1.07, p <.001), WFNS grade (OR:2.095, 95%, Cl:1.87-2.35, P<.001), occurrence of vasospasm (OR:2.90, 95% Cl:1-94-4.34, P< .001) and aneurysm size larger than 12 mm (OR: 2.215,95% Cl:1.20-4.10, P=0.11) were independent predictors of outcome after 6 months. Of the 321 poor grade patients (WFNS score >3), 171 (53,3%) were overweight. Of these, 21.6% attained a favorable outcome compared with 35.3% of normal-weight patients (P=.006). Based on the BMI, obesity seems to be negligible for outcome after SAH compared with the impact of SAH, the patient's age, the occurrence of vasospasm, or aneurysm size. [15]

Another recent study of Tawk et al. [20] investigated 274 consecutive patients admitted with SAH between 2008 and 2012. After performing a multivariate analysis adjusting for an age, the older age was associated with worsened severity and that BMI was not noticeably associated with severity bleeding or functional outcome in patients with SAH.

Although the obesity paradox correlation has limited evidence patients with intracranial aneurysms appear to overlap other vascular conditions as heart ischemic disease and stroke. The reason for the paradox has yet to be defined and the related mechanisms are still unknown. It appears to be the same underlying mechanism observed in hypercholesterolemia and regular physical exercise and weight of loss. [21]

A better nutrition and increased metabolic reserve appear to confers a kind of protection against endotoxin inflammatory cytokines and survival advantages. The exercise associated with good nutrition not only preserves muscle strength and its vascular dynamics, reducing circulating glucose, thereby increasing the effectiveness of insulin released as improving appetite and mood. Futures and more consistent studies are needed.

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CAPÍTULO XI

Artigo a ser Submetido para Publicação na Revista Circulation

Artigo a ser Submetido para Publicação na Revista Circulation

Submission to *Circulation*

The arterial variants of Willis circle and vessels related and its effect on carotid siphon aneurysms genesis

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Short title: *{Bozzetto Ambrosi}* : Variants of Wills circle and carotid siphon aneurysms genesis

Word count: The total word count of the manuscript, including the title page, abstract, text, references ?

Subject Codes: Please select from here www.ahajournals.org/site/misc/subject_codes.xhtml

Abstract

BACKGROUND: Populated-based, crossing-matched and flow computational studies have suggested a correlation between arterial variations of Willis circle and the development of an intracranial aneurysm. Asymmetric A1 segment, posterior cerebral artery (PCA) dominance and other minor variants e.g sharper angle bifurcations, vessel duplications and fenestrations has been demonstrated to leading to accelerated degenerative changes in the vessel wall at several locations either in the anterior or posterior circulation. Specific studies about hemodynamic changes correlated to arterial variants of the circle of Willis and carotid siphon aneurysms has been not addressed yet.
OBJECTIVE: To characterize the role of arterial variants of the circle of Willis as particularly implicated in the genesis of aneurysms within the circumference of the carotid siphon. At the same time, a regression analysis to overcome significant imbalance between men and women in both with respect to the aneurysm location and the presence of arterial variants of Willis polygon.
METHODS: A case-control study was conducted evaluating individuals with unilateral carotid siphon aneurysms treated between 2002 and 2014 (n = 178 patients/aneurysms, 154 females, 24 males) at the Department of Interventional Neuroradiology, Hospital Beaujon, France and compared with a control healthy group (n = 210 patients, 142 females, 68 males) and a combined cohort with contralateral healthy siphon and control healthy patients (n=468 patients, 372 females, 96 males). The presence of A1 or Fetal PCA dominance or both associated were assessed.
RESULTS: Contrary to expectations, there was an inverse relationship between the presence of aneurysms somewhere in the circumference of the siphon and arterial variants of Willis circle. Both A1/Fetal PCA dominance were founded in 3/178(1.6%) patients of the group with a unilateral aneurysm (3/178) and in 13 of 178 of the contralateral healthy siphons (OR=0.2176, p = 0.0189). A1 dominance was demonstrated in 11 of 24 healthy male siphons and 1 of 24 males with unilateral carotid siphon aneurysm (OR 0.514, p <0.0070) and in 44 females with 154 healthy siphons vs. 11 females with 154 unilateral aneurysms (OR 0.192, p <0.0001). **DISCUSSION:** The high association of A1/Fetal PCA in healthy siphons denotate a probable protective effect of this association. The lower frequency of carotid siphon aneurysms in certain locations might relate with a greater resistance and increased capacity of adaptation against the wall hemodynamic disorder.
CONCLUSION: Anatomical variants high flow-related appear to be relevant protection factor of carotid siphon aneurysms. This new concept can help in screening and treatment strategy of the intracranial aneurysms. Therefore, more studies involving flow measurements might be considered for better assessment of the blood circulation.
KEYWORDS: Willis circle, *circulus arteriosus cerebri*, intracranial aneurysms, carotid siphon, genesis

Introduction

The intracranial aneurysms are abnormal local vascular dilatations occurring more frequently within the arteries of Willis polygon and its vessels related. [1-3] Aneurysms that

develop on the circumference of the carotid siphon are quite diversified and complex surgical techniques are needed for either its microsurgical or endovascular repair. [4-13] Although the natural history of intracranial aneurysms remains not elucidated, current evidence have showed that hemodynamic and geometric factors seem to be possible cofactors of the evolutionary process involving endogenous and local factors (weakness and vulnerability) in the destructive remodeling of the arterial wall and aneurysms formation. [14-17]

Populations and crossing matched studies performed in several locations as ACA(Anterior cerebral artery) and PCoA(Posterior communicating artery) indicate that asymmetry in the arteries of the circle of Willis and other geometric changes as sharper bifurcation angles has been demonstrated in the flow studies as playing an important role in the aneurysm development.[14-20]At the same time, authors investigating the relationship between variations of the Willis polygon and analyzing the risk of aneurysm formation, have detected a correlation between the known difference between men and women for anatomic variants which appear to be correlated with the difference in the distribution of aneurysms. [21,22]

We conduct a study detecting A1 or P1 dominance between siphons with and without aneurysms in a series of patients were referred for carotid siphon aneurysm neuroendovascular management and comparing with a matched sampling of contralateral healthy siphon and a series of healthy regression-adjusted sample from a high-performing French university center, and reference center for intra-cranial aneurysms.

Methods

An observational, descriptive and quantitative, case-control survey was conducted from January 2011 until October 30, 2014, within the Department of Interventional Neuroradiology at Beaujon University Hospital, France. The research was developed in accordance with the ethical standards for research involving human subjects (CAAE 47075215.1.0000.5208).

From a daily updated database of patients with intracranial aneurysms treated by the department between February 2002 until October 2014, only patients with unilateral carotid siphon aneurysms were included in this study. An aneurysm was considered within the carotid siphon when located in any point of siphon circumference or corresponding to

Bouthilier[24] C4-6 segment of each ICA analysed (C2-C4 segment in Fischer classification[25]) as shown in Figure 1.

Following healthy patients were recruited between January 2011 and October 2014 whose angiographic studies of four vessels have no showed evidence of brain aneurysms, "blebs" or other related vascular malformations and were analyzed prospectively. Patients with incomplete arteriographical examinations or not allowing proper analysis were excluded. Also patients with bilateral carotid siphon aneurysms were considered in a separated group called “mirror” for further analysis.

Data collection

Patient demographical data, such as age and gender, and history of subarachnoid haemorrhage were reviewed. Data from pre-treatment angiograms, including 2- and 3-dimensional rotations used to locate aneurysms in the siphon (and harbored in the nine most frequent locations as Figure 1) [26], as well as the type of syphon (based on a lateral view of Huber’s modified description[27], in seven subtypes) were analyzed and recorded, as well as any anatomical variations and collateral circulation.

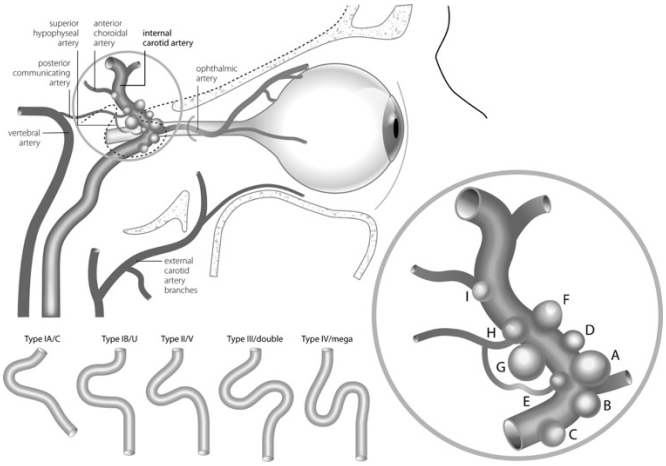

Figure 1. A. **B.**

Procedure

All carotid siphons studied were categorized in five group as either: *i)* **Group 1**, carotid siphon with "unique" aneurysm, *ii)* **Group 2**, both carotid siphon with aneurysms labeled as "mirror"; *iii)* **Group 3** , healthy contralateral siphon; *iv)* **Group 4**, both healthy carotid siphons; *v)* **Group 5**, healthy combined group.

All configuration of circle of Willis were assessed by reviewing of several images of Digital Subtraction Angiography (DSA) of the cervical or intracranial vasculature, 3D-reconstruction, intra-arterial vasoCT, arterial perfusion, 2D and 3D flow acquisitions which were performed in each patient during surgical pre and post-assessment. The presence of anterior communicating artery (ACoA), both A1, P1 segments and posterior communicating arteries (PCoA) were recorded. We classified each Willis circle for the presence of A1 or Fetal posterior cerebral artery (PCA) dominance or both. A1 dominance was defined as the contralateral branch was not visible or a diameter < 1 mm. PCA fetal was defined when the PCA originates from the ICA, completely (without connection with basilar artery) as well partially (with small connection from basilar artery).

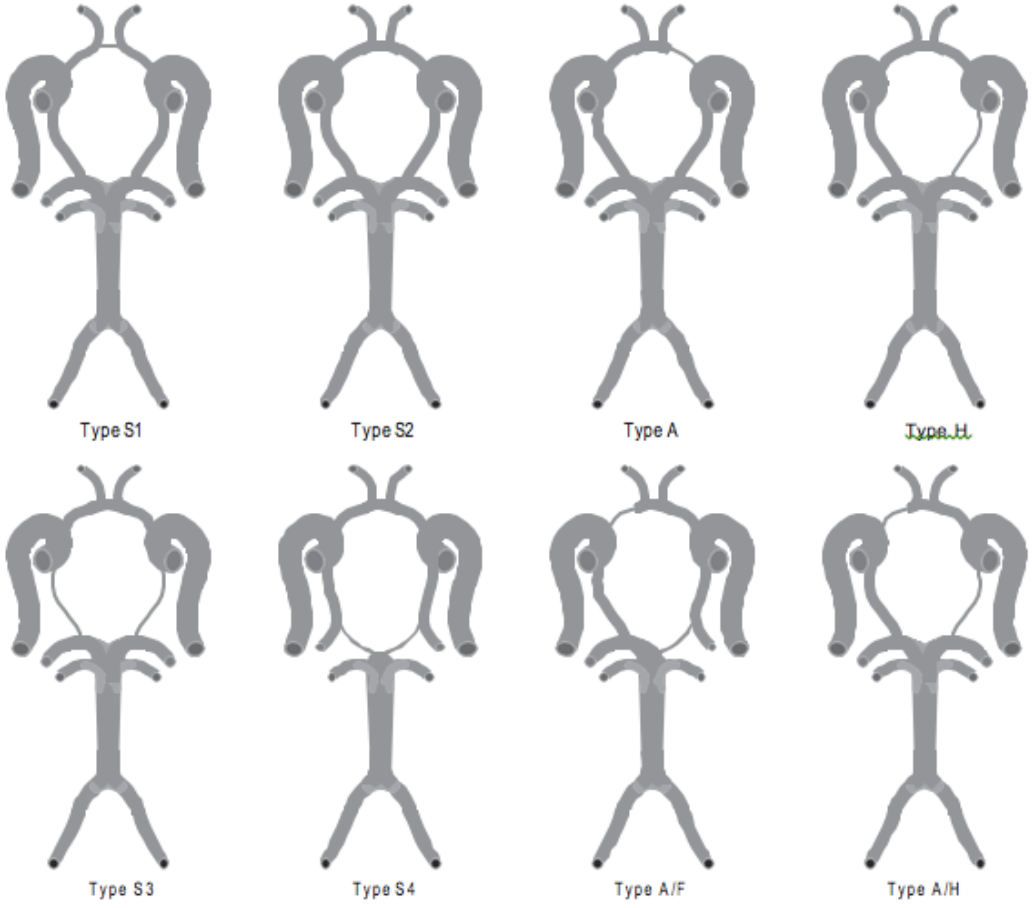

Figure 2. Different Willis Circle configurations.

Posteriorly, data will be stored in an Excel ® spreadsheet and then analyzed using the SPSS ® 23 version:

Baseline characteristics of analyzed groups

A total of 262 patients (230 female and 32 male) with a mean admission age of 50.47 ± 12.9 years (range 16-84) were diagnosed and treated of carotid siphon aneurysms between

2002 and 2014 at the Department of Interventional Neuroradiology, Hospital Beaujon, France. Of this number, 40 patients (18.5%) had a history of subarachnoid bleeding. The control healthy group were composed of 210 patients (142 females and 68 males) with mean admission age of 47.99 ± 16.774 years (range 16-84) and resulting in a combined cohort with contralateral healthy siphon (n=472 patients, 372 females, 96 males).

The **table 1** illustrates the results regarding gender analysis and summarizes the main demographic features of five group studied. The aneurysm group showed a female preponderance of 154/178(86.5%). However, the mirror group had the greater predominance with 76/84(90.5%) females. The healthy control after reformatting had a group 142/210(67,6%) of females and the final sample reached in the combined group was composed of 296/388(76.2%) females.

Statistical Analysis

Statistical analysis was performed using Statistical Analysis Software (SAS) version 23 (SAS Institute Inc., Cary, NC 27513-2414, USA). For continuous variables, demographic and clinical variables are reported as mean and median, showing the standard error and 95% confidence interval. For categorical variables, data were presented in terms of numbers and percentages. Statistical analyses were performed using the Pearson chi-square test, and the Fisher exact test used to determine the statistical inference for categorical variables, based on the outcome variable. Data were deemed statistically significant at $p<0.05$.

Results

Of the 1038 carotid siphons analysed, the presence of Fetal PCA was demonstrated in 282/1038 (27.16%) of total of siphons studied and respectively in 44/178(24.7%) of both groups with unilateral carotid siphon aneurysm and its contralateral healthy siphon. The mirror m healthy and combined groups showed respectively 12/84(14.3%), 69/210(32.8%) and 113/388(29.12%) of Fetal PCA dominance.

Regarding A1 dominance, it was demonstrated in 217/1038 (20.9%) of total of carotid siphons and successively in 12/178(6.7%) of siphons with a unilateral aneurysm, 11/84(13.0%) of mirror siphon group, 55/178(30.8%) of control healthy siphons, 42/210(20.0%) of healthy controls, 97/388(25.0%) of combined healthy groups.

Our analysis showed A1 dominance significantly greater in siphon without aneurysms demonstrated in 42/210(20%) versus unilateral aneurysms 12/178 (6.7%), OR= 0.2892, $p<0.0003$ as illustrated in **Table 2**. The same preponderance of A1 dominance is noted comparing unilateral aneurysm (12/178=6,7%) versus healthy siphon (55/178=30.8%),

OR=0.1617, p<0.0001 (**Table 3**). The A1 dominance was significantly more frequent in circle of Willis of females with normal siphons.

