Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2019;47:303–308
DOI: 10.1159/000502334

Received: January 25, 2019
Accepted: July 23, 2019
Published online: August 16, 2019

Cerebral Perfusion and the Occurrence of Nonfocal Transient Neurological Attacks

Eline A. Oudeman[a, c] Esther E. Bron[b] Renske M. Van den Berg-Vos[c]
Jacoba P. Greving[d] Geert Jan Biessels[a] Catharina J.M. Klijn[a, e]
L. Jaap Kappelle[a] on behalf of the Heart-Brain Connection Consortium

[a]Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [b]Department of Biomedical Imaging, Erasmus MC, Rotterdam, The Netherlands; [c]Department of Neurology, OLVG West, Amsterdam, The Netherlands; [d]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [e]Department of Neurology, Donders Institute for Brain, Cognition, and Behavior, Center for Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands

Keywords
Nonfocal transient neurological attacks · Cerebral perfusion · Quantitative magnetic resonance angiography · Heart failure

Abstract
Introduction: Nonfocal transient neurological attacks (TNAs) are associated with an increased risk of cardiac events, stroke and dementia. Their etiology is still unknown. Global cerebral hypoperfusion has been suggested to play a role in their etiology, but this has not been investigated. We assessed whether lower total brain perfusion is associated with a higher occurrence of TNAs. ***Methods:*** Between 2015 and 2018, patients with heart failure were included in the Heart Brain Connection study. Patients underwent brain magnetic resonance imaging, including quantitative magnetic resonance angiography (QMRA) to measure cerebral blood flow (CBF). We calculated total brain perfusion of each participant by dividing total CBF by brain volume. Patients were interviewed with a standardized questionnaire on the occurrence of TNAs by physicians who were blinded to QMRA flow status. We assessed the relation between total brain perfusion and the occurrence of TNAs with Poisson regression analysis. ***Results:*** Of 136 patients (mean age 70 years, 68% men), 29 (21%) experienced ≥1 TNAs. Nonrotatory dizziness was the most common subtype of TNA. Patients with TNAs were more often female and more often had angina pectoris than patients without TNAs, but total CBF and total brain perfusion were not different between both groups. Total brain perfusion was not associated with the occurrence of TNAs (adjusted risk ratio 1.12, 95% CI 0.88–1.42). ***Conclusion:*** We found no association between total brain perfusion and the occurrence of TNAs in patients with heart failure.

Introduction

Nonfocal transient neurological attacks (TNAs) are characterized by an acute onset of neurological signs or symptoms, such as unsteadiness, confusion or bilateral weakness [1]. In contrast to transient ischemic attacks (TIAs), the signs and symptoms of TNAs cannot be attributed to one specific arterial territory of the brain [1, 2].

KARGER

E-Mail karger@karger.com
www.karger.com/ced

Eline Anna Oudeman
Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus
University Medical Center Utrecht, Utrecht University
Heidelberglaan 100, NL–3584 CX Utrecht (The Netherlands)
E-Mail e.a.oudeman@umcutrecht.nl

TNAs are not a diagnostic entity, and the lack of a specific ICD code for TNA, for example, through the use of medical registries, makes it harder to study this topic. However, TNAs have been found to be associated with an increased risk of cardiac events, stroke, and dementia [1, 3]. Prevalence rates of TNAs vary highly between populations, ranging from 2% in the preceding 3 years in healthy participants aged 55 years or older to 45% in the preceding 6 months in patients with a recent TIA or nondisabling ischemic stroke with carotid or vertebral artery stenosis [4, 5]. In a population-based study, TNAs were associated with smoking, hypertension, and angina pectoris [4].

Consensus on the etiology of TNAs and its pathogenesis is still lacking. Both transient and chronic global cerebral hypoperfusion have been suggested to be an important causal factor [3, 6]. However, as there is no clear evidence to support this hypothesis, debate remains [3, 6].

Patients with heart failure are at increased risk of cerebral hypoperfusion, which is thought to be mediated through a reduced cardiac output, and related to the New York Heart Association (NYHA) classification and duration of heart failure [7–10]. We therefore investigated the occurrence of TNAs and their association with cerebral perfusion in patients with heart failure. We hypothesized that, in these patients, a recent TNA is related to chronic global cerebral hypoperfusion.

