ARTIGO DE REVISÃO

TROMBOSE AGUDA DE STENT CAROTÍDEO - UMA ENTIDADE CLÍNICA RARA?

ACUTE CAROTID STENT THROMBOSIS - A RARE CLINICAL ENTITY?

Andreia Coelho¹,², Miguel Lobo¹, Clara Nogueira¹,², Jacinta Campos¹,², Rita Augusto¹,², Nuno Coelho¹,², Ana Carolina Semião¹, João Pedro Ribeiro², Alexandra Canedo¹,²

1. Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar de Vila Nova de Gaia e Espírito Santo
2. Faculdade de Medicina da Universidade do Porto

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RESUMO

Introdução: A trombose aguda de stent carotídeo (ACST), que se define de acordo com o Academic Research Consortium como o evento que ocorre nas primeiras 24 horas após o procedimento, é descrita como uma complicação rara de stenting carotídeo mas tem consequências potencialmente catastróficas. A European Society for Vascular Surgery atualizou as suas guidelines concluindo que trombólise e o abciximab poderão ser eficazes, mas não fornece recomendações terapêuticas específicas. O objetivo deste artigo foi sumarizar a evidência existente relativa à etiologia e abordagem de ACST.

Métodos: Uma revisão de literatura foi realizada usando a base de dados MEDLINE.

Resultados: Não são reportados dados relativos à taxa de incidência de ACST nos grandes ensaios clínicos randomizados publicados. Em cohorts publicados, a taxa de incidência varia entre 0,5 a 0,8% na maioria dos estudos, mas pode atingir os 33% em contexto agudo pós-acidente vascular cerebral (AVC). Considerando a etiologia, podemos subdividir em 2 categorias principais: causas sistêmicas e complicações técnicas. No primeiro caso, a não adesão / resistência aos antiagregantes plaquetários foram as causas mais reportadas, enquanto que nas complicações técnicas inclui-se a dissecação da artéria carótida e a protrusão do placa. De salientar também que dual layer stents foram associados a maior risco de ACST. Existem três abordagens principais para o ACST: farmacológica, endovascular e cirúrgica. A abordagem farmacológica inclui a hipocoagulação, a trombólise e a trombólise facilitada, apesar de o papel das duas últimas continuar por esclarecer.

O tratamento endovascular foi a abordagem mais comum para ACST intraprocedimento: trombectomia mecânica com ou sem trombólise facilitada concomitante. As opções cirúrgicas incluíram endarterectomia carotídea com explantação do stent, que foi também o bail-out após mau resultado com tratamento endovascular, atingindo excelentes taxas de recanalização. Nos casos de ACST assintomáticos, o tratamento conservador com hipocoagulação foi unânime.

Discussão: Como conclusão, o ACST é provavelmente uma entidade clínica subestimada associada a múltiplos fatores de risco. A decisão relativa à melhor abordagem deve depender se o ACST ocorre intraprocedimento ou não, da constatação ou não de deterioração do estado neurológico e da experiência do centro. Estudos adicionais devem ser realizados para melhor definir a abordagem ideal.

Palavras-chave
Estenose carótida; Doença Carótida; Stents; Trombose da artéria carótida;

ABSTRACT

Introduction: Acute carotid stent thrombosis (ACST), defined according to the Academic Research Consortium as occurring in the first 24 hours after the procedure, is described as an exceedingly rare complication of CAS but it can lead to catastrophic outcomes. A review of literature was performed using the MEDLINE database.

