Cerebral Circulation - Cognition and Behavior 5 (2023) 100169

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

Lower haemoglobin concentrations are associated with impaired cognition in patients with carotid artery occlusion

Sanne Kuipers [a,*], Sean W. Willemse [a], Jacoba P. Greving [b], Esther E. Bron [c], Robert J. van Oostenbrugge [d], Matthias J.P. van Osch [e], Geert Jan Biessels [a], L. Jaap Kappelle [a], Heart-Brain Connection Consortium

[a] Department of Neurology, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht, the Netherlands
[b] Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Radiology & Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands
[d] Department of Neurology, Maastricht University Medical Centre, Maastricht, the Netherlands
[e] Department of Radiology, Leiden University Medical Centre, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Anaemia
Carotid artery occlusion
Cerebral blood flow
Cognition
Haemoglobin

ABSTRACT

Background: Patients with carotid artery occlusion (CAO) are vulnerable to cognitive impairment (CI). Anaemia is associated with CI in the general population. We hypothesized that lower haemoglobin is associated with cognitive impairment (CI) in patients with CAO and that this association is accentuated by cerebral blood flow (CBF).

Methods: 104 patients (mean age 66±8 years, 77% men) with complete CAO from the Heart-Brain Connection study were included. Anaemia was defined as haemoglobin < 12 g/dL for women and < 13 g/dL for men. Cognitive test results were standardized into z-scores (using a reference group) in four cognitive domains. Patients were classified as cognitively impaired when ≥ one domain was impaired. The association between lower haemoglobin and both cognitive domain z-scores and the presence of CI was assessed with adjusted (age, sex, education and ischaemic stroke) regression models. Total CBF (measured with phase contrast MRI) and the interaction term haemoglobin*CBF were additionally added to the analyses.

Results: Anaemia was present in 6 (6%) patients and was associated with CI (RR 2.54, 95% CI 1.36; 4.76). Lower haemoglobin was associated with the presence of CI (RR per minus 1 g/dL haemoglobin 1.15, 95% CI 1.02; 1.30). This association was strongest for the attention-psychomotor speed domain (RR for impaired attention-psychomotor speed functioning per minus 1 g/dL haemoglobin 1.27, 95% CI 1.09;1.47) and ß for attention-psychomotor speed z-scores per minus 1 g/dL haemoglobin -0.19, 95% CI -0.33; -0.05). Adjustment for CBF did not affect these results and we found no interaction between haemoglobin and CBF in relation to cognition.

Conclusion: Lower haemoglobin concentrations are associated with CI in patients with complete CAO, particularly in the domain attention-psychomotor speed. CBF did not accentuate this association. If validated in longitudinal studies, haemoglobin might be a viable target to prevent cognitive deterioration in patients with CAO.

Introduction

Carotid artery occlusion (CAO) can be found in nine percent of patients with transient ischaemic attacks (TIAs) or ischaemic stroke [1]. Asymptomatic CAO is speculated to be more common, although its prevalence is largely unknown [2]. Due to either thrombo-embolisms or haemodynamic impairment patients with CAO are prone to develop ischaemic stroke [1]. Apart from stroke, patients with CAO have an increased risk of cognitive impairment (CI), with a prevalence up to 71% [3]. CI in patients with CAO has been attributed to cerebral infarction or white matter lesions [3]. Besides vascular brain injury, CI in these patients may also be caused by hemodynamic impairment without structural brain abnormalities [4], but studies exploring this showed conflicting results [3].

Another factor that might contribute to the development of CI in patients with CAO, but has not yet been studied in that setting, is anaemia. Haemoglobin is an important determinant of oxygen carrying

* Corresponding author at: Department of Neurology G03.232, University Medical Centre Utrecht, Heidelberglaan 100, Utrecht, 3508 GA Utrecht, the Netherlands.
E-mail address: s.kuipers-2@umcutrecht.nl (S. Kuipers).

https://doi.org/10.1016/j.cccb.2023.100169
Received 17 October 2022; Received in revised form 1 April 2023; Accepted 9 June 2023
Available online 24 June 2023

Abbreviations and acronyms

CAO	carotid artery occlusion
CBF	cerebral blood flow

capacity of the blood, that is known to influence cerebral blood flow (CBF) by cerebral auto-regulation [5–7]. If compensation mechanisms fail, lower haemoglobin concentrations and disturbed cerebral hemodynamic may lead to ischaemia [8]. Previous studies found an association between lower haemoglobin concentrations (anaemia) and worse cognitive functioning in the general (elderly) population [9–11] and in patients with various clinical conditions such as renal disease [12], heart failure [13] and acute ischaemic stroke [14,15]. We hypothesized that lower haemoglobin concentrations are associated with CI in patients with CAO and that this association is accentuated by CBF due to inadequate compensation for additional cerebral hypoperfusion.

