Blood pressure and risk of cognitive impairment. The role of vascular disease in neurodegeneration.

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Abstract

Background: Both cerebral vascular disorders and cognitive decline increase in incidence with age. The role of cerebral vascular disease and hemodynamic changes in the development of cognitive deficits is controversial. The objective of this study was to assess cardiovascular response during cardiac stress testing in neurologically asymptomatic individuals who developed cognitive impairment several years after the cardiac stress testing.

Methods: This is a retrospective cohort study of patients who underwent cardiac stress testing between January 2001 and December 2010. Patients were followed up until May 2015 and we selected those who developed cognitive dysfunction including dementia, mild cognitive impairment and subjective cognitive decline, after the stress test. Heart rate and blood pressure both at rest and at peak exercise and the mean R-R interval at rest were recorded. For each patient who developed cognitive impairment, we selected one matched control who did not show cognitive decline by the end of the follow-up period.

Results: From this cohort of 7224 patients, 371 developed cognitive impairment; of these, 186 (124 men) met the inclusion criteria and 186 of the other patients were selected as matched controls. During follow-up, cognitive impairment appeared 6.2 ± 4.7 years after the cardiac stress test. These patients who subsequently developed cognitive impairment had significantly lower at-rest systolic, diastolic and mean blood pressure than controls ($p<0.05$). Further, compared with controls, their maximum heart rate was significantly higher at peak exercise and both systolic and diastolic blood pressures increased significantly more during exercise.

Conclusion: The results from this study suggest that differences in cardiovascular response to stress are present in the preclinical phase of cognitive decline, serving as a potential risk factor for cognitive impairment. These findings challenge the potential use of blood pressure and heart rate variability at rest and during cardiac stress assessment as a risk factor for cognitive impairment.

1. Introduction

Cognitive disorders are becoming one of the most prevalent health issues in the developing countries, and in recent years, major efforts have been focused on identifying risk factors involved in cognitive decline. Among them, impaired blood pressure control and cerebrovascular damage have been associated with an increased risk of developing dementia[1,2] as uncontrolled blood pressure may lead to vascular brain damage and consequently impairment of cognitive function.

Specifically, several studies have reported a U-shaped relationship between blood pressure and cognitive function[1,3–8]. In fact, low basal blood pressure seems to be associated with appearance of dementia[1], mild cognitive impairment (MCI)[9], subjective cognitive decline[10] and poor cognitive performance on the MMSE (MiniMental State Examination)[11]. These findings can be explained by the relative parieto-temporal hypoperfusion created by low blood pressure. In this regard, individuals with hypotension also had worse cognitive performance[12], and worse cognitive function has been observed after standing[13]. This might be related to lower blood pressure, especially diastolic, with consequent transient fronto-parietal hypoperfusion during orthostatic challenge. In contrast, individuals with high systolic blood pressure and pulse rate were found to obtain better MMSE scores[14]. On the other hand, midlife systolic hypertension induces arterial stiffness, poor compliance[15] and a progressive reduction in baroreceptor sensitivity[16] which have been associated with cerebral white matter disease[10] and elevated plasma levels of Aβ40[3]. Therefore, both hypertension, as a risk factor for cerebrovascular damage, and also low late-life diastolic blood pressure may be recognised as risk factors for the development of dementia[17]. These findings suggest the possibility of controlling a possible cause of brain degeneration years before the cognitive decline appears.

All these findings indicate that blood pressure can be used as a preclinical biomarker for cognitive impairment. In patients who develop dementia, cognitive impairment is preceded by 3 to 6 years by a reduction in blood pressure, especially systolic[18]. We hypothesized that some of these disturbances may be present under stress in the preclinical phase of cognitive decline, and that vascular instability precedes cognitive impairment. The aim of this study was to retrospectively assess cardiovascular response during cardiac stress testing (CST) in a cohort of neurologically asymptomatic individuals who developed cognitive impairment several years after the CST was performed. The results of this study might be helpful to identify individuals who are at risk of developing cognitive impairment and clarify whether the cardiac response to stress is present in this preclinical phase of cognitive decline.