Results: There are no reported data relative to the incidence of ACST in the large clinical trials published. In cohorts published, the incidence rate varies between 0.5 to 0.8% in the majority of studies, but it can reach 33% in the context of acute stroke (AVC). Considering the etiology, we can subdivide into 2 main categories: systemic causes and technical complications. In the first case, the lack of adherence / resistance to antiplatelet agents were the most reported causes, while in technical complications includes dissection of the carotid artery and protrusion of the plaque. It should be highlighted that dual layer stents were associated with a higher risk of ACST. There are three main approaches for ACST: pharmacological, endovascular and surgical. The endovascular approach was the most common for ACST intraprocedural: mechanical thrombectomy with or without facilitated thrombolysis concomitantly. The surgical options included carotid endarterectomy with explantation of the stent, which was also used as bail-out after poor results with endovascular treatment, achieving excellent recanalization rates. In cases of ACST asymptomatic, the conservative treatment with anti-coagulation was unanimous.

Discussion: As conclusion, ACST is probably an underappreciated clinical entity associated with multiple risk factors. The decision relative to the best approach depends on whether the ACST occurs intraprocedural or not, the assessment or not of deterioration of the neurological state and the experience of the center. Additional studies should be performed to better define the approach ideal.

*Autor para correspondência.
Correio eletrónico: andreiasmpcoelho@gmail.com (A. Coelho).
neurologic consequences. The European Society for Vascular Surgery updated guidelines state that thrombolysis and intravenous abciximab may be effective, but provide no specific recommendations.
Given the lack of data concerning the optimal management, the purpose of this review was to evaluate the current literature and report on ACST aetiology and management strategies.

**Methods:** Literature review was performed in the MEDLINE database.

**Results:** No data on ACST is evident in large randomized controlled trials. ACST incidence rate ranges from 0.5–0.8%, reaching as high as 33% in acute settings.
Considering aetiology, it can be subdivided into two main groups: systemic causes and technical complications. In the first antiplatelet non-compliance/resistance were the most reported while in the latter carotid artery dissection and plaque protrusion were the most common causes. Dual layer stents have been associated with greater risk for ACST in the literature. There are three main approaches for ACST: pharmacologic, endovascular and surgical. Pharmacologic management included anticoagulation, thrombolysis and facilitated thrombolysis. A role for thrombolysis and facilitated thrombolysis is still to be determined. Endovascular treatment was the most common approach in intraprocedural ACST. Mechanical thrombectomy and thrombus aspiration with or without simultaneous facilitated thrombolysis. Surgical options included carotid endarterectomy with stent implantation which was a bail-out after failed endovascular treatment with excellent recanalization rates. In asymptomatic ACST conservative management with anticoagulation was unanimous.

**Discussion:** As a conclusion, ACST is probably an underestimated clinical entity associated with multiple risk factors. Decision on the best approach depends if ACST occurs intraprocedural or afterwards, on the development of neurologic status deterioration and on centre’s experience. Additional studies must be undertaken to better define optimal management.

**Keywords**
Carotid stenosis [MeSH Terms], Carotid Artery Diseases [MeSH Terms], Stents [MeSH Terms], Carotid Artery Thrombosis [MeSH Terms]

**INTRODUCTION**

Stroke remains nowadays the leading cause of death and permanent disability in Portugal. Data from DGS (Direção Geral de Saúde) estimates an incidence of 2 cases/1000 habitants/year, with 30% mortality within the first year and 40% of permanent disability in first year survivors.(3)
Carotid bifurcation atherosclerotic disease is one of the most common cerebrovascular culprits.(4) Management options for carotid atherosclerotic disease depend on whether carotid disease is symptomatic or asymptomatic and on patient’s surgical risk. Options include best medical treatment (BMT) alone or associated with carotid artery revascularization with open carotid endarterectomy (CEA) and carotid artery stenting (CAS). Traditionally, CEA has been the gold standard for management of both symptomatic and asymptomatic high-grade carotid artery stenosis, and original indications for CAS were limited to anatomically and physiologically high-risk patients.(5) However, the minimally invasive nature, shorter procedure and patient-recovery times, and expanded pool of physicians capable of performing the procedure, have popularized CAS beyond its original indications.(5)

