

## Evaluation of Systolic and Diastolic Hypotension in Dementia with Lewy Bodies and Alzheimer's Disease

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### ABSTRACT

**BACKGROUND:** Orthostatic hypotension (OH) can be seen in as many as 30% to 50% of the elderly population as well as in dementia. OH is part of the autonomic dysfunction in dementia with Lewy bodies (DLB) and prevalent in the majority of these patients. It is also suggested to be a negative prognostic factor for survival in DLB. A detailed interpretation of the 10-minute orthostatic blood pressure measurement has shown prolonged orthostasis in DLB compared with other dementias. The type of OH (systolic and diastolic) has not been separately investigated in different dementias.

**OBJECTIVES:** The aims of this study were to analyze the type of orthostatic hypotension, systolic and/or diastolic, in different dementia groups compared with normal controls.

**PATIENTS AND METHODS:** One-hundred fifty-six individuals, 52 with DLB, 50 with Alzheimer's disease (AD), 54 AD with vascular components (AD<sub>vasc</sub>), and 62 normal controls, were included. As part of each patient's routine clinical dementia investigation, systolic and diastolic blood pressure measurements were examined in the supine position, immediately after standing up, and after 1, 3, 5, and 10 minutes of standing. OH was defined as a blood pressure drop of 20 mmHg systolic or 10 mmHg diastolic, and the type of OH—systolic, diastolic or both—was defined.

**RESULTS:** Orthostatic hypotension was severely underdiagnosed before the dementia investigation with only 2% to 4% in the dementia groups, while we found that 69% of DLB, 50% of AD<sub>vasc</sub>, 38% of AD, and 13% of normal controls had OH. A combination of systolic and diastolic OH was the most common type of OH both in the DLB (67%) and AD<sub>vasc</sub> (48%) groups, while systolic OH was the most common type in AD (63%) as well as in normal controls (63%). Mini Mental State Examination scores differed significantly ( $P < 0.001$ ) between the group with no OH ( $25.2 \pm 4.8$ ) and the group with combined systolic and diastolic OH ( $22.0 \pm 4.8$ ).

**CONCLUSION:** Patients with DLB showed a greater proportion of combined systolic and diastolic hypotension. This might suggest a more complex OH than in patients with AD or elderly controls, possibly exacerbating the clinical picture in DLB. Further investigations of the relevance of these findings and the relation to clinical symptoms are needed.

**KEYWORDS:** dementia with Lewy bodies, Alzheimer's disease, orthostatic hypotension, dysautonomia

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## Introduction

Orthostatic hypotension (OH) is found in almost 50% of members of elderly populations who have various disorders such as cardiac failure, diabetes mellitus, Parkinson's disease, and multisystem atrophy, compared with healthy elderly individuals in whom the prevalence is less than 5% and increases with age.<sup>1-4</sup> Patients with dementia and patients with dementia with Lewy bodies (DLB), in particular, are at high risk to develop OH related to involvement of both the central nervous system (CNS) and postganglionic sympathetic lesions.<sup>5</sup>

DLB is the second most common neurodegenerative dementia after Alzheimer's disease (AD) with a clinical prevalence of 15% to 20% of all dementia cases.<sup>6</sup> The core symptoms of DLB are spontaneous parkinsonism, recurrent detailed visual hallucinations, and fluctuations in attention and alertness, with episodes of reduced responsiveness, daytime drowsiness, and increased sleepiness.<sup>7</sup> In addition, DLB patients exhibit REM (rapid eye movement) sleep behavior disorder (RBD).<sup>7-9</sup> The DLB patients are difficult to treat since they have psychotic symptoms but severe sensitivity to neuroleptics.<sup>10</sup> They also tend to respond less favorably to treatment with dopamine agonists.<sup>11</sup> DLB patients often have autonomic failure, manifested by repeated falls, syncope, and loss of consciousness.<sup>7</sup> Several of the above-mentioned symptoms could be expressions of OH. Dementia, OH, and risk of falling are all factors that increase with age; these imply high health related costs and great suffering for patients as well as for relatives.<sup>12-15</sup>