Table 1 – Characteristics of five groups studied

	Group 1 (One Siphon)	Group 2(Mirror Siphon)	Group 3(Healthy Siphon)	Group 4 (Healthy Patient)	Group 5 (Combined Group)	Total
Fetal PCA	44/178(24.7%)	12/84(14.3%)	44/178(24.7%)	69/210(32.8%)	113/388(29.12%)	282/1038(27.16%)
A1 dominance	12/178(6.7%)	11/84(13.0%)	55/178(30.8%)	42/210(20.0%)	97/388(25.0%)	217/1038(20%)
Both	3/178(1.6%)	1/84(1.2%)	8/210(3.8%)	13/178(7.3%)	21/388(5.4%)	46/1038(0.4%)
Age	49.84±12.299	51.10±13.846	49.84±12.299	47.99±16.774	49.95±14.886	49.74±14.020
Females	154/178(86.5%)	76/84(90.5%)	154/178(86.5%)	142/210(67.6%)	296/388(76.2%)	822/1038(79.19%)
Total	178/178(100%)	84/84(100%)	178/178(100%)	210/210(100%)	388/388(100%)	1038/1038(100%)

Table 2 – Comparison between siphon with unilateral siphon aneurysm and healthy patients.

	Sample 1	Sample 4	p-value	OR(95%Cl)	Total
Fetal PCA	44/178(24.7%)	69/210(32.8%)	0.0795	0.6710 (0.4296-1.0481)	113/388 (29.12%)
Females	40/154(25.9%)	48/142(33.8%)	0.1418	0.6871 (0.4165-1.1336)	88/296 (29.72%)
Males	4/24(16.6%)	21/68 (30.8%)	0.1857	0.4476 (0.1361-1.4720)	24/92 (26.08%)
A1 Dominance	12/178(6.7%)	42/210(20.0%)	0.0003*	0.2892 (0.1470-0.5687)	54/388(13.91%)
Females	11/154(7.1%)	32/142(22.5%)	0.0003*	0.2644 (0.1276-0.5480)	43/296(14.52%)
Males	1/24 (4.1%)	10/68(14.7%)	0.2575	0.2957 (0.0359-2.4370)	11/92(11.95%)
Both	3/178(1.6%)	8/210(3.8%)	0.2214	0.4329 (0.1131-1.6569)	11/388(2.8%)
Females	2/154(1.3%)	7/142(4.9%)	0.0906	0.2538(0.518-1.2425)	9/296(3.0%)
Males	1/24(4.1%)	1/68(1.5%)	0.4499	2.9565(0.1777-49.2004)	2/92(2.1%)

Table 3 – Characteristics of five samples studied.

	Group 1	Group 3	p-value	OR(95%Cl)	Total
Fetal PCA	44/178(24.71%)	44/178(24.71%)	1	1 (0.6178 -1.6187)	88/356(24.71%)
Females	40/154(25.97%)	40/154(25.97%)	1	1 (0.6009- 1.6643)	80/308(20.61%)
Males	4/24(16.60%)	4/24(16.60%)	1	1 (0.2191-4.5640)	8/48(16.60%)
A1 Dominante	12/178(6.70%)	55/178(30.80%)	<0.0001*	0.1617(0.0830- 0.3149)	67/356(18.82%)
Females	1/154(7.10%)	44/154(28.60%)	<0.0001*	0.1923(0.0949 -0.3896)	44/308(14.28%)
Males	1/24 (4.20%)	11/24 (45.80%)	0.0070	0.0514(0.0059-0.4443)	12/48(25.00%)
Both	3/178(1.60%)	13/178(7.30%)	0.0189*	0.2176(0.0609-0.7773)	16/356(4.50%)
Females	2/154(1.30%)	11/154(7.20%)	0.0221*	0.1687(0.0367-0.7742)	13/308(4.20%)
Males	1/24(4.10%)	2/24(83.30%)	0.5584	0.4783(0.0404- 5.6578)	3/48(6.25%)

Comparing the healthy patient group with unilateral aneurysm group showed 8/210(3.8%) versus 3/178(1.6%), OR 0.4329 (0.1131-1.6569), p=0.2214. While mirror group, there was no statistical significant regarding A1 dominance respectively have a frequency of 12/84 (14.28%), and 11/84 (13.0%) of Fetal PCA dominance.

Table 3 illustrates regarding both dominances associated comparing unilateral aneurysms group (3/178=1.60%) versus healthy control siphon (13/178=7.30%), p = 0.0189, OR = 0.2176 which showed a statistically significant difference. Regarding A1 dominance also was statistically significant. When compared separately only males, the healthy siphon group (11/24) versus group aneurysm (1/24) showed significance p <0.0070, OR 0.0514. The same comparing only females, siphon healthy (44/154) vs. siphon with aneurysm group (11/154), p <0.0001, OR = 0.192.

Discussion

In this study we present our experience that represent one the biggest series of carotid siphon aneurysms described in the literature. [1-3] Many advances and progresses has been made the techniques, materials and biotechnologies related to aneurysms management. [1-3] However, we emphatize the importance should be given to understand the genesis and pathogenic process with a better clinical utility. Therefore, we addressed a study with the use of cerebral hemodynamics in prediction of genesis of carotid siphon aneurysms. To our knowledge, this is the first time a balanced case control study of female predominance is used to study the Willis circle asymmetry.

We substantially tried to remove bias from our analysis. Horishowi and colleagues when analysing retrospectively 131 patients with intracranial aneurysms and comparing with 440 healty patients found that ACoA aneurysms were significantly related to the A1 hypoplasia and ICA aneurysms to PCA dominance. They found that male patients who did not harbor aneurysms tended to do not have A1 hypoplasia, whereas women had a significantly greater incidence of PCA fetal dominance. Their results demonstrated a sex-linked difference in anatomical variations may be correlated to the well-known sex-linked difference in aneurysm distribution. Neto and colleagues alsoevaluated the anatomical variants in the carotid siphon and of the circle of Willis in patients with aneurysms and found higher incidency of PCoA aneurysms in females (p<0.05), and ACoA in males (p<0.1). Also they demonstrated higher incidence of Fetal PCO in patients with PCoA aneurysms (24 *versus* 8%, p<0.05) and patients with ACoA aneurysm with higher incidence of A1 hypoplasia (p<0.0001, OR=32.13,

95%CI 12.95–79.71) and lower frequency of fetal-type PcomA compared to their control counterparts (p=0.0125).

Our study showed interesting results. There was an inverse relationship between the presence of aneurysm somewhere in the circumference of the carotid siphon and association with both types of circle of Willis with A1 and Fetal PCA dominance. Our results are in line with previous studies and suggested a possible protective effect of these associations.

Regarding the possible relationship between anatomical variations and intracranial aneurysms development, Padget was among the first to highlight by perfoming series studies comparing embryological abnormalities with aneurysms and without aneurysms. Kayembe et al comparing and studied macroscopically 44 complete circle of Willis and detected higher incidence of anatomical variations in the aneurysm series than in the control circles without aneurysm and founded a correlation between asymmetrical proximal segment of ACA and aneurysms of ACoA and the similar correlation in asymmetric PCoA and aneurysms of ICA-PCoA junction. Willis polygon hemodynamic appear to play important role to intracranial aneurysms genesis. However, they founded a limitating factor as most of such studies were unsatisfactory because of their methodology, that is poor handling of statistical data, lack of control series.

More recent studies with populations and crossing matched studies in several locations as ACA and PCoA has showed evidences that a circle of Willis asymmetric either congenital or acquired is a risk factor for the development, growth and recurrence of aneurysms there hemodynamic stress producing degenerative lesions leading to hyperdynamic flow.

In our adjusted case control analysis, we have a paired control sample to decrease effectthe sex differences in arterial anatomy for a long time. Moreover, variations in the anatomy of the circle of Willis were divided into too many subtypes, and such complicated classifications obscured or even overlooked the sex difference. In only one MR angiography study of the circle of Willis, a sex difference was observed in the diameters of the ACoA, ICA, BA, and MCA, which were greater in men than in women, whereas the mean diameter of the PCoA was greater in women.

The differences between men and women may be related to the constitutional factors and with the proper nutrition. Fetal circulation aneurysms had a lower frequency of these polygons that there will be greater resistance to the likely cause a hemodynamic disorder that excessive wear and vibrations result in structural fatigue and rupture of the internal elastic lamina and, therefore, lead to the formation brain aneurysm.

On the other hand, patients with hypoplastic A1 appear to have less capacity to adapt to hyperdynamic flow patterns as a result of abnormal high flow states or other collateral pathways which could accelerate degenerative changes in the vessel wall and subsequent development of aneurysms.

Previous studies describe that following a circle of Willis asymmetric either congenital or acquired would be a risk factor for the development of aneurysms there hemodynamic stress producing degenerative lesions leading to hyperdynamic flow. There some questions still without response. Does the lack of colateralidade due to lack of dominant A1/fetal PCOM would generate a stream of disorder that could lead to the formation of aneurysms.? The same phenomenon that occurs when ligation of one of the carotid arteries (considered an effective treatment for carotid artery aneurysm), has been associated with the induction of hemodynamic changes, which can be potentially responsible for the formation of new contralateral aneurysms by retrograde flow?

In this series case studies detected a similar case of a 62 year old patient with left carotid siphon aneurysm treatment history handled by the parent vessel occlusion and presented dysplastic aneurysms in the contralateral siphon. Subsequent research with DSA with opacification of the right internal carotid artery showed multiple aneurysms in the contralateral siphon.

Ryan et al described recently that asymmetric white matter disease, referring as well to hypoperfusion mechanism in the development of chronic ischemic pathology or small vessel disease or incomplete. Although there is a standard anatomy and hemodynamic, there are a range of individual differences between arteries, these differences occur depending on the age, genetic influence morphology and likely not yet understood.

Comparing the cerebral aneurysms with thoracic aortic aneurysms that are frequent in men. There is a clear difference between aortic diameter and the female and male arterial stiffness. In any age, men have aortas larger diameter than women, 39 though the absolute difference in diameter of the infrarenal aorta is only ≈1.4 mm.40 There is also a more pronounced dependent increase in diameter observed after age 45 to 54 years in men than in women. Thus, if a diameter of 3 cm is used as an AAA definition, the prevalence of age groups 45 to 54 and 75 to 84 years has increased from 2.6% to 19.8%, compared with men 0.5% to 5.2% in women. This increase, age dependent on the diameter of the aorta is accompanied by a compensatory increase in wall thickness to minimize the increase in tension in the circumferential wall, but compensatory response is higher in women than in men. Other arteries, including the common femoral artery, are smaller in women, which may affect the

suitability for endovascular treatment in the presence of AAA. In any age, healthy men are also more rigid aortas than women, but this may not be independent of the lower aorta diameters in men However, it has been suggested that smoking causes much greater rigidity of the aorta in women than in men .com stiffer aortas of larger diameter are more prone to age-dependent increases in diameter without sufficient compensatory thickening of the aorta, it is not surprising that AAA is more common in men than in women. However, partly due to its lower height, the morphology of AAA in women may be different from that in men; for example, women have shorter and angled AAA than men.

Seeking to understand the pathophysiology of carotid siphon aneurysms that related to anatomical, morphological, embryological factors.

Our study also showed a significant female preponderance regarding intracranial aneurysms which increase with the increasing number of aneurysms and is correlated among them certain locations, the carotid siphon. (Sarti et. al, 1991, Silva Neto et al., 2012) In populations more than 50 years, the increased prevalence in women can approach a ratio of 2: 1 or greater has been associated with low estrogen. (Longstreth et al 1994;. Vlak et al, 2011;. Defillo et al, 2014) and carotid siphon in particular aneurysms occurring in the two siphons make up more than 90% of the cases as evidenced in this study. This also corrobates with sex-effect aneurysm development.

However, there are several points from this complex to elucidate the evolutionary process involving own anatomy (which conditions provide the exact point source of aneurysms most often associated bifurcations). What aspects of vascular geometry (curves and angles) would provide that the hemodynamic status with endogenous factors related to the vascular wall (weakness and vulnerability) could be co-factors in this process.

It is likely that changes in morphology in large pots as the main trunk and adaptability of internal carotid arteries would be responsible for development of carotid siphon aneurysms.

Given all the facts and ideas trying to find out in which environment the aneurysm would form, some key points could help us: is there any correlation between the pattern of the geometry of the circle of Willis and certain subtypes of intracranial aneurysms. Apparently not, our analysis did not find arguments justifying the tortuosity of the siphon with aneurysms subtypes.

On the other hand certain hemodynamic patterns of the polygon of Willis seem to justify a higher screening and perhaps a preventive treatment?

Finally, this paradigm to our current and future directions must turn to the understanding of the genesis and natural history of intracranial aneurysms and then be able to predict

treatment response modifiers stents flow at the same time having a better understanding of changes in flow circle of Willis. This should also contribute to the understanding of the pathophysiology and point primarily to a more effective direction in the detection and prevention of intracranial aneurysms.

Like any research, the limitations are evident to the few. The main difficulty was to control the biases and have a control group as identical as possible to the affected group. However it may be an area to be explored in the future. Another issue will also examine the banal variants as the fenestration, the size differences between the segments of the arteries etc

We had a bias with respect to frequency of siphon aneurysms subtypes, because our center and reference deals with more complex cases and had few cases of aneurysms of the posterior communicating artery that are theoretically the most frequently found.

Conclusions

This little research on the morphology and hemodynamics of carotid siphon aneurysms basically comparing groups of siphon with unilateral aneurysms versus siphon without aneurysms and healthy patients showed relevant findings. Our research involved a quite representative population (greater series of carotid siphon aneurysms described in the literature) and might open the door for more controlled and multicenter studies to develop in the near future. Also, it contributed to a resumption of studies regarding the carotid siphon and the pathophysiology of intracranial aneurysms.

Other relevant contributions are that: So far as it detected anatomical variations, there are no specific screening protocols, most cases are treated as normal variant of the abnormality. More studies are required to establish future protocol of screening and strategic of treatment and including new tools of hemodynamic studies.

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CAPÍTULO XII

Discussão

4 DISCUSSÃO

A morfologia e a hemodinâmica vascular tem tido recentemente uma ampla utilização e expansão na investigação e terapêutica aneurismática, particularmente depois da introdução dos stents modificadores de fluxo para uso clínico. Temos presenciado uma evolução da hemodinâmica cerebral como instrumento clínico na decisão do tratamento. Além disso, cada dia se tem mais interesse em entender fisiopatogenicamente os aneurismas intracranianos. Conforme ilustramos na Figura 20, evoluímos desde visão de raio X proporcionada pelos primeiros exames contrastados realizados por Moniz, passando pelo uso das ferramentas hemodinâmicas modernas no presente e caminhamos para uma visão futurista que nos permitirá conhecer em detalhes o interior das moléculas.

