

# The impact of carotid revascularization on cognitive function

## *O impacto da revascularização carotídea sobre a função cognitiva*

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### Abstract

The concept that carotid disease may compromise cognitive function was initially proposed by Fisher in 1951, based on an autopsy case. However, some topics involving cognitive function remain controversial, such as its correlation with carotid obstructive disease. So, the authors of this review evaluate the impact of carotid revascularization on cognitive function and the repercussions of the revascularization technique (carotid stenting vs. endarterectomy) chosen. It was clear from the literature reviewed that carotid stenosis is related to a decline in cognitive function over time. However, controversy still remains over the impact of carotid revascularization on cognitive function. With relation to the technique employed (carotid stenting vs. endarterectomy), the majority of studies found no difference between the two techniques in terms of overall cognitive outcome.

**Keywords:** carotid stenosis; therapy; carotid endarterectomy; cognition.

### Resumo

A noção de que a doença carotídea pode comprometer a função cognitiva foi proposta inicialmente por Fisher, em 1951, baseado em um caso de necropsia. Porém, alguns tópicos envolvendo a função cognitiva permanecem controversos, tais como sua correlação com a doença obstrutiva da carótida. Nesse sentido, os autores desta revisão buscam avaliar o impacto da revascularização carotídea e a repercussão da técnica de revascularização empregada (endarterectomia *versus* angioplastia carotídea) sobre a função cognitiva. A partir da literatura levantada, ficou claro que as estenoses carotídeas estão relacionadas com o declínio cognitivo ao longo do tempo, mas ainda há controvérsia no que se refere ao impacto da revascularização carotídea sobre a função cognitiva. Quanto à técnica empregada (angioplastia *versus* endarterectomia carotídeas), a maioria dos estudos não demonstrou distinção entre as duas técnicas quanto ao desfecho cognitivo geral.

**Palavras-chave:** Estenose das carótidas; terapia; endarterectomia das carótidas; cognição.

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## ■ INTRODUCTION

The concept that carotid disease may compromise cognitive function was initially proposed by Fisher in 1951, based on an autopsy case.<sup>1,2</sup> He postulated that occlusive carotid disease could provoke a state of dementia and proposed restoration of anterograde flow to reverse the condition. This insight contributed to the first carotid reconstruction (1951)<sup>1,3</sup> and later to the first carotid endarterectomy (CEA)<sup>1,4,5</sup> in patients who had suffered a stroke and had internal carotid stenosis, which introduced CEA as an important option for stroke management.<sup>1</sup>

The term Cognitive Function (CF) is used to describe the way in which a person produces and controls their mental and behavioral processes such as thinking, learning, remembering, solving problems and memorizing.<sup>1</sup> The basic distinction between cognitive deficit and neurological deficit is that the second relates to a loss of localized sensory or motor function – such as the ability to move a limb – whereas the first relates to loss of a system, such as the ability to remember new facts. Studies suggest that one in three North Americans experience a stroke, dementia or both at some point during their lives,<sup>6,7</sup> and that 64% of individuals who suffer a cerebrovascular event will develop dementia.<sup>6,8</sup> Among the elderly, the risk of dementia increases fourfold after an ischemic stroke.<sup>6,9</sup>

Studies have clearly shown that people with isolated cognitive deficits are at greater risk of having problems at work, have greater difficulty with day-to-day activities, are dependent on others and are poor drivers.<sup>1,10,11</sup>

However, certain subjects relating to CF remain controversial, including its correlation with obstructive carotid disease. For this reason, the present review was conducted with the object of analyzing the impact of carotid revascularization and the repercussions of which carotid revascularization technique is chosen (CEA vs. carotid artery stenting).

## ■ METHOD

The methodology employed was a bibliographic review, attempting to answer the following questions:

- Does carotid revascularization have an impact on cognitive function?
- Is there a difference between the two different intervention techniques (endarterectomy and carotid stenting)?

