Original research article

EUROPEAN STROKE JOURNAL

# Nonfocal transient neurological attacks in patients with carotid artery occlusion

European Stroke Journal
2019, Vol. 4(1) 50–54

DOI: 10.1177/2396987318818779
journals.sagepub.com/home/eso
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## Abstract

**Introduction:** Nonfocal transient neurological attacks (TNAs) are episodes with atypical, nonlocalizing cerebral symptoms. We examined the prevalence of nonfocal TNAs, in patients with and without carotid artery occlusion (CAO).

**Methods:** We included 67 patients with CAO and 62 patients without CAO. In both groups, patients had a history of transient ischemic attack (TIA) or nondisabling ischemic stroke in the anterior circulation that had occurred >6 months before inclusion. Patients without CAO did not have ipsilateral or contralateral carotid artery stenosis of ≥50%. All patients were interviewed with a standardized questionnaire on the occurrence of nonfocal TNA symptoms during the preceding six months. We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for the occurrence of ≥1 and ≥2 different nonfocal TNAs after adjustments for age, sex, systolic blood pressure and time interval between most recent TIA or ischemic stroke and administration of the questionnaire.

**Results:** Forty-three of all patients (33%) had had one or more nonfocal TNAs in the preceding six months. Nonrotatory dizziness (24%) was reported most often. The prevalence of ≥1 nonfocal TNAs was not significantly different between patients with and without CAO (39% vs. 27%; adjusted RR 1.47, 95% CI 0.83–2.61), but the prevalence of ≥2 or more different nonfocal TNAs was higher in patients with CAO (16% vs. 3%; adjusted RR 4.77, 95% CI 1.20–18.98). In patients with CAO who also had a contralateral carotid or vertebral artery steno-occlusion, nonfocal TNAs occurred more often than in patients without any carotid or vertebral artery steno-occlusion (46% vs. 27%; adjusted RR 2.22, 95% CI 1.08–4.60 for ≥1 and 21% vs. 3%; adjusted RR 8.27, 95% CI 1.83–37.32 for ≥2 nonfocal TNAs).

**Conclusions:** Patients with CAO more often experienced multiple nonfocal TNAs than patients without CAO.

## Keywords

Internal carotid artery, carotid artery occlusion, transient neurological attacks

Date received: 20 July 2018; accepted: 10 November 2018

## Introduction

Nonfocal transient neurological attacks (TNAs) are defined as attacks with atypical, nonlocalizing cerebral symptoms such as unsteadiness, confusion or bilateral weakness.[1,2] Patients with nonfocal TNAs are at higher risk of cardiac events, stroke and dementia than patients without nonfocal TNAs.[2,3] Even though they are by no means benign, the underlying pathophysiology of nonfocal TNAs is still poorly understood. Both cerebral ischemia and cerebral hypoperfusion have been suggested to play a role.[1,3–5] Factors that might contribute to cerebral hypoperfusion are severe obstruction of cerebropetal arteries and impaired

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cerebral autoregulation.[6] We therefore hypothesized that in patients with carotid artery occlusion (CAO), nonfocal TNAs are more prevalent than in patients without CAO.

## Methods

### Study population and design

We selected patients from two prospective observational cohort studies.[7,8]

Patients with CAO were selected from the Heart-Brain Connection (HBC) study, which is a multicenter cohort study in the Netherlands that focusses on the relation between cardiovascular and hemodynamic measures and cognitive impairment.[7] From all consecutive patients with CAO who participated in the HBC study from November 2014 to March 2017 (data release 1 October 2017), we included all patients with CAO who had experienced an ipsilateral transient ischemic attack (TIA) or nondisabling ischemic stroke more than six months before inclusion. CAO was defined as a complete occlusion of the internal carotid artery and was measured either with ultrasound, magnetic resonance angiography or computed tomography angiography.

Patients without CAO were selected from the Second Manifestations of ARTerial disease (SMART) study from November 2015 until September 2017. The SMART study is a cohort study executed by a single academic hospital in the Netherlands, including patients with vascular risk factors or clinical manifest vascular disease.[8] Eligible patients had a history of TIA or nondisabling ischemic stroke of the anterior circulation that had occurred more than six months before inclusion and did not have a stenosis of the ipsilateral or contralateral carotid artery of $\geq$50% on ultrasound. Imaging of the internal carotid arteries was performed $<$1 year before inclusion into our study.

In both groups, patients were independent in activities of daily living (modified Rankin Scale of 0–3).

The HBC study and SMART study were approved by the Ethics Committee of the Leiden UMC and UMC Utrecht, respectively.[7,8] All patients provided written informed consent.