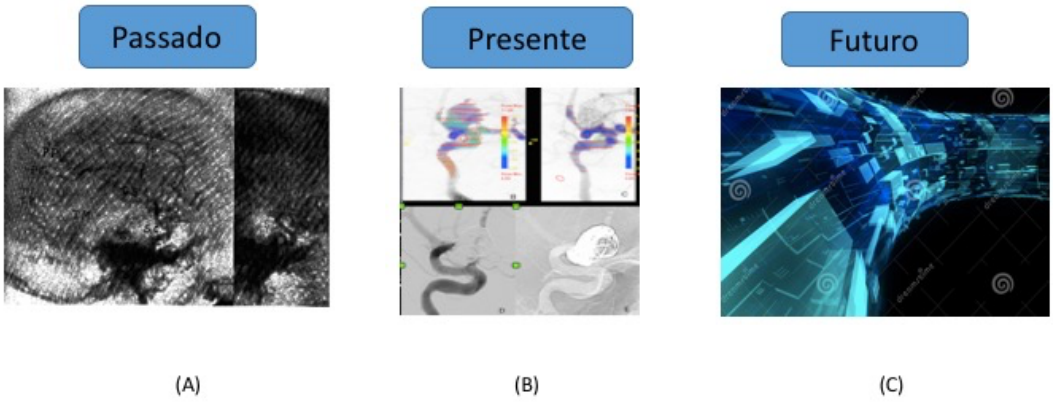


Figura 20 – Imagem radiográfica de Moniz (A) Imagem angiográfica com estudo de fluxo (B) Imagem extraída da internet (C).

Com o aprimoramento das técnicas de diagnóstico e tratamento percebeu-se que a cura obtida após a colocação do clip cirúrgico, quando os neurocirurgiões davam por terminado nem sempre acontece. Acredita-se cada vez mais o aneurisma intracraniano é uma doença que acomente a parede vascular e talvez tenha repercussões em toda circulação e hemodinâmica cerebral.

Nosso estudo utilizou-se a própria circulação cerebral (exames angiográficos) para analisar de uma forma mais simples e prática a hemodinâmica cerebral. Realizou-se uma análise de sifões de pacientes com aneurismas *versus* sifões de pacientes controles sem aneurismas. Enquanto os poucos outros estudos da literatura utilizaram acompanhando a

tendência os modelos de silicone para avaliar as geometrias vasculares obtidas a partir de seres humanos.

Nossa análise de distribuição de fluxo no polígono de Willis foi feita através da análise da presença de assimetrias de hipo ou hiperfluxo, a presença da hipoplasia de A1 e PCA fetal. Nesta experiência em particular, observou-se que os controles tem mais frequência de PCA fetal e A1 dominante denotando que a presença de uma circulação fetal pode ser sinômimo de hiperfluxo e consequente proteção na formação de aneurismas intracranianos.

Nos sifões com aneurismas houve uma maior incidência de assimetrias de hipofluxo denotando um estado de degeneração e adaptação avançada da circulação cerebral. Particularmente, sugerindo que a configuração do sifão/polígono de Willis é diferente com aneurisma comparado com pacientes sem aneurisma. Outra investigação realizada foi com relação a posição dos aneurismas e o círculo de Willis (analisando o risco de formação do aneurisma dentro do sifão) correlacionaram a diferença conhecida entre os homens e as mulheres para a presença de aneurismas e de variantes anatômicas. Isso parece também estar correlacionados com a diferença a distribuição dos aneurismas como um todo.

Nosso cuidado analítico foi em relação à obtenção de um grupo controle que se aproximasse do grupo mais afetado pelos aneurismas do sifão unilaterais, no caso mulheres com polígonos assimétricos.

Observou-se uma relação inversa entre a presença de aneurisma em algum ponto da circunferência do sifão e o polígono de Willis tipo A1 e P, provavelmente devido ao efeito protetor dessas duas associações. O que denota que a fisiopatologia dos aneurismas do sifão carotídeo que se relaciona com fatores anatômicos-morfólogicos-embriológicos. Não foi surpresa ter encontrado essa frequência maior em mulheres nos aneurismas em espelho, onde a questão anatômica embriológica parece bem mais evidente. Provavelmente exista um processo de crescimento e desenvolvimento dos aneurismas do sifão carotídeo diferente comparando homens e mulheres.

Acredita-se que os fatores morfológicas e hemodinâmicos possam estar correlacionados entre si. As diferenças entre homens e mulheres podem estar relacionadas com os fatores constitucionais e com a própria nutrição. Os polígonos com circulação fetal tiveram menor frequência de aneurismas. Será que nesses polígonos existe uma resistência maior contra o provável distúrbio hemodinâmico que causaria um desgaste excessivo e vibrações resultam em fadiga estrutural e ruptura da lâmina elástica interna e, por conseguinte, levam à formação do aneurisma cerebral. Está bem estabelecido que existe uma preponderância feminina para aneurismas intracranianos que aumentam com o aumento do

número dos aneurismas e está correlacionado com certas localizações dentre elas, o sifão carotídeo (Sarti et. Al, 1991).

Em populações com mais de 50 anos, o aumento da prevalência em mulheres pode aproximar-se de uma proporção de 2 para 1, ou maior do que tem sido associado com baixo estrogênio. (Longstreth et. al 1994; Vlak et al, 2011; Defillo et al., 2014) e em aneurismas do sifão carotídeo particularmente ocorrendo nos dois sifões perfazem mais de 90% dos casos conforme evidenciamos nesse estudo. Isso corrobora com as evidências que mostram que a distribuição aneurismática é correlacionada com o sexo.

Por outro lado, será que pacientes com hipoplasia de A1 parecem ter menor capacidade de adaptar-se a padrões de fluxo hiperdinâmicos como um resultado de estados de alto fluxo anormais ou outras vias colaterais aceleraranDo as alterações degenerativas na parede dos vasos e subsequente desenvolvimento dos aneurismas. Isso tinha sido observado previamente nos seguintes estudos Milenkovic descreveu que um polígono de Willis assimétrico tanto congênito como adquirido seria um fator de risco para o desenvolvimento de aneurismas se existe estresse hemodinâmico produzindo lesões degenerativas levando ao fluxo hiperdinâmico (Milenkovic et al, 1995).

Será que a falta de colateralidade decorrente da falta de A1 dominante/ PCOM fetal geraria um distúrbio de fluxo que poderia levar a formação com aneurismas. O mesmo fenômeno que certamente ocorre quando ligamos uma das artérias carótidas (considerado um tratamento eficaz para aneurismas da artéria carótida), tem sido associado com a indução de alterações hemodinâmicas, que podem ser potencialmente responsáveis pela formação de novos aneurismas contralaterais por fluxo retrógrado (Arampeola, 2010).

Na população geral, a incidência e distribuição de configurações assimétricas do polígono de Willis varia entre 15 e 22%. A presença de assimetria indica uma relação clara entre as alterações morfológicas que ocorrem como um resultado da configuração assimétrica, e desordem de relações hemodinâmicas para poder fornecer suprimento adequado através da colaterais. A incidência significativamente maior de assimetria em relação às mudanças aneurismáticas sobre os vasos sanguíneos cerebrais, sugerem que o fluxo de sangue no cérebro é adaptável às necessidades de perfusão mais elevadas. Desordens hemodinâmicas e anormalidades de fluxo devido a mudanças ultra-estruturais nas paredes dos vasos sanguíneos possivelmente desencadeiam uma cascata de mecanismos de adaptação patológica da parede e levando a formação de aneurismas.

Os estudos recentes sugerem também que polígonos assimétricos teriam maior doença da substância branca, referindo-se assim para o mecanismo hipoperfusão no desenvolvimento de patologia isquêmica crônica ou a doença dos pequenos vasos ou lacunar.

Apesar de haver um padrão na anatomia e hemodinâmica, existem uma gama de diferenças individuais entre as artérias, essas diferenças ocorrem dependendo da idade, morfologia e provável influência genética que ainda não entendemos.

Comparando os aneurismas cerebrais com os aneurismas da aorta torácica que são frequentes em homens. Existe uma clara diferença entre o diâmetro aórtico e a rigidez arterial femininas e masculinas. Em qualquer idade, os homens têm aortas de maior diâmetro do que as mulheres, embora a diferença absoluta no diâmetro da aorta infra só é ≈1.4mm. Há também um aumento dependente da idade mais acentuada de diâmetro observado após 45 a 54 anos nos homens do que em mulheres. Assim, se um diâmetro de 3cm é utilizado como uma definição de AAA, a prevalência entre os grupos de idade 45 a 54 anos e 75 a 84 anos aumentou de 2,6% para 19,8%, em comparação com os homens de 0,5% a 5,2 % nas mulheres. Este aumento, dependente da idade no diâmetro da aorta é acompanhada por um aumento compensatório na espessura da parede para minimizar o aumento da tensão na parede circunferencial, mas a resposta compensatória é maior em mulheres do que nos homens. Outras artérias, incluindo a artéria femoral comum, são menores nas mulheres, que podem afetar a adequação para o tratamento endovascular na presença de um AAA. Em qualquer idade, homens saudáveis também têm aortas mais rígidas do que as mulheres, mas isto pode não ser independente dos diâmetros da aorta inferiores em homens. No entanto, tem sido sugerido que o tabagismo provoca muito maior rigidez da aorta em mulheres do que em homens.Com aortas mais rígidas, de maior diâmetro que são mais propensas a aumentos dependentes da idade de diâmetro sem espessamento da aorta compensatória suficiente, não é de estranhar que AAA é mais comum em homens do que em mulheres. No entanto, em parte devido à sua menor estatura, a morfologia da AAA em mulheres pode ser diferente da que nos homens; por exemplo, as mulheres têm mais curtos e mais angulados AAA do que homens.

Recentes estudos tem mostrado uma correlação entre a variabilidade morfológica e hemodinâmica do sifão carotídeo e a formação de aneurismas. (Lee, 2008; Silva Neto, 2012) As áreas de fluxo turbulento são susceptíveis a fraqueza e causariam alterações morfológicas na parede vascular do sifão carotídeo. Assim como, alterações hemodinâmicos causados pela variabilidade do polígono de Willis e do sifão carotídeo podem estar associados ao desenvolvimento de aneurismas.

CAPÍTULO XIII

Conclusão e Considerações Finais, Limitações da Pesquisa, Perpectivas Atuais e Futuras Direções

5 CONCLUSÃO E CONSIDERAÇÕES FINAIS

Cada vez fica mais evidente que existe uma forte correlação entre a morfologia vascular e a hemodinâmica cerebral com os seus aneurismas relacionados. Essa tese de doutorado incluiu o minucioso estudo da morfologia vascular do sifão carotídeo e sua relação com as mudanças de fluxo do polígono de Willis e suas ramificações. Os resultados indicaram que a hemodinâmica cerebral e os processos envolvidos devem as nossas direções atuais e perspectivas futuras para o melhor entendimento da gênese e história natural dos aneurismas intracranianos, onde será possível também prever uma melhor resposta ao tratamento com os stents modificadores de fluxo e ao mesmo tempo da evolução da própria lesão aneurismática. Isso também deve contribuir para a compreensão da fisiopatologia como um todo e apontar principalmente para uma direção mais eficaz dentro da problemática atual.

As principais conclusões e considerações dos estudos dessa tese relacionam-se com o entendimento da morfologia e hemodinâmica dos aneurismas intracranianos, particularmente dos aneurismas que surgem na circunferência do sifão carotídeo e são resumidas a seguir.

No **estudo 1**, que foi demonstrado no capítulo IV, o resultado final obtido foi de que o uso das biotecnologias tem gerado expectativas no entendimento da gênese e do desenvolvimento dos aneurimas intracranianos e consequente no seu manejo estratégico. No entanto, baseado nas evidências encontradas revisando sistematicamente a literatura, poucos estudos validados foram identificados e apenas pequenas amostras quando estudamos especificamente o sifão carotídeo foram validadas até então. Esses estudos existentes são essencialmente baseadas em estudos de fluxo aneurismático *in vitro* dedicados à análise da hemodinâmica vascular e outros analisando a angulação do sifão propriamente dito (Piccinelli et al., 2011, Valen-Sendstad et al., 2014; Lauric et al., 2014). Finalmente, os refinamentos tecnológicos tem drasticamente por outro lado melhorado o estudo de fluxo aneurismático visando a sua incorporação dentro do contexto clínico.

No **estudo 2**, que foi demonstrado no capítulo V, conclui-se que apesar das evoluções e refinamentos tecnológicos obtidos dentro do cenário diagnóstico e terapêutico, os aneurismas que surgem dentro da circunferência do sifão carotídeo, que são os mais frequentemente tratados por via endovascular permanecem um desafio. O puro e simples

diagnóstico clínico-radiológico desses aneurismas detentores de uma morfologia e geometria peculiar ainda persiste um desafio. Os sintomas de apresentação muitas vezes se confundem e são quase impossível de diferenciá-los dos achados incidentais. Mais estudos são indicados, que visem subdividir os aneurismas do sifão carotídeo em diferentes subgrupos correlacionados através de rigoroso e minucioso estudo.

No **estudo 3**, que foi demonstrado no capítulo VI, conclui-se que historicamente as técnicas endovasculares foram introduzidas para tratar os aneurimas do sifão carotídeo inoperáveis e progressivamente viram a se tornar-se a técnica de escolha de tratamento. O tratamento endovascular obviou a microcirurgia devido sua comprovada eficácia e segurança demonstrada face a cirurgia convencional aberta. A técnica de remodelamento com balão revolucionou o tratamento dos aneurismas intracranianos com colo largo. No entanto, as técnicas de tratamento endovascular em meados de 2010 sofreram uma grande mudança com a introdução dos novos stents modificadores de fluxo visando corrigir e compensar os distúrbios hemodinâmicos e morfológicos vasculares.

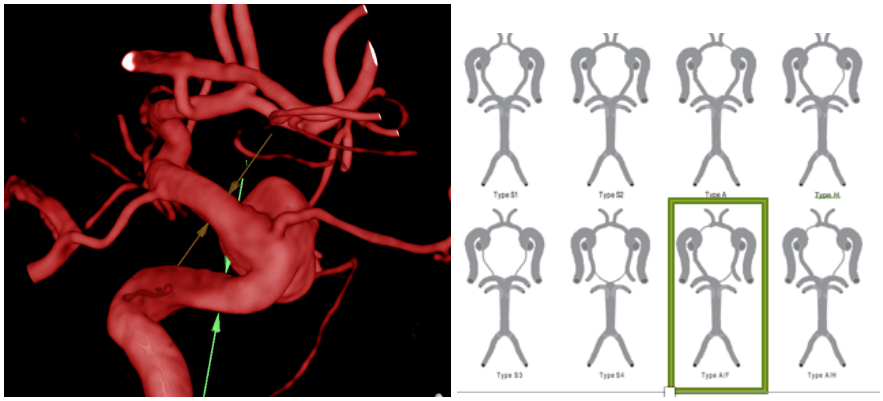
No **estudo 4**, que foi demonstrado no capítulo VII, conclui-se que através de nova classificação tridimensional geométrica proposta, identificamos e agrupamos os subtipos mais prevalentes com base em áreas de susceptibilidade usando marcos de microcirurgia e radiológicos e correlacionando com morfologia do sifão carotideo. Os resultados indicaram que esses aneurimas apesar da diversidade a ser mais frequente na curva ascendente de um sifão carotídeo. Estudos são necessários correlacionados os diferentes subtipos de aneurismas do sifão carotídeo e do próprio sifão com padrões morfológicos e funcionais.

No **estudo 5**, que foi demonstrado no capítulo VIII, as considerações feitas que examinar o uso de hemodinâmica cerebral não é fácil porque há elementos de confusão como fatores constitucionais ou características da doença e da estrutura arterial como hemodinâmica vascular, efeito do gênero na formação de aneurismas intracranianos. Como anteriormente tinha-se mostrado, há uma diferença ligada ao sexo em variações anatômicas e isso está ligado à distribuição anatômica de aneurismas (Ghods et al, 2012.); porém não sabe-se se esses dois elementos estão correlacionados. Certamente estudos controlados devem ajudar no melhor entendimento dessa problemática. Outras questões-chave seriam: existe alguma correlação entre o padrão diferente de geometrias no círculo de Willis e os vasos relacionados com alguns subtipos de aneurismas intracranianos? Talvez algumas anomalias do círculo arterial de Willis justificariam seu rastreamento e tratamento preventivo? Seria o próprio aneurisma o ponto de gatilho dentro da hemodinâmica cerebral ou vice-versa, uma doença congenitamente adquirida?