Articles were located by searching the PubMed electronic database. A retrospective search was run covering publications from 1951 to 2013 using the following keywords: carotid endarterectomy; carotid

stenting; cognitive changes; cognitive function. Results were restricted to articles published in English.

Articles of interest identified by the initial search strategy were first independently assessed by two of the authors. In order to avoid the risk of excluding any studies that could be important to the review, a consensus meeting was held and then both reviewers chose all the titles they had identified as potentially relevant to the object of study, irrespective of whether or not an abstract was available. Once relevant titles had been selected, the full texts of the articles were acquired and each article was assessed against a protocol covering the following topics: study type, sample, type of intervention used, results observed. All longitudinal, prospective and retrospective articles, meta-analyses and review articles that met the criteria were included. Articles not yet published, comments and editorials, case reports and cross-sectional studies were all excluded. Articles with very similar content were also excluded, giving priority to the first authors to publish on subject and/or those who described larger or more recent samples. The studies were chosen on the basis of the likelihood of their answering the research questions guiding this bibliographic review. On this basis, 189 articles were initially identified and 67 of them were selected and analyzed for this review.

## ■ RESULTS

### **Mechanisms behind cognitive changes after carotid revascularization**

Carotid artery stenosis is recognized as a risk factor for cognitive impairment.<sup>6,12</sup> However, the results of studies involving the effects of revascularization on cognition are controversial.<sup>6,13</sup> If, on one hand, intervention for carotid stenosis should be beneficial because it restores cerebral blood flow,<sup>2,6</sup> on the other hand, one review has suggested that carotid revascularization leads to a decline in cognitive function because of other mechanisms related to the patients operated and the technique employed.<sup>1</sup>

Patient-related factors include prior cerebral injury manifest as stroke, prior silent cortical infarct, prior white matter damage and morphology of atherosclerotic plaques.<sup>1</sup>

Factors related to the technique employed include microembolization, further cerebral microinfarcts, duration of cerebral hypoperfusion and incidence of systemic hypotension during revascularization.<sup>1</sup>

## Silent cerebral microinfarcts and cognitive decline

The Rotterdam study showed that silent infarcts in healthy elderly people, identified by magnetic resonance imaging (MRI), doubled the risk of developing dementia and reduced CF over follow-up.<sup>1,14</sup> These findings were confirmed by other important studies.<sup>15-17</sup>

On the other hand, surgical or catheter manipulation of the aorta during cardiac procedures can cause cerebral injuries secondary to microembolization.<sup>1,18,19</sup> The postoperative cognitive decline observed in these patients has been related to these microemboli.<sup>1,20-22</sup>

Along the same lines, other studies have demonstrated that manipulation of the carotid artery during revascularization can cause atheroembolization with consequent silent cerebral microinfarcts.<sup>1,23-25</sup>

Transcranial Doppler (TCD) can differentiate gaseous from particulate microembolic material during revascularization procedures.<sup>26,27</sup> Gaunt et al.<sup>28</sup> showed that the occurrence of more than ten particulate microemboli during initial dissection for CEA is associated with cognitive decline. Differentiation of the more clinically relevant particulate emboli from gaseous emboli using multifrequency TCD monitoring techniques should therefore be encouraged.<sup>26,28,29</sup>

A study published in 2011 used TCD monitoring to identify approximately 15 microemboli (SD of 22) during CEA; 319.3 (SD of 110.3) during carotid artery stenting (CAS) with a distal filter, and 184.2 (SD of 110.5) during CAS using reverse flow as cerebral protection method. The differences between CEA and both CAS techniques were considered significant. However, the difference between the two CAS techniques was not significant, very probably because of the small number of patients studied (14, 14 and 5, respectively).<sup>30</sup>