Nowadays, according to the 2017 update to European Society for Vascular Surgery (ESVS) Carotid and Vertebral Artery Disease Guidelines, CAS and BMT may be considered in symptomatic or asymptomatic carotid artery disease (ClassIb Level of evidence B)(2)
Acute carotid stent thrombosis (ACST), defined according to the Academic Research Consortium as occurring in the first 24 hours after the procedure(6), is described as an exceedingly rare complication of CAS even though it can lead to catastrophic neurologic consequences. However, this may be grossly underestimated as randomized controlled trials (RCTs) published on CAS are omission regarding this complication. A follow-up study on ACST using serial Computed Tomography Angiography (CTA) revealed that the occurrence rate of acute or subacute in-stent thrombosis among 23 cases of CAS reached 43.5%. The eccentric hypodense area in the stent lumen was thrombotic material, most of which resolved within 12 weeks owing to endogenous thrombolysis.(7)
Management of ACST and the outcome after successful rescue of carotid thrombosis remain currently unclear.(7)
Given the lack of data concerning the optimal management, the purpose of this review was to evaluate the current literature and report on ACST aetiology and management strategies.
METHODS

Literature review was performed in the MEDLINE database with the following query: (acute carotid stent thrombosis) OR (carotid artery stenting AND acute thrombosis) OR (acute carotid stent occlusion) in order to identify manuscripts on the subject. Additionally, relevant randomized controlled trials published on CAS were reviewed in order to identify reports on ACST incidence.

RESULTS

Data from CAS RCTs

Data from Table 1 summarizes the main RCT’s published concerning CAS safety comparing it with carotid endarterectomy (CEA). All RCT reported complications such as stroke and myocardial infarction as primary endpoints, but none report on ACST.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Clinical criteria for CAS</th>
<th>n</th>
<th>ACST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheim, D. et al (10)</td>
<td>2017</td>
<td>Asymptomatic</td>
<td>68</td>
<td>No data</td>
</tr>
<tr>
<td>SPACE-2 (8)</td>
<td>2016</td>
<td>Asymptomatic</td>
<td>197</td>
<td>No data</td>
</tr>
<tr>
<td>ACT-1 (10)</td>
<td>2016</td>
<td>Asymptomatic</td>
<td>1089</td>
<td>No data</td>
</tr>
<tr>
<td>CREST (11)</td>
<td>2011</td>
<td>Asymptomatic + Symptomatic</td>
<td>1262</td>
<td>No data</td>
</tr>
<tr>
<td>ICSS (12)</td>
<td>2010</td>
<td>Symptomatic</td>
<td>855</td>
<td>No data</td>
</tr>
<tr>
<td>SAPPHIRE (13)</td>
<td>2008</td>
<td>30% Symptomatic</td>
<td>167</td>
<td>No data</td>
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<tr>
<td>EVA-3S (14)</td>
<td>2008</td>
<td>60% Symptomatic</td>
<td>265</td>
<td>No data</td>
</tr>
<tr>
<td>SPACE (15)</td>
<td>2008</td>
<td>Symptomatic</td>
<td>613</td>
<td>No data</td>
</tr>
<tr>
<td>Brooks, et al (16)</td>
<td>2004</td>
<td>Asymptomatic</td>
<td>43</td>
<td>No data</td>
</tr>
<tr>
<td>CAVATAS (17)</td>
<td>2001</td>
<td>Asymptomatic + Symptomatic</td>
<td>251</td>
<td>No data</td>
</tr>
</tbody>
</table>

ACST Incidence Rate

ACST incidence rate is very difficult to establish as the main RCT’s on CAS do not report this complication (Table 1). Data on ACST incidence rate come from observational studies only, with a reported incidence of 0.5–0.8% in most studies. (1,10–12) The biggest reported series includes 674 patients, with an ACST incidence rate of 0.59%. (10) There are however reports of incidence rates reaching as high as 33%, when CAS is performed in acute phase post stroke. (10–24)