2. Patients And Methods

2.1. Participants

We conducted a single-centre retrospective study of patients who underwent CST at the University Clinic of Navarra over a 10-year period (between January 2001 and December 2010). After the CST, the participants were clinically followed up by their attending physicians until December 2015 and we identified those who had developed cognitive dysfunction. Patients diagnosed with subjective cognitive decline (SCD), MCI or dementia were selected for this study provided that they met the following eligibility criteria: (a) adequate clinical information to allow follow-up of at least 24 months, and (b) the diagnosis of cognitive impairment having been established by a neurologist, applying the established criteria[19 – 21], including blood tests, brain magnetic resonance imaging (MRI) or computed tomography (CT), and neuropsychological tests.

Patients were excluded if they had: (a) a diagnosis of cognitive impairment when the CST was performed; (b) cognitive impairment diagnosed on the same day as the CST (individuals referred to our Neurology Department for a check-up because they reported symptoms of memory loss); (c) a history of cardiac disease, including arrhythmias and coronary artery disease; or (d) depression or other psychiatric illnesses, obstructive sleep apnoea, multiple sclerosis, or epilepsy. The rationale for the last set of exclusion criteria (d) was that previous research has indicated that cardiac autonomic tone as reflected by heart rate variability (HRV) is altered in patients with these conditions (depression[22], obstructive sleep apnoea, multiple sclerosis[23], and epilepsy[24]).

For each patient diagnosed with cognitive impairment, we selected a control participant from the CST cohort who had follow-up data and did not show cognitive decline by the end of the follow-up period. Controls were individually matched for sex, age, body mass index, hypertension (yes/no), type 2 diabetes (yes/no), smoking habit (yes/no), dyslipidaemia (yes/no) and antihypertensive drug use (yes/no), to control for confounding factors.

2.2. Measures

CST was indicated for patients who complained of chest pain or dyspnoea or who had relevant vascular risk factors (smoking, hypertension, type 2 diabetes, or dyslipidaemia). The stress was induced by exercise on a treadmill according to the Bruce protocol[25] and the American Heart Association Statement for CST[26]. A Schiller Cardiovit CS-200 ergometer (Schiller AG, Baar, Switzerland) and an MTM 1500 treadmill machine (Schiller AG) were used for the exercise testing. The session started with 5 minutes of seated rest. At the end of this rest period, Blood Pressure (BP) was recorded from the right arm only. Electrocardiogram and heart rate (HR) were monitored continuously and BP was measured during the last 30 seconds of each stage. The treadmill test was stopped when participants reached peak exercise. An active cool down was used, and vital signs were recorded every minute post-exercise for 5 minutes. The measurements obtained during the CST and subsequently analysed were: systolic, diastolic and mean blood pressure at rest and at peak exercise, HR at rest and at peak exercise, the percentage of the theoretical maximum HR, and the increase in systolic and diastolic blood pressure after the exercise, as well as the mean R-R interval.

2.3. Statistical analysis

Data collection and analyses were carried out between January and December 2017. Blood pressure and HR at rest and at peak exercise were assessed. Data are expressed as means ± standard deviations unless otherwise indicated. Characteristics of patients and controls were compared using a pair samples t test. For comparisons of two or more means (e.g., HR or BP readings during the CST), an analysis of variance (ANOVA) was performed. The Tukey test was used to compare differences between each pair of means with appropriate adjustment for the multiple testing. In all cases, statistical significance was defined as $P < 0.05$. All analyses were performed using STATA software, version 14.