In line with these findings, another research group compared asymptomatic patients submitted to CEA or to CAS with distal filtering (20 and 23 patients, respectively) and found a significant difference, with detection of cerebral microinfarcts by diffusion MRI much more frequent when using CAS (21% vs. 0%).<sup>31</sup> Roh et al. compared CEA to CAS,<sup>32</sup> observing that both neurological events and new lesions seen on MRI were more common in the CAS group. Rapp et al.<sup>33</sup> reported on a series of 48 patients submitted to 54 CAS procedures with excellent clinical results, but with a considerable number of new lesions on diffusion MRI. While these lesions are very often uncorrelated with clinical changes,

studies have demonstrated that repeated embolic injuries have cumulative effects.<sup>31,34</sup>

Notwithstanding, the influence that these differences may have on the neurocognitive results of carotid revascularization has not yet been fully explained, since large-scale studies were focused on strokes.<sup>1</sup> A study of heart surgery patients demonstrated that embolic events during operations were related to memory deficits.<sup>26,35</sup> By extrapolation, this finding might also be of relevance to carotid revascularization patients.

## Hemodynamic changes and repercussions for cognitive function

Carotid revascularization improves cerebral blood flow, which can translate into an improvement in CF.<sup>1,26,36-39</sup> Borroni et al.<sup>39</sup> identified a subset of their CEA patients who had moderate vascular dementia and showed that 60% of this subset enjoyed cognitive improvement after surgery. This potential benefit could be achieved for all patients, irrespective of revascularization technique.

However, all of the techniques involve transitory attenuation of cerebral blood flow,<sup>1</sup> and some studies have related this to transitory or persistent cognitive deficits.<sup>1,26,38,40-44</sup> Carotid endarterectomy is generally associated with longer periods of ipsilateral carotid flow privation (mean duration of 337 seconds) than CAS (mean duration of 26 seconds;  $p < 0.001$ ).<sup>43</sup>

A study with patients submitted to heart surgery demonstrated that hypoperfusion during the procedure was related to attention deficit.<sup>35</sup> This finding is also of relevance to patients undergoing carotid revascularization procedures, since these operations also involve a certain degree of hypoperfusion.

Cerebral hypoperfusion is defined as cerebral blood flow below 30% of normal flow.<sup>23,26,44</sup> The most widely used strategies intended to avoid hypoperfusion during CEA are either a selective shunt (guided by cerebral monitoring using continuous electroencephalogram, TCD or neurological examination) or a universal shunt.<sup>26,41,44-46</sup> More recently, cerebral oximetry, bispectral index and evoked potentials are also being used for cerebral monitoring during surgery at some centers.<sup>24,47,48</sup>

Additionally, another event that can occur in relation to both types of revascularization procedure is systemic hypotension, defined as a drop in systemic systolic pressure of  $>30$  mmHg, compared with baseline,<sup>26,45</sup> which is more frequent with CAS (more than 68% of patients),<sup>49-52</sup> and is associated with elevated levels of biochemical markers (S100B) of glial injury.<sup>53</sup>

Although CAS involves shorter periods of blood flow privation, it appears to cause greater hemodynamic instability when compared with CEA. The combined impact of these competing factors has not yet been fully investigated.<sup>1</sup>

### **Cognitive changes after carotid revascularization: endarterectomy vs. carotid angioplasty**

Systematic reviews conducted by Lunn et al. and Irvine et al. demonstrate the complete absence of consensus on cognitive outcomes after CEA.<sup>54,55</sup> They found that 16 out of 28 studies analyzed demonstrated improved CF after CEA, but that the remaining 12 either did not detect improvements or even found evidence of a decline in CF.