Aetiology

Aetiology for ACST is usually subdivided in 2 main groups: Local/technical causes and systemic causes. In the latter group, antiplatelet non-compliance is systematically identified as the most important potentially preventable cause for ACST. (10) Other causes include antiplatelet resistance and hypercoagulable states (such as thrombocytopenia, diabetes mellitus and heparin resistance) and antiplatelet resistance. (22) Standard antiplatelet therapy recommendation is dual antiplatelet therapy with aspirin and clopidogrel preoperatively that should be continued for at least one month, followed by clopidogrel thereafter. In acute setting, loading doses of both clopidogrel and aspirin as well as intravenous continuous administration of a third antiaggregant (GPIb/IIIa inhibitor) are usually administered. Most operators administer 5000 IU of intravenous heparin prior to the procedure. (25) Aspirin resistance has been defined clinically as the development of thrombotic and vascular events although therapeutic doses of aspirin are given. On the other hand, clopidogrel resistance has been defined as the continued activity of the target of clopidogrel (platelet P2Y12 receptors) despite the adequate antiplatelet therapy. (25) Fifi et al reported aspirin resistance prevalence of 5.2% and clopidogrel resistance of 36.5% among 96 patients who underwent neurovascular stenting. (26) Recent data however, recommend against routine testing for clopidogrel and ASA resistance as randomized trials have failed to demonstrate any benefit of platelet function monitoring to adjust therapy. (27) Technical causes include vessel dissection, severe plaque protrusion, early stent restenosis and stent underexansion. Furthermore, deployment of the stent and balloon angioplasty ruptures the luminal plaque, exposing thrombogenic material, thereby potentially promoting thrombosis both locally within the stent and remotely at the distal protection device. Descriptions in the literature of sequential occlusion of distal protection device and carotid stent exist. (28) Also concerning technical complications, type of carotid stent deserves special consideration. ICSS RCT reported significantly lower 30-day risks of death/stroke in CAS patients where closed cell design stents were used (5.1%), versus 9.5% in patients where open cell designed stents were used (OR 10.53, 95% CI 0.31–0.91, p < 0.02). (12) The rationale for this difference is the greater risk for plaque protrusion during CAS with open cell stents in unstable plaques. Plaque protrusion is strongly associated with ischemic complications. (29)
Open cell stents have also been associated with greater incidence of post-procedural complications.\(^{(30)}\)

Regarding micromesh or dual layer stents, there is currently no evidence that they reduce procedural risks after CAS.\(^{(29)}\)

The rationale for this stent is the increased flexibility and conformability and improved device navigation when compared to closed-cell stents. Open cell stent platform enables device to conform to difficult anatomy, while closed cell lattice can trap atherosclerotic/thrombotic material and prevent protrusion. However, regarding the risk for ACST associated with dual layer stents, in a single report in the setting of emergency CAS with intra-cranial thrombectomy, the dual layer Casper RX, Microvention, Tustin, CA was reported to have a significantly higher rate of acute occlusion with odds ratio of 21.3 (43% vs. 3.7%; p = 0.0001).\(^{(26)}\)

**Diagnosis**

Post-CAS surveillance is extremely variable between studies, which may explain in part the differences in ACST incidence between studies, as asymptomatic ACST may be missed. In patients with multiple risk factors for ACST, examination with ultrasound Doppler at least twice in the first week after CAS has been recommended.\(^{(31)}\)

**Management**

Decision on the best approach should depend on 3 main factors: whether ACST occurs intra-procedural or afterwards, on the presence or absence of neurologic status deterioration and finally on the center’s and surgeon’s experience. Management options can be subdivided into 3 main categories: pharmacologic, endovascular and surgical treatment. Pharmacologic treatment includes anticoagulation, GP IIb/IIIa Inhibitors, thrombolysis and facilitated thrombolysis. Anticoagulation may be used alone or as an adjuvant, but in asymptomatic cases, conservative management with anticoagulation alone was an unannounced option in studies.\(^{(38)}\)

