Addendum I: Overview of DCVA Heart-Brain Connection crossroads (HBCx)

Project overview

Heart-Brain Connection (HBC1): 2013-2018
Research leaders: prof. dr. M.A. van Buchem & prof. dr. M.J.A.P. Deamen
Heart-Brain Connection crossroads (HBCx): 2019-2024
Research leaders: prof. dr. M.J.A.P. Daemen & prof. dr. G.J. Biessels

Overall scientific summary HBC1 and HBCx

Cardiovascular disease and dementia are closely related. Cognitive impairment is common among people with cardiovascular or cerebrovascular disease. One in three dementia cases is attributable to vascular injury. This potentially preventable vascular burden in cognitive impairment is referred to as Vascular Cognitive Impairment (VCI).

Central hypothesis of the Heart-Brain Connection programme: hemodynamic changes are an important and potentially reversible cause of vascular cognitive impairment.

In the first CVON Heart-Brain Connection (HBC1) programme we have established:

- A national interdisciplinary collaborative network to study, diagnose and treat VCI
- A comprehensive diagnostic heart-brain axis protocol for hospital- and population-based studies as well as animal studies, addressing the role of hemodynamics in VCI.

Our findings in HBC1 clearly confirmed the importance of the heart-brain axis in VCI. HBC1 explored the etiological role of hemodynamic factors in VCI, particularly addressing flow (i.e. cardiac output, large artery flow, cerebral perfusion). We found that flow is important, but does not fully explain VCI. Therefore, additional dimensions of hemodynamics also need to be considered.

The HBC-crossroads (HBCx) programme that started in 2019 further builds on the central hypothesis that hemodynamic changes are an important and potentially reversible cause of VCI, now taking a more multidimensional (i.e. crossroads) approach to hemodynamics, also addressing flow regulation and variability and factors that modulate the impact of hemodynamic disturbances in VCI.

We evaluate the role of hemodynamics in VCI in:

- Key cardiac conditions (atrial fibrillation, valvular disease, heart failure/venous congestion)
- Vascular factors (blood pressure variability, vascular reactivity, endothelial (dys)function)

- The primary cerebral co-morbidity of VCI, amyloid pathology (i.e. assess interplay hemodynamics and amyloid)

We will also address age, sex, and environment as modulating factors.

Our ambitions are to identify treatable targets, further improve the diagnostic protocols and analyses, translate research tools to diagnostic applications, and provide integrated heart-brain care for patients. The framework of HBCx includes mechanistic studies, proof of concept treatment studies targeting hemodynamics, and the implementation of the HBC concept in heart-brain clinics in daily care. We build on the rich HBC1 dataset, refine the analyses and will also establish new cohorts and link up with other existing cohort studies such as RACE-V.

Theme and ambitions HBCx

The ultimate benefit of studying vascular contributions to cognitive decline and dementia (i.e. Vascular Cognitive Impairment - VCI) is that vascular disease is an important and currently the only modifiable cause of dementia. Cardiovascular disease can be targeted both in prevention programs in the general population, in vulnerable patients at risk of VCI, and in symptomatic patients. The ambition of the HBC-program is to clarify the role of cerebral hemodynamics in VCI to identify cardiovascular targets for prevention and treatment of VCI and to identify those individuals who may benefit most from such treatments at an early stage. The choice to focus on hemodynamics was extensively discussed in the application of the HBC1 program. In short, there is ample evidence that adequate cerebral perfusion is a prerequisite for optimal cognitive functioning. A number of studies have observed cerebral hypoperfusion in different types of dementia. Cerebral perfusion is a function of cardiac output, arterial stiffness, patency of cerebropetal arteries, cerebral vasomotor reactivity, and patency of small cerebral vessels. For each of these parameters, there is evidence that, if changed, it can affect cognition [1]. Cardiac factors such as cardiac failure and vascular factors such as atherosclerotic and steno-occlusive disease of cerebropetal arteries challenge the blood supply to the brain, small vessel diseases put the brain at risk for changes in perfusion pressure by limiting the cardiovascular reactivity and stiffening of the aorta challenges the brain by an increased deposition of pulsatile energy in its microvasculature. These mechanisms coexist in many patients and they probably act synergistically in terms of leading to functional and structural brain changes. If and how these interactions occur, and how they result in VCI is still unknown.