3. Results

Population of the study

In total, 9259 CSTs were performed between January 2000 and December 2010 at the University Clinic of Navarra on 7224 patients, some patients undergoing several CSTs. From this cohort, 371 patients had developed cognitive impairment by December 2015, and of these, 186 met inclusion criteria. Specifically, 47 had dementia, 57 MCI (54 amnestic MCI and 3 non-

amnestic MCI) and 82 subjective cognitive decline. Concerning the aetiology of the dementia, 23 patients met diagnostic criteria for Alzheimer's disease, while 7 had mixed dementia, 5 vascular dementia, 4 Parkinson's disease/dementia complex, 4 dementia with Lewy bodies, 2 primary progressive aphasia and 2 the behavioural variant of frontotemporal dementia. The flow diagram in Figure 1 summarizes the number of individuals at each stage of the study. Interestingly, seven patients with subjective cognitive decline and eight with MCI had progressed to dementia (due to Alzheimer's disease) by the end of the follow-up period.

Most of the 186 patients were men, and most were overweight as indicated by the high mean body mass index; the overall mean age was 63 ± 9 years. At least 50% of the study population had hypertension, dyslipidaemia and/or a smoking habit. The mean time from the CST to the diagnosis of cognitive impairment was 6.2 ± 4.7 years, being shorter in the case of MCI than subjective memory decline and dementia (5.5 versus 6.5 years) and in the case of men than women (6 vs. 6.5 years). As expected, there were no differences in age, sex, vascular risk factors or treatment between patients and controls, because they were matched ($p>0.05$). Characteristics of all participants at the time of CST are summarized in Table 1.

Comparisons of cardiovascular measures among groups

Overall, patients who developed cognitive impairment had significantly lower values of systolic, diastolic and mean blood pressure at rest, than controls. Subgroup analysis showed that these differences compared to controls were also significant in patients with objective cognitive decline (both dementia and MCI groups), as well as in the patients with SCD ($p<0.05$). We did not find any differences between groups in basal HR ($p>0.05$). These data are summarized in Table 2.

At peak exercise, there were no differences in blood pressure between patients who developed cognitive impairment and controls ($p>0.05$). Interestingly, the increase in systolic and diastolic blood pressure observed during exercise was larger in patients who developed cognitive impairment overall, and in the subgroup with objective cognitive decline (dementia and MCI) than in controls ($p<0.05$). In participants who developed SCD, only the increase in diastolic blood pressure during exercise was significantly larger than in controls ($p<0.05$).

In addition, at peak exercise, patients who developed cognitive impairment had a significantly higher HR than controls. Again, subgroup analysis showed that as compared to controls these differences were also significant in patients with objective cognitive decline (both dementia and MCI), and patients with SCD ($p<0.05$).

Discussion

We here demonstrate that changes in blood pressure profile and cardiovascular response to cardiac stress might precede the appearance of cognitive decline. In this retrospective analysis of the CST performed on 7224 patients with no cognitive complaints, we found that 186 individuals had developed cognitive impairment, including MCI, dementia or subjective cognitive decline cognitive after a follow-up period of 6 years. Interestingly, these groups of patients differed in basal blood pressure and, after exercise, significant differences were also found in maximal HR and increases in both systolic and diastolic blood pressure ($p<0.05$). Patients who developed cognitive impairment had lower systolic, diastolic and mean blood pressure at rest than the control group ($p<0.05$), and these differences are not explained by anti-hypertensive drugs or the presence of vascular risk factors, as patients and controls were matched for vascular risk factors, including antihypertensive drug use and presence of hypertension itself.

At peak exercise, patients who subsequently developed cognitive dysfunction also had a lower basal blood pressure and after exercise there were no differences in maximum systolic or diastolic blood pressure. A greater increase in HR and in systolic and diastolic blood pressure were observed, indicating that the baroreflex is intact in this group. Hence, the cardiovascular response to exercise is characterized by a greater increase in systolic and diastolic blood pressure from basal values and a larger increase in maximum HR. That is, we found that differences in cardiovascular profile are already present years before the diagnosis of dementia is established.