This study aims to assess the association between haemoglobin and cognitive performance in patients with complete CAO, and ascertain whether CBF accentuates this association.

Materials and methods

Patient population

We included patients from the Heart-Brain Connection Study, an observational multicentre cohort study that aims to determine the influence of haemodynamic parameters on CI. The rationale and methods were described previously [16].

As a model of haemodynamic compromise, we included patients with a complete CAO. Patients were recruited between September 2014 and September 2017 from three outpatient clinics in The Netherlands. All patients had a symptomatic or asymptomatic complete internal carotid artery (ICA) occlusion as confirmed by ultrasound, MR angiography and/or CT angiography. Further inclusion criteria were age of 50 years or older and the ability to undergo cognitive testing and other study procedures (such as imaging). Patients were excluded if they had an ischaemic stroke or TIA in the three months prior to inclusion, if they were scheduled to undergo carotid surgery or if they had other psychiatric or neurological disorders that could affect cognitive performance [16].

All participants provided written informed consent. The Medical Ethics Review Committee of the Leiden UMC performed central approval. Local medical ethical committees of all sites approved the local performance of the study.

Patient characteristics

Patient demographics were registered by trained physicians or research nurses using a standardized interview and physical examination. Level of education was ranked according to the Verhage criteria [17].

All patients underwent blood tests to determine haemoglobin concentration in g/dL, haematocrit levels as a ratio (L/L) and estimated glomerular function rates in mL/1.73m^2. Anaemia was defined according to the World Health Organization criteria: haemoglobin concentrations $<$12 g/dL for women and haemoglobin concentrations of $<$13 g/dL for men [18]. An elevated haemoglobin concentration was defined as $>$15.5 g/dL for women and $>$17.5 g/dL for men.

MRI protocol and assessment of CBF

MRI of the brain was performed with 3T scanners (Philips Ingenia and Philips Achieva). We acquired 3D T1-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging and phase-contrast (PC) imaging. PC scans were obtained with a resolution 1.17 $\times$ 1.17 $\times$ 5 mm^3. Relevant contrast parameters were: TR = 12 ms; TE = 8.2 ms; flip angle = 10°; velocity encoding = 200 cm/s; untriggered; 10 averages [16]. PC scans of the cerebropetal arteries were used to quantify the total CBF. The circumferences of the left and right carotid artery and the basilar artery were manually drawn using the flow analysis tool of Mass software [19]. The cross-sectional area was multiplied with the flow velocity in order to obtain the volume flow rate (in mL/min) of each blood vessel. The sum of the flow rates was used to calculate the total blood flow to the brain (in mL/min). Total flow of the brain was divided by the total brain volume and multiplied by 100 in order to obtain the CBF in ml/100 g/min. Total brain volume was defined as the sum of grey and white matter volume and was calculated with an automated pipeline (Quantib brain, Rotterdam, the Netherlands) after manual exclusion of infarcts and other pathologies.

Neuropsychological assessment

All patients underwent a standardized neuropsychological assessment, based on the Dutch Parelsnoer Initiative [20]. Results of the neuropsychological assessment have been compiled in four different domains: memory, language, attention-psychomotor speed and executive functioning. The supplementary table shows an overview of the neuropsychological test protocol. All test scores were standardized into z-scores using reference participants (n = 128, mean age: 65.6 $\pm$ 7.4 years, 53% men), who were recruited amongst spouses and relatives of patients (detailed methods are described previously [21]). Global cognitive functioning was calculated as an average z-score across domains. We considered a domain as impaired when the z-score was ≤ -1.5 [16,21]. Patients were classified as cognitively impaired when at least one domain was impaired.

