

## Invasive treatment of asymptomatic extracranial carotid stenosis. A conceptual approach

*Tratamento invasivo da estenose assintomática da carótida extracraniana.  
Uma abordagem conceitual*

Ricardo Cesar Rocha Moreira<sup>1</sup>

In the second decade of the XXI century, a vast body of knowledge (>4,800 articles listed in Medline) has been accumulated on all aspects of extracranial carotid disease. Out of this wealth of information, scientific Societies all over the world have proposed guidelines for the management of cerebrovascular disease.<sup>1-4</sup>

Current guidelines have reached nearly a consensus on the role of invasive treatment in symptomatic patients with extracranial carotid stenosis.<sup>5</sup> However, in asymptomatic patients, there is much uncertainty as to whether invasive treatments - carotid endarterectomy (CEA) and carotid angioplasty with stenting (CAS) - reduce stroke risk. The benefit of adding an invasive treatment to Best Medical Therapy (BMT) is currently the most controversial issue in the management of patients with asymptomatic extracranial carotid stenosis.<sup>6</sup>

The author proposes an alternate approach to the issue of which patients with asymptomatic carotid disease can benefit from invasive treatment. The knowledge accumulated in over a century of studies can be summarized in a few concepts, from which a framework can be formed.<sup>7</sup> The conceptual framework can be used as a provisional tool to make clinical decisions, when guidelines are not clear or applicable to an individual patient.

The first concept can be stated as follows: “the vast majority of individuals with extracranial carotid lesions are asymptomatic and will remain asymptomatic for life.” This concept is based on over 50 long-term prospective studies that followed patients with carotid plaques on medical treatment.<sup>5,8</sup> Those studies have shown that patients with asymptomatic carotid atherosclerosis have a much higher risk of ischemic cardiac events and long-term mortality, compared with the population at large.<sup>8</sup> This concept leads to two corollaries: the presence of an asymptomatic carotid plaque is a strong marker of systemic atherosclerosis; and all patients in whom a carotid plaque is detected

should be placed on BTM and followed closely for progression of their atherosclerotic disease.<sup>3,4,8</sup>

The second concept refers to risk: “Patients with asymptomatic carotid atherosclerosis on BMT have a low risk of developing an ischemic cerebral vascular accident (CVA).” A recent meta-analysis of 49 long-term studies showed that the overall risk of ischemic brain events in patients on medical management is below 1% per year of follow-up.<sup>9</sup> Nevertheless, a minority of patients with asymptomatic carotid lesions will develop brain ischemia. The quest for physicians involved in care of patients with asymptomatic carotid atherosclerosis is finding which patients are at higher-than-average risk of developing brain ischemic events.<sup>4-6</sup>

The third concept refers to benefit: “The benefit of invasive treatment of asymptomatic extracranial carotid atherosclerosis is limited to a subgroup of patients with high-risk lesions.” Namely, vulnerable carotid plaques. The characteristics that define a vulnerable plaque include: a large lipid-laden core, a thin fibrous cap, inflammation in and/or around the plaque, vasavosorum neovascularization, and intraplaque hemorrhage.<sup>10</sup> Vulnerable plaques are particularly prone to develop plaque events. The most common events: plaque ulceration, intraplaque hemorrhage and plaque rupture result in extrusion of atheromatous contents into the arterial lumen, causing embolization to the distal arterial bed. Distal embolization from events within a carotid plaque is the main mechanism of brain ischemia, and can present clinically as transient ischemic attack (TIA) and ischemic cerebral vascular accident (CVA).<sup>4,10</sup> The other mechanism of brain ischemia related to the plaque is internal carotid artery occlusion, that can be caused by an plaque event such as hemorrhage or by progression of a plaque to high-degree or subocclusive stenosis, with subsequent thrombosis.<sup>10</sup>

A number of studies have been conducted in asymptomatic carotid patients on BMT in order to

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identify factors that increase the risk of a cerebral ischemic event.<sup>4,11</sup> In those studies, the following clinical or imaging factors have been found to be associated with statistically significant increased risk of late stroke in asymptomatic patients with a 60-99% extracranial carotid stenosis:

- Silent brain infarction on CT scan;
- Progression of degree of stenosis on serial Doppler ultrasonography exams;
- Plaque area in computerized plaque analysis: the larger the plaque, the larger the risk;
- Size of juxta-luminal hypoechoic (or echolucent) area within the carotid plaque;
- Intraplaque hemorrhage on MR imaging;
- Impaired CVR - cerebral vascular reserve - on transcranial ecodoppler;
- Predominantly echolucent plaque on Doppler ultrasonography;
- Spontaneous embolization on transcranial ecodoppler;
- Spontaneous embolization on transcranial ecodoppler, plus echolucent plaque;
- Contralateral carotid occlusion or contralateral clinical cerebral ischemia (TIA or CVA).

Over the next 5 to 10 years, the ongoing prospective studies will provide hard data on the significance of those clinical and imaging risk factors and will probably change current recommendations on the invasive treatment of asymptomatic extracranial carotid stenosis.<sup>12</sup> While this new information is not available, the question “Which patients can benefit of invasive treatment for asymptomatic extracranial carotid stenosis ?” can be answered using the conceptual framework presented above:

1. A carotid atherosclerotic plaque is a strong marker of systemic atherosclerosis. All patients with a significant plaque should be on BMT and followed closely for cardiovascular ischemic events;
2. Invasive treatments - CEA or CAS - should be offered only to asymptomatic patients on BMT whose plaques present with or progress to high-degree/subocclusive stenosis; and to patients in whom clinical or imaging evaluation suggests a vulnerable plaque with high-risk of triggering cerebral ischemia.

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# Tratamento invasivo da estenose assintomática da carótida extracraniana. Uma abordagem conceitual

## *Invasive treatment of asymptomatic extracranial carotid stenosis. A conceptual approach*

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Nesta segunda década do século XXI, um vasto corpo de conhecimento (> 4,800 artigos listados no MEDLINE) já foi acumulado em todos os aspectos da doença da carótida extracraniana. A partir desta riqueza de informação, Sociedades científicas de todo o mundo vêm propondo diretrizes para o manejo da doença cerebrovascular<sup>1-4</sup>.

As diretrizes mais recentes são quase consensuais quanto ao manejo dos pacientes sintomáticos com aterosclerose da carótida extracraniana<sup>5</sup>. Contudo, em pacientes assintomáticos, há muita incerteza se os tratamentos invasivos - endarterectomia da carótida (EAC) e angioplastia da carótida com stent (ACS) - reduzem o risco de isquemia cerebral. O benefício de se indicar um tratamento invasivo além do Tratamento Clínico Otimizado (TCO) é atualmente a questão mais controversa no manejo de pacientes com estenose assintomática da carótida extracraniana<sup>6</sup>.

O autor propõe uma abordagem alternativa para responder à questão de quais são os pacientes com doença carotídea assintomática que podem se beneficiar dos tratamentos invasivos. O conhecimento acumulado ao longo de mais de um século pode ser resumido em uns poucos conceitos, com os quais se pode formar uma estrutura<sup>7</sup>. A estrutura conceitual pode então ser usada como uma ferramenta provisória para a tomada de decisões clínicas, quando diretrizes não são claras ou aplicáveis em um caso em particular.

O primeiro conceito pode ser enunciado da seguinte forma: “a vasta maioria dos indivíduos com estenoses da carótida extracraniana são assintomáticos e vão permanecer assintomáticos por toda a vida”. Este conceito é baseado em mais de 50 estudos prospectivos de longo prazo, que seguiram pacientes com placas significativas de carótida sob tratamento clínico<sup>5,8</sup>. Os estudos mostraram que pacientes com estenoses assintomáticas das carótidas tinham um risco elevado de eventos cardíacos isquêmicos e mortalidade alta a longo prazo, comparados com

a população em geral<sup>8</sup>. Este conceito leva a dois colorários: a presença de uma placa assintomática de carótida é um forte marcador de aterosclerose sistêmica; e todos os pacientes em quem uma placa de carótida é detectada devem ser submetidos a TCO e seguidos de perto para progressão da sua doença aterosclerótica<sup>3,4,8</sup>.