No **estudo 6**, que foi demonstrado no capítulo IX, as considerações feitas foram que apesar da escassez de estudos, as variações na própria anatomia vascular do polígono de Willis associadas com a geometria vascular parecem desencadear um processo de desgaste excessivo e vibrações que resultariam em fadiga estrutural e ruptura da lâmina elástica interna das arterias intracranianas levando a formação dos aneurismas intracranianos. A análise das variantes arteriais embriológicas do polígono de Willis e seus ramos poderá se tornar uma técnica potencialmente útil para o entendimento da gênese e na avaliação dos resultados do tratamento dos aneurismas intracranianos.

No **estudo 7**, que foi demonstrado no capítulo X, considerou-se que a existe uma forte correlação entre a obesidade paradoxal com aneurismas intracranianos e que isso parecem se sobrepor com outras condições vasculares, como a doença cardíaca e o acidente vascular cerebral isquêmico. A razão para o paradoxo ainda não foi elucidado e os mecanismos relacionados ainda são desconhecidos. Parece que o mecanismo subjacente seria o mesmo que observado na hipercolesterolemia e o uso do exercício físico regular para a perda de peso. Certamente, uma melhor nutrição e uma maior reserva metabólica confeririam uma espécie de protecção contra as citocinas inflamatórias ou endotoxinas e consequentemente aumentado as chances de sobrevivência. O exercício associado com uma boa alimentação, não só preserva a força muscular e sua dinâmica vasculares, mas leva a redução de glicose circulante, aumentando assim a eficácia da insulina liberada como melhorando o apetite e humor. Futuros estudos correlacionados são esperados.

No **estudo 8**, que foi demonstrado no capítulo XI, realizou-se um estudo caso controle envolvendo grupos de sifões com aneurismas *versus* pacientes saudáveis sem aneurismas ou sifões sem aneurismas. Conclui-se que ao mesmo tempo que existem fatores que facilitam a gênese dos aneurismas intracranianos (hipoplasia de A1, duplicações, fenestrações...) foram encontrados fatores protetores como certas configurações do polígono de Willis com a presença da A1 dominante e da PCA fetal dentro da circulação cerebral conforme ilustrado na Figura B abaixo.



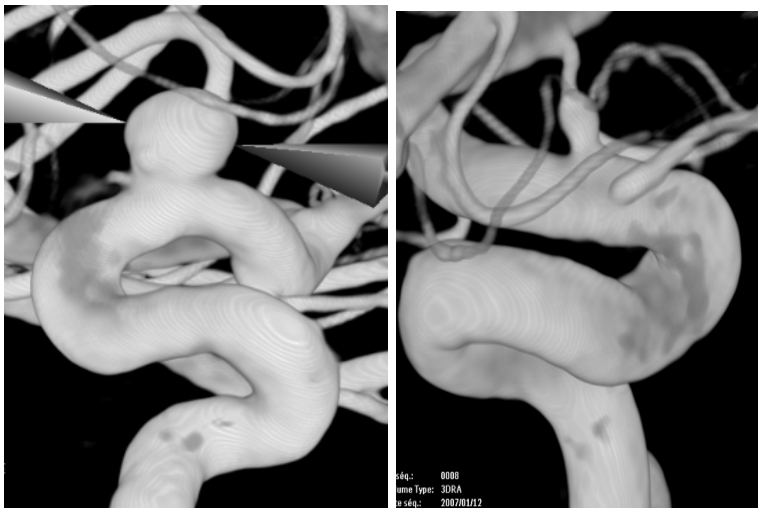
(A) (B)

Figura 21 – Estudo tridimensional arteriográfico da artéria carótida interna direita de uma paciente com aneurisma do sifão carotídeo em posição paraclinóide (A) Figura esquemática das diferentes configurações do polígono de Willis e enfatizando o subtipo que parece ser protetor (B).

Por outro lado, isso corrobora com estudos recentes os quais têm proposto que a ausência congênita da capacidade anastomóstica do círculo de Willis é correlacionada com outras doenças cerebrovasculares como doenca microangiopática, referindo-se assim para o mecanismo hipoperfusão no desenvolvimento de patologia isquêmica crênica ou doença cerebrovascular pequeno vaso (Ryan et al., 2015). Outra doença conhecida relacionada com o fluxo tem sido demonstrada após a ligação da artéria carótida conforme já comentamos anteriormente. Este procedimento foi realizado durante longo tempo para o tratamento de aneurismas gigantes do sifão carótideo como a técnica de escolha antes do desenvolvimento de terapia neuroendovascular. No entanto, este tipo de procedimento tem sido associado com a formação de aneurismas intracranianos *de novo* e em remodelação vascular induzida pelo fluxo (Gao et al., 1981). Estudos experimentais sobre a ligadura da carótida demonstraram que existiria um fluxo sanguíneo compensatório após a oclusão da carótida com remodelamento patológico secundário. O desenvolvimento adaptativo de fluxo ao longo do círculo de Willis resultaria na formação de um aneurisma da artéria carótida contralateral (Tutino et al., 2014). Nossa pesquisa envolveu população bastante representativa (maior série de aneurismas do sifão carotídeo descrita na literature até o presente) e poderá abrir a porta para mais estudos controlados e multicêntricos se desenvolvam num futuro próximo. Além disso, contribuiu para a retomada dos estudos sobre o sifão carótideo e da sua fisiopatologia, bem como dos aneurismas intracranianos.

Outras contribuições relevantes são foram as seguintes:

1) Na medida em que detectam-se variações anatômicas, não há protocolos de rastreio específicos, a maioria dos pacientes diagnosticados são tratados como variante normal da anormalidade. Mais estudos são necessários para o desenvolvimento de protocolos de rastreio e de estratégia do tratamento, incluindo de estudos hemodinâmicos.
2) Evidências mostram que as variações anatômicas observadas no círculo de Willis poderiam desempenhar um papel na gênese dos aneurismas intracranianos e ao mesmo tempo podem ter um fator protetor. Isso suporta o uso da hemodinâmica como preditor clínico e instrumento de decisão no diagnóstico e manejo dos aneurismas do sifão carotídeo.
3) Ao mesmo tempo, os autores investigaram a relação entre o círculo de Willis e o risco de formação de aneurisma detectando que também há uma correlação entre a diferença conhecida entre os homens e as mulheres para a presença anatômica das variantes que também parecem estar correlacionados com a diferença da distribuição dos aneurismas. É bem provável que mudanças na morfologia em grandes vasos como o tronco principal e da capacidade de adaptação das artérias carótidas internas seria responsável pela formação dos aneurismas do sifão.
4) Aneurismas em geral tem se mostrado mais como da uma doença da parede vascular. Os stents *flow diverters* foram desenvolvidos para atuar no endotélio do vaso e criando uma nova parede vascular. Além disso, acreditamos que não seja apenas uma doença local, mas os aneurismas podem ser apenas um ponto de gatilho da doença em toda a hemodinâmica cerebral que se desenvolve na circulação cerebral congenitamente ou adquirida.
5) Dado a todos esses fatos e idéias na tentantiva de desvendar em que ambiente o aneurisma se formaria, alguns pontos-chaves poderiam ajudar-nos: existe alguma correlação entre o padrão da geometria do círculo de Willis e certos subtipos de aneurismas intracranianos. Aparentemente não, nossa análise não encontrou argumentos justificando a tortuosidade do sifão com subtipos de aneurismas. Ainda não sabemos se existiria talvez uma terapia especifica ou condições especificas que desencaderiam diferentes aneurismas na mesma localização no mesmo paciente como podemos observar na **Figura 22** abaixo. Por outro lado certos padrões hemodinâmicos do polígono de Willis parecem justificar uma maior triagem e talvez um tratamento preventivo?



(A) (B)

Figura 22 – Estudo arteriográfico da artéria carótida interna direita de uma paciente jovem com acufenos e aneurisma do sifão carotídeo em posição oftálmica direita (A) Estudo arteriográfico da artéria carótida contralateral de uma paciente com aneurisma do sifão carotídeo em posição oftálmica esquerda (B).

6 LIMITAÇÕES DA PESQUISA

A principal dificuldade foi de controlar os viéses e ter um grupo controle o mais idêntico possível do grupo afetado. Porém pode ser uma área a se explorar no futuro. Outra questão será analisar também as banais variantes como as fenestrações, as diferenças de tamanho entre os segmentos das artérias etc... que não foram detalhadamente estudados. Tivemos um viés com relação a frequência dos subtipos de aneurismas do sifão carotídeo, porque nosso centro sendo de referência trata os casos mais complexos e poucos casos de aneurismas da artéria comunicante posterior foram relatados que são teoricamente os mais frequentemente encontrados.

7 PERSPECTIVAS ATUAIS E FUTURAS DIREÇÕES

Nos últimos anos, tem se visto significantes avanços biotecnológicos no diagnóstico e no tratamento dos aneurismas intracranianos em geral, incluindo os aneurismas do sifão carotídeo. Têm sido visto muitas pesquisas se centrando nas técnicas, e pouca importância parece ser dada a entender a gênese e processo patogênico. Muitos avanços foram feitos com as novas biotecnologias tanto no diagnóstico como no tratamento, mas uma melhor correlação clinica é esperada.

Mudanças na morfologia vascular do sifão carotídeo correlacionado com aneurismas intracranianos influenciariam não apenas na escolha da técnica endovascular, mas nos resultados, por exemplo quando nos deparamos com um caso de recanalização.

Esse conceitos e resultados obtidos certamente também poderão ser aplicadso a outras localizações de aneurismas principalmente da circulação anterior se consideramos a origem embriológica vascular.

Esses aneurismas do sifão carotídeo são muito provavelmente um processo dinâmico, onde se deve levar em conta todos esses fatores anatômicos-morfológicos-hemodinâmicos que caracterizam a geometria do aneurisma e da circulação arterial.

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ANEXO I

Normas para Submissão ao International Archives of Medicine

Template para formatação do artigo submetido ao International Archives of Medicine

Author guidelines

Contents

Any manuscript submitted to a iMedPub journal and any book published with iMedPub must be original. The manuscript/book, or substantial parts of it, must not be under consideration by any other journal/publisher.

In general, the manuscript/book should not have already been formally published. However, we allow preprint publication and postacceptance peer-review.

In any case where there is the potential for overlap or duplication we require that authors are transparent. Any potentially overlapping publications should be declared on submission and, where possible, uploaded as additional files with the manuscript. Any overlapping publications should be cited. The Editors of iMedPub journals reserve the right to judge potentially overlapping or redundant publications on a case-by-case basis.

Format

Most articles published in iMedPub Journals will be organized into the following sections: title, authors, affiliations, abstract, introduction, methods, results, discussion, references, acknowledgments, and figure legends. Uniformity in format will help readers and users of the journal. We recognize, however, that this format is not ideal for all types of studies. If you have a manuscript that would benefit from a different format, please contact the editors to discuss this further. Although we have no firm length restrictions for the entire manuscript or individual sections, we urge authors to present and discuss their findings concisely.

Title

The title should be specific to the study yet concise, and should allow sensitive and specific electronic retrieval of the article. It should be comprehensible to readers outside your field. Avoid specialist abbreviations if possible. Titles should be presented in title case, meaning that all words except for prepositions, articles, and conjunctions should be capitalized. If the paper is a randomized controlled trial or a meta-analysis, this description should be in the title.

Examples:

Climate Change and Increased Spread of Malaria in Sub-Saharan Africa A Cluster-Randomized Controlled Trial of a Nurse-Led Intervention after Stroke Please also provide a brief "running head" of approximately 40 characters.

Authors and Affiliations

Provide the first names or initials (if used), middle names or initials (if used), surnames, and affiliations—department, university or organization, city, state/province (if applicable), and country—for all authors. One of the authors should be designated as the corresponding author. It is the corresponding author's responsibility to ensure that the author list, and the summary of the author contributions to the study are accurate and complete. If the article has been submitted on behalf of a consortium, all consortium members and affiliations should be listed after the Acknowledgments.

Abstract

The abstract is divided into the following four sections with these headings: Title, Background, Methods and Findings, and Conclusions. It should contain the all following elements, except for items in square brackets, which are only needed for some study types. Please use the same format for abstracts submitted as presubmission inquiries.

Background

This section should describe clearly the rationale for the study being done. It should end with a statement of the specific study hypotheses and/or study objectives.

Methods and Findings

Describe the participants or what was studied (eg cell lines, patient group; be as specific as possible, including numbers studied). Describe the study design/intervention/main methods used/What was primarily being assessed eg primary outcome measure and, if appropriate, over what period.

[If appropriate, include how many participants were assessed out of those enrolled eg what was the response rate for a survey.]

[If critical to the understanding of the paper, describe how results were analysed, ie which specific statistical tests were used.]

For the main outcomes provide a numerical result if appropriate (it nearly always is) and a measure of its precision (e.g. 95% confidence interval). Describe any adverse events or side effects.Describe the main limitations of the study.

Conclusions

Provide a general interpretation of the results with any important recomendations for future research.

[For a clinical trial provide any trial identification numbers and names (e.g. trial registration number, protocol number or acronym).]

Introduction

The introduction should discuss the purpose of the study in the broader context. As you compose the introduction, think of readers who are not experts in this field. Include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned so that a non-expert reader can delve into these issues further. The introduction should conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved.

Methods

This section should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established protocols may simply be referenced. Detailed methodology or supporting information relevant to the methodology can be published on our Web site.

This section should also include a section with descriptions of any statistical methods employed. These should conform to the criteria outlined by the Uniform Requirements, as follows: "Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important quantitative information. Discuss the eligibility of research participants. Give details about randomization. Describe the methods for and success of any blinding of observations. Report complications of treatment. Give numbers of observations. Report losses to observation (such as dropouts from a clinical trial). References for the design of the study and statistical methods should be to standard works when possible (with pages stated) rather than to papers in which the designs or methods were originally reported. Specify any general-use computer programs used."

Results

The results section should include all relevant positive and negative findings. The section may be divided into subsections, each with a concise subheading. Large datasets, including raw data, should be submitted as supporting files; these are published online alongside the accepted article. The results section should be written in past tense.

As outlined in the Uniform requirements, authors that present statistical data in the Results section, should "...specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Define statistical terms, abbreviations, and most symbols."

Discussion

The discussion should be concise and tightly argued. It should start with a brief summary of the main findings. It should include paragraphs on the generalisability, clinical relevance, strengths, and, most importantly, the limitations of your study. You may wish to discuss the following points also. How do the conclusions affect the existing knowledge in the field? How can future research build on these observations? What are the key experiments that must be done?

References

The International Committee of Medical Journal Editors offers guidance to authors in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication. The recommended style for references is based on the National Information Standards Organization NISO Z39.29-2005 (R2010) Bibliographic References as adapted by the National Library of Medicine for its databases. Details are inCiting Medicine. (Note Appendix F which covers how citations in MEDLINE/PubMed differ from the advice in Citing Medicine.) Sample references typically used by authors of journal articles are provided below.