Methods

Study Population and Design

Between September 2015 and August 2018, 162 patients with heart failure were recruited from cardiology outpatient clinics in the Netherlands. Inclusion criteria were an established diagnosis of heart failure that had been clinically stable for at least 6 months. Heart failure was defined according to the European Cardiology Society Guidelines as both symptoms and signs typical of heart failure with objective evidence of a structural or functional abnormality of the heart at rest on routine echocardiography [11]. All patients were 50 years or older and independent in daily living. Among others, exclusion criteria were a contraindication to undergo magnetic resonance imaging (MRI) and atrial fibrillation at the moment of inclusion [12].

The current study is embedded in the Heart Brain Connection (HBC) study, a multicenter cohort study that focusses on cardiovascular and hemodynamic contributions to cognitive impairment [12]. Detailed information on the rationale and design has been described elsewhere [12]. The HBC study was approved by the Ethics Committee at the Leiden University Medical Center. All participants provided written informed consent.

Patient Characteristics

Patients were assessed by a trained physician or research nurse using a standardized interview on demographics, vascular risk factors, and the occurrence of nonfocal symptoms in the preceding 6 months (Table 1) [1, 12]. TNAs were defined as attacks of 1 or more nonfocal symptoms with an acute onset, a minimum duration of 30 seconds and a maximum duration of 24 h. The interviewer was blinded to the quantitative magnetic resonance angiography (QMRA) flow status. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, and characteristics of heart failure were derived from medical records. Systolic and diastolic blood pressures were measured on the left and right arm with an automatic blood pressure monitor; the mean of these 2 readings was used for analyses.

Table 1. Predefined nonfocal neurological symptoms with occurrence of each nonfocal symptom in the past 6 months

Nonfocal symptoms	Number (%)
Unconsciousness	4 (14)
Confusion	1 (3)
Amnesia	1 (3)
Unsteadiness	4 (14)
Bilateral leg weakness	2 (7)
Blurred vision	3 (10)
Nonrotatory dizziness	22 (76)
Paresthesias	4 (14)

All symptoms should have an acute onset, a minimum duration of 30 s and a maximum duration of 24 h.

Assessment of MRI and QMRA Flow Status

Patients underwent brain MRI, including QMRA [13–15]. MRI was performed on 3T scanners with a standardized protocol (Philips Ingenia, Philips Achieva and Philips Gemini; Philips Medical Systems, Best, the Netherlands). We acquired T1-weighted sequences (resolution = $1 \times 1 \times 1$ mm^3, duration = 6 min 47 s, MP-RAGE; repetition time [TR] = 8.2 ms; echo time [TE] = 4.5 ms; shot interval = 3,000 ms; flip angle = 8°; inversion delay = 990 ms) and fluid-attenuated inversion recovery sequences (resolution $1.11 \times 1.11 \times 1.11$ mm^3, duration = 4 min 43s, TR = 4,800 ms, TE = 313 ms, inversion time 1.650 ms, turbo spin-echo factor 182). A neuroradiologist, who was blinded to clinical information, rated all MRI scans on the presence of brain infarction.

For flow measurement, QMRA was performed [13–15]. On a sagittal angiographic MRI scout image, a transverse imaging plane perpendicular both to the precavernous portion of the internal carotid arteries and to the middle part of the basilar artery was chosen for a 2D gradient-echo phase contrast sequence (resolution $1.17 \times 1.17 \times 5$ mm^3, duration = 0.43 s, TR = 12 ms, TE = 8.2 ms, flip angle = 10°, velocity encoding = 200 cm/s, untriggered, 10 averages).

Assessment of Brain Volume, Total Cerebral Blood Flow and Total Brain Perfusion

For assessment of brain volume, a fully automated brain tissue and white matter hyperintensity segmentation method were combined with manual segmentation of brain volumes and infarcts based on T1-weighted and fluid attenuated inversion recovery sequencing scans [16]. Total brain volume (in mL) was corrected for infarcts and calculated by adding up gray and white matter volumes [16].