From its initiation in 2013 the HBC1 program has focused on the following objectives:

- Founding a national interdisciplinary collaborative network for the study of VCI to support a true multidisciplinary and consensus-based approach to research and the clinical management of VCI.
- Establish a comprehensive diagnostic protocol in hospital- and population-based studies as well as in animal studies, to enable to study the role of hemodynamic factors along the heart-brain axis
- Establish the role of hemodynamics in VCI, in particular flow along the heart brain axis, through clinical studies [2] in patients with exemplar hemodynamic phenotypes, i.e. patients with chronic heart failure (HF), carotid occlusive disease (COD), and memory clinic patients with clinically manifest VCI.

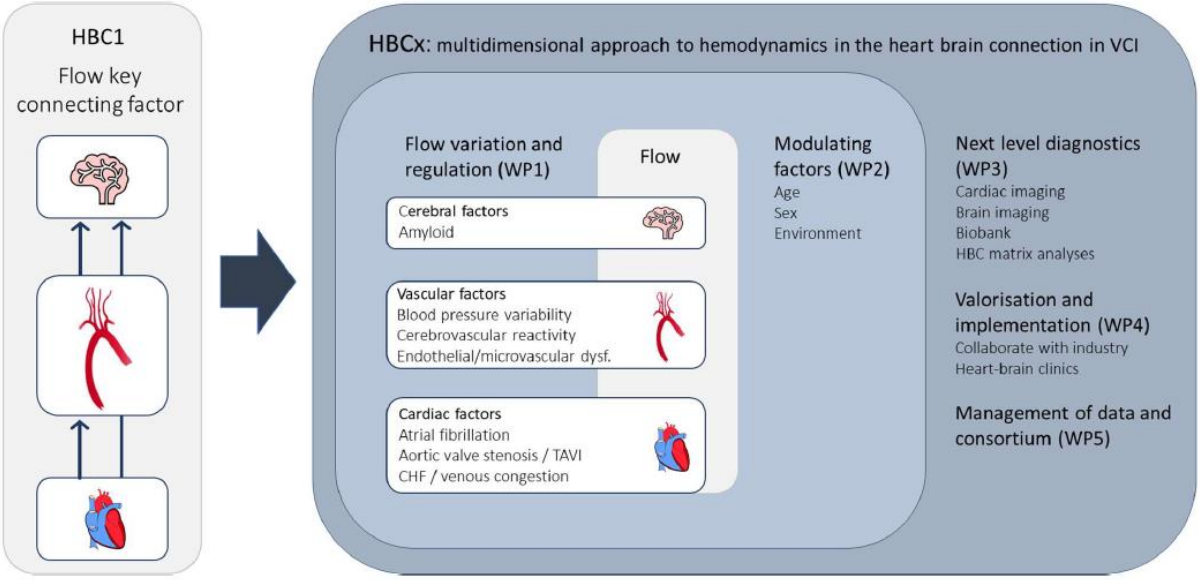
In HBC1 we implemented a standardized detailed MRI protocol to assess cardiac and large artery function, in particular flow, atherosclerotic load and cerebral perfusion in all patient groups and controls. Impact on the brain was assessed with structural brain MRI and thorough tests of cognitive

function. We also started a proof of concept clinical intervention study [3], that aimed to improve cardiovascular health and cerebral flow in patients with VCI through an exercise program. In addition, we used epidemiological data from the Rotterdam study to establish the impact of cardiovascular disease on cognition at the population level and explore the role of hemodynamics in unselected subjects. Finally, we used animal studies to dissect the mechanisms involved and to reveal novel leads for interventions.

In HBCx we expand our views on hemodynamics in the Heart-Brian connection. In HBC1 we deliberately took a rather **monodimensional approach to hemodynamics** and tested the specific hypothesis that cerebral hypoperfusion is a key factor in the connection between cardiovascular function and cognition. In this essential first step to unravel the role of hemodynamics (HD) in the heart brain connection in VCI we zoomed in on patients with exemplar conditions of impaired flow/perfusion: we studied patients with chronic heart failure (CHF) to explore the impact of flow disturbances at the level of the heart on VCI, patients with COD to explore the impact of flow disturbances at the level of large arteries and memory clinic patients with VCI to explore the impact of flow disturbances at the level of the brain itself.