Articles in Journals

1. Standard journal article
   List the first six authors followed by et al. (Note: NLM now lists all authors.)
   Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.
   As an option, if a journal carries continuous pagination throughout a volume (as many medical journals do) the month and issue number may be omitted.
   Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.
2. More than six authors:
   Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.
3. Optional addition of a database's unique identifier for the citation: [Edited 12 May 2009]
   Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7. PubMed PMID: 12140307.
   Forooghian F, Yeh S, Faia LJ, Nussenblatt RB. Uveitic foveal atrophy: clinical features and associations. Arch Ophthalmol. 2009 Feb;127(2):179-86. PubMed PMID: 19204236; PubMed Central PMCID: PMC2653214.
4. Optional addition of a clinical trial registration number: [Added 12 May 2009]
   Trachtenberg F, Maserejian NN, Soncini JA, Hayes C, Tavares M. Does fluoride in compomers prevent future caries in children? J Dent Res. 2009 Mar;88(3):276-9. PubMed PMID: 19329464. ClinicalTrials.gov registration number: NCT00065988.

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   Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.
6. Both personal authors and organization as author (List all as they appear in the byline.) [Edited 12 May 2009]
   Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. J Urol. 2003;169(6):2257-61.
   Margulies EH, Blanchette M; NISC Comparative Sequencing Program, Haussler D, Green ED. Identification and characterization of multi-species conserved sequences. Genome Res. 2003 Dec;13(12):2507-18.
7. No author given
   21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.
8. Article not in English [Edited 12 May 2009]
   Ellingsen AE, Wilhelmsen I. Sykdomsangst blant medisin- og jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785-7. Norwegian.
9. Optional translation of article title (MEDLINE/PubMed practice):
   Ellingsen AE, Wilhelmsen I. [Disease anxiety among medical students and law students]. Tidsskr Nor Laegeforen. 2002 Mar 20;122(8):785-7. Norwegian.
10. Volume with supplement
    Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache. 2002;42 Suppl 2:S93-9.
11. Issue with supplement
    Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12.
12. Volume with part
    Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. Int J Psychoanal. 2002;83(Pt 2):491-5.
13. Issue with part
    Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumors. J Vasc Interv Radiol. 2002;13(9 Pt 1):923-8.
14. Issue with no volume
    Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. Clin Orthop. 2002;(401):230-8.
15. No volume or issue
    Outreach: bringing HIV-positive individuals into care. HRSA Careaction. 2002 Jun:1-6.
16. Pagination in roman numerals
    Chadwick R, Schuklenk U. The politics of ethical consensus finding. Bioethics. 2002;16(2):iii-v.
17. Type of article indicated as needed
    Tor M, Turker H. International approaches to the prescription of long-term oxygen therapy [letter]. Eur Respir J. 2002;20(1):242.
    Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. Drug Alcohol Depend. 2002;66 Suppl 1:S105.
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    Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. J Clin Psychiatry. 2002;63(2):169. Retraction of: Feifel D, Moutier CY, Perry W. J Clin Psychiatry. 2000;61(12):909-11.
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    Starkman JS, Wolder CE, Gomelsky A, Scarpero HM, Dmochowski RR. Voiding dysfunction after removal of eroded slings. J Urol. 2006 Dec;176(6 Pt 1):2749. Partial retraction of: Starkman JS, Wolter C, Gomelsky A, Scarpero HM, Dmochowski RR. J Urol. 2006 Sep;176(3):1040-4.
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22. Article republished with corrections
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2. Editor(s), compiler(s) as author
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Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. Proc Natl Acad Sci U S A. Forthcoming 2002.

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2. Journal article on the Internet [Edited 12 May 2009] Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle
3. Optional presentation (omits bracketed phrase that qualifies the journal title abbreviation): Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle
4. Article with document number in place of traditional pagination: Williams JS, Brown SM, Conlin PR. Videos in clinical medicine. Blood-pressure measurement. N Engl J Med. 2009 Jan 29;360(5):e6. PubMed PMID: 19179309.
5. Article with a Digital Object Identifier (DOI): Zhang M, Holman CD, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752. PubMed PMID: 19129307; PubMed Central PMCID: PMC2615549.
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13. Contribution to a blog: Mantone J. Head trauma haunts many, researchers say. 2008 Jan 29 [cited 2009 Feb 13]. In: Wall Street Journal. HEALTH BLOG [Internet]. New York: Dow Jones & Company, Inc. c2008 - . [about 1 screen]. Available from: http://blogs.wsj.com/health/2008/01/29/head-trauma-haunts-many-researchers-say/. Campbell A. Diabetes and alcohol: do the two mix? (Part 2). 2008 Jan 28 [cited 2009 Feb 13]. In: Diabetes Self-Management Blog [Internet]. New York: Diabetes Self-Management. [2006 Aug 14] - . 2 p. Available from:http://www.diabetesselfmanagement.com/blog/Amy_Campbell/Diabetes_and_Alcohol_Do_the_Two_Mix_Part_2 Reider J. Docnotes: Health, Technology, Family Medicine and other observations [Internet]. [place unknown]: Jacob Reider. 1999 - . CRP again ...; 2004 Apr 2 [cited 2009 Feb 13]; [about 1 screen]. Available from:http://www.docnotes.com/2004/04/crp-again.html

Acknowledgments

People who contributed to the work, but do not fit the criteria for authors should be listed in the Acknowledgments, along with their contributions. You must also ensure that anyone named in the acknowledgments agrees to being so named.

Details of the funding sources that have supported the work should be confined to the funding statement. Do not include them in the Acknowledgments.

Funding

This section should describe sources of funding that have supported the work. Please also describe the role of the study sponsor(s), if any, in study design; collection, analysis, and interpretation of data; writing of the paper; and decision to submit it for publication.

Competing and conflicting Interests

It is important to consider this carefully. If you don't declare a conflict of interest and you are subsequently found to have one your paper will lose credibility. Conversely, full disclosure of conflict of interest does not prevent a paper being published but does allow you to be open with your readers. This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, we will print a statement to this effect. For guidelines on what is and what is not conflict of interest have a look at http://grants.nih.gov/grants/policy/coi/

Abbreviations

Please keep abbreviations to a minimum. List all non-standard abbreviations in alphabetical order, along with their expanded form. Define them as well upon first use in the text. Non-standard abbreviations should not be used unless they appear at least three times in the text.

Nomenclature

The use of standardized nomenclature in all fields of science and medicine is an essential step toward the integration and linking of scientific information reported in published literature. We will enforce the use of correct and established nomenclature wherever possible:

We strongly encourage the use of SI units. If you do not use these exclusively, please provide the SI value in parentheses after each value.
Species names should be italicized (e.g., Homo sapiens) and the full genus and species must be written out in full, both in the title of the manuscript and at the first mention of an organism in a paper; after that, the first letter of the genus name, followed by the full species name may be used.
Genes, mutations, genotypes, and alleles should be indicated in italics. Use the recommended name by consulting the appropriate genetic nomenclature database, e.g., HUGO for human genes. It is sometimes advisable to indicate the synonyms for the gene the first time it appears in the text. Gene prefixes such as those used for oncogenes or cellular localization should be shown in roman: v-fes, c-MYC, etc.
The Recommended International Non-Proprietary Name (rINN) of drugs should be provided.
Accession Numbers
All appropriate datasets, images, and information should be deposited in public resources. Please provide the relevant accession numbers (and version numbers, if appropriate). Accession numbers should be provided in parentheses after the entity on first use. Suggested databases include, but are not limited to:

ArrayExpress
BioModels Database
Database of Interacting Proteins
DNA Data Bank of Japan [DDBJ]
EMBL Nucleotide Sequence Database
GenBank
Gene Expression Omnibus [GEO]
Protein Data Bank
UniProtKB/Swiss-Prot
ClinicalTrials.gov
In addition, as much as possible, please provide accession numbers or identifiers for all entities such as genes, proteins, mutants, diseases, etc., for which there is an entry in a public database, for example:

Ensembl

Entrez Gene
FlyBase
InterPro
Mouse Genome Database (MGD)
Online Mendelian Inheritance in Man (OMIM)
Providing accession numbers allows linking to and from established databases and integrates your article with a broader collection of scientific information.

Figures

If the article is accepted for publication, the author will be asked to supply high-resolution, print-ready versions of the figures. Please ensure that the files conform to our Guidelines for Figure and Table Preparation when preparing your figures for production. After acceptance, authors will also be asked to provide an attractive image to highlight their paper online. Figures may be published under a Creative Commons Attribution License, which allows them to be freely used, distributed, and built upon as long as proper attribution is given. Please do not submit any figures that have been previously copyrighted unless you have express written permission from the copyright holder to publish under the CCAL license.

Figure Legends

The aim of the figure legend should be to describe the key messages of the figure, but the figure should also be discussed in the text. An enlarged version of the figure and its full legend will often be viewed in a separate window online, and it should be possible for a reader to understand the figure without switching back and forth between this window and the relevant parts of the text. Each legend should have a concise title of no more than 15 words. The legend itself should be succinct, while still explaining all symbols and abbreviations. Avoid lengthy descriptions of methods.

Virtual Slides

Authors must include virtual slides into their manuscripts when including microscopic preparations. These will be administered by DiagnomX, scanned and hosted by Huron Technologies International, Inc, Canada, Leica Microsystems, Germany, or Motic Medical Diagnostic Systems, China. The slides will be displayed with an easy to use viewing tool and an individual image data bank for your own use. If you wish to include virtual slides in your manuscript please indicate this in the "Comments to Editor" field on submission form.

Tables

All tables should have a concise title. Footnotes can be used to explain abbreviations. Citations should be indicated using the same style as outlined above. Tables occupying more than one printed page should be avoided, if possible. Larger tables can be published as online supporting information. Tables must be cell-based; do not use picture elements, text boxes, tabs, or returns in tables. Please ensure that the files conform to our Guidelines for Figure and Table Preparation when preparing your tables for production.
Requirements for figures and tables
1) When you submit an article; tables and figures must be submitted as separate files

2) Tables must be in Word.doc format

3) Line Graphs should be in or tif or eps formats, and resolution of 900-1200 dpi. If you are unsure about this, please send us the graph in Microsoft excel format and we will convert it into eps or tif formats.

4) Photographs containing no text must be in jpg or tif formats with resolution of 500+ dpi. If you do not have tif or eps, please submit as jpg.

5) Images which contain a combination of text and picture elements must be jpg or tif or eps formats with resolution of 500-1200 dpi. If you do not have tif or eps, please submit as jpg.

**** Generally, we will NOT accept any images with resolution below 300 dpi. You must submit at least in jpg format, that way we can change it into any other format accordingly.

**** Please note that all images must be big (greater than the intended size) and of high resolution.

For more information regarding the image quality requirements, please visit:http://www.ncbi.nlm.nih.gov/pmc/about/PMC_Filespec.html#Image_File_Requirements

Please note that we will be strictly enforcing these conditions and files which fail to conform to these requirements will not be considered for publication.

Multimedia Files and Supporting Information

We encourage authors to submit essential supporting files and multimedia files along with their manuscripts. All supporting material will be subject to peer review, and should be smaller than 10 MB in size because of the difficulties that some users will experience in loading or downloading files of a greater size. If your material weights more than 10 MB, please provide it by email: info@imed.pub

Supporting files should fall into one of the following categories: Dataset, Figure, Table, Text, Protocol, Audio, or Video. All supporting information should be referred to in the manuscript with a leading capital S (e.g., Figure S4 for the fourth supporting information figure). Titles (and, if desired, legends) for all supporting information files should be listed in the manuscript under the heading "Supporting Information."

Supporting files may be submitted in a variety of formats, but should be publication-ready, as these files are not copyedited. All video files should be submitted as AVI or Quicktime files.

Assistance

Any other feature not stated in this guidelines should follow the Uniform Requirement for Manuscriptsof the ICMJE. You can also read more at info for authors in iMedPub Journals or contact us at info@imed.pub

ANEXO II

Normas para publicação na Revista Neurobiologia

Normas para publicação na Revista Neurobiologia

Forma dos artigos

A revista **NEUROBIOLOGIA** possui sua própria formatação, baseada no modelo padrão da área de saúde, que é o VANCOUVER, cuja característica principal é que as referências são organizadas por ordem de citação e não por ordem alfabética. Assim, em vez de aparecer o (s) sobrenome (s) do (s) autor (es) no texto, os autores devem colocar a numeração de forma sobrescrita, correspondendo a ordem que foi citada no texto.

Os autores devem submeter o original em processador de Word, fonte 12 (Arial). O texto deve conter, nesta ordem:

1) **Apresentação (página de rosto):**

a) Título sintético e preciso, com até 100 caracteres. Deve ser centralizado, em **negrito** e em espaço simples. O título deve ser sugestivo, chamando a atenção para o conteúdo e não se restringindo a um aspecto estritamente descritivo. A não ser em manuscritos referentes a aspectos particulares de uma região não passíveis de extrapolação para a população geral, deve ser evitada, no título, a descrição da região de procedência do estudo.

b) Autor: nome e sobrenome, este como desejado para indexação;

c) Informações complementares: nome da instituição em que foi feito o estudo, cidade e país; grau e cargo do autor; declaração de conflito de interesses; financiadora; endereço postal e eletrônico para correspondência.

2) **Resumo:**

a) Artigos Originais, Artigos de Revisão e Notas Históricas: até 150 palavras em letra Arial no tamanho 10 e com espaçamento simples, contendo uma pequena introdução, objetivo, metodologia (sujeitos avaliados, instrumentos de avaliação, tratamento estatístico), resultados e conclusão;

b) Cartas e Opiniões não têm Resumo.

3) **Resumo e Palavras-Chave**: devem ser colocados, nessa ordem, depois do nome dos autores, antes do texto. Os nomes dos autores em Arial, tamanho 10 e em itálico.

4) **Texto:**

a) Artigos Originais: até 3000 palavras, excluindo-se as referências, contendo: introdução e objetivo; método (sujeitos e procedimentos, referência explícita quanto ao cumprimento das normas éticas aplicáveis, incluindo o nome da Comissão de Ética que aprovou o estudo e o Consentimento no caso de trabalhos com seres humanos); resultados; discussão; agradecimentos; referências;

b) Artigos de Revisão: até 5000 palavras, sem contar as referências, incluindo análise de dados de outros autores ou metanálise, avaliação crítica dos dados da literatura e considerações baseadas em sua experiência pessoal;

c) Notas Históricas: até 1000 palavras, excluindo-se as referências;

d) Cartas: até 500 palavras, excluindo-se as referências;

e) Opiniões: até 400 palavras;

f) Resumos de Teses: até 200 palavras.

5) **Tabelas:**

a) Artigos e Artigos de Revisão: até 5, apresentadas em páginas separadas, constando: número de ordem, título e legenda. Não usar barras para separar linhas ou colunas;

b) Cartas e notas históricas: até 2, com formato semelhante ao descrito para os artigos.

6) **Ilustrações:**

a) Artigos e Artigos de Revisão: até 3, gráficos ou fotos, de boa qualidade, com legendas em páginas separadas; reproduções de ilustrações publicadas: anexar autorização da publicadora e do autor;

b) Cartas e Notas Históricas: até 2, com formato semelhante ao descrito para os artigos;

7) **Referências:**

a) Artigos Originais: até 30, restritas àquelas essenciais ao conteúdo do artigo;

b) Artigos de Revisão: até 60;

c) notas históricas: até 10;

d) Cartas e Opiniões: até 5.

As referências devem:

1) Ser numeradas (VANCOUVER) na ordem consecutiva de sua citação ao longo do texto;

2) Incluir todos os autores quando até 6; quando 7 ou mais, listar os 3 primeiros, seguidos de "*et al*.". Sempre que aparecer qualquer termo em latim ou em outro idioma que não seja o português, deve aparecer em *itálico*.

Modo de fazer a citação:

a) Artigos: Autor (es). Título. Periódico ano; volume: páginas inicial-final (com todos os dígitos);
b) Livros: Autor (es) ou editor (es). Título. Edição, se não for a primeira. Tradutor (es), se for o caso. Cidade em que foi publicado: publicadora, ano: páginas inicial-final;
c) Capítulos de livros: Autor (es). Título. Editor (es) do livro e demais dados sobre este, conforme o item anterior;
d) Resumos: Autor (es). Título, seguido de (Abstract). Periódico ano; volume (Suplemento e seu número, se for o caso): página(s). Quando não publicado em periódico: Título da publicação. Cidade em que foi publicada: publicadora, ano, página(s);
e) Livro ou texto on-line: autor (es). Título. Disponível em: www ... (nome do site). Acessado em (mês, dia e ano);
f) Comunicações pessoais só devem ser mencionadas no texto, entre parênteses. As referências que constam dos artigos publicados neste número servem para orientação.

ANEXO III

Normas para publicação na Revista Anatomical Record

Normas para Publicação na Revista Anatomical Record

FORM

The manuscript should have uniform style according to ***The Anatomical Record***, as detailed below. It should be written in English and be as concise as possible, without omitting relevant results. Literature surveys, overly detailed methods, or extensive bibliographies will not be published.
Supplemental material will be published electronically by ***The Anatomical Record***. However, supplemental material is limited to video clips, 3-D files, sound files, and/or description of detailed methods. Not permitted as supplementary material is primary data (results), such as digital images, schemas, or data tables. Primary data are to be included as part of the manuscript files so that reviewers can evaluate the data. The editorial office will look at uploaded files and if digital image files, schema files, or data table files are uploaded as supplemental material, the editorial office will contact the corresponding author to correct the submission. Review will be delayed until the correction is made to the uploaded submission.
Text should be supplied in a format compatible with Microsoft Word for Windows. Mac users are asked to save their files with their appropriate file extension (i.e., .doc, .xls, .tif, .eps, etc.). For example, when saving a Word document on a Mac, please add a suffix of ".doc". **ScholarOne Manuscripts (formerly known as Manuscript Central) does NOT accept .pdf files**.
Abbreviations and style of references are contained in the current edition of the CBE style manual (sixth edition, 1994, Council of Biology Editors, Inc., Suite 230 N. Michigan Ave., Chicago, IL 60601). Spelling reference is to the current edition of Webster's International Dictionary. In items of nomenclature, this journal adheres to the principles specified in Nomina Anatomica, Nomina Embryologica, Nomina Anatomica Veterinaria, and Nomina Anatomica Avium, where appropriate.

Manuscripts should be subdivided into the following sequence:

Title Page
Abstract
Text
Acknowledgments
Literature Cited
Footnotes
Tables
Figure Legends

Each subdivision should start on a new page.

Title page: The first page of the manuscript should include:
Title of paper
Full name of author(s)
Institutional affiliation and complete address
Telephone and facsimile numbers and e-mail address of the corresponding author
Running title not to exceed 45 letters and spaces
Individual and address to whom correspondence concerning manuscript should be sent
All grant information in the following format: Grant sponsor(s): _____; Grant number(s): _____.

Abstract: Submit an abstract of 250 words or less that will serve in lieu of a concluding summary. The abstract must be written in complete sentences. It should concisely state the significant findings without reference to the rest of the paper. Append three to eight key words at the end of the abstract for the purposes of citing your work by the secondary services.
Text: This is divided into an Introduction, Materials and Methods, Results, and Discussion sections.
Literature Cited:
Text references to literature should be arranged chronologically by author's name followed by year of publication:

. . . studies by Gheerbrandt et al., (2005) reveal
. . . studies by Geisler and Uhen (2005) shown

. . . a recent report (Buchholtz, 2007)
. . . (Uhen, 2007)

When references are made to more than one paper by the same author, published in the same year, they are to be designated in the text as (Kelley, 1970a,b) and in the literature list as follows:

Kelley RO. 1970a. An electron microscopic study of mesenchyme during development of interdigital spaces in man. Anat Rec 168:43-54.
Kelley RO. 1970b. Fine structure of apical, digital and interdigital cells during limb morphogenesis in man. In: Proceedings of the VIIth International Congress of Electron Microscopy. Vol. III: p 381-382.

Literature Cited is to be arranged alphabetically in the following style: Author's name (or names), year of publication, complete title, volume, and inclusive pages.

Journal:
Bartsiokas A. 2002. Hominid cranial bone structure: a histological study of Omo 1 specimens from Ethiopia using different microscopic techniques. Anat Rec 267:52-59.
Bräuer G, Collard M, Stringer C. 2004. On the reliability of recent tests of the Out of Africa hypothesis for modern human origins. Anat Rec 279:701-707.
Broadfield DC, Holloway RL, Mowbray K, Silvers A, Yuan MS, Márquez M. 2001. Endocast of Sambungmacan 3 (Sm 3): a new Homo erectus from Indonesia. Anat Rec 262:369-379.
Bruner E, Manzi G. 2005. CT-based description and phyletic evaluation of the archaic human calvarium from Ceprano, Ital. Anat Rec 285:643-657.
Bush EC, Simons EL, Allman JM. 2004. High-resolution computed tomography study of the cranium of a fossil anthropoid primate, Paraphithecus grangeri: new insights into the evolutionary history of primate sensory systems. Anat Rec 281:1083-1087.
Martin RD, MacLarnon AM, Phillips JL, Dobyns WB. 2006. The Flores hominid: new species or microcephalic dwarf? Anat Rec 288:1123-1145.

Book Chapter:
Depew MJ, Tucker AS, Sharpe PT. 2002. Craniofacial development. In: Rossant J, Tam PPL, editors. Mouse Development: Patterning, Morphogenesis and Organogenesis. San Diego: Academic Press. p 421-498.
Book:
Sternberger LA. 1986. Immunocytochemistry. 3rd ed. New York: John Wiley & Sons.
Footnotes: Number footnotes to the text consecutively. The corresponding reference numbers must be clearly indicated in the text. Additional references to the identical footnote must be numbered with the next consecutive number, for example:
[1] Material used for this experiment was . . .
[2] provided by . . .
[3] See footnote 2, page . . .
Type table footnotes directly beneath the table and number them 1, 2, 3 etc. They must not be numbered in sequence with text footnotes.

Tables: All tables must be cited in the text and have titles. Table titles should be complete but brief. Information other than that defining the data should be presented as footnotes. Since tabular matter is expensive to reproduce, it should be simple and uncomplicated with as few vertical and horizontal rules as possible.
Figure legends: All figures must be cited in the text and must have legends. Number figures, including charts and graphs, consecutively throughout the text. Give text references to figures only in terms of the figure number. Whenever possible, integrate figures into the text. Group figures to fit a single page with their appropriate legend. References to relevant text passages can often reduce the length of legends and avoid redundancy.
Abbreviations: Spell out all nonstandard abbreviations the first time used. Abbreviations for all figures should be listed alphabetically and placed before the first figure in which they are mentioned, e.g.,

AchE	Acetylcholinesterase
CP	Cortical Plate
Smc	Primary somatosensory cortex

V Ventral

Digital Illustrations: ***The Anatomical Record*** is known for its free-of-charge publication of high-quality figures. To maintain this level of quality, it is necessary to require images to be submitted and processed with this goal in mind. Therefore, when preparing digital art, please submit figures in separte .tif or .eps file formats, with the following attributes:

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- 300 DPI/PPI for picture-only (without text of any kind) figure files
- 600 DPI/PPI for figures containing pictures and lie elements (i.e., text labels, thin lines, arrows, etc.)
- 1200 DPI/PPI for black and white images such as line drawings, graphs, or charts

Scaling, cropping, and rotating should be performed in the originating application. To ensure that your figures will not be too large to upload, be sure to adjust the height and width to approximately 2500 pixels. If the figure(s) does not meet the specifications shown above (including not exceeding the maximum size of 2500 pixels), please use graphics software (e.g., Adobe Photoshop or Illustrator) to modify the figure(s).

ATTENTION AUTHORS: Please verify that figure files meet the printer's specifications for format and resolution, at the time that you submit the original version of your manuscript. **Note that .tif (or .eps) file formats for figures (black and white, color, and grayscale) is recommended.** We recommend creating your graphics, with all fonts and scale bars included, using Photoshop, Illustrator, or Freehand and then uploading the figure files into ScholarOne Manuscripts (formerly known as Manuscript Central). File formats that are NOT acceptable are JPG/JPEG, GIF, ONG, PCX, PNG, XBM, Word, and Excel. **For further guidance on preparing digital figure files, authors are encouraged to visit http://cjs.cadmus.com/da/applications.asp** . Figure files that do not conform to the required format and resolution will delay review of your manuscript, because the editorial office will return the files to you for correction before sending your manuscript to reviewers.

Cover Illustrations: Authors are encouraged to submit CMYK color figures for consideration as cover illustrations. These figures must be submitted with the manuscript, preferably sized to 21 x 26 cm, with 600 DPI/PPI resolution.

Care and Use of Experimental Animals: ***The Anatomical Record*** and the American Association of Anatomists require that all studies involving experimental animals be conducted in a humane manner and in accordance with all local, state and federal guidelines for the care and utilization of laboratory animals. Husbandry of the animals must meet the NIH Guidelines for the Care and Use of Laboratory Animals. Each manuscript must include details of the a) food and water regimen, b) light cycles, c) appropriate tranquilizers, analgesics, anesthetics, and care performed in association with all surgical procedures, d) manner by which the animals were euthanized, including drugs and their dosages, and e) written assurance that an Institutional Animal Care and Use Committee (or equivalent) approved the protocol.

Protection of Human Subjects: ***The Anatomical Record*** and the American Association of Anatomists also require that all studies involving human subject adhere to the principles of the Declaration of Helsinki or research in Human Beings. Each manuscript must include details of the a) number of subjects, b) age, c) gender, d) women, children and other minorities, e) inclusion and exclusion criteria, and f) written assurance that an Institutional Review Board (or equivalent) approved the protocol.

AAA Guidelines for Research Involving Human Subjects and Vertebrate Animals: The authors signify by submission of their manuscript that research involving use of human subjects—including research for educational studies— has been conducted according to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, unless regulated by more restrictive state or local laws. Research involving vertebrate animals must adhere to AAA's Guiding Principles in the Care and Use of Animals. For investigations involving human subjects or vertebrate animals, a statement of protocol approval from an Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC) or its equivalent, respectively, must be included in the Methods section of the paper. Editors/Associate Editors are expected to refuse papers in which evidence of adherence to these principles is not stated explicitly.

MISCELLANEOUS

- Do not hyphenate words at the end of the lines.
- Corrections to the manuscript should be typed or printed legibly in ink.
- Do not begin sentences with abbreviations.
- Spell out the word Figure in the text except when it appears in parentheses: Figure 2, (Figs. 4-6).

- Always spell out numbers when they stand as the first word in a sentence, abbreviations cannot follow such numbers. Numbers indicating time, weight and measurements are to be in Arabic numerals when followed by abbreviations (e.g., 2mm; 1sec; 3ml). In general, write out the numbers one to ten in the text. All higher numbers should be given as numerals.
- The metric system should be used for all measurements, weights, etc.
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- It is the current policy to underwrite all normal black-and-white tabular and illustration costs.

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ANEXO IV

Normas para publicação na Revista Perspectivas Médicas

Normas para Publicação na Revista Perspectivas Médicas

Periódico científico oficial da Faculdade de Medicina de Jundiaí, a Revista Perspectivas Médicas tem como objetivo a apresentação de trabalhos de qualidade na área experimental básica e das áreas de saúde.

Os trabalhos poderão ser originais, revisões, comunicações curtas, relatos de caso, cartas ao editor e outras. The Perpectivas Médicas (Perspect. Med.) is the official Journal of the Jundiaí Medical School, Jundiaí, São Paulo, Brazil. Its main objective is to contribute for development of basic sciences and clinical sciences by publishing high-quality scientific articles produced by researchers all over the world. The works will be able to be original papers, revisions, short communications, accounts of case, letters to the editor and other.

Os trabalhos devem ser encaminhados ao Corpo Editorial preferencialmente na forma eletrônica no item submissão, após conferir todas as normas editoriais através do endereço: http://www.fmj.br/revista_online.asp ou para o endereço abaixo com cópia em CD: Corpo Editorial da Revista Perspectivas Médicas - Rua Francisco Telles, 250, Bairro Vila Arens, Jundiaí, São Paulo, CEP: 13202-550. Tel.: (11) 4587-1095. ou pelo e-mail: perspectivasmedicas@fmj.br Princípios Gerais: As normas deverão ser obedecidas com rigor para que o trabalho seja encaminhado para avaliação com vistas à sua publicação. Os trabalhos devem ser inéditos, escritos preferencialmente em português, podendo ser aceitos também em espanhol ou inglês (se interessar os autores podem enviar além da submissão on-line do artigo em português, uma versão completa do mesmo em idioma estrangeiro pelo email da revista), todos com aprovação em Comitê de Ética em Pesquisa oficial da Instituição e ainda não publicado de forma completa em outro veículo de divulgação científica. Deve enquadrar-se em uma das diferentes seções, a saber: Artigos Originais: investigação experimental básica ou clínica, contendo título (100 caracteres ou 20 palavras no máximo) e palavras-chave (ambos em português e inglês), autor(es) - máximo de seis, principal titulação e Departamento, resumo (até 250 NORMAS DE PUBLICAÇÃO Página | 2 palavras), abstract, introdução e objetivos, material e métodos, resultados, discussão e conclusões, agradecimentos e referências bibliográficas. Revisões (máximo de 3000 palavras): artigo que sumariza o conhecimento atual em determinado campo e período, devendo incluir título e palavras-chave (ambos em português e inglês), autor(es) e titulação, resumo, abstract, introdução e objetivos, materiais e métodos, resultado da pesquisa, discussão e conclusões, agradecimentos e referências bibliográficas. Comunicações Curtas (máximo de 2000 palavras): artigos práticos, curtos e objetivos incluindo aspectos pessoais, devendo seguir a estrutura de um artigo original. Relatos de Caso (máximo de 2000 palavras): relato de um caso ou de uma série de casos, com justificada razão para publicação como raridade, aspectos inusitados, evolução atípica e/ou nova terapêutica, devendo seguir a estrutura de um artigo original. Cartas ao Editor (máximo de uma lauda): perguntas, respostas, comentários e opiniões a respeito de outros artigos publicados. Outras: destinada a ideias e inovações, terapêutica, normas e rotinas e atualizações, devendo seguir a estrutura de uma comunicação curta. Forma de apresentação dos artigos: Os artigos devem ter a seguinte formatação: folhas de tamanho A4 (210 x 297 mm), em uma coluna, com margens 2,0 cm, em fonte arial 12 e espaço duplo. Todas as páginas devem ser numeradas, em caso da forma impressa, na borda superior direita a partir da identificação. Deve-se observar: -Título em português e inglês com no máximo 100 caracteres, contando os espaços e símbolos. -Nome do autor(es) no máximo de 6 e excepcionalmente até 10 para trabalhos originais de grande monta. -Data, nome dos autores e respectivas assinaturas, quando da forma impressa. - Seção para a qual o trabalho deverá ser avaliado e área do conhecimento. -Palavras-chave e Key words, deverão ser no máximo de 6 e mínimo de 3, em português, espanhol e inglês, em letras minúsculas e usando os descritores em Ciências da Saúde (DeCS) e o Medical Subject Headings (M e S H) acessáveis pelo endereço: http://www.bireme.org.br ou http://decs.bvs.br ou www.nlm.nih.gov. -Nome do autor (es) identificado(s) com asterisco e logo abaixo a(s) titulação(ões) (Exemplo: Professor Doutor entre outros) e local(is) de realização do trabalho (Exemplo: Laboratório, Departamento, Instituto entre outros), bem como cidade, estado e país de origem. -Artigo ainda não publicado. -Relatar conflitos de interesse através do texto seguinte: Conflito de interesse; sim ou não e enviar carta ao e-mail: perspectivasmedicas@fmj.br declarando: Os autores do artigo, assinados abaixo (assinatura eletrônica), intitulado (título completo), declaram não ter nenhum potencial conflito de interesse em relação ao Página | 3 presente artigo, submetido à revista Perspectivas Médicas. Além disso, todos concordam com o conteúdo em questão. - Endereço completo para correspondência, incluindo telefone e e-mail. -Fonte de Financiamento. A partir da primeira página, numerá-las em seqüência no canto superior direito (em caso de submissão na forma impressa) seguindo a estrutura, a saber: -Resumo em português e Abstract em inglês contendo no máximo 250 palavras, fazendo referência à essência do assunto. -Introdução e objetivos, material e métodos, resultados, discussão e conclusões, seguidos de agradecimentos e suporte financeiro e referências bibliográficas. Todas as referências citadas no corpo do texto deverão ser numeradas, entre parênteses e sobrescritas, por ordem de aparecimento no texto. -Tabelas, Figuras e Quadros As tabelas, figuras e quadros devem montadas em slides do Power Point e salvas em formato “apresentação”, versão compatível ao Office 2003 em arquivo único e ser anexado durante a submissão on-line em seu devido lugar e com a respectiva legenda no corpo do texto no final dos resultados, sendo que as mesmas devem ser planejadas para serem apresentadas com tamanho aproximado de 13 cm de largura por 13 cm de altura podendo variar de acordo com o formato do plate. O título ou legenda