It is widely accepted that cerebral hypoperfusion leads to functional oligoaemia, hypoxia, oxidative stress, a decrease in ATP synthesis, synaptic dysfunction, and neuroinflammation. All these events cause disruption of the blood-brain barrier and provoke biochemical changes such as pericyte damage, microvascular degeneration, increased deposition of basement membrane

proteins and perivascular amyloid, accumulation of thrombin and fibrin and secretion of multiple neurotoxic and inflammatory factors such as interleukin 1-6, tumour necrosis factor-alpha, and hypoxia-inducible factor 1, resulting in beta-amyloid deposits[27]. Interestingly, all these changes have also been reported in damaged myocardium[28]. The damage provoked by vascular changes may cause microangiopathy, macroangiopathy, cerebral hypoperfusion and consequently cognitive deficits including promoting or accelerating neurodegeneration[27]. This hypothesis is supported by single photon emission computed tomography and magnetic resonance imaging studies that have shown changes in brain perfusion in the amygdala, insular cortex, anterior cingulated cortex and hippocampus[29].

We here hypothesize that the blood pressure profile may be a risk factor itself for neurodegeneration. In this work, we investigated whether cardiovascular changes are present before the appearance of cognitive impairment, seeking to identify potentially modifiable risk factors and explain how cardiovascular response to exercise affect cognitive performance. Changes in cardiovascular function are linked to age, vascular rigidity, smoking and other vascular risk factors but also to a secondary response to other risk factors such as hypertension. As a matter of fact, high blood pressure is a risk factor for cognitive impairment in midlife, whereas it becomes protective in late life, when low diastolic pressure is associated with cognitive impairment, due to brain hypoperfusion. Our results are consistent with previous reports that patients with cognitive impairment have lower systolic and diastolic blood pressure than controls before they develop clinical cognitive symptoms[10,18] and the decline in blood pressure takes place around 3 years before the dementia is clinically evident[18]. Low blood pressure may reflect insufficient sympathetic response, due to the damage of the peripheral sympathetic nervous system, which mainly controls blood flow and arterial pressure, whereas the sympathetic cardiac innervation, involved in the control of the HR, is unaffected. In line with this hypothesis, orthostatic intolerance and hypotension have been also linked to dementia, through reductions in cerebral blood flow[30], cerebral hypoperfusion[10] and higher levels of white matter hyperintensities on neuroimaging. The underlying mechanism in this scenario is related to orthostatic intolerance and hypotension, without a compensatory increase in HR[16], causing reductions in cerebral blood flow.

Impaired cerebral autoregulation in ageing contributes to this phenomenon, characterized by hypotension in late life[8] that may be present in patients with cognitive dysfunction. Blood pressure changes and lack of cerebrovascular and cardiovascular regulation lead to brain hypoperfusion and hypoxia resulting in brain damage, manifested clinically as cognitive decline. Therefore, chronic cerebral hypoperfusion and small vessel disease may contribute to cognitive impairment[31], and some of these changes may be present years earlier, and not necessarily associated with autonomic dysfunction.

We observed lower BP, at least, a few years before cognitive decline, but with preserved capacity of the heart to increase the HR (intact baroreflex) during exercise. This is an interesting point, as compared with other neurodegenerative disorders such as Parkinson Disease (PD), we describe that there is still a compensatory response with the ability to increase the frequency, while in PD there is chronotropic insufficiency[32].

In patients with cognitive impairment, the vasomotor tone fails, and there is a dysfunction in the peripheral regulation of the sympathetic arteries, causing brain hypoperfusion. The process starts some years before memory loss is present, causing over the years cerebral hypoperfusion and ischemic lesions that may contribute to cognitive disturbances. On the other hand, in patients with vascular risk factors, hypertension may be present during midlife, causing continuous vascular damage and vessel rigidity, leading to ischemic lesions. We therefore recommend treating vascular risk factors including high blood pressure, optimising antihypertensive treatment seeking to avoid hypotension.

Longitudinal studies with longer observational periods and 24-hour monitoring of diurnal and nocturnal changes in blood pressure and HRV would be interesting in order to explore the changes in cardiac response with age and how to adjust therapy to prevent brain damage. There is a need for prospective studies investigating the role of blood pressure changes, including orthostatic hypotension, in cognitive dysfunction.

Declarations

Standard Protocol Approval

This study was approved by the Institutional Review Board of the University of Navarra. Patients had been informed that their data may be used for scientific purposes and had given their informed consent.

Competing interests

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

The authors declare that they have not conflict of interest.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

MCA and MR have contributed with conception and design of the research. MT, LI, MR and BE have contributed with acquisition of data. MT, MR and MCA have contributed with the analyses. RLP supervised the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages.

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Abbreviations

ANOVA: Analysis of variance

BP: Blood Pressure

CST: Cardiac Stress Testing

CT: Computed Tomography

HR: Heart Rate

HRV: Heart Rate Variability

MCI: Mild Cognitive Impairment

MMSE: MiniMental State Examination

MRI: Magnetic Resonance Imaging

PD: Parkinson Disease

SCD: Subjective Cognitive Decline

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Tables

Table 1. Sample characteristics at the time of cardiac stress testing overall and by final diagnosis.

Measures	**Controls (n=186)**	**CI after CST (n=186)**	**Dementia after CST (n=47)**	**MCI after CST (n=57)**	**SCD after CST (n=82)**
Age, years	62.8 ± 9.3	62.8 ± 8.9	68.3 ± 6.5	64.7 ± 9.4	58.3 ± 7.6
Gender, men (%)	124 (66)	124 (66)	28 (59)	42 (73)	54 (65)
Body mass index, kg/m^2	26.1 ± 7.3	26.9 ± 4.1	26.0 ± 3.9	27.8 ± 4.0	27.0 ± 4.0
Hypertension, yes (%)	106 (56)	106 (56)	32 (68)	33 (57)	41 (50)
Type 2 diabetes mellitus, yes (%)	59 (31)	59 (31)	20 (42)	23 (40)	16 (19)
Smoking, yes (%)	93 (50)	93 (50)	20 (42)	34 (59)	39 (47)
Dyslipidaemia, yes (%)	132 (70)	132 (70)	33 (70)	45 (78)	54 (65)

Continuous variables are represented as mean ± standard deviation.

CI, cognitive impairment; CST, cardiac stress testing; MCI, mild cognitive impairment; SCD: subjective cognitive decline.

Table 2. Cardiac stress test and heart rate variability measures overall and by subgroups.