GP IIb/IIIa inhibitor abciximab administered both intravenously (iv) or catheter directed intra-arterially, has been reported to reconstitute acutely occluded stents.\(^{(39)}\)

Thrombolysis has been referenced in ESVS guidelines as worth of consideration in ACS.\(^{(35)}\)

The combined therapeutic regimen consisting of dethrombosis (GP IIb/IIIa inhibitors) and fibrinolysis (as alteplase) - termed “facilitated thrombolysis” can improve reconstitutive rates even further. Steiner-Boeker et al described ‘facilitated thrombolysis’ as a rescue therapy for in-stent thrombosis. In their case report they used locally administered intra-arterial tPA plus abciximab and additional heparin with restoration of blood flow occurring within 15 min. They argued that this method could provide a more rapid means to restore blood flow, thereby minimizing potential adverse neurologic sequelae.\(^{(39)}\)

The literature remains sparse on effective and reliable endovascular treatment strategies should medical therapy fail. Thrombectomy with devices such as the Penumbra System (PS; Penumbra, Alameda, Calif) was first used for recanalization of acute intracranial large arterial vessels, however it has a potential to resolve ACST during CAS. Nevertheless if ACST is caused by severe plaque protrusion caution is warranted.\(^{(34)}\)

Dhall et al described successful simultaneous direct thrombosis with the guiding sheath with facilitated thrombolysis for inprocedural ACST.\(^{(32)}\)

Setacci et al described 2 cases of successful thrombectomy by careful aspiration. The entire clot was pulled out by using forceps and an aspirator, and an excellent runoff was achieved without the need to remove the stent.\(^{(37)}\)

In-stent PTA performed under distal protection without additional placement of stent was described in one case successfully.\(^{(37)}\)

Stent-in-stent has been described more often with encouraging results.\(^{(36)}\)

The management of ACST may require emergent definite surgical repair, particularly when neurologic status deterioration ensues or as a bailout after failed endovascular revascularization attempt. Stent removal and CEA is effective in rapid reestablishment of cerebral perfusion and neurologic status improvement, but there are concerns with the time-consuming aspect of this procedure. Also emergent CEA in an acute post-CAS setting is associated with higher morbidity associated with dual-antiplatelet therapy and anticoagulation and greater risk for cranial nerve damage.\(^{(37)}\)

**DISCUSSION**

There is an astonishing variability in ACST incidence rate in the literature. This is probably due to two main factors. The first is the difference is in post-CAS surveillance with some centers performing routine ultrasound Doppler follow-up while others only reporting ACST in symptomatic patients. The second is the difference between included patients in different case series, with acute phase stenting seemingly associated with increased risk.

In patients with neurological deterioration, surgical management was able to achieve recanalization through removal of thrombogenic material. But there were some concerns regarding time-consuming aspects of surgical approach and increased morbidity in such circumstances. Endovascular treatment including thrombectomy, thromboaspiration, PTA-in-stent and stent-in-stent could be applied quickly during the procedure. But, long-term efficacy is still debatable. A role for thrombolysis and facilitated thrombolysis is still to be determined.
In the absence of RCTs, it is difficult to compare the efficacy of different treatment modalities. The critical prognostic points of this potentially devastating complication are the initial clinical presentation expressing the grade of ischemic brain damage, the accurate and timely recognition of the thrombosis and the prompt restoration of oxygenated blood flow into the viable tissue at risk of infarction (ischemic penumbra). Prompt revascularization remains the key to the successful outcome in symptomatic patients and can also justify discrepancies between delayed successful recanalization of the thrombosed stent and functional recovery. In asymptomatic patients, conservative management with anticoagulation still seems the safest option.

As a conclusion, ACST is probably an underestimated clinical entity associated with a multiplicity of factors. Additional studies must be undertaken to better define optimal management.

REFERENCES