### Study parameters

All patients were interviewed by a trained physician or research nurse with a standardized questionnaire on the occurrence of eight nonfocal symptoms in the preceding six months (Table 1). Nonfocal TNAs were defined as attacks of one or more nonfocal signs or symptoms with an acute onset, a minimum duration of 30 s and a maximum of 24 h. The classification of nonfocal symptoms was adapted from the Rotterdam Study.[1,2] Symptoms that were compatible with a different diagnosis, such as migraine or epilepsy, were excluded from the analysis. The researcher who completed the interview was aware of the presence or absence of CAO in each patient.

**Table 1.** Occurrence of different types of nonfocal TNA symptoms in the past six months.

| Nonfocal symptoms, *n* (%) | Carotid occlusion ($n = 67$) | No carotid occlusion ($n = 62$) |
|---|---|---|
| Blurred vision | 6 (9%) | 2 (3%) |
| Bilateral leg weakness | 4 (6%) | 1 (2%) |
| Unsteadiness | 6 (9%) | 0 (0%) |
| Nonrotatory dizziness | 18 (27%) | 13 (21%) |
| Paresthesias | 0 (0%) | 4 (7%) |
| Unconsciousness | 4 (6%) | 0 (0%) |
| Confusion | 2 (3%) | 0 (0%) |
| Amnesia | 1 (2%) | 0 (0%) |

TNA: transient neurological attack.

In addition, we recorded demographic and clinical characteristics, including the presence of vascular risk factors, use of antihypertensive, lipid lowering, antiplatelet or anticoagulant medication, blood pressure, side of symptomatic CAO and presence of other extracranial arterial stenosis.

### Statistical analysis

We calculated the prevalence of nonfocal TNAs in both patient groups. We assessed the association between CAO and the occurrence of nonfocal TNAs with Poisson regression analysis with robust standard errors.[9] We calculated crude and adjusted risk ratios (RR) with corresponding 95% confidence intervals (CIs) for the occurrence of $\geq$1 and $\geq$2 different nonfocal TNAs. Adjustments were made for age, sex, systolic blood pressure and time interval between most recent TIA or ischemic stroke and questionnaire, as these factors were considered a priori to be potential confounders of the association between CAO and the occurrence of nonfocal TNAs. Subgroup analyses were performed in patients without steno-occlusion of the vertebral arteries, and in patients with CAO who also had had a contralateral carotid or vertebral artery steno-occlusion versus patients without any carotid or vertebral artery steno-occlusion.

## Results

We included 67 patients with CAO and 62 patients without CAO. Mean age was 66 ($\pm$9) years. Patients with CAO were more often male, had more vascular

**Table 2.** Patient characteristics.

| | Carotid occlusion ($n = 67$) | No carotid occlusion ($n = 62$) |
|---|---|---|
| Age in years, mean (SD) | 65.3 (±7.9) | 65.8 (±9.8) |
| Male sex, *n* (%) | 51 (76%) | 37 (60%) |
| Hypertension, *n* (%) | 52 (78%) | 39 (63%) |
| Hyperlipidemia, *n* (%) | 61 (91%) | 24 (39%) |
| Current smoking, *n* (%) | 17 (25%) | 11 (18%)[a] |
| Diabetes mellitus, *n* (%) | 21 (31%) | 11 (18%) |
| History of, *n* (%) | | |
| Myocardial infarction | 9 (13%) | 5 (8%) |
| Peripheral arterial disease | 21 (31%) | 2 (3%) |
| TIA (including amaurosis fugax) | 50 (75%) | 22 (36%) |
| Ischemic stroke | 38 (57%) | 42 (68%) |
| Medication use, *n* (%) | | |
| Antiplatelet | 56 (84%) | 48 (77%) |
| Anticoagulant | 6 (9%) | 10 (16%) |
| Antihypertensive | 47 (70%) | 32 (52%) |
| Lipid lowering | 59 (88%) | 50 (81%) |
| Systolic blood pressure in mmHg, mean (SD) | 152.1 (±21.1) | 136.3 (±15.0)[b] |
| Diastolic blood pressure in mmHg, mean (SD) | 82.7 (±12.1) | 80.3 (±10.8)[b] |
| Stenosis of extracranial cerebral arteries, *n* (%) | | |
| Contralateral ICA stenosis ≥50% or occlusion | 13 (20%)[c] | NA |
| VA stenosis ≥50% or occlusion | 15 (23%)[c] | 3 (5%) |
| Side of symptomatic carotid occlusion, *n* (%) | | |
| Right | 31 (46%) | NA |
| Left | 30 (45%) | NA |
| Both | 6 (9%) | NA |
| Interval between most recent TIA or ischemic stroke and questionnaire in years, median (IQR) | 3.7 (1.9–8.9) | 1.8 (1.0–10.5) |