OH is defined as a sustained reduction of systolic blood pressure of 20 mmHg or a diastolic drop of 10 mmHg within 3 minutes of standing from supine position.<sup>16,17</sup> Population-based studies have reported that the mortality rate was higher in individuals with OH than in those without OH.<sup>18,19</sup> OH has also recently been suggested to be a negative prognostic factor with shorter survival in DLB patients.<sup>20</sup> The orthostasis in DLB is prolonged compared with AD and normal controls.<sup>21</sup> One way of describing OH further is to divide it into "initial OH" (blood pressure drop between 1 and 3 minutes of standing) and "delayed OH" (blood pressure drop between 5 and 45 minutes of standing).<sup>22</sup> There might also be a potential to use both the systolic and diastolic definition of OH to characterize the orthostatic reaction. This may ultimately lead to new clinical implications, such as support in the differentiation between dementia diagnoses and treatment strategies.

The aims of this study were (1) to analyze type of OH (systolic and/or diastolic) and (2) to relate the findings to dementia diagnosis.

## Patients and Methods

**Patients.** The AD and AD with smaller vascular components (ADvasc) patients were recruited from the Malmö Alzheimer's study<sup>23</sup> and exhibited mild-to-moderate disease. All patients diagnosed with DLB (n = 52) at the clinic during the same study interval were included. Each DLB patient was

age matched with patients with AD (n = 50) and ADvasc (n = 54) from the Malmö Alzheimer's study. The patients were investigated with Mini Mental State Examination<sup>24</sup> (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale<sup>25</sup> (ADAS-cog) and A Quick Test (AQT).<sup>26</sup> The cognitive tests were mainly used to support a cognitive deficit as part of the dementia diagnosis. The cognitive test profiles were supportive of the diagnoses, for example, frontosubcortical and visuospatial deficiencies in DLB and memory dysfunction in AD in accordance with the clinical diagnostic criteria.

The diagnoses were given as part of routine clinical investigation prospectively using the *National Institute of Neurological and Communicative Disorders and Stroke* and the *Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA) criteria for probable AD<sup>27</sup> and the 1996 consensus criteria for probable DLB.<sup>8</sup> The DLB patients exhibited at least 2 of 3 core criteria (parkinsonism, visual hallucinations, and fluctuations in attention and wakefulness). The majority of the patients had their diagnosis and baseline visit before the revised DLB criteria were published 2005.<sup>7</sup> Vascular components were defined as any smaller vascular lesion at brain imaging but not clinically relevant to be categorized as vascular dementia. Examples of lesions were minor periventricular white matter lesions and/or infarcts of 1 mm not in strategic areas.

All patients attended the Neuropsychiatric Clinic (now Memory Clinic), Malmö, Skåne University Hospital, Sweden, and were evaluated with a detailed clinical investigation. All patients were included in long-term follow-up programs at the clinic, and the baseline investigations were used for this study material. This included medical history, physical and neurological examination, and tests of cognitive function such as Mini Mental State Examination (MMSE),<sup>24</sup> blood and cerebrospinal fluid (CSF) sampling, brain computed tomography (CT), echocardiography (ECG), and 10-minute orthostatic blood pressure measurements.

Sixty-two healthy volunteers with absence of memory complaints or any other cognitive symptoms were recruited through advertisements. The controls also went through physical examination including orthostatic blood pressure measurement and cognitive testing. Exclusion criteria for the controls were cognitive impairment, active neurological, or psychiatric disease.

The study was approved by the Regional Ethical Review Board of Lund University. All patients and caregivers gave informed consent.

**Blood pressure measurements.** The orthostatic blood pressure measurement was performed in accordance with a standardized scheme using a validated digital sphygmomanometer (Omron M5-1, Lidingo, Sweden) over the brachial artery.<sup>28</sup> The blood pressure and pulse rate were recorded after at least 10 minutes of rest in a supine position, immediately after standing, and after 1, 3, 5, and 10 minutes of standing yielding 6 measurement points for each patient. OH was defined as a reduction of systolic blood pressure (SBP) of



at least 20 mmHg or a reduction of diastolic blood pressure (DBP) of at least 10 mmHg.<sup>16,17</sup> In the evaluation of OH, both patients with complete (all 6 measurement points) and incomplete orthostatic measurements were included to avoid selection of only those patients with normal blood pressure reactions.