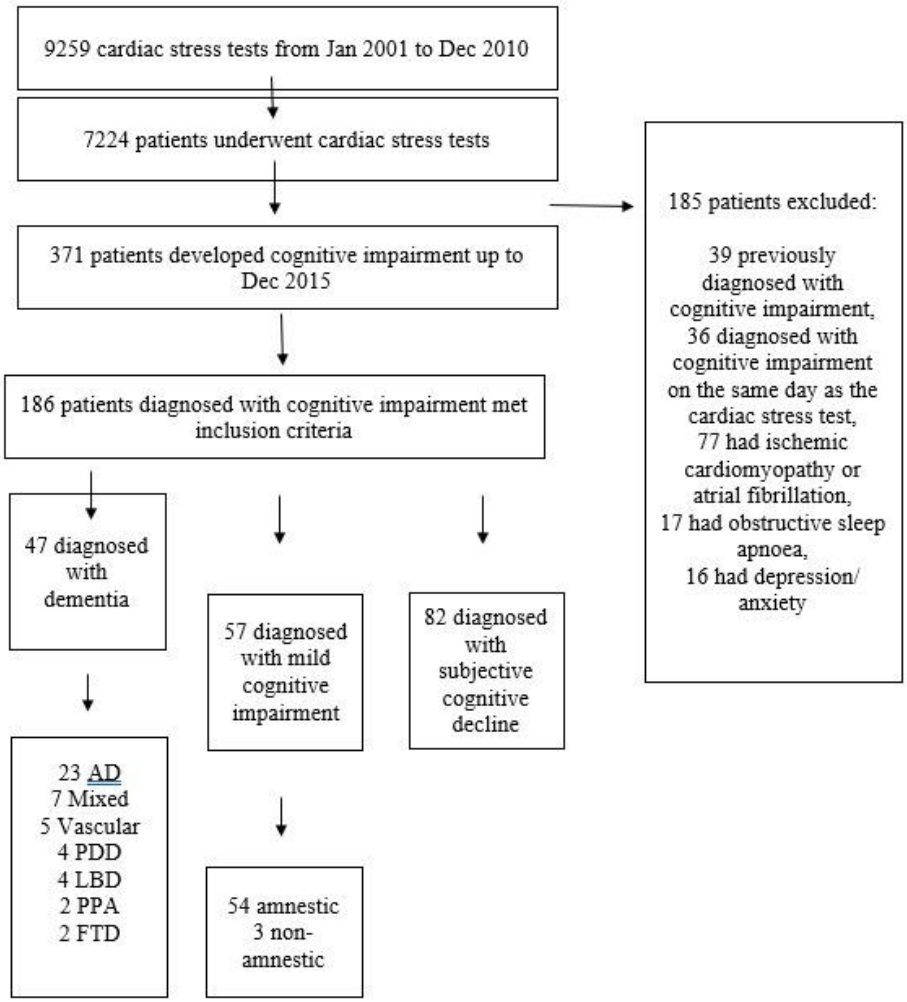
	Controls (n=186)	CI after CST (n=186)	Sig.[a]	Controls (n=104)	Dementia+MCI after CST (n=104)	Sign.[a]	Controls (n=82)	SCD after CST (n=82)	Sign.[a]
Basal HR, bpm	78.0±13.7	78.6±13.7	0.703	78.2±14.3	78.3±13.1	0.703	77.8±12.9	78.9±12.8	0.575
Basal SBP, mmHg	128.9±19.5	123.6±18.5	**0.001**	131.2±19.2	126.2±19.7	**0.001**	126.0±19.7	120.2±16.5	**0.014**
Basal DBP, mmHg	78.5±11.3	75.5±9.8	**0.002**	78.3±10.5	75.1±10.4	**0.002**	78.7±12.3	76.0±9.1	**0.046**
Basal MBP, mmHg	94.7±14.0	91.5±11.7	**0.006**	95.7±13.3	92.1±12.3	**0.006**	93.4±14.8	90.8±10.8	**0.018**
Max HR, bpm	137.1±30.2	144.6±26.2	**0.002**	131.4±30.2	138.5±28.3	**0.002**	144.3±28.7	152.4±21.0	**0.024**
Max SBP, mmHg	177.0±32.7	179.2±30.7	0.479	174.7±34.0	175.9±30.7	0.479	180.0±30.9	183.4±30.4	0.466
Max DBP, mmHg	87.4±15.6	88.2±12.5	0.585	86.5±15.6	86.6±13.1	0.585	88.6±15.6	90.2±11.5	0.423
Max MBP, mmHg	117.4±19.5	118.6±16.5	0.824	116.5±20.2	116.2±16.5	0.824	118.6±18.6	121.6±16.2	0.260
D SBP, mmHg	48.3±32.9	55.0±30.5	**0.029**	43.6±34.6	49.5±32.5	**0.029**	54.3±29.7	62.0±26.5	0.096
D DBP, mmHg	9.3±13.1	12.7±10.1	**0.005**	8.9±14.8	11.6±10.8	**0.005**	9.9±10.5	14.1±9.1	**0.005**
Mean R-R interval, ms	876.9±159.4	909.7±168.0	0.058	862.6±150.4	904.8±179.1	0.058	895.2±169.4	916.1±153.8	0.396

Continuous data are reported as mean ± standard deviation.

(a) Paired samples t-test

bpm, beats per minute; CI, cognitive impairment; CST, cardiac stress testing; DBP, diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; MCI, mild cognitive impairment; MHR, maximum heart rate; SBP, systolic blood pressure; SCD, subjective cognitive decline.

Figures



AD, Alzheimer's disease; FTD, frontotemporal dementia; LBD, Lewy bodies disease; PDD, Parkinson's disease dementia; PPA, primary progressive aphasia.

Figure 1

This flow diagram summarizes each stage of the study.