SD: standard deviation; TIA: transient ischemic attack; ICA: internal carotid artery; VA: vertebral artery; IQR: interquartile range; NA: not applicable.
[a]Missing in $n = 1$ (2%).
[b]Blood pressure was measured before administration of questionnaire (<1 year earlier).
[c]Missing in $n = 3$ (5%).

risk factors and had higher systolic blood pressure than those without CAO (Table 2). Seven (11%) of patients with CAO had a contralateral asymptomatic carotid artery stenosis of ≥50% and six (9%) had a contralateral CAO. Fifteen (23%) patients with CAO also had >50% stenosis of a vertebral artery.

Table 1 summarizes the different nonfocal symptoms. Forty-three of all patients (33%) had had one or more nonfocal TNAs in the preceding six months (Supplementary Figure 1). The prevalence of at least one nonfocal TNA was not significantly different between patients with and without CAO (39% vs. 27%; adjusted RR 1.47, 95% CI 0.83–2.61; Table 3). However, the prevalence of two or more different nonfocal TNAs was significantly higher in patients with CAO (16% vs. 3%; adjusted RR 4.77, 95% CI 1.20–18.98; Table 3).

Exclusion of patients with vertebral artery steno-occlusion ($n = 21$, 16%) yielded comparable results (Table 3). In a post-hoc analysis, nonfocal TNAs occurred more often in patients with both CAO and a contralateral carotid or vertebral artery steno-occlusion ($n = 28$) than in patients without any carotid or vertebral artery steno-occlusion ($n = 59$) (46% vs. 27%; adjusted RR 2.22, 95% CI 1.08–4.60 for ≥1 and 21% vs. 3%; adjusted RR 8.27, 95% CI 1.83–37.32 for ≥2 nonfocal TNAs) (Table 4).

## Discussion

We found that one-third of patients with a distant history of TIA or nondisabling ischemic stroke of the anterior circulation experienced nonfocal TNAs in the preceding six months. The prevalence of multiple nonfocal TNAs was higher in patients with CAO than in those patients without CAO. Also, the prevalence of one or more nonfocal TNAs was higher in patients with CAO who also had a contralateral carotid or vertebral artery steno-occlusion than in patients without any cerebropetal steno-occlusion.

Studies on the prevalence of nonfocal TNAs are limited. In a previous population-based study, 2% of

**Table 3.** Occurrence of nonfocal TNAs in the past six months in patients with and without CAO, and in the subgroup of patients without vertebral artery stenosis or occlusion.

| All patients | Carotid occlusion ($n = 67$) | No carotid occlusion ($n = 62$) | RR crude (95% CI) | RR adjusted (95% CI) |
|---|---|---|---|---|
| Occurrence of $\geq$1 different TNA symptoms, *n* (%) | 26 (39%) | 17 (27%) | 1.42 (0.86–2.34) | 1.47 (0.83–2.61)[a] |
| Occurrence of $\geq$2 different TNA symptoms, *n* (%) | 11 (16%) | 2 (3%) | 5.09 (1.17–22.06) | 4.77 (1.20–18.98)[b] |
| **No VA steno-occlusion** | **Carotid occlusion ($n$=49)** | **No carotid occlusion ($n$=59)** | **RR crude (95% CI)** | **RR adjusted (95% CI)** |
| Occurrence of $\geq$1 different TNA symptoms, *n* (%) | 16 (33%) | 16 (27%) | 1.20 (0.67–2.15) | 1.08 (0.56–2.10)[a] |
| Occurrence of $\geq$2 different TNA symptoms, *n* (%) | 8 (16%) | 2 (3%) | 4.82 (1.07–21.64) | 4.02 (0.99–16.35)[b] |

TNA: transient neurological attack; CAO: carotid artery occlusion; RR: risk ratio; CI: confidence interval; VA: vertebral artery.
[a]Adjusted for age, sex, systolic blood pressure, time interval between most recent TIA or ischemic stroke and questionnaire.
[b]Adjusted for systolic blood pressure, time interval between most recent TIA or ischemic stroke and questionnaire.