Heyer et al. compared the CF of 80 patients who underwent CEA with controls who had had orthopedic surgery. They found a decline in one out of four cognitive tests and when all test results were analyzed together, there was a significant decline in overall scores for the CEA group. This study was limited by follow-up that was short and incomplete.<sup>56</sup>

The first studies of which we are aware involving CAS emphasized its neurocognitive consequences, but CAS methodology evolved and now includes stent placement and the use of cerebral protection devices.<sup>1,57</sup> The most common form of cerebral protection is placement of a filter in the distal internal carotid before conducting angioplasty of the carotid bifurcation and was developed to reduce microembolization, but the method is not able to completely eliminate the occurrence of this phenomenon. This fact has been explained by the lack of protection during instrumentation of the aortic arch and passage of the guide wire past the carotid lesion and by failure to capture all emboli after installing the filter.<sup>30,58,59</sup> Proximal occlusion and reverse flow are other potential alternatives for these deficits, since both cerebral protection devices are installed before manipulation of the lesion and both involve stopping anterograde flow in the internal carotid.<sup>30</sup>

A study conducted in 2006<sup>60</sup> of 40 patients submitted to CAS with a cerebral protection device used mini mental state examinations to test CF, reported improvements after CAS, which is a trend that has also been observed by other authors.<sup>61</sup> However, another group of researchers<sup>62</sup> compared a group of 24 patients who underwent CAS with a control group of patients submitted to coronary angioplasty and concluded that CAS could be responsible for a moderate cognitive decline over the short term.

Analysis of studies that have compared one carotid revascularization technique with another revealed that there is still a great deal of controversy.<sup>6,31,63-67</sup> Capoccia et al. conducted a non-randomized study in which they respected clinical and anatomic criteria to indicate either CEA (20 patients) or CAS (23 patients) and administered mini mental state examinations over the short and medium term to both groups, concluding that CF worsened in the second group only. The authors detected a positive relationship between this finding and a higher rate of lesions detected within 24 hours using diffusion magnetic resonance (0% versus 21%, respectively).<sup>31</sup>

Feliziani et al. conducted a study including analysis of cognitive aspects of asymptomatic individuals submitted to carotid revascularization (24 patients operated using the CAS technique versus 22 patients using the CEA technique). They investigated three questions related to CF, as follows: 1- To what extent does revascularization itself affect CF, irrespective of the technique employed? 2- What is the behavior of CF over time (3 and 12 months after operating)? 3- Which is the best technique in terms of CF? They assessed CF in several different domains: memory; attention and executive functions; and constructive and visuospatial abilities. In relation to the first and third questions: there were no statistically significant results. In relation to the second question, the performance of patients who had undergone CAS deteriorated over time in constructive and visuospatial abilities.<sup>6</sup>

Lal et al. studied asymptomatic patients submitted to CEA (25 individuals) or CAS (21 individuals) and conducted tests of several domains of cognition during the immediate postoperative period and 4 to 6 months after the procedures. They concluded that there was cognitive improvement after both techniques and that there was no difference in overall test results between the two techniques. However, analysis of domain-specific scores showed that CEA resulted in a reduction in memory, while CAS patients exhibited worsened psychomotor velocity.<sup>63</sup>

In contrast, Takaiwa et al. studied 26 patients (15 operated with CAS and 11 operated by CEA) and concluded that although there was no statistical difference between the two techniques in terms of CF, there were improvements in the domains 'memory' and 'attention' after carotid revascularization and these improvements were sustained over time (12 months).<sup>64</sup>

Studies that have investigated this subject vary greatly in terms of the following aspects: the point in time at which tests are administered; use of specific

tests; use of control groups; duration of postoperative follow-up period; number of patients studied; and severity of stenoses operated.<sup>1</sup>

## CONCLUSIONS

The literature reviewed makes it clear that carotid stenoses are related to cognitive decline over time. There is still much controversy with relation to the impact carotid revascularization has on CF. Microembolizations and hemodynamic fluctuations that can occur during carotid interventions contribute to worsening the performance of revascularized patients in cognitive tests. However, there is no consensus among the most up-to-date studies on this trend. There are high quality studies that have confirmed a reduction in cognitive performance, but many others have shown stability or even improvements in performance.

The majority of studies that compared endarterectomy to carotid stenting did not detect a difference between the two techniques in terms of overall cognitive outcome. Further studies are needed to investigate the impact of carotid revascularization on the several different domains of cognition.

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