Total cerebral blood flow (CBF, in mL/min) was calculated from the phase-contrast images. Regions of interest were manu-

Table 2. Characteristics and QMRA flow status of patients with and without TNAs

	No TNA (n = 107)	≥1 TNAs (n = 29)	p value
Characteristics			
Gender, male	77 (72)	15 (52)	0.04
Age, years	70±10	69±9	0.59
Current smoking	15 (14)	5 (17)	0.91
Diabetes mellitus	18 (17)	3 (10)	0.36
Hyperlipidemia	47 (44)	15 (54)	0.38
Hypertension	55 (51)	16 (57)	0.59
Angina pectoris	14 (13)	12 (41)	0.001
History			
Myocardial infarction	54 (50)	16 (55)	0.65
TIA	8 (8)	5 (17)	0.11
Ischemic stroke	5 (5)	2 (7)	0.63
Blood pressure, mm Hg			
Systolic	135±18	135±16	1.00
Diastolic	76±10	77±13	0.71
NYHA classification			0.35
Class I	49 (46)	8 (28)	
Class I–II	17 (16)	6 (21)	
Class II	30 (28)	13 (45)	
Class II–III	6 (6)	1 (3)	
Class III	5 (5)	1 (3)	
Duration of heart failure, years	4±1	3±1	0.18
LVEF (percentages)	43±8	44±9	0.47
MRI/QMRA findings			
Visible brain infarcts	44 (41)	11 (38)	0.76
Total CBF, mL/min	556±159	592±164	0.29
Total brain volume, mL	1,093±109	1,077±115	0.55
Total brain perfusion, mL/min/100 mL	51.2±15.2	54.9±13.7	0.25

Numbers are n (%) or mean ± SD.

MRI/QMRA, magnetic resonance imaging/quantitative magnetic resonance angiography; TNA, nonfocal transient neurological attack; TIA, transient ischemic attack; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CBF, cerebral blood flow.

ally drawn closely around the vessel lumens of both internal carotid arteries and the basilar artery using the flow analysis tool of Mass software (Division of Image Processing, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands) [14]. Flow velocities were multiplied by the cross-sectional area of the regions of interest to obtain volume flow rates (in mL/min). The flow through the 3 vessels was then summed to calculate total CBF (in mL/min).

We calculated total brain perfusion (in mL/min per 100 mL) by dividing each individual's total CBF (in mL/min) by brain volume (in mL) and multiplying the result by 100.

Statistical Analysis

Descriptive analyses characterize the study population of heart failure patients with and without TNAs. Differences were determined with independent sample t tests, chi-square-tests, or Fisher's exact tests when appropriate.

We assessed the relation between total brain perfusion and TNAs with Poisson regression analysis with robust standard errors (SEs). We calculated crude and adjusted risk ratios (RR, expressed per standard deviation (SD)) with corresponding 95% CIs for the occurrence of ≥1 TNAs. Adjustments were made for age, sex, and angina pectoris, as these factors were considered a priori to be potential confounders of the association between total brain perfusion and TNAs.

Results

A total of 162 patients with heart failure were included in the HBC study. After exclusion of 7 patients (4%) with missing questionnaires on nonfocal symptoms and 19 patients (12%) with unreliable measures of total brain perfusion, 136 patients (mean age 69.9 years [SD 9.6], 67.6% male) remained for analyses. Characteristics of the study population are described in Table 2. Twenty-nine patients (21%) had experienced ≥1 TNAs in the preceding

6 months. Of these 29 patients, 21 patients experienced 1 TNA and 8 patients experienced 2 or more TNAs (median 1, interquartile range 1–2). Nonrotatory dizziness was the most common subtype of TNA (Table 1). Patients with TNAs were more often female (48 vs. 28%, $p = 0.039$) and more often had angina pectoris (41 vs. 13%, $p = 0.001$) than patients without TNAs. Patients with and without TNAs were comparable with respect to age and vascular risk factors. Furthermore, LVEF, duration of heart failure, and NYHA classification did not differ between patients with and without TNAs.

Total CBF, total brain volume, and total brain perfusion were similar between patients with and without TNAs (Table 2). Total brain perfusion was not associated with the occurrence of TNAs (crude RR 1.20, 95% CI 0.92–1.56; adjusted RR 1.12, 95% CI 0.88–1.42).