**Table 4.** Occurrence of nonfocal TNAs in the past six months in patients with CAO and VA or contralateral carotid steno-occlusion and in those without CAO and without VA steno-occlusion.

| | Carotid occlusion[a] ($n = 28$) | No steno-occlusion[b] ($n = 59$) | RR crude (95% CI) | RR adjusted (95% CI) |
|---|---|---|---|---|
| Occurrence of $\geq$1 different TNA symptoms, n (%) | 13 (46%) | 16 (27%) | 1.71 (0.96–3.05) | 2.22 (1.08–4.60)[c] |
| Occurrence of $\geq$2 different TNA symptoms, n (%) | 6 (21%) | 2 (3%) | 6.32 (1.36–29.36) | 8.27 (1.83–37.32)[d] |

TNA: transient neurological attack; CAO: carotid artery occlusion; VA: vertebral artery; RR: risk ratio; CI: confidence interval.
[a]Patients with both CAO and a contralateral carotid artery steno-occlusion or vertebral artery steno-occlusion.
[b]Patients without steno-occlusion of the carotid and vertebral arteries.
[c]Adjusted for age, sex, systolic blood pressure, time interval between most recent TIA or ischemic stroke and questionnaire.
[d]Adjusted for systolic blood pressure, time interval between most recent TIA or ischemic stroke and questionnaire.

patients (>55 years) experienced a nonfocal TNA in the preceding three years.[1] In another hospital-based study, nonfocal symptoms occurred more frequently in patients with a recent TIA or nondisabling ischemic stroke; 20% of patients without carotid or vertebral artery stenosis, 36% of patients with carotid artery stenosis and 54% of patients with vertebral artery stenosis experienced nonfocal TNAs in the six months preceding the cerebral ischemic event.[10] Our findings are compatible with these results.

Although we can only hypothesize, the higher prevalence of multiple nonfocal TNAs in patients with versus without CAO might be caused by cerebral hypoperfusion due to CAO. Our finding that these differences in prevalence were even more profound in patients with both CAO and a contralateral carotid or vertebral artery steno-occlusion supports a hemodynamic etiology.

Our study has some limitations. To start, although we tried to make the group without CAO comparable to the CAO group with regards to vascular risk factors and risk of ischemic stroke by including only patients with a distant history of TIA or nondisabling ischemic stroke as our control population, vascular risk factors and previous vascular diseases were more often present in the CAO group. Although we cannot rule out residual confounding, we have adjusted our analysis for those variables that we considered potential confounders of the association between presence of CAO and occurrence of nonfocal TNAs. Second, the time interval between the most recent cerebral ischemic event and administration of the questionnaire was longer in patients with CAO than in patients without CAO. Patients with a more recent event may have been more aware of what symptoms they experienced in the previous six months which may have underestimated the prevalence of nonfocal TNAs in patients with CAO. However, this would only have enhanced the difference between patients with and without CAO and adjustment for this time interval did not have a large influence on the effect estimates. Third, the diagnosis of a nonfocal TNA can be difficult and the questionnaire was administered by several different unblinded interviewers which carries the risk of misclassification. However, we used a standardized questionnaire and systematically asked for nonfocal TNAs. Last, we had no detailed information regarding diagnostic examinations in patients with nonfocal TNAs

and as such could not be completely sure that other diagnoses were ruled out.

In conclusion, our study indicates that nonfocal TNAs are highly common in patients with a distant TIA or nondisabling stroke. Patients with CAO experience multiple nonfocal TNAs more often than patients without CAO. Since nonfocal TNAs are highly prevalent and it is unknown whether they should be a reason to adapt clinical management, future research is needed to understand underlying mechanisms and prognosis.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Heart Brain Connection (HBC) consortium is supported by the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation (CVON 2012-06 HBC), the Netherlands Organisation for Health Research and Development and the Royal Netherland Academy of Sciences. CJM Klijn is supported by grants from the Dutch Heart Foundation (2012T077) and ZonMW (015008048).The SMART study is supported by a grant from the University Medical Center Utrecht.

### Ethical approval

The HBC study and SMART study were approved by the Ethics Committee of the Leiden UMC and UMC Utrecht, respectively.

### Informed consent

Written informed consent was obtained from all participants.

### Guarantor

EAO, EJV and LJK.

### Authors' contribution

EAO and EJV performed the interviews and data extraction; EAO, EJV, JPG, AA and LJK designed the study plan and were involved in data analysis and interpretation of the results. EAO and EJV wrote the first version of the manuscript. All authors contributed to revision of the manuscript and gave final approval to submit the manuscript for publication.

### Acknowledgements

We gratefully acknowledge the contribution of researchers and participants of the SMART Study Group and HBC Study Group.

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## Appendix

Collaborators of the Heart Brain Connection study are R.J. van Oostenbrugge, H.P. Brunner-La Rocca, A.C. van Rossum, M.A. van Buchem, A. de Roos, W.M. van der Flier, W.J. Niessen, R.J. an der Geest, M.A. Ikram, P.J. Koudstaal, M. Daemen, M.J.P. van Osch.

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