Statistical analysis

Linear regression was used to describe the association between minus 1 g/dL haemoglobin concentration and cognitive domain z-scores (global cognition and the four aforementioned cognitive domains). Poisson regression analysis with robust standard errors was used to describe the association between minus 1 g/dL haemoglobin concentration or the presence of anaemia and CI. The associations were expressed as ß (95% CI) per minus 1 g/dL haemoglobin for continuous outcomes (domain z-scores) and Risk Ratio's (95% CI) per minus 1 g/dL haemoglobin for dichotomous outcomes (impaired cognition). In both the linear and poisson regression models adjustments were made for age, sex, education and history of ischaemic stroke (models A). Additionally, we applied a Bonferroni adjustment to correct for testing multiple cognitive domains [22]. To ascertain whether total CBF accentuates the association between haemoglobin and cognition, CBF and the interaction term haemoglobin*CBF were subsequently added to the analyses (models B). All statistical analyses were performed with R (version 1.3.1093).

Results

A total of 105 patients with CAO were included in the HBC study. After exclusion of one patient with missing haemoglobin concentration and neuropsychological test scores, 104 patients (mean age 66.2 $\pm$ 8.1 years, 77% men) remained for analyses. Patient characteristics are summarized in Table 1. The mean education score was 5.0 $\pm$ 1.2. Sixty-three patients (61%) had a right-sided occlusion of the ICA and 14 patients (13%) had a bilateral ICA occlusion. In 89 patients (86%), the occlusion was symptomatic. Fifty-four patients (52%) had a history of ischaemic stroke and 77 (74%) patients had a history of TIA. Mean haemoglobin concentration was 14.5 $\pm$ 1.5 g/dL. The majority (93%) of the patients had a haemoglobin concentration within the normal range.

Table 1
Baseline characteristics.

Characteristics	
Age (years), mean (sd)	66.2 (8.1)
Male sex, n (%)	80 (77)
Education score (7 levels), mean (sd)a	5.0 (1.2)
Hypertension in medical history, n (%)	81 (78)
hypertension at physical examination ≥140/90 mmhg, n (%)	72 (70)
hypercholesterolaemia in medical history or use of lipid lowering drugs, n (%)	96 (92)
Current smoking, n (%)	28 (27)
Diabetes mellitus in medical history, n (%)	31 (30)
Body mass index of ≥ 30, n (%)	28 (27)
History of TIA, n (%)[b]	77 (74)
History of ischaemic stroke, n (%)[b]	54 (52)
Right-sided internal carotid occlusion, n (%)	63 (61)
Bilateral internal carotid occlusion, n (%)	14 (13)
Symptomatic internal carotid occlusion, n (%)	89 (86)
Contralateral internal carotid stenosis (>50%), n (%)	12 (12)
Common carotid stenosis (>50%) or occlusion, n (%)	18 (17)
Vertebral artery stenosis (>50%) or occlusion, n (%)	30 (29)
Haemoglobin concentration (g/dL), mean (sd)	14.5 (1.5)
Anaemia, n (%)[c]	6 (6)
Elevated haemoglobin concentrations, n (%)[d]	1 (1)
Haematocrit (L/L), mean (sd)	0.43 (0.04)
eGFR <60 mL per 1.73m^2, n (%)	12 (12)
Total CBF (ml/100 g/min), mean (sd) (available in 96 patients)	45.5 (12.0)

Data are presented as mean (sd) or number (percentage).
CBF: cerebral blood flow; eGFR: estimated glomerular filtration rate; TIA: transient ischaemic attack.
[a]Education was assessed with the system of Verhage, ranging from 1 to 7 (low to high education).
[b] Some patients had both a history of TIA and ischaemic stroke.
[c] Anaemia was defined as a haemoglobin concentration of <12 g/dL for women and <13 g/dL for men.
[d] Elevated haemoglobin concentration was defined as >15.5 g/dL for women and >17.5 g/dL for men.

Anaemia was present in 6 patients (6%) (1 female and 5 males). One male patient had a slightly elevated haemoglobin concentration, of 17.6 g/dL. Data regarding total CBF was missing in 8 patients (8%) due to MRI logistics. Mean total CBF was 45.5 ± 12.0 ml/100 g/min.

The mean global cognitive functioning z-score was −0.53±0.67, with the lowest scores for the domain attention-psychomotor speed (mean z-score −0.87±1.11). CI was present in 36% of the patients, also most commonly involving the domains attention-psychomotor speed (23%) and memory (16%) (Table 2).

Presence of anaemia ($n = 6$) was associated with CI (age, sex, education and history of ischaemic stroke adjusted RR 2.54, 95% CI 1.36; 4.76, $p = 0.004$). Lower haemoglobin concentration was associated with the presence of CI (age, sex, education and history of ischaemic stroke adjusted RR per minus 1 g/dL haemoglobin 1.15, 95% CI 1.02; 1.30). This association was strongest for the domain attention-psychomotor speed (adjusted RR for impaired attention-psychomotor speed functioning per minus 1 g/dL haemoglobin 1.27, 95% CI 1.09; 1.47). Assessment of the relation between lower haemoglobin concentration and worse attention-psychomotor z-scores showed the same results (adjusted ß per minus 1 g/dL haemoglobin −0.19, 95% CI −0.33;−0.05) (Fig. 1 and Table 3 'models A'). After correction for testing multiple cognitive domains the association between anaemia and CI (corrected $p = 0.02$) and the associations between lower haemoglobin concentrations and worse cognitive functioning on the attention-psychomotor speed domain remained significant (corrected $p = 0.03$ for the linear model and $p = 0.01$ for the dichotomous model). Additional adjustments for total CBF did not change the results (Table 3 'models B'). Haemoglobin concentrations were inversely associated with total CBF (age and sex adjusted ß per minus 1 g/dL haemoglobin 2.22 ml/100 g/min, 95% CI 0.57; 3.86). There was no interaction between haemoglobin concentration and total CBF in relation to cognitive functioning in z-scores and presence of CI (p-values for interaction terms > 0.05).

Table 2
Unadjusted cognitive test results.

Cognitive outcome	Impaired, n (%)[a]	Z-score, mean (sd)
Global cognitive functioning[b]	37 (36)[c]	−0.53 (0.67)
Memory	17 (16)	−0.59 (1.24)
Language	4 (4)	−0.33 (0.56)
Attention-psychomotor speed	24 (23)	−0.87 (1.11)
Executive functioning	3 (3)	−0.35 (0.75)

Data are presented as number (percentage) of patients with impaired cognitive domains (cognitive domain z-score of 1.5 or lower) and mean (sd) z-scores.
[a] Patients were classified as cognitively impaired when at least one domain was impaired. We considered a cognitive domain as impaired when the z-score was equal or below −1.5. Patients that for example had impaired functioning on the memory domain could also had impaired functioning on other domains.
[b] Global cognitive functioning is the average z-score across the compound z-scores of memory, attention-psychomotor speed language, and executive functioning.
[c] n=10 patients had 2 or 3 impaired cognitive domains.

Discussion

This study shows that lower haemoglobin concentrations are independently associated with worse cognitive performance in patients with complete CAO, particularly in the cognitive domain attention-psychomotor speed. Total CBF did not accentuate the association between haemoglobin and cognition in these patients.

To the best of our knowledge, this is the first study on the association between haemoglobin concentration and cognition in patients with CAO. Our findings are largely in line with previous studies that assessed an association between low haemoglobin concentrations or anaemia and cognition in the general (elderly) population [9–11] and various clinical conditions [12–15]. A detailed comparison between our results and these previous studies is difficult, due to important differences in co-morbidities and in the prevalence of both anaemia and CI. In contrast to our findings, several population-based studies described a more inverted U-shaped association between haemoglobin concentration and cognitive functioning [9,10]. We could not assess an association between higher haemoglobin concentration and worse cognitive functioning, probably because our study had only one patient with an elevated haemoglobin concentration.

Against our hypothesis, CBF did not accentuate the observed association between haemoglobin and cognition: adjustment for CBF did not affect the results and we found no interaction between haemoglobin concentration and CBF in relation to cognition. Nevertheless, apart from cognition, haemoglobin concentration was inversely associated to total CBF, suggesting that the majority of the patients in our study did have the ability to compensate for lower haemoglobin concentrations with an increase in CBF. These findings supplement information in our understanding of the physiologic response of the brain to a decrease of haemoglobin concentration. However, as cerebral autoregulation is an active process that acts constantly, the cross-sectional design of this study and especially that CBF was measured in a resting, supine position might increase the risk for misinterpretation of the role CBF plays in the mechanism linking haemoglobin to cognition.

Longitudinal studies are needed to determine whether anaemia is causally linked to worse cognitive performance or whether anaemia is merely a marker of conditions associated with CI, such as frailty and declining health status. If the association between anaemia and worse cognitive performance is proven to be causal in patients with CAO, there may be an opportunity for prevention of cognitive deterioration through correction of reversible forms of anaemia in patients with CAO.

An important strength of this study is the relatively large number of clinically stable patients with CAO. Also, some limitations have to be

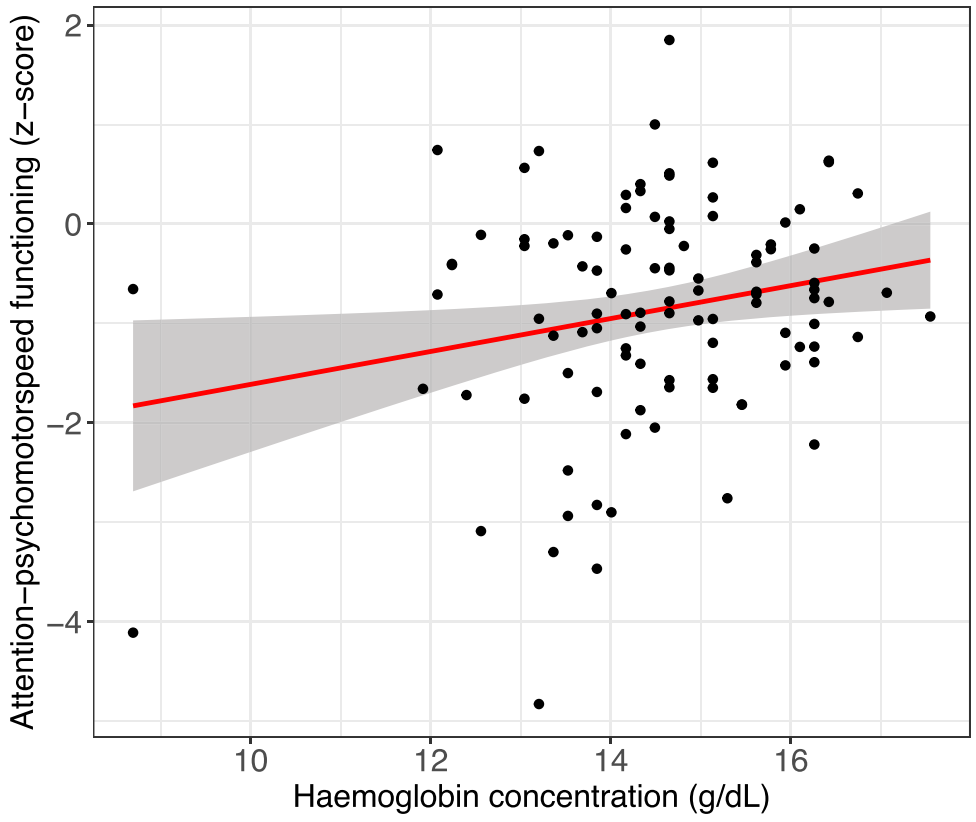

Fig. 1. Association between haemoglobin concentration and attention-psychomotor speed functioning
Legend: Plot showing the adjusted (for age, sex, education and history of ischaemic stroke) association between haemoglobin concentration (g/dL) and attention-psychomotor speed functioning (z-score), $\beta = 0.19$, p-value <0.01.

Table 3
Association between minus 1 g/dL haemoglobin concentration and cognitive outcome.

Cognitive outcome	Models A[a]				Models B[b,c]			
	ß (95% CI)	p	Risk Ratio (95% CI)	p	ß (95% CI)	p	Risk Ratio (95% CI)	p
Global cognitive functioning[d]	−0.07 (−0.15; 0.01)	0.08	1.15 (1.02; 1.30)	0.02	−0.08 (−0.16; 0.01)	0.08	1.16 (1.00; 1.35)	0.05
Memory	−0.09 (−0.24; 0.07)	0.27	1.07 (0.80; 1.41)	0.68	−0.11 (−0.27; 0.06)	0.21	1.09 (0.82; 1.45)	0.56
Language	0.01 (−0.07; 0.09)	0.78	0.62 (0.38; 1.02)	0.06	0.01 (−0.07; 0.09)	0.81	n/a[e]	n/a
Attention-psychomotor speed	−0.19 (−0.33; −0.05)	0.007[f]	1.27 (1.09; 1.47)	0.002[f]	−0.17 (−0.32; −0.02)	0.02	1.32 (1.06–1.65)	0.01
Executive functioning	−0.02 (−0.12; 0.08)	0.74	1.04 (0.39; 2.77)	0.92	−0.04 (−0.15; 0.07)	0.51	1.05 (0.32–3.44)	0.94

Data showing the association between haemoglobin concentration and cognitive outcome presented as ß (95% CI) per minus 1 g/dL haemoglobin for continuous outcomes (domain z-scores) and Risk Ratio's (95% CI) per minus 1 g/dL haemoglobin for dichotomous outcomes (impaired cognition).