Discussion

This study shows that, in heart failure patients, there is no difference in total brain perfusion as measured by QMRA between patients with and without TNAs. Our results do not support the often-presumed hypothesis that global cerebral hypoperfusion is associated with the occurrence of TNAs.

Most previous studies that focused on the etiology of TNAs have investigated the relation between TNAs and different markers of cardiac disease [3, 6, 17]. Even though TNAs were associated with a higher risk of major cardiac events than TIAs, NT-proBNP levels were not significantly higher in patients with TNAs than in patients with TIAs [3, 6]. These findings are comparable with our results, as duration of heart failure, LVEF, and NYHA classification did not differ between patients with and without TNAs. Furthermore, previous studies found no relation between TNAs and arrhythmias on 24-h ECG monitoring, nor between TNAs and atrial fibrillation [4, 17, 18]. In our study, known atrial fibrillation was an exclusion criterion, but the incidence of TNAs was still relatively high among patients with heart failure. Furthermore, we found no difference in visible brain infarcts on MRI between patients with and without TNAs, supporting previous findings that the role of cardio-embolism in the etiology of TNAs is relatively small.

Another study found acute focal cerebral ischemia as measured with MR diffusion weighted imaging within 7 days after a TNA in about a quarter of patients [19]. This suggests that focal cerebral ischemia might play a role. From a clinical point of view, TNAs cannot be explained by a focal deficit in the brain. This is enhanced by the nonfocal nature of signs and symptoms accompanying TNAs, which makes it difficult for patients to express the signs and symptoms they have experienced. Even though focal cerebral ischemia is likely to play a role in the etiology of TNAs, the causal pathway between TNAs and focal ischemic lesions remains unclear. Whether these ischemic lesions are caused by embolism, local vasculopathy or hypoperfusion remains unanswered.

Studies on the prevalence of TNAs are limited. Still, our study showed a relatively high prevalence (21%) of TNAs in the preceding 6 months. In a population-based study, 2% of patients 55 years or older experienced a TNA in the preceding 3 years [4]. However, in a hospital-based study, nonfocal symptoms occurred more frequently in patients with a recent TIA or nondisabling ischemic stroke [5]. In this study, 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 6 months preceding the ischemic event [5]. We could not attribute the relatively high prevalence of TNAs in our study to cerebral hypoperfusion as a consequence of heart failure, nor to the duration of heart failure, the LVEF or NYHA classification as these characteristics of heart failure did not differ between patients with and without TNAs. Although we can only hypothesize, the relatively high prevalence of TNAs in patients with heart failure might be related to the relatively high prevalence of hypertension and angina pectoris in our patient population, as these factors were previously associated with the occurrence of TNAs in a population-based study [4].

Our finding that TNAs occurred more often in females than in males is different from a previous study in which similar male-female ratios were found in patients with TNAs, patients with TIAs, and in control participants without any neurological attacks [1]. These differences might depend on the classification of nonfocal symptoms that was used in each study as we have used "blurred vision" instead of "positive visual phenomena" and only "unconsciousness" instead of both "decreased consciousness and unconsciousness" [1]. Besides, we did not include "unwell feelings" as a TNA [1].

Our study has some limitations. First, our results may have been influenced by recall bias as we could have missed TNAs that were not remembered by the patient. However, we used a standardized questionnaire that covered a broad spectrum of nonfocal symptoms. Second, we did not measure cerebral perfusion at the very moment of a TNA. Therefore, transient global cerebral hypoperfu-

sion cannot be excluded as the cause of TNAs. We have no data on which activities were undertaken during each TNA or on the duration of TNAs in our cohort. However, as TNAs typically last <1 h, measuring cerebral perfusion during a TNA is difficult [4]. Third, flow measurement by QMRA does not allow region specific assessment of cerebral perfusion, which precludes identification of local areas of hypoperfusion. Fourth, because we studied patients 50 years or older with heart failure, the generalizability to a broader group of patients with TNAs is limited. However, our patient population was chosen deliberately, as patients with heart failure are vulnerable for cerebral hypoperfusion through a compromised cardiac output [7–10].