In HBC1 we indeed showed the importance of the heart brain connection in VCI, COD and CHF patients as 18-35% of CHF and COD patients have minor to major VCI and 9-15% of COD and VCI patients have signs of chronic heart failure [4]. Moreover, the Rotterdam study shows that myocardial infarction, atrial fibrillation (AF) and subclinical markers of cardiac dysfunction predispose to cerebral damage and dementia [5-10].

One important lesson that we learned from the results of HBC1 is that cerebral perfusion measured as a static parameter does not explain in full the relation between the heart and the brain in VCI. In HBCx we therefore added **two new dimensions to the hemodynamic concept of HBC1** to further build on our **central hypothesis that hemodynamic changes are an important and potentially reversible cause of VCI.** While in HBC1 we primarily focused on the role of hypoperfusion, we now address variability and regulation of cerebral perfusion as well as factors that modulate the impact of hemodynamics on the brain.



As illustrated in the figure above the first dimension added to flow as a connecting factor is variation and regulation of flow (WP1). The second dimension added are factors that modulate the impact of hemodynamic changes on the brain (WP2).

Flow variation and regulation (WP1) is studied within the HBC framework (i.e. at the level of the heart, vessels, and brain) and -similar to HBC1- in exemplar patient groups. This provides us the opportunity to leverage and build on the framework and data collected in HBC1. For the **heart (WP1a)** we will include patients with atrial fibrillation (AF), patients with aortic valve constriction and its replacement by Transcatheter aortic valve implantation (TAVI) and study venous congestion in CHF patients. AF is a growing public health problem, having reached epidemic proportions. There is also growing evidence that AF is independently associated with cognitive impairment and dementia [5, 11-13]. Mechanisms are still largely unknown, but HD instability and effects on cerebral perfusion have been reported [14,15]. Of note AF is hypothesized to be a vascular disease, i.e. is caused by coronary macro- and-/or microvascular alterations, a hypothesis that is currently tested in the CVON RACE V consortium. This offers a unique opportunity to join efforts, clarify the hemodynamic (HD) and vascular contribution of AF to VCI and increase the awareness of cardiologists for the heart brain connection. Aortic valve stenosis is used as a model system how cerebral blood flow (CBF) is altered by obstructed aortic valve blood flow and how TAVI improves CBF and the condition of the brain. In a pilot study brain integrity and cognition in aortic stenosis and after TAVI were already explored. First results show that TAVI indeed leads to an increase in cardiac output and CBF in selected patients. These observations are expanded in HBCx. Venous congestion (VC), often secondary to CHF, significantly contributes to organ dysfunction elsewhere in the body, for example in liver and kidneys [16]. Limited, indirect data suggest that VC might also impact the brain and as such play a role in VCI. VC may thus be another important - yet unexplored – HD link between heart and brain.

Two **regulating vascular factors (WP1b)** that are well known to influence CBF and are addressed in HBCx are blood pressure variability and cerebrovascular reactivity. Blood pressure variability (BPV) is associated with an increased cardiovascular mortality, possibly because of increased arterial stiffness, impacting vascular elasticity and reactivity. Data from the Rotterdam study collected in HBC1 show that increased BPV is associated with cognitive decline [17] and with dementia [18] and has been linked to structural lesions in the brain [19]. The nature of the relation between BPV and both functional and structural lesion in the brain is however not fully understood and will be explored in HBCx. Data of the Rotterdam study collected in HBC1 show that reduced cerebrovascular reactivity is associated with an increased risk of developing dementia [20]. In HBCx we will further develop a method to measure cerebrovascular reactivity at the tissue level, by transforming the traditional tilt table test into an MRI-compatible setup with a lower body negative pressure box. By also measuring the neurovascular response in a similar manner as in HBC1, multiple regulation pathways can be probed. In HBC1 we identified several novel molecular targets on intracranial human ECs. We selected those targets that are functionally linked to HD. As the endothelium plays a crucial role in the regulation of CBF, we will use these markers to dissect basic molecular mechanisms of CBF regulation and to screen for novel endothelial based biomarkers and molecular targets for intervention.

