THE RELATIONSHIP BETWEEN CEREBROVASCULAR RESERVE AND RISK OF STROKE IN PATIENTS WITH CAROTID MACROANGIOPATHY

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Rezumat:

Introducere
Tulburările în rezerva cerebrovasculară (CVR) au fost asociate cu un risc crescut de evenimente ischemice și pot stratifica riscul de accident vascular la pacienții cu un grad ridicat de stenoză sau ocluzie a arterei carotide interne (ICA). Scopul acestui studiu a fost acela de a realiza o trecere în revistă a datelor din literatura de specialitate privind asocierea dintre tulburările în rezerva cerebrovasculară (CVR) și riscul de accident vascular cerebral.

Metode
Studiul literaturii de specialitate (incluzând studii de urmărire a pacienților de minimum un an), urmat de măsurări ale nivelului de bază al CVR, efectuate via orice modalitate, și măsurile primare luate în cazul accidentului vascular și/ai accidentului ischemic tranzitoriu (TIA) la pacienții cu stenoză sau ocluzie a arterei carotide interne (ICA)

Rezultate
Autorii au gasit o relație pozitivă semnificativă între tulburările în CVR cu producerea viitoare de accident vascular. Analizele au arătat că asocieră dintre tulburările în CVR și riscul viitor de atac ischemic sau tranzitoriu rămânând semnificativ în ciuda măsurărilor de prevenire a patologiei simptomatice sau asimptomatice, stenoze sau ocluzii, ori metode de testare a CVR.

Concluzii
Perturbările CVR sunt puternic asociate cu riscul crescut al evenimentelor ischemice în stenoza de carotidă ori ocluzie și acest lucru poate fi util pentru stratificarea de risc.

Cuvinte-cheie: risc de accident ischemic tranzitoriu (TIA), risc de accident vascular cerebral, rezervă cerebrovasculară, reactivitatea cerebrovasculară, meta-analiză, review sistematic

Abstract:

Introduction
Impairments in Cerebrovascular reserve (CVR) have been associated with increased risk of ischemic events and may stratify stroke risk in patients with high grade internal carotid artery (ICA) stenosis or occlusion. The aim of this study was to perform a literature data review concerning the association of CVR impairment and risk of stroke.

Methods
The literature search (including studies with minimum one year patient follow up with baseline CVR measures performed via any modality and primary outcome measures of stroke and/or TIA) has been made to evaluate the association of impairments in CVR with future stroke or transient ischemic attack (TIA) in patients with high grade ICA stenosis or occlusion.

Results
The authors have found a significant positive relationship between impairment of CVR and development of stroke. Subset analysis showed that this association between CVR impairment and future risk of stroke/TIA remained significant regardless of ischemic outcome measure, symptomatic or asymptomatic disease, stenosis or occlusion, or CVR testing method.

Conclusions
CVR impairment is strongly associated with increased risk of ischemic events in carotid stenosis or occlusion and may be useful for stroke risk stratification.

Key words: TIA, risc for stroke, cerebrovascular reserve, cerebrovascular reactivity, metaanalysis, systematic review
Introduction

It is well known the fact that atherosclerotic disease occurs frequently at the common carotid artery bifurcation. Such extracranial atherosclerotic disease accounts for 15 to 20% of ischemic strokes. Traditional imaging-based risk assessment of stroke, focused on defining the degree of arterial narrowing, has not taken into account downstream hemodynamic effects distal to the stenosis and the cerebrovascular reserve (CVR).

For example, when carotid stenosis is severe and reduces cerebral perfusion pressure (CPP), autoregulation of the vasculature will maximally dilate the cerebral arterioles to maintain cerebral blood flow (CBF). With further reduction in CPP and maximally dilated arterioles, the CBF will also decrease and potentially increase the risk of stroke.

In symptomatic severe ICA stenosis, carotid endarterectomy (CEA) has been shown to significantly lower the risk of ipsilateral cerebral infarction. The benefit of CEA is less clear in patients with asymptomatic high grade stenosis. For example, in the Asymptomatic Carotid Surgery Trial, the modest 5.4% reduction in absolute stroke risk at 5 years in patients with asymptomatic carotid stenosis who were treated with CEA requires serious consideration of the risks of surgery, including local surgical expertise in the procedure.

In such a population, integration of cerebral hemodynamics such as CVR or oxygen extraction fraction derived from positron emission tomography (PET) into assessment of stroke risk could potentially help isolate a group of patients who might most benefit from surgical revascularization.

On the other hand, further risk stratification may improve prognosis and motivation for adherence to medical therapy in patients with asymptomatic occlusion, as indications for surgical revascularization in this group also remain unclear with a recent randomized trial showing no benefit of surgical revascularization relative to medical therapy.