Strengths of our study are that we, for the first time, report the frequency of TNAs in the specific population of patients with heart failure. Furthermore, all data were systematically collected by trained physicians or research nurses.

In conclusion, our findings do not support global hypoperfusion of the brain as a risk factor for TNAs. Further studies are needed to unravel the possible mechanisms leading to TNAs.

Acknowledgments

We gratefully acknowledge the contribution of researchers and participants of the HBC consortium [12].

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The 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 Netherlands Academy of Sciences. C.J.M.K.: is supported by grants from the Dutch Heart Foundation (2012T077) and ZonMw (015008048).

References

1 Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA. 2007 Dec;298(24):2877–85.
2 A classification and outline of cerebrovascular diseases. II. Stroke. 1975 Sep-Oct;6(5):564–616.
3 Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J; The Dutch TIA Study Group. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. Lancet. 1992 Sep;340(8820):630–3.
4 Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. Stroke. 1997 Apr;28(4):768–73.
5 Compter A, Kappelle LJ, Algra A, van der Worp HB. Nonfocal symptoms are more frequent in patients with vertebral artery than carotid artery stenosis. Cerebrovasc Dis. 2013;35(4):378–84.
6 Plas GJ, Jurg SD, Brusse-keizer M, Dippel DW, Koudstaal PJ, den Hertog HM. N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) levels are increased in patients with transient ischemic attack accompanied by nonfocal symptoms. J Am Heart Assoc. 2015 Dec;4(12):pii:e002072.
7 Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke. 2001 Nov;32(11):2530–3.
8 Choi BR, Kim JS, Yang YJ, Park KM, Lee CW, Kim YH, et al. Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol. 2006 May;97(9):1365–9.
9 Paulson OB, Jarden JO, Godtfredsen J, Vorstrup S. Cerebral blood flow in patients with congestive heart failure treated with captopril. Am J Med. 1984 May;76(5 5B):91–5.
10 Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow. Anesthesiology. 2015 Nov;123(5):1198–208.
11 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul;37(27):2129–200.
12 Hooghiemstra AM, Bertens AS, Leeuwis AE, Bron EE, Bots ML, Brunner-La Rocca HP, et al.; Heart-Brain Connection Consortium. The missing link in the pathophysiology of vascular cognitive impairment: design of the Heart-Brain study. Cerebrovasc Dis Extra. 2017;7(3):140–52.
13 Dolui S, Wang Z, Wang DJ, Mattay R, Finkel M, Elliott M, et al. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. J Cereb Blood Flow Metab. 2016 Jul;36(7):1244–56.
14 Spilt A, Box FM, van der Geest RJ, Reiber JH, Kunz P, Kamper AM, et al. Reproducibility of total cerebral blood flow measurements using phase contrast magnetic resonance imaging. J Magn Reson Imaging. 2002 Jul;16(1):1–5.
15 Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Vrooman HA, Hofman A, et al. Total cerebral blood flow and total brain perfusion in the general population: the Rotterdam Scan Study. J Cereb Blood Flow Metab. 2008 Feb;28(2):412–9.
16 de Boer R, Vrooman HA, van der Lijn F, Vernooij MW, Ikram MA, van der Lugt A, et al. White matter lesion extension to automatic brain tissue segmentation on MRI. Neuroimage. 2009 May;45(4):1151–61.

17 de Bono DP, Warlow CP, Hyman NM. Cardiac rhythm abnormalities in patients presenting with transient non-focal neurological symptoms: a diagnostic grey area? Br Med J (Clin Res Ed). 1982 May;284(6327):1437–9.

18 Plas GJ, Booij HA, Brouwers PJ, Brusse-Keizer M, Koudstaal PJ, Dippel DW, et al. Nonfocal symptoms in patients with transient ischemic attack or ischemic stroke: occurrence, clinical determinants, and association with cardiac history. Cerebrovasc Dis. 2016;42(5-6):439–45.

19 van Rooij FG, Vermeer SE, Góraj BM, Koudstaal PJ, Richard E, de Leeuw FE, et al. Diffusion-weighted imaging in transient neurological attacks. Ann Neurol. 2015 Dec;78(6):1005–10.