O segundo conceito é referente ao risco: “Pacientes com aterosclerose carotídea assintomática sob TCO têm um risco muito baixo de desenvolver acidente vascular cerebral (AVC) isquêmico”. Uma meta-análise recente de 49 estudos de longo prazo mostra que, no geral, o risco de eventos isquêmicos cerebrais dos pacientes sob tratamento clínico é menos de 1% por ano de seguimento<sup>9</sup>. Mesmo assim, uma minoria dos pacientes com lesões assintomáticas da carótida vão desenvolver isquemia cerebral. A missão dos médicos envolvidos em cuidar de pacientes com estenose assintomática da carótida é descobrir quais pacientes tem risco mais elevado de desenvolver eventos isquêmicos cerebrais<sup>4-6</sup>.

O terceiro conceito se refere a benefício: “O benefício do tratamento invasivo da aterosclerose assintomática de carótida extracraniana se limita a um subgrupo de pacientes com lesões de alto risco”. Especificamente, placas de carótida vulneráveis. As características que definem uma placa vulnerável incluem: um núcleo grande rico em lipídios; uma capa fibrose tênue; inflamação dentro ou ao redor da placa; neovascularização nos vasos vasorum; e hemorragia intraplaca<sup>10</sup>. Placas vulneráveis são particularmente propensas a desenvolver eventos intraplaca. Os eventos mais comuns: ulceração da placa, hemorragia intraplaca e ruptura da placa resultam em extrusão do conteúdo ateromatoso na luz arterial, causando embolização para o leito arterial distal. Embolização distal a partir de eventos intraplaca é o principal mecanismo de isquemia cerebral, e pode se apresentar clinicamente como com ataque isquêmico transitório (AIT) ou com acidente vascular cerebral

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isquêmico (AVC)<sup>4,10</sup>. O outro mecanismo de isquemia cerebral relacionado ao evento intraplaca é oclusão da carótida interna, que pode ser causada por um evento intraplaca, como uma hemorragia, ou por progressão da placa para estenose de alto grau/suboclusiva, com trombose subsequente<sup>10</sup>.

Uma série de estudos foram conduzidos em pacientes assintomáticos sob TCO para tentar identificar fatores que aumentam o risco de um evento isquêmico cerebral<sup>4,11</sup>. Nestes estudos, os seguintes fatores clínicos e de imagem foram associados com aumento estatisticamente significativo do risco de isquemia tardia em pacientes assintomáticos com estenose da carótida de 60-99%:

- Infarto cerebral silencioso à TAC - tomografia computadorizada;
- Progressão do grau de estenose em exames seriados de ecodoppler;
- Área da placa em análise computadorizada (quanto maior a placa, maior o risco);
- Tamanho da área hipoeecóica (ou ecolucente) justaluminar dentro da placa;
- Hemorragia intraplaca na imagem por Ressonância Magnética;
- Reserva vascular cerebral reduzida no ecodoppler transcraniano;
- Placa predominantemente ecolucente no exame de ecodoppler;
- Embolização espontânea no Doppler transcraniano;
- Embolização espontânea no Doppler transcraniano, mais placa ecolucente;
- Oclusão da carótida contralateral ou isquemia cerebral sintomática contralateral.

Nos próximos 5 a 10 anos, os estudos prospectivos em andamento vão gerar dados sólidos quanto ao significado destes fatores clínicos e de imagem, que provavelmente vão mudar as recomendações atuais para o tratamento invasivo da estenose assintomática da carótida extracraniana<sup>12</sup>. Enquanto estas informações novas não estiverem disponíveis, a questão “Quais pacientes podem se beneficiar do tratamento invasivo da estenose assintomática da carótida extracraniana?” pode ser respondida com o uso da estrutura conceitual descrita acima:

1. A placa de ateroma da carótida é um forte marcador de aterosclerose sistêmica. Todos os pacientes com uma placa significativa devem ser colocados

em TCO e seguidos cuidadosamente, pelo alto risco de eventos isquêmicos cardiovasculares;

2. Tratamentos invasivos - EAC ou ACS - devem ser indicados apenas em pacientes assintomáticos que se apresentam com ou progridem para estenoses de alto grau/suboclusivas; e em pacientes nos quais a avaliação clínica e de imagem sugerem uma placa vulnerável, com alto risco de provocar isquemia cerebral.

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