There have been two main approaches to measuring CVR. One approach attempts direct CBF measurements of the brain tissue with flow sensitive imaging techniques such as positron-emission tomography (PET), nuclear medicine (NM) techniques, CT perfusion, or MR perfusion before and after a vasodilatory stimulus. The second approach involves transcranial Doppler (TCD) measurement of flow velocities (typically in the middle cerebral artery) distal to a lesion both before and after a vasodilatory stimulus, with the increase flow velocity considered a surrogate for CVR. Vasodilatory stimuli include increasing levels of CO2 (such as with breath holding or inhalation of CO2 gas mixtures) and pharmacologic challenge with acetazolamide. It is difficult to draw reliable conclusions about the role of CVR in predicting stroke based on individual research studies in the literature given their relatively small sample sizes.

While there have been attempts to summarize stroke risk based on existing studies evaluating CVR impairment in specific patients with a particular modality, there have been no recent attempt at a systematic review and meta-analysis of the entire literature across all patient populations and modalities has been performed.

It is important to improve our understanding of the role of CVR in patients with carotid artery stenosis for determining stroke prevention regimens. The purpose of this study was to perform a systematic literature review and meta-analysis in order to summarize the association of CVR impairment and stroke risk. Most imaging-based risk assessments of stroke or TIA rely on the degree of arterial narrowing with the highest incidence of stroke associated with the most severe narrowing.

The yearly incidence of stroke varies from approximately 1.2 to 5.9% per year for asymptomatic ICA stenosis to about 10% per year for symptomatic ICA occlusion. Though these estimates are integral to current treatment and stroke prevention paradigms, most consensus recommendations do not include assessments of cerebral hemodynamics in their management algorithms.

In this systematic review and meta-analysis of 1061 independent CVR tests in 991 unique patients with carotid stenosis or occlusion with a mean follow up of 32.7 months, baseline CVR impairment was associated with increased risk of stroke/TIA.

Authors findings suggest a positive relationship between baseline CVR impairment and future ischemic events, with a pooled odds ratio suggesting that patients with impaired CVR are approximately 4 times more likely to develop stroke or TIA. To our knowledge, though there have been two previous published meta-analyses of the role of CVR in predicting future stroke risk, one was limited in scope as it examined only 3 studies limited to patients with asymptomatic disease and another was performed in 1997 before a majority of the current studies in the meta-analysis were published and was focused instead on baseline CBF impairment.

Our literature search found 5 studies limited to asymptomatic patients, and is the first study to evaluate the effect of CVR impairment across different disease characteristics and by combining studies that used different methods to measure CVR. Importantly, the authors of this study suggests that CVR impairment is strongly associated with stroke or TIA in both high grade stenosis and occlusion, as well as in asymptomatic and symptomatic patients.

These findings suggest that, in combination or in addition to the risk of embolic stroke arising from carotid atheromatous plaque, these patients face stroke risk from hypoperfusion in vascular territories where vasodilatory capacity is maximally exhausted.

The choice of modality for evaluating CVR varies. The authors have found the association between CVR impairment and risk of stroke conserved across testing modality (TCD or NM techniques) as well as the nature of the vasodilatory stimulus (acetazolamide or variation in inspired CO2 levels). TCD is relatively inexpensive and fairly widely available, but does not provide additional...
information of the brain parenchyma and is technically impossible in some cases due to lack of acoustic windows. Modalities which measure brain tissue perfusion, such as NM techniques, often have limited use in the clinical setting due to expense, availability and low spatial and temporal resolution.

Though there are radiation and cost considerations for newer cross sectional methods such as CT and MRI perfusion techniques, to our knowledge no prospective studies assessing CVR impairment and stroke risk have been performed with these newer modalities, so their utility requires further investigation. Our study has some limitations that should be considered. Though no studies in the review described any differences in risk factors or treatment that might explain differences between normal and impaired CVR groups, an explicit statistical correction of these risk factors occurred in a majority 9 of 13 but not all of the studies. In addition, no methodology for blinding of investigators to the CVR results was explicitly made in a majority of the studies. Study endpoints (stroke or TIA) were defined variably by authors with many aggregating these outcomes and preventing a distinction between minor versus disabling stroke. In addition, definitions of normal versus impaired CVR and symptomatic versus asymptomatic disease varied, and though some similarities existed, no one standard definition could be applied across all studies. Similarly, more precise description of the severity of stenosis (percentages) and timing of this measurement relative to CVR determination was reported in a variable fashion and was difficult to generalize. Lastly, due to the nature of the data available for statistical analysis, assessment of risk per unit of time as a hazard ratio could not be performed. Authors conclusion is that association between CVR impairment and risk of stroke/TIA is robust across many patient subsets and methods of CVR assessment suggesting an important potential role in stroke/TIA risk assessment. The feasibility of integrating routine CVR measurements into the care of patients with carotid stenosis or occlusion and validation of newer methods of CVR using cross-sectional imaging techniques requires continued investigation.

References:


