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Original Paper

The Missing Link in the Pathophysiology of Vascular Cognitive Impairment: Design of the Heart-Brain Study

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Keywords

Cerebral hypoperfusion · Cardiovascular dysfunction · Cognitive decline · Heart failure · Carotid occlusive disease · Cerebral blood flow · Small vessel disease

Abstract

Background: Hemodynamic balance in the heart-brain axis is increasingly recognized as a crucial factor in maintaining functional and structural integrity of the brain and thereby cognitive functioning. Patients with heart failure (HF), carotid occlusive disease (COD), and vascular cognitive impairment (VCI) present themselves with complaints attributed to specific parts

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of the heart-brain axis, but hemodynamic changes often go beyond the part of the axis for which they primarily seek medical advice. The Heart-Brain Study hypothesizes that the hemodynamic status of the heart and the brain is an important but underestimated cause of VCI. We investigate this by studying to what extent hemodynamic changes contribute to VCI and what the mechanisms involved are. Here, we provide an overview of the design and protocol. ***Methods:*** The Heart-Brain Study is a multicenter cohort study with a follow-up measurement after 2 years among 645 participants (175 VCI, 175 COD, 175 HF, and 120 controls). Enrollment criteria are the following: 1 of the 3 diseases diagnosed according to current guidelines, age ≥50 years, no magnetic resonance contraindications, ability to undergo cognitive testing, and independence in daily life. A core clinical dataset is collected including sociodemographic factors, cardiovascular risk factors, detailed neurologic, cardiac, and medical history, medication, and a physical examination. In addition, we perform standardized neuropsychological testing, cardiac, vascular and brain MRI, and blood sampling. In subsets of participants we assess Alzheimer biomarkers in cerebrospinal fluid, and assess echocardiography and 24-hour blood pressure monitoring. Follow-up measurements after 2 years include neuropsychological testing, brain MRI, and blood samples for all participants. We use centralized state-of-the-art storage platforms for clinical and imaging data. Imaging data are processed centrally with automated standardized pipelines. ***Results and Conclusions:*** The Heart-Brain Study investigates relationships between (cardio-)vascular factors, the hemodynamic status of the heart and the brain, and cognitive impairment. By studying the complete heart-brain axis in patient groups that represent components of this axis, we have the opportunity to assess a combination of clinical and subclinical manifestations of disorders of the heart, vascular system and brain, with hemodynamic status as a possible binding factor.

Introduction

With the rapid aging of the population, the prevalence of cognitive decline and dementia increases [1–4]. Although Alzheimer disease is the most common cause of dementia, vascular disease is increasingly recognized as an independent contributor to cognitive impairment [1]. The term vascular cognitive impairment (VCI) has been introduced to describe the complete spectrum of cognitive disorders (mild and major) associated with and due to cerebrovascular disease [1, 5–8]. VCI can be the result of irreversible structural damage to the vascular system in the brain [9]. Based on that view, treatment for VCI is often restricted to secondary prevention by treating risk factors, such as high blood pressure [10]. Recent findings suggest that cerebral hypoperfusion can also hinder the function of the brain before structural damage occurs [9]. The latter is supported by the finding that nondemented patients with cardiovascular disease show cognitive decline [11] and that in patients with heart failure (HF) cognitive functioning can be enhanced by improving cardiac function [12–14]. Furthermore, the observation of cognitive impairment in carotid occlusive disease (COD) suggests a relationship between reduced cerebral blood flow (CBF) and cognitive functioning [15]. Thus, cardiac and (cerebro-)vascular pathology affecting CBF might influence cellular functions in the brain before structures are altered. Exploring the contribution of cardiac and (cerebro-)vascular pathology to brain alterations is important, because it could identify treatment targets for patients with cognitive impairment due to this type of pathology in the foreseeable future. Medication that improves hemodynamics, such as antihypertensive medication, is available at this moment. However, trials assessing the efficacy of such therapies in VCI are currently lacking. This is due to an incomplete understanding of the mechanisms involved and to the lack of research that identifies patients who will benefit most [1, 16, 17]. Since health care and research are usually

Textbox 1

The Heart-Brain Connection consortium
The Heart-Brain Connection consortium consists, in addition to the Heart-Brain Study, of preclinical, experimental, and clinical trial research. Here we briefly describe these studies and how they are connected to the clinical study. 1 Within the data of the Rotterdam Study [58], a large prospective cohort study in the city of Rotterdam, the Netherlands, we investigate the heart-brain link from a population-based perspective. If we can demonstrate putative causal associations, this extends the importance of cardiac function and cerebral hemodynamics for brain disease to an asymptomatic population. 2 In a preclinical program, we focus on the senescence accelerated mouse (SAMP8) model to test the link between cardiovascular function, cerebral blood flow, and cognition in combination with potential genetic aggravating factors [59–62]. This mouse model shows cardiac hypertrophy as well as heart failure. This study advances our insight into the importance of hemodynamics for brain function, as well as the interplay between systemic hypoperfusion and disturbed local vessel function. 3 We perform an additional observational imaging study performed on a 7-tesla MRI scanner. With this ultra-high-field MRI we evaluate novel techniques assessing intracranial small vessel pulsatility and microvascular functioning to explore their value as novel etiologic, diagnostic, and prognostic biomarkers for VCI. 4 We conduct a randomized controlled trial aimed at improving cerebral perfusion (as measured with MRI-based arterial spin labeling) in elderly patients with VCI through aerobic exercise, while taking into account a potential modulatory effect of cardiac output [63]. This proof-of-principle RCT may show that improvement of the cerebral perfusion can lead to improved cognitive functioning in patients with VCI.
MRI, magnetic resonance imaging; RCT, randomized, controlled trial; SAMP8, senescence accelerated mouse; VCI, vascular cognitive impairment.

organized in a monodisciplinary way, cardiovascular status tends to be neglected in patients presenting with cognitive impairment in memory clinics and, vice versa, cognitive disorders are often neglected in patients presenting with cardiovascular disease in cardiology or vascular medicine departments. Moreover, guidelines for diagnostic protocols that provide a combined comprehensive assessment of the cardiovascular and cerebral structure and function are lacking. The Heart-Brain Study is part of a larger Heart-Brain Connection consortium (www.heart-brain.nl) [18], covering preclinical, experimental, and clinical trial research (Textbox 1). The Heart-Brain Study hypothesizes that the hemodynamic status of the heart and the brain is an important, but underestimated cause of VCI. We aim to assess the association between (cardio-)vascular and hemodynamic factors in the heart and the brain in relation to cognitive function. Our objectives are to assess (1) the association between cardiovascular parameters and cognitive function, (2) the association between cardiovascular parameters and brain structure and perfusion, and (3) the association between brain structure and perfusion and cognitive function. We study these objectives in patients with HF, COD, and VCI, both cross-sectionally as well as longitudinally. By studying the complete heart-brain axis in patient groups that present themselves with complaints attributed to specific parts of the heart-brain axis, we have the opportunity to assess a combination of clinical and subclinical manifestations of disorders of the heart, vascular system, and brain, with hemodynamic status as a possible binding factor. Here, we describe the design and study protocol of this multidisciplinary study, in which cardiologists, epidemiologists, neurologists, neuropsychologists, radiologists, image processing experts, and MR physicists work together to study the hemodynamic status of the heart and the brain as an important, but underestimated determinant of VCI.

Table 1. Overview of data collection per assessment moment

	Baseline	Follow-up 1 year[a]	Follow-up 2 years
Informed consent	X		
Clinical assessment	X		X
Neuropsychological assessment	X	X	X
Brain MRI	X		X
Cardiac MRI	X		
Blood	X		X
Cerebrospinal fluid[b]	X		
Echocardiography[c]	X		X
24-hour blood pressure[d]	X		
Cause of death for deceased patients		X	X

[a] Only for patients with vascular cognitive impairment; [b] Performed in the routine clinical setting in VU University Medical Center; [c] Available in Maastricht University Medical Center and VU University Medical Center; [d] Available in Maastricht University Medical Center, University Medical Center Utrecht, and VU University Medical Center.

Methods

Study Design

The Heart-Brain Study is a prospective study with a follow-up measurement after 2 years. Five Dutch university medical centers collaborate: Erasmus Medical Center (ErasmusMC) in Rotterdam, Leiden University Medical Center (LUMC) in Leiden, Maastricht University Medical Center (MUMC) in Maastricht, University Medical Center Utrecht (UMCU) in Utrecht, and VU University Medical Center (VUmc) in Amsterdam. Participants have been enrolled from September 2014 onwards. For an overview of the data collection see Table 1.

Participants

Patients with VCI, COD, and HF are recruited from cardiology, memory, and neurology outpatient clinics from four sites: LUMC, MUMC, UMCU, and VUmc. In each patient group, 175 patients are recruited, yielding a total sample size of 525 patients. In addition, 120 controls undergo the same study procedures as patients. Eligible participants are selected according to the inclusion and exclusion criteria (Table 2). Written informed consent is obtained prior to participation in the study.

Baseline Assessment

Clinical Data and Assessment

The following measures are collected and saved as a core clinical dataset:

- Sociodemographic factors, including age, sex, educational level, and social situation.
- Vascular risk factors including hypertension, diabetes, hyperlipidemia, smoking, overweight, and extensive alcohol use.
- Medical, neurologic, cardiovascular, and family history.
- Current medication.
- Physical examination with particular attention to clinical signs of volume overload (e.g., pitting edema, rales) and heart murmur.
- Duplicate blood pressure measurement on one occasion (sitting, lying, and standing).
- Resting 12-lead electrocardiography.
- Anthropometry, physical performance, and physical activity [19, 20].

Table 2. Inclusion and exclusion criteria of patients with VCI, COD, and HF and controls for the Heart-Brain Study

General selection criteria for all patient groups

Inclusion criteria
- Age 50 years or older
- Able to undergo cognitive testing
- Independence in daily life

Exclusion criteria
- Contraindication for MRI or unable to undergo MRI protocol due to physical condition
- Life-threatening disease with life expectancy less than 3 years other than VCI, COD, or HF
- A clinical diagnosis of dementia is not a contraindication for participation in this study; however, clinical evidence of a neurodegenerative disease other than VCI or AD (such as frontotemporal dementia, Lewy body disease, or hypokinetic rigid syndrome) is an exclusion criterion
- Another neurologic or psychiatric diagnosis that affects cognitive performance or testing, such as severe traumatic brain injury or substance abuse
- Participation in ongoing trials for therapeutic interventions including randomized controlled trials and clinical trials of investigational medicinal products
- Plan to move out of the region within the next 3 years
- Atrial fibrillation at the moment of inclusion (of note, [paroxysmal] atrial fibrillation in the history is not an exclusion criterion). PVCs exceeding 10% of the total number of heartbeats, e.g., a heart rate of 60/min and >6 PVCs

Additional selection criteria for patients with VCI

Inclusion criteria
- Cognitive complaints
- Clinical Dementia Rating ≤1 and Mini-Mental State Examination ≥20

Furthermore, at least one of the following criteria should be present:
- On brain MRI moderate to severe white matter lesion (Fazekas >1) and/or (lacunar) infarct(s) and/or intracerebral (micro-)hemorrhage(s)
- On brain MRI mild white matter lesions (Fazekas = 1) and at least two of the following vascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, or clinically manifest vascular disease (>6 months ago). Clinically manifest vascular disease comprises peripheral arterial disease, myocardial infarction, percutaneous coronary intervention/coronary artery bypass graft, and/or stroke

Exclusion criteria
- n/a

Additional selection criteria for patients with COD

Inclusion criterion
- Significant stenosis (>80%) or occlusion of the internal carotid artery as visible on MR angiography

Exclusion criterion
- Plan for carotid surgery

Additional selection criteria for patients with HF

Inclusion criteria

This study includes HF patients irrespective of left ventricular ejection fraction and coronary artery disease

HF according to European Cardiology Society guidelines:
- Symptoms typical of HF (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)
- Signs typical of HF (tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly)
- Objective evidence of a structural or functional abnormality of the heart at rest on routine echocardiography
- Stable clinical situation for at least 6 months

Exclusion criteria
- n/a

Additional selection criteria for controls

Inclusion criteria
- n/a

Exclusion criterion
- A diagnosis of VCI, COD, and HF, i.e., a control may participate when one or two diagnoses are present

AD, Alzheimer disease; COD, carotid occlusive disease; HF, heart failure; MRI, magnetic resonance imaging; PVC, premature ventricular contraction; VCI, vascular cognitive impairment.

Table 3. Neuropsychological assessment and measures of neuropsychiatry and general functioning

Test/questionnaire	Domain
Cognitive functioning	
Mini-Mental State Examination (MMSE) [44]	Global cognition
15-Word Auditory Verbal Learning Test [45]	Episodic memory
Total recall	
Delayed recall	
Recognition	
Visual Association Test (VAT), short version [46]	Implicit associative visual learning
Digit Span, extended version [47]	
Forward	Attention
Backward	Working memory
Trail Making Test (TMT) [48]	
Part A	Information processing speed, attention
Part B	Response inhibition, executive functioning
Stroop Color-Word Test (SCWT) [49]	
Card I and II	Information processing speed, attention
Card III	Concept shifting, executive functioning
Fluency, 60 s (animals) [50, 51]	Verbal fluency, semantic memory
Letter-Digit Substitution Test (LDST) [52]	Information processing speed, attention
General functioning and neuropsychiatry	
Clinical Dementia Rating Scale (CDR) [53]	Severity of cognitive impairment
Amsterdam IADL Questionnaire [54]	Functional status
Disability Assessment of Dementia (DAD) [55]	Functional status
Geriatric Depression Scale-15 (GDS-15) [56]	Depressive symptoms
Starkstein Apathy Scale [57]	Symptoms of apathy

CDR, Clinical Dementia Rating scale; DAD, Disability Assessment Dementia; GDS-15, Geriatric Depression Scale-15; IADL, Instrumental Activity of Daily Living; LDST, Letter-Digit Substitution Test; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; SCWT, Stroop Color-Word Test; VAT, Visual Association Test.

Cognitive Functioning

All participants undergo an extensive and standardized neuropsychological assessment, based on the Dutch Parelsnoer Initiative [21]. This test battery covers global cognitive functioning and four major cognitive domains including memory, language, attention-psychomotor speed, and executive functioning (Table 3). All test scores are standardized into *z*-scores and subsequently combined into cognitive domains. We rate a cognitive domain as impaired when the *z*-score is below –1.5. Patients are classified as cognitively normal when no domains are impaired, with minor cognitive impairment with one domain impaired, and with major cognitive impairment with more than one domain impaired.

In addition to cognitive functioning, we assess general functioning, activities of daily living, depressive symptoms, and apathy (Table 3).

MRI

MRIs are acquired on Philips Ingenia 3T scanners at LUMC and UMCU, a Philips Achieva 3T scanner at MUMC, and a Philips Gemini 3T PET-MR scanner at VUmc (Philips, Best, The Netherlands). The MRI protocol consists of a cardiac, vascular, and brain protocol (Table 4). The brain protocol includes T1-weighted, fluid-attenuated inversion recovery (FLAIR) images and susceptibility-weighted imaging (SWI). Cerebral perfusion is measured with arterial spin labeling [22] and phase-contrast flow measurements. The sequences measuring perfusion

Table 4. MRI protocol

Organ	Pathophysiological phenomenon	Parameter	MR technique	Duration, min:s	Resolution, mm^3	Relevant contrast parameters
Brain	Structural status	Atrophy (brain volumes)	1. T1-weighted	6:47	1×1×1	MP-RAGE; TR 8.2 ms; TE 4.5 ms; shot interval 3,000 ms; flip angle 8°; inversion delay 990 ms
		WMH + infarcts	2. FLAIR	4:43	1.11×1.11×1.11	TR 4,800 ms; TE 313 ms; TI 1,650 ms; TSE factor 182
		Microbleeds	3. SWI	2:30	0.8×0.8×1.6	3D gradient echo; TR 45 ms; TE 31 ms; flip angle 13°; EPI factor 3
	Perfusion at rest	Whole brain perfusion at rest	4. ASL	6:05	3×3×7	pCASL; label duration 1,800 ms; postlabeling delay 1,800 ms; background suppression; multislice 2D; single shot EPI readout
	Cerebral blood flow	Total cerebral blood flow	5. Phase-contrast flow measurement	0:43	1.17×1.17×5	TR 12 ms; TE 8.2 ms; flip angle 10°; Venc 200 cm/s; untriggered; 10 averages
Aorta	Aorta stiffness	Pulse wave velocity	6. Aorta QFlow	1:47	2.5×2.5×8	TR 4.7 ms; TE 2.8 ms; flip angle 10°; Venc 150 cm/s; number of heart phases dependent on heart rate; temporal resolution 5 ms
Heart	Functional status	Systolic function	7. Short-axis multi-slice cine SSFP	3:00	1.5×1.6×8.0	TR 3.1 ms; TE 1.55; flip angle 45°; 40 heart phases; 67 phase percentage; breath-hold; number of slices dependent on size of LV (range 12–16 slices)
		Diastolic function	8. Phase contrast mitral inflow	2:00	2.5×2.5×8.0	TR 4.4 ms; TE 2.8 ms; flip angle 10°; 40 heart phases; Venc 150 cm/s
		Cardiac output	Comes with 7			
	Structural status	LV mass	Comes with 7			
		LV volume	Comes with 7			

ASL, arterial spin labeling; EPI factor, echo-planar imaging factor; FLAIR, fluid attenuation inversion recovery; LV, left ventricular; MP-RAGE, magnetization-prepared rapid acquisition gradient echo; pCASL, pseudo-continuous arterial spin labeling; Qflow, quantative flow; SSFP, steady-state free precession; SWI, susceptibility-weighted imaging; TE, echo time; TI, inversion time; TR, repetition time; TSE factor, turbo spin-echo factor; Venc, velocity encoding; WMH, white matter hyperintensities.

are performed in the same scan session as the structural sequences. The heart protocol includes short-axis multislice cine steady-state free precision (SSFP), aorta QFlow images, and phase-contrast mitral flow measurements. Scans are screened by local radiologists for clinically relevant incidental findings.

Blood and Cerebrospinal Fluid Markers

We investigate systemic and organ-specific blood biomarkers that relate to functional or structural abnormalities in components of the heart-brain axis. For systemic biomarkers, we assess biomarkers related to processes involved in HF, atherosclerosis, and VCI. We focus on abnormalities in lipid metabolism, insulin resistance/dysglycemia, inflammation, and anemia. For markers reflecting pathogenic processes in organ-specific components of the heart-blood vessels-brain axis, we assess markers of HF and cardiac fibrosis, and remodeling of blood vessel pathology and of Alzheimer-type pathology.

Cerebrospinal fluid is collected for patients with VCI in the routine clinical setting in VUmc for determination of amyloid-beta 1–42, total tau, and hyperphosphorylated tau-18 [23]. Participants are asked to give separate informed consent for DNA storage for future genetic analyses.

Echocardiography

We use standard clinical Doppler-echocardiographic equipment to measure the complete standard clinical array including structures as well as systolic and diastolic function of both ventricles, atrial dimensions, and valve function, as recommended by the European and

American Societies of Echocardiography [24, 25]. Transthoracic echocardiography is performed in standard parasternal, apical, and subcostal views. Echocardiography is performed in MUMC and VUmc.

24-Hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure monitoring is performed, using validated blood pressure monitors from Microlife (Microlife Corporation Europe, Widnau, Switzerland). 24-hour blood pressure measurements have been shown to be of better prognostic value for cardiovascular events and more reproducible than conventional office BP measurements [26]. 24-hour ambulatory blood pressure is performed in MUMC, UMCU, and VUmc.

Follow-Up Assessment

Two years after baseline assessment, all participants are invited for a second visit which includes neuropsychological testing, brain MRI, and collection of blood samples. Echocardiography is included when performed at baseline. In addition, clinical data on disease incidence and admission to hospital or nursing home between the first and last visit are collected by history taking. For participants with cognitive problems or when the history of the participant is considered less reliable, additional history is obtained from next of kin and/or the general practitioner. For deceased participants, the cause of death is obtained from Central Agency for Statistics Netherlands (CBS) and general practitioners. Patients with VCI additionally undergo follow-up of neuropsychological testing after 1 year. We evaluate cognitive decline based on the difference in the cognitive domain *z*-scores (for more information, see section Cognitive Functioning above).

Data Collection, Processing, and Storage

We use centralized state-of-the-art storage platforms for clinical (OpenClinica, LLC, Waltham, MA, USA) and imaging data (Extensible Neuroimaging Archive Toolkit [XNAT]). Imaging data are processed centrally with automated standardized pipelines. For an elaborate description, see online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000480738).

Sample Size Considerations

With a sample size of 175 patients in each patient cohort we can detect associations in which the determinant explains 4% or more of the variance in the dependent variable (i.e., the equivalent of a correlation coefficient of 0.2 or more with alpha 0.05, power 90%), taking 10–20 relevant covariates into account. Assuming that the dropout rate will not exceed 25% over 2 years, we have 80% power to detect associations of the same strength at follow-up.

Statistical Analysis

Cross-Sectional Relations

Regression analyses are used to investigate the independent associations between measures of cerebral perfusion and blood flow, structural brain abnormalities (brain atrophy, white matter hyperintensities, infarcts, and microbleeds), and cognitive performance. Also, regression analyses are used to investigate the relationship between cardiovascular parameters (cardiac output, systolic and diastolic function of the ventricle, blood pressure, pulse wave velocity, aortic and carotid stiffness) and cerebral perfusion and blood flow (arterial spin labeling and phase-contrast flow measurements) at baseline.

Prospective Relations

To investigate prospective relations of baseline cardiovascular and cerebral perfusion and flow measures with change in brain MRI abnormalities and cognitive functioning, we use regression models with brain volume and change in cognitive performance at follow-up as the dependent variables and cardiovascular parameters and brain perfusion and blood flow at baseline as the independent variables.

Since the main analyses have an etiologic focus, appropriate adjustment for confounding factors is performed. All abovementioned associations are examined in each patient cohort (VCI, COD, or HF) separately, comparing groups with controls. Finally, we pool all data and perform linear regression analyses, taking into account potential effect modifications by cohort [27].

Ethical Considerations

The Medical Ethics Review Committee of the LUMC performed central approval of the Heart-Brain Study (number P.14.002). Subsequently, local boards of the UMCs approved the local performance of the study. The Heart-Brain Study is performed in accordance with the declaration of Helsinki (version 2013) and the Medical Research Involving Human Subjects Act (WMO).

Current Status and Time Line

The first participant was included in September 2014, the inclusion period finalizes in 2017, and the last follow-up measurement will be in 2018. The first baseline results are expected in 2017, the longitudinal results in 2019.

Results and Conclusion

The Heart-Brain Study hypothesizes that the hemodynamic status of the heart and the brain are important, but underestimated determinants of VCI. Previous studies have investigated components of the heart-brain axis in (prospective cohorts of) healthy people [28–33], patients with HF [12, 13, 34–39], and COD [40–43]. These studies have found circumstantial evidence that cardiac and cardiovascular pathology affecting CBF and perfusion in the brain may influence brain function before structures are irreversibly damaged. It is currently unknown how often hemodynamic changes based on cardiovascular pathology occur in patients with cognitive impairment. Various cardiovascular factors, such as cardiac output, blood pressure, pulse wave velocity, and aortic and carotid stiffness, may influence CBF. On the other hand, in VCI a lower CBF could also be related to a decreased need of blood by an already affected brain. Little is known about how these factors, separate or in concert, influence cognitive performance. The Heart-Brain Study is unique because of the integrated approach that we use to investigate relationships between (cardio-)vascular factors, the hemodynamic status of the heart and the brain, and cognitive impairment, in three patient groups that represent components of the heart-brain axis. While zooming in on one component of the heart-brain axis we assess the other components and how they are interconnected. This way, we assess both clinical and subclinical manifestations of disorders of the heart, vascular system, and brain, with hemodynamic status as a possible binding factor along the heart-brain axis. This integrated approach may show light on the mechanisms involved in these relationships. To study the relationships as clearly as possible we chose to exclude patients with current atrial fibrillation at the time of inclusion, since atrial fibrillation may lead to unpredictable hemodynamic changes. This exclusion might lead to limited generalizability of this study. However, the patient groups mainly function as a model of specific parts of the

heart-brain axis, i.e., hemodynamic components possibly leading to chronic cerebral hypoperfusion.

We perform extensive phenotyping using a comprehensive and standardized MRI protocol that has been developed to measure structure and function of both the heart and the brain. Alongside, a platform for data storage and image processing is developed in which both automatic and manual quality assessment procedures are implemented. Quantification of imaging biomarkers of the heart, brain, and cerebropetal arteries is performed with existing and newly developed automated software. With this study, we provide a foundation for an interdisciplinary collaborative network for the study of the heart-brain axis that will lead to a true multidisciplinary and consensus-based approach of clinical management of cognitive impairment in patients with HF, COD, and VCI. The close collaboration between departments of cardiology and neurology opens possibilities for future heart-brain clinics, through which implementation of newly developed diagnostic tools and treatment options can be optimized. With this approach we meet the clinical and research need for centers of excellence with transdisciplinary programs within and between centers [1, 16, 17].

In addition to the Heart-Brain Study, in the Heart-Brain Connection consortium [18] we perform preclinical, experimental, and clinical trial studies that further increase the understanding of the mechanisms underlying the relationship between hemodynamic status and cognitive functioning (Textbox 1).

In conclusion, in the Heart-Brain Study we test the hypothesis that the hemodynamic status of the heart and the brain is an important, but underestimated cause of VCI offering promising opportunity for treatment. Moreover, we develop a novel, clinically feasible diagnostic protocol including a comprehensive MRI protocol that assesses the heart, the vascular system, and the brain. This protocol can be used for identifying patients suitable for future trials as well as monitoring treatment effects. Finally, we provide a foundation for an interdisciplinary collaboration for the study of VCI that will lead to a true multidisciplinary and consensus-based approach of the clinical management of VCI.

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Disclosure Statement

W.J. Niessen is cofounder, part-time Chief Scientific Officer, and stock holder of Quantib BV. Other authors declare that there are no competing interests. None of the authors have direct or indirect relationships with the Netherlands CardioVascular Research Initiative.

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