Alzheimer pathology is the exemplar condition from the **brain perspective (WP1c).** While it is clear that the effects of Alzheimer and vascular pathologies on the brain are additive, these processes may also interact. In fact, amyloid can accumulate in vessels disturbing vascular reactivity [21] and, conversely, there are indications that disturbances in brain perfusion can induce amyloid deposition.

We have ample experience with advanced amyloid biomarker studies, including Amyloid-PET, which quantifies and visualized amyloid in the brain and a recently introduced Simoa immunoassay platform, to reliable measure neuroproteins in blood. In the setting of the HBCx framework this will provide us with a unique opportunity to study how amyloid contributes to VCI and to explore the links between amyloid and HD.

Factors that modulate the impact of hemodynamic factors on the brain (WP2): While the work in WP1 will reveal how and to what extent HD factors affect CBF, cognition and brain structure, WP2 will reveal in which individuals HD disturbances have most impact on the brain, thus placing them most at risk of VCI. In this WP the modulating effects of age, sex and environment on the HD factors studied in WP1 are addressed. While it is obvious to address age as a modulating factor – people of advanced age are at greatest risk of both cardiovascular disease and dementia – there is very little existing data on potential modulating effects of sex in VCI. This is surprising because during aging, the cardiac and vascular anatomy and physiology changes differentially in women and men. This sex-specific "vascular ageing" is suggested to explain sex-differences in vascular risk factor profiles as well as manifestations of cardiovascular disease. Moreover, there is accumulating evidence of sex-specific patterns of disease manifestations of Alzheimer's type dementia and it has been postulated that better appreciation of these sex differences are crucial for the development of a "precision medicine" approach for that condition [22]. Yet, such sex differences have hardly been explored in VCI. HBCx is the perfect platform to fill in this knowledge gap.

Next level diagnostics (WP3) focuses on advanced imaging analysis techniques and biobanking to support our studies and to generate next level diagnostics and biomarkers of VCI. We will further develop automated tools for the quantitative analyses of cardiac and brain MRI. These tools will support the HBCx program and their diagnostic and prognostic properties will be studied.

Valorization of data and technology collected and developed in the HBC consortium and **Implementation of the HBC concept in heart brain clinics (WP4)** aims to accelerate the development of novel therapeutic and diagnostic tools in collaboration with industry partners, and to rapidly employ the HBC concept in routine patient care.

HBCx: Hemodynamic changes are an important and potentially reversible cause of VCI			
WP1 Flow variation and regulation along the heart brain axis in VCI	**WP2** Modulating factors	**WP3** Next level diagnostics	**WP4** Valorisation and implementation
WP1a Cardiac factors: atrial fibrillation; aortic valve stenosis/TAVI; heart failure/venous congestion WP1b Vascular factors: Blood pressure variability; CBF regulation Endothelial derived biomarkers WP1c Cerebral factors: Amyloid	• Age • Sex • Environment	• Cardiac imaging • Brain imaging • HBC matrix analyses • Biobank	• Collaborate with industry • Heart-brain clinics
WP5 management of data and consortium			

Our overarching objectives are to:

- Further establish the role of hemodynamics (HD), also beyond hypoperfusion, in VCI
- Earlier detect the patient at risk for developing VCI by improved diagnostic tools and analyses and
- implementation of the HBC approach in routine patient care
- Identify treatable targets

Our short-term ambitions (5 years) for this theme are:

- To identify those HD factors that play a key role in VCI and can be targets for intervention.

- To understand the contribution of factors that modulate the impact of HD on cognition, such as age, sex and the environment to refine the integrated care in the heart-brain clinics (early recognition), and to precise the targets for intervention
- To deliver novel markers of treatable targets (e.g. amyloid and novel markers in plasma, MRI
- signatures of early cardiovascular disease, but also cognitive screening in cardiac population)
- To improve patient care by implementing the HBC approach/concept in routine patient care offering integrated care in heart-brain clinics
- To spread the importance of the HBC concept in the (inter)national patient, clinical and research field and include patients and private partners herein.

Our long-term ambition (2030-2035) are:

- Improved understanding of the contribution of HD in the pathophysiology of VCI
- Early detection of the chronic CVD patient at risk of VCI
- Novel treatment strategies for CI in the CVD patient targeting HD factors
- Changing clinical diagnostic and therapeutic guidelines for the chronic CVD patient at risk for VCI
- 25% reduction of VCI in CVD patients

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