em caso de figuras (salvas em jpg) deverão ser colocados sob as figuras e juntos das mesmas, no mesmo arquivo do Power Point, ou como já citado, no corpo do texto no final dos resultados, lembrando de colocar a mesma identificação com a figura (numero arábico). Também deverá constar na legenda da figura o valor da sua ampliação direta (Exemplo: 100x) ou na forma de barra micrométrica. Os títulos das tabelas, gráficos e quadros devem ficar sobre os mesmos, devendo seguir processo semelhante ao das figuras, exemplificado abaixo. Tabela 1: Comparação das médias e variâncias do consumo de proteínas e gorduras em gestantes diabéticas. - Referências Bibliográficas As referências devem ser numeradas e apresentadas seguindo a ordem de inclusão no texto, segundo o estilo Vancouver (http://www.icmje.org). É imprescindível ao enviar seu artigo conferir estas normas, sendo sujeito ao não aceite de artigos sem a devida revisão. As abreviações das revistas devem estar em conformidade com o index medicus/medline (list of journals indexed in índex medicus) ou pelo site http://www.nlm.nih.gov/. É sugerido utilizar revistas indexadas. Todas as referências devem ser digitadas, separadas por vírgula, sem espaço e sobreescritas no corpo do texto e se forem citadas mais de duas referências em seqüência, apenas a primeira e a última devem ser digitadas, sendo separadas por um traço (exemplo: 5-8). É sugerido que as citações de livros, resumos e home page, devam ser evitadas, e juntas não devem ultrapassar a 10% do total das referências. Os editores sugerem também a citação de artigos publicados na revista Perspectivas Médicas. Exemplos Periódicos: Página | 4 - Até seis autores 1.Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7. - Mais de seis 1.Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6. Programas e Órgãos: 1.Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance . Hypertension. 2002;40(5):679-86. Livros: 1.Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4ª ed. St. Louis: Mosby; 2002. Capítulo de Livro: 1.Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editores. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113. Tese 1.Tannouri AJR, Silveira, P G. Campanha de prevenção do AVC: doença carotídea extracerebral na população da grande Florianópolis. [categoria]. Florianópolis: Universidade Federal de Santa Catarina, Curso de Medicina, Departamento de Clínica Médica; 2005. Internet: 1.Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [periódico na Internet]. 2002 Jun [acesso em 2002 Aug 12];102(6):[aproximadamente 3 p.]. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawat ch.htm Julgamento dos Artigos: A avaliação pelos pares (peer review) será realizada em todos os trabalhos submetidos à revista Perspectivas Médicas (Perspect. Med.), tendo que atender às normas para publicação, assim como ao escopo e política editorial. Os trabalhos serão avaliados sob anonimato durante todo o processo de julgamento, cada trabalho será avaliado por dois árbitros da área para análise do mérito científico e da contribuição do estudo, em caso de dúvidas, o editor poderá solicitar a colaboração de um terceiro profissional, expert na área, que conste ou não conste do corpo de revisores. Somente serão encaminhados aos revisores os artigos que estejam rigorosamente de acordo com as normas e elementos básicos à publicação. O aceite será feito na originalidade e contribuição científica para a área. Os assessores farão sugestões gerais sobre o trabalho e decidirão se o mesmo deve ser: aprovado, aprovado com correções menores, aprovado com correções maiores ou recusado. O artigo com correções passará por novo processo de avaliação. Os pareceres serão encaminhados ao editor-chefe ou co-Página | 5 editor, o qual encaminhará resposta aos autores, via eletrônica com o aceite ou correções sugeridas para reformulação e prazo de entrega. Em caso de trabalhos recusados, os autores receberão os pareceres e o referido julgamento. Qualquer caso omisso será resolvido pelos editores, sempre norteados pelos comentários dos assessores. Após a aprovação do trabalho os autores receberão uma carta de aceite do artigo para publicação, sendo este em formato padrão sem custo nenhum aos autores. Direitos Autorais A revista terá todos os direitos, inclusive de tradução em todos os países signatários da Convenção Internacional sobre Direitos Autorais. A reprodução total ou parcial em outros periódicos deverá mencionar a fonte e dependerá da autorização prévia da revista, sendo proibida para fins comerciais. DECLARAÇÃO Enviar ao e-mail: perspectivasmedicas@fmj.br a declaração prévia atrelada à possível publicação: “Declaramos para fins de publicação na revista Perspectivas Médicas, que o presente artigo (Título) não foi e não será publicado em outro veículo de divulgação científica até o final da apreciação pelo Corpo Editorial. Igualmente, declaramos que todas as informações apresentadas no presente artigo estão de acordo com a opinião de todos os autores”. Todos os autores deverão assinar e datar.

ANEXO V

Normas para publicação na Revista Clinical Nutrition & Dietetics (IJCND)

Normas para Publicação na Revista Clinical Nutrition & Dietetics (IJCND)

Manuscript Preparation Guidelines

Manuscript Title

The title should be limited to 30 words or less and should not contain abbreviations. The title should be a brief phrase describing the contents of the paper.

Author's information

Complete names and affiliation of all authors, including contact details of corresponding author (Telephone, Fax and E-mail address*).

Note: The corresponding author should be marked with (*).

Abstract

The abstract should be clearly written, well informative and briefly state the scope of the research. It should be citation free. The Abstract of the manuscript approximately 300 words, must be structured into separate sections and a short description of the study. Abbreviations should be avoided while writing the abstract.

Background: The purpose of the study.

Methods: How the study was performed and statistical tests used.

Results: The main findings.

Conclusion: Brief summary and potential implications**.**

Note: This necessary to keep a focus on title & abstract while writing the manuscript. The title & abstract are the most visible part of a manuscript while inviting a reviewer to evaluate the manuscript and database search. So the title & abstract must be as concise, accurate, informative and readable as possible.

Keywords

A list in alphabetical order not exceeding ten words or short phrases, excluding words used in the title. All the keywords must be included in the content of the manuscript. (E.g. keyword 1, keyword 2, keyword 3...)

Units, symbols and abbreviations

Authors are requested to use the International System of Units for all measurements. The mathematical expressions should contain symbols, no abbreviations are allowed. If the paper contains many symbols, it is recommended that they should be defined as early in the text as possible.

Scientific names should be given the Latin names of each species in full, together with the authority for its name, at first mention in the main text. Subsequently, the genus name may be abbreviated, except at the beginning of a sentence. If there are many species, cite a Flora or checklist which may be consulted for authorities instead of listing them in the text. Do not give authorities for species cited from published references. Give priority to scientific names in the text (with colloquial names in parentheses, if desired).

Background/Introduction

This section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state and should include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field.

Materials & Method

The materials & method section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. The references should be properly cited for the given published procedures. This section may each be divided by subheadings or may be combined. All the material should be shortlisted with required the quantity. If the materials are obtained from any laboratories, it should acknowledge properly in the manuscript. Generic drug names should generally be used, If the materials are obtained from any laboratories, it should acknowledge properly in the manuscript. The instruments or lab used for the experiment and their application details clearly explained.

Results and Discussion

This section may each be divided by subheadings or may be combined. The results section should provide complete details of the experiment that are required to support the conclusion of the study. This section should present clearly but precisely the experimental findings. Only results essential to establish the actual point of the work should be included. Numerical data should be analyzed using appropriate statistical tests. State the results and draw attention in the text to important details shown in tables and figures.

When preparing the discussion section we strongly advise that you pay particular attention to principal findings, a discussion of the validity of the observations, a discussion of the findings in light of other published work dealing with the same or closely related subjects, and a statement of the possible significance of the work.

Conclusions

This should clearly explain the main conclusions of the work highlighting its importance and relevance.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

Author's contributions

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should:

1. The substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.
2. Involvement in drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

Acknowledgements

If any acknowledgments are there, it should be included at the very end of the paper before the references. This section includes acknowledgment of people, grant details, funds, etc.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Funding/Financial Disclosure

The author should describe the sources of funding that have supported their work. Please include relevant grant numbers and the URL of any funder's Web site.

References

All references must be numbered consecutively, in square brackets E.g.: [1] or [1,5-7,28], in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Authors are requested to provide at least one link for each reference.

Note: Only published or accepted manuscripts, datasets, clinical trial registration records and abstracts should be included in the reference list. Papers that have been submitted but not yet accepted should not be cited. Limited citation of unpublished work should be included in the body of the text only as "unpublished data". All "personal communications" citations should be supported by a letter from the relevant authors.

Example of the reference style

Published Papers

1. Layman LC (2013) Clinical genetic testing for Kallmann syndrome. J Clin Endocrinol Metab 98: 1860-1862. (DOI Number)

2. Dai J, Liu B, Ngoi SM, Sun S, Vella AT, et al. (2007) TLR4 hyperresponsiveness via cell surface expression of heat shock protein gp96 potentiates suppressive function of regulatory T cells. J Immunol 178: 3219-3225. (DOI Number)

Accepted/unpublished papers

Format will be same as published papers, instead of the page numbers "In press".

Books

Dormandy T (1999) The White Death: A History of Tuberculosis. (1st edition), New York: New York University Press, USA, 433 p.

Book Chapters

Hu Z (2010) Advanced Visualization, Analysis, and Inference of biological Networks using VisANT. In: Wang E (Ed) Cancer Systems Biology, CRC Press, USA, pp. 323-350.

Conference proceedings

Minuesa G, Erkizia I, Arimany-Nardi C, Pastor-Anglada M, Clotet B, et al. (2012) The Intracellular Disposition of Raltegravir Is Dependent on P-gp (ABCB1) Activity and Is Significantly Reduced in Primary CD4+ P-gphigh T Cells, Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections.

Workshop

Siccardi M, D'Avolio A, Bonora S, Baietto L, Gatti D, et al. (2009) Combined effect of SLCO1B1 521T>C, PXR 63396C>T and ABCB1 3435C>T on the achievement of therapeutic concentrations of unboosted atazanavir, Proceedings of the 10th International Workshop on Clinical Pharmacology of HIV Therapy.

Clinical trial registration

Withes JA (2010) A study of intravesical TMX-101 in subjects with Non-Muscle-Invasive Bladder Cancer, Current Controlled Trials. (DOI Number)

Figures

Upon submission of an article, authors are supposed to include all figures in the manuscript .doc, .docx, TIFF and JPEG format. All figures should be cited in the manuscript in a proper sequence (Figure 1, Figure 2). The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure there should be legends and the figure also be discussed in the text of the manuscript.

Note: The responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

Tables and captions

Tables submitted for publication should be included at the very end of the manuscript file (.doc, .rtf, .tex). Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Supplementary Files

We provide unlimited storage space for the author work, so that the author will not left out with any information to share with the scientific community (No page limit). We encourage authors to provide datasets, tables, Audio, video, or other information as supplementary files to support the research work. The supplementary file size should not more than 10 MB.

Supplementary files can be in any format, and will be downloadable from the final published article as supplied by the author. All supporting material will be subject to peer review.

Supplementary files should be named "*Supplementary file 1*" and so on and should be referenced explicitly by file name within the body of the article.

Supported Supplementary file formats

Additional documentation : PDF (Portable Document Format), PPT (Power Point Presentation)

Animations: SWF (Shockwave Flash)

Video : MP4 (MPEG 4)

Tabular data : XLS, XLSX (Excel Spreadsheet), CSV (Comma separated values)

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ANEXO VI

Normas para publicação na Revista Circulation

Normas para publicação na Revista Circulation

Circulation considers all types of original research articles, including experiments conducted in human subjects, laboratory animals, and in vitro. Specific content areas of interest are as follows: arrhythmia, cardiovascular surgery, congenital heart disease, coronary heart disease, epidemiology, exercise physiology, genetics, health services and outcomes research, heart failure, hypertension, imaging, interventional cardiology, molecular cardiology, pediatric cardiology, pericardial disease, preventive cardiology, stroke, transplantation, valvular heart disease, and vascular medicine.

General Preparation Instructions

1 Maximum Word Length: 7000 words
2 Word count includes title page, abstract, text, references, tables, and figure legends.
3 Maximum Number of References: 50
4 Maximum Number of Figures and Figure Legends: 8
5 Manuscript should be typed double-spaced, including title page, abstract, text, references, figure legends, and tables. Text should only appear on one side of the page. Acceptable formats are Word or WordPerfect.
6 Leave a 1-inch margin on all sides. Do not use justified margins.
7 Cite references, figures, and tables in numeric order. For review, it is preferred if figures are embedded within the main manuscript file, rather than uploaded individually. For publication, see acceptable figure requirements under "Accepted Manuscripts" below.
8 Use SI units of measure. A more conventionally used measurement may follow in parentheses. Make all conversions before manuscript submission.
9 Please provide sex-specific and/or racial/ethnic-specific data when appropriate, in describing the outcomes of epidemiologic analyses or clinical trials, or specifically state that no sex-based or racial/ethnic-based differences were present.
10 Consult the American Medical Association Manual of Style, 10th ed, New York, Oxford University Press, 2007, for style.
11 Manuscripts must conform to the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (http://www.icmje.org/).
12 Assemble the manuscript in this order: Title Page, Abstract, Text, Acknowledgments, Funding Sources, Disclosures, References, Figure Legends, Tables, and Figures.

Title Page

The title page (page 1, do not number) should contain these elements:

1. Full title
2. First author’s surname and short title (not to exceed 50 characters, including spaces)
3. Authors’ names, academic degrees, and affiliations
4. Name and complete address for correspondence (include street name and address as well as post office box, and address for reprints if different from correspondence)
5. Fax number, telephone number, and email address
6. The total word count of the manuscript, including the title page, abstract, text, references, tables, and figures legends
7. The Journal Subject Codes pertaining to the article. Please refer to the Subject Code List.