[a] Models A include haemoglobin concentration in g/dl, age, sex, education and a history of ischaemic stroke as dependant variables and cognitive outcome (domain z-scores or impaired cognition) as independent variable. Additionally, we applied a Bonferroni adjustment to correct for testing multiple cognitive domains.

[b] Models B: same as model A but adding total CBF as dependant variable.

[c] To assess the interaction between haemoglobin concentration and total CBF, the interaction term (haemoglobin*CBF) was additionally added to models B. We found no interaction between haemoglobin and total CBF in relation to cognitive outcome (p-values for interaction terms all >0.05).

[d] Global cognitive functioning is the average z-score across the compound z-scores of memory, attention-psychomotor speed, language, and executive functioning. Overall, patients were classified as cognitively impaired when at least one domain was impaired.

[e] Not applicable because of overfitting.

[f] After correction for testing multiple cognitive domains these associations remained significant.

recognized. The cross-sectional design of this study precludes us to draw conclusions on pathophysiological mechanisms and to study the relation between haemoglobin and cognitive functioning over time. Furthermore, because of the low number of patients with anaemia in this study, the association between the presence of anaemia and CI has to be interpreted with caution. Also, at first sight the data points in the scatterplot of the association between haemoglobin concentration and attention-psychomotor speed z-scores may not convince to represent a 'perfect' straight line. We have checked the assumptions for linear regression and concluded that the datapoints are around a straight line. In addition, we found a normal distribution and variances of residuals. Moreover, given that all our findings point in the same direction, we are convinced of a relation between haemoglobin concentration and attention-psychomotor speed functioning. Another limitation is the absence of information about the aetiology of lower haemoglobin concentrations (such as mean corpuscular volume, iron status and medical diagnosis of anaemia) and other co-morbidities or medication use affecting rheology. Eight percent of the CBF values were missing because of logistic reasons, which means that this probably has not influenced our results. An alternative acquisition method for CBF would have been arterial spin labelling (ASL) MRI. However, we have chosen not to use ASL-MRI for this study, since the accuracy of ASL-MRI can be influenced

by haemoglobin concentrations [23,24] and by transit time effects as frequently observed in CAO [25]. As far as we know, PC imaging is not influenced by haemoglobin concentrations. Besides CBF, the estimated cerebral oxygen delivery would have been an interesting parameter in our study, however we did not have information about the oxygen saturation of our patients. It would have been interesting to study the relation between haemoglobin concentration and patterns of CI, but the number of patients with more than one impaired cognitive domain was too small to test this is our study. We performed an extensive neuropsychological assessment with a performance of $\leq$1.5 SD below the mean as cut-off demarcating CI. Other studies might have used other cut-offs [26], which may influence the estimated prevalence of CI. However, the high prevalence of CI in our study corresponds to previous literature amongst patients with CAO [3]. Additionally, severe depression might have affected the cognitive performance of our patients. However, in case of psychiatric or neurological diseases that may affect cognitive performance, patients were excluded. Therefore, we do not expect that mood disorders substantially have influenced the cognitive test results. Also, anaemia often is associated with fatigue. Therefore, the relation between lower haemoglobin and worse cognitive functioning may have been mediated by fatigue. However, this study did not aim to study underlying mechanisms of the association between haemoglobin and cognition. Finally, the use of a relatively limited neuropsychological test battery for the domain executive functioning might partially explain the relatively low number of patients with impaired executive functioning in our study.

In conclusion, we found that lower haemoglobin concentration is independently associated with worse cognitive performance in patients with complete CAO, particularly in the domain attention-psychomotor speed. CBF did not accentuate the association between haemoglobin and cognition in patients with CAO. Longitudinal studies are needed to determine whether haemoglobin is a viable treatment target in order to ameliorate cognitive function.

Declaration of Competing Interest

M.J.P. van Osch receives research support from Philips.

Funding Sources

This work is part of the Heart-Brain Connection crossroads (HBCx) consortium of the Dutch CardioVascular Alliance (DCVA). HBCx has received funding from the Dutch Heart Foundation under grant agreements 2018–28 and CVON 2012–06.

Acknowledgement

We gratefully acknowledge the contribution of researchers and participants of the HBCx consortium.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2023.100169.

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