Abstract and Key Words

- Do not cite references in the abstract
- Limit use of acronyms and abbreviations. Define at first use with acronym or abbreviation in parentheses.
- Be concise (250 words maximum)
- Use the following headings:

1 Background—rationale for study
2 Methods and Results—brief presentation of methods and presentation of significant results; please include sample size

3 Conclusions—succinct statement of data interpretation

4 When applicable, include a fourth heading, "Clinical Trial Registration." Please list the URL, as well as the Unique Identifier, for the publicly accessible website on which the trial is registered.

- Insert 3 to 5 Key Words after abstract. Please refer to the Key Word List .

Text

- Typical main headings include Methods, Results, and Discussion.
- Number pages.
- Abbreviations must be defined at first mention.
- MethodsPlease note that the print version of the Methods and Results should be able to stand alone and should provide sufficient information for the reader to understand the basic methods of the study and to review the fundamental findings in a mechanistic way.
- Experimental animals: State the species, strain, number used, and pertinent descriptive characteristics. When describing surgical procedures, identify the preanesthetic and anesthetic agents used and the amounts, concentrations, routes, and frequency of administration of each. Paralytic agents are not considered acceptable substitutes for anesthetics. For other invasive procedures on animals, report the analgesic or tranquilizing drug used. If none were used, provide justification for exclusion.
- Human studies: Indicate that the study was approved by an institutional review committee and that the subjects gave informed consent.
- Drugs and Devices: In the Methods, the complete name and location of the manufacturer must be supplied for all reagents, equipment, and devices used. In all other instances, the generic rather than trademark names of all drugs and devices.
- Independent Data Access and Analysis: The Editors consider it preferable for investigators to have direct access to the primary data in a clinical trial (raw and derived datasets) when reporting results of the trial. Alternatively, an independent party with an academic affiliation who has access to the primary data may serve as the analyst for the investigators. It is recognized that for logistical reasons these options may not be possible in all instances. At a minimum, the authors should have the ability to query any aspect of the data either directly or through an independent analysis. However, the Editors reserve the right to ask for additional information from the corresponding author regarding measures that were taken to minimize bias and verify the integrity of the primary data and any analyses performed.
- Guidelines for Clinical Trials: In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors (Circulation. 2005;111:1337 and http://content.nejm.org/cgi/content/full/NEJMe078110), all clinical trials in Circulation must be registered in a public trials registry at or before the onset of participant enrollment. This requirement applies to all clinical trials that begin enrollment after July 1, 2005 and applies to all clinical trials, including Phase 1 studies. Any research study that prospectively assigns human participants or groups of humans to one or more health-related intervention(s) to evaluate the effects on health outcomes is considered a clinical trial. The special report, The Proposed Rule for U.S. Clinical Trial Registration and Results Submission published in The New England Journal of Medicine, can be consulted for the guidance. Those who are uncertain whether their trial meets the ICMJE definition of a clinical trial should err on the side of registration if they wish to seek publication.The registry must be accessible to the public at no charge, searchable, open to all prospective registrants, and managed by a not-for-profit organization. The registry must include the following information: a unique identifying number, a statement of the intervention(s), study hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target

number of subjects, funding source, contact information for the principal investigator, and key dates (registration date, start date, and completion date). The registry sponsored by the United States National Library of Medicine (http://www.clinicaltrials.gov) meets these requirements and is recommended by the editors.Other registries are acceptable if they meet these requirements. In addition to http://www.clinicaltrials.gov, the following registries are recommended by the ICMJE:

A http://isrctn.org
B http://www.umin.ac.jp/ctr/index/htm/
C http://www.anzctr.org.au/Default.aspx
D http://www.trialregister.nl/trialreg/index.asp

- In accordance with the ICMJE's recommendation, we will also accept registration of clinical trials in any of the primary registers that participate in the World Health Organization's International Clinical Trial Registry Platform. Primary registers are WHO-selected registers managed by not-for-profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to the WHO. Please note that registration in any WHO partner registers is insufficient. The authors will be requested to provide the exact URL and unique identification number for the trial registration at the time of submission. Since this information will be published, we ask that you include a fourth heading in your abstract: "Clinical Trial Registration Information". Please list the URL, as well as the unique identifier, for the publicly accessible web site on which the trial is registered in this section. Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a flow diagram presenting the enrollment, intervention allocation, follow-up, and data analysis with number of subjects for each (http://www.consort-statement.org/?o=1011). Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomized clinical trial. Results posted in the same clinical trials registry in which the primary registration resides will not be considered prior publication if they are presented in the form of a brief abstract (≤500 words) or a table.
- Guidelines for Meta-Analyses: See "Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting," JAMA. 2000;283:2008-2012.
- Guidelines for Studies on Diagnostic Tests:See "The STARD Statement for Reporting Studies of Diagnostic Accuracy: Explanation and Elaboration," Ann Intern Med. 2003;138:40-44.
- Guidelines for Human Phenotype-Genotype Association or Linkage Studies:

A Reporting issues:

1 Report process for selecting genes and SNPs.
2 Report Hardy-Weinberg statistics or p-values and method of calculating same.
3 Refer to existing public domain websites for the Human Gene Ontology name and the rs number for SNPs.
  - http://www.ncbi.nlm.nih.gov/projects/SNP/
  - http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Snp
4 Describe genotyping methods. If numerous primers have been used, please include them in an online supplement.

B False positive and false negative concerns. Given well-described problems with both false positive and false negative associations, phenotype-genotype association studies should meet some or all of the criteria below:

1 Phenotype is clearly defined, is heritable, and if a quantitative phenotype is reported, reproducibility data are provided.

2 The sample size is adequate to detect a SNP or haplotype with a modest effect. For genotype–trait associations, provide an estimate of the effect size that could be detected with power 0.80 or higher with the allele frequency and sample size reported.

3 Since multiple statistical testing methods are frequently used in genotyping–phenotyping studies, please include specifics of the primary model(s) tested. Nonessential secondary models may be published as electronic data supplements. Clinically relevant confounders should be included in multivariable models or residuals.

C Review criteria for human linkage studies. Manuscripts should include the following:

1 Identifying plausible candidate genes under the linkage peak.

2 Follow-up fine mapping to narrow the region of linkage, and/or genotyping some of the candidate genes under the linkage peak.

3 Replication data from another sample.

• Guidelines for Genomic and Proteomic Studies:

A Preparation of Data Submitted: Data should follow the MIAME checklist (for more information see http://www.mged.org/Workgroups/MIAME/miame_checklist.html).

B Accessibility of Data: Authors of papers that include genomic, proteomic, or other high-throughput data are required to make their data easily accessible for the reviewers and the editors during the review process.

1 You may submit your data to the NCBI gene expression and hybridization array data repository (GEO, http://www.ncbi.nlm.nih.gov/geo/) and provide the GEO accession number; or

2 You may provide a link to a secure or publicly accessible website which hosts the data. Prior to publication, the data must be submitted and an accession number obtained. Access to the information in the database must be available at the time of publication. GEO has a web-based submission route, suitable for a small number of samples, or a batch submission tool (called SOFT). GEO is accessible from http://www.ncbi.nlm.nih.gov/geo/. The submission FAQ is available at http://www.ncbi.nlm.nih.gov/projects/geo/info/faq.html.

• Guidelines for Proteins and Nucleic Acid Sequences:

• Newly reported nucleotide or protein sequences must be deposited in GenBank or EMBL databases, and an accession number must be obtained. Access to the information in the database must be available at the time of publication. Authors are responsible for arranging release of data at the time of publication. The authors must also provide a statement in the manuscript that this sequence has been scanned against the database and all sequences with significant relatedness to the new sequence identified (and their accession numbers included in the text of the manuscript).

A GenBank

B GenBank Submissions

C National Center for Biotechnology Information

D 8600 Rockville Pike, Building 38A

E Room 8N-805

F Bethesda, MD 20894

G Tel: (301) 496-2475

H On the web at: http://www.ncbi.nlm.nih.gov/Genbank/index.html

I EMBL Nucleotide Sequence Submissions

J European Bioinformatics Institute

K Hinxton Hall
L Hinxton, Cambridge CB10 1SD, UK
M Tel.: 44-1223-494401; Fax: 44-1223-494472
N e-mail: support@ebi.ac.uk
O On the web at: http://www.ebi.ac.uk
P DNA Data Bank of Japan
Q Center for Information Biology
R National Institute of Genetics
S Mishima, Shizuoka, 411, Japan
T Tel.: 81-559-81-6853; Fax: 81-559-81-6849
U On the web at: http://www.ddbj.nig.ac.jp

- Submission to any data bank is sufficient to ensure entry in all.

Acknowledgments

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Funding Sources

- All sources of support for the research should be listed under this heading.
- All grant funding agency abbreviations should be completely spelled out, with the exception of the NIH.

Disclosures

All potential conflicts of interest must be stated within the text of the manuscript, under this heading. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock,membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products. Other areas of real or perceived conflict of interest could include receiving honoraria or consulting fees or receiving grants or funds from such corporations or individuals representing such corporations.

Please state "None" if no conflicts exist.

References

- Accuracy of reference data is the responsibility of the author.
- Verify all references against original sources.
- List all authors for each reference; do not use “et al.”
- Example of a good reference:

1 Smith HJ, Allen S, Yu W, Fard S. This is the title. Circulation. 2004;104:276-308.

2 Please note that if you use reference software tools (e.g., EndNote or Reference Manager), they do not always match our style and you may need to manually correct your references.

- Cite references in numeric order according to first mention in the text. In the text, ensure accuracy of spelling and details of publication, i.e., the text citation should match the reference information.
- Personal communications, unpublished observations, and submitted manuscripts are not legitimate references. They must be cited in the text only (not in the reference list) as follows: author name, degree(s) held, unpublished data, year.

- Abstracts may be cited only if they are the sole source and must be identified in the reference as "Abstract."
- References must be from a full-length publication in a peer-reviewed journal.
- "In-press" citations must have been accepted for publication and the name of the journal or book publisher must be included.

Figures

8) Figure parts should be clearly labeled. Letters and locants must be uniform in size and style within each figure, and when possible, between figures. (The font size must be 10 point or higher.)
9) Avoid headings on the figure. Heading information should appear in the figure legend.
10) Line art should not contain hair lines, which are hard to reproduce.
11) Supply a scale bar with photomicrographs.
12) Provide double-spaced copy for figure legends on a separate page.
13) Symbols and abbreviations must be defined in the figure or its legend.
14) Limit white space between the panel and panel label.
15) Figures should be sized as close as possible to their final print size. Please note that very few figures qualify for a 2-column format.

Tables

6) Begin each table on a separate page, double-spaced. Please remember that tables prepared with Excel are not accepted unless embedded within your text document.
7) The table number should be Arabic, followed by a period and brief title.
8) Use same size type as in text.
9) Supply a brief heading for each column.
10) Indicate footnotes in this order: *, †, ‡, §, ||, #, **.
11) Do not use vertical lines between columns. Use horizontal lines above and below the column headings and at the bottom of the table only. Use extra space to delineate sections within the table.
12) Abbreviations used in the table must be defined in a footnote to the table.

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Online Data Supplements are encouraged as an enhancement to the print Methods section. This optional section provides an opportunity to present supporting materials to the manuscript. Please note that all supplements undergo peer review and must be submitted with the original submission of the manuscript.

Online Data Supplements can consist of the following:

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6) Additional Figures
7) Additional Tables
8) Video Files

If citations are made in an Online Data Supplement, the supplement must contain its own Reference Section, with references numbered sequentially beginning with the number 1. Please try to keep the individual file size to 10 MB or less to facilitate easier downloading for readers.

A combined PDF of your supplemental data must be provided. The first page of this PDF should include the heading, "SUPPLEMENTAL MATERIAL." Please note that this single PDF would include all of the supplemental material related to your manuscript, except for the Video or Movie files. The supplemental material to be included in this PDF is as follows: Supplemental Methods, Supplemental Tables, Supplemental Figures and Figure Legends, and Supplemental References. Lastly, the legends for the Video files should also be included in this PDF. Please upload this PDF to your author area.

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Correspondence

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5.1. Response to Reviewers
5.2. Tracked Changes version of the manuscript
5.3. Clinical Perspective Summary

3) All Author Information, including

1. First and Last Names
2. Affiliations
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The four steps of the submission process are: Files, Manuscript Information, Validate, and Submit. The four steps each contain sub-steps that can be accessed by clicking on their respective tabs. Navigating through this "Tab View" will save any entered information each time a new tab is clicked (or the boxes "Save and Continue" and "Next" are clicked). Each step and sub-step is listed below:

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ANEXO VII

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Carta do Doutorado Sanduíche

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DECLARAÇÃO DE EX-BOLSISTA

Brasília, 19 de Maio de 2015,

Declaramos, para os devidos fins, que o(a) interessado(a) abaixo, foi bolsista da Capes e realizou Doutorado Sanduíche/PDSE, no exterior, conforme os dados abaixo:

BOLSISTA: PATRICIA BOZZETTO AMBROSI
Nº PROCESSO: 1873/13-0
PERÍODO DA BOLSA: 05/2013 a 04/2014
INSTITUIÇÃO: UNIVERSITÉ PARIS DIDEROT - PARIS VII
PAÍS: FRANÇA
ÁREA: BIOTECNOLOGIA.

Atenciosamente,

ADI BALBINOT JÚNIOR
Coordenador-Geral de Monitoramento e Acompanhamento de Resultados

ANEXO VIII

Carta de Utilização de Dados

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Pr Jacques MORET PROFESSEUR DES UNIVERSITÉS --- PRATICIEN HOSPITALIER

ADJOINT
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Dr Léon IKKA
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CHEF DE CLINIQUE
Dr Jildaz CAROFF

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Madame Pascale LABLE TEL: 01 40 87 52 37
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Madame Angèle HODEBOURG TEL: 01 40 87 53 13

LETTRE DU CONSENTEMENT AVEC AUTORISATION POUR L'UTILISATION DES DONNÉES

Je soussigné, le Professeur Jacques MORET, chef du service de Neuroradiologie Interventionnelle, certifie autoriser le chercheur Docteur PATRICIA BOZZETTO AMBROSI à effectuer son projet de recherche: “Morphologie et hémodynamique des anévrysmes du siphon carotidien” sur la base de données de mon Service dans le cadre du stage doctorale de sa thèse de Sciences à la Université Fédérale de Pernambuco au Brésil, qui est sous la supervision du Pr. MARCELO VALENÇA. Ces données pourront être utilisées par le Docteur PATRICIA BOZZETTO AMBROSI pour des publications scientifiques.

Ce projet vise à caractériser les aspects anatomo-radiologiques, morphologiques et hémodynamiques des anévrysmes du siphon carotidien ainsi que les facteurs anatomiques liés à l'apparition de ces anévrysmes.

Cette autorisation est subordonnée au respect des exigences du décret 466/12 et ses annexes, le chercheur s'engage à utiliser les données personnelles des sujets de recherche, exclusivement à des fins scientifiques, tout en assurant la confidentialité et la non-utilisation des informations au détriment des individus et / ou des communautés.

Avant de commencer la collecte de données, le chercheur présente à l'institution l'avis, dûment approuvé, émis par le comité d'éthique de la recherche avec des sujets humains, accrédités au CEP de système/ CONEP.

Paris, le 7 juillet 2015

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Hôpital Beaujon
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