Only values from subjects standing by themselves without assistance were recorded. Other reasons for not completing the measurement were apparatus failure and unwillingness to participate. This resulted in the exclusion of 15 patients (AD,  $n = 7$ ; DLB,  $n = 5$ ; ADvasc,  $n = 3$ ). These patients did not differ according to age and sex from the included patients.

In total, the study comprised of 203 subjects: 141 (156 minus 15) dementia patients and 62 normal controls.

**Statistical analysis.** Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) software version 20.0 (International Business Machines Corp, Armonk, NY). The majority of variables such as age, blood pressure, and pulse rate were normally distributed. The possible differences between the means were analyzed with independent  $t$  tests for two groups and with 1-way analysis of variance (ANOVA) for 3 or more independent groups. For nonnormally distributed variables, such as pulse differences,

the corresponding statistical methods, Mann-Whitney  $U$  and Kruskal-Wallis tests, were used. All analyses are presented without Bonferroni corrections. For dichotomous or categorical variables the  $\chi^2$  test was used. Logistic regression analyses were performed to identify which factors influenced the presence of and type of OH. The independent factors investigated were gender, age, diagnosis (AD, ADvasc, DLB, and normal controls), arterial hypertension, heart disease, and arteriosclerosis; treatment with antihypertensive medication, aspirin, antidepressants, antipsychotics, anxiolytics, and sedatives; and the MMSE.

## Results

The demographics of this study are shown in Table 1. Male gender was significantly more prevalent in the DLB group compared with the other diagnostic groups. The normal controls were younger, on average, than the dementia groups. The normal controls had less treatment with antidepressive and antipsychotic medication compared with the other groups. Antipsychotic or sedative medications were more common in the DLB group compared with the AD and ADvasc groups. There was no significant difference in mean MMSE score among the dementia groups. MMSE (mean  $\pm$  standard

**Table 1.** Demographics.

	DLB (n = 51)	AD (n = 50)	ADvasc (n = 54)	NC (n = 62)	p VALUE
<b>Age (years),</b> mean $\pm$ SD (range)	76 $\pm$ 6 (54–89)	76 $\pm$ 7 (52–86)	76 $\pm$ 6 (57–89)	73 $\pm$ 8 (60–94)	AD vs NC $p = 0.047$ ADvasc vs NC $p = 0.013$ DLB vs NC $p = 0.017$
<b>Sex, female</b>	23 (44%)	38 (76%)	34 (63%)	41 (66%)	DLB vs AD $p = 0.001$ DLB vs ADvasc $p = 0.041$ DLB vs NC $p = 0.015$ AD vs ADvasc $p = ns$
<b>Previous diagnosis of hypertension</b>	18 (35%)	10 (20%)	17 (32%)	12 (21%)	ns
<b>Previous diagnosis of hypotension</b>	1 (2%)	1 (2%)	2 (4%)	0 (0%)	ns
<b>MMSE</b> mean $\pm$ SD (range)	22.0 $\pm$ 4.9 (10–29)	21.8 $\pm$ 4.6 (6–28)	22.4 $\pm$ 4.4 (13–30)	29.1 $\pm$ 1.5 (24–30)	NC vs DLB $p < 0.001$ NC vs AD $p < 0.001$ NC vs ADvasc $p < 0.001$ AD vs ADvasc ns AD vs DLB ns DLB vs ADvasc ns
<b>Antidepressive treatment</b>	26 (51%)	19 (38%)	23 (43%)	3 (5%)	NC vs DLB $p < 0.001$ NC vs AD $p < 0.001$ NC vs ADvasc $p < 0.001$ AD vs ADvasc ns AD vs DLB ns DLB vs ADvasc ns
<b>Antipsychotic/sedative treatment</b>	28 (55%)	17 (34%)	18 (33%)	1 (2%)	DLB vs AD $p = 0.028$ DLB vs ADvasc $p = 0.021$ AD vs ADvasc $p = ns$ NC vs DLB $p < 0.001$ NC vs AD $p < 0.001$ NC vs ADvasc $p < 0.001$
<b>Antihypertensive treatment</b>	19 (37%)	15 (30%)	24 (44%)	23 (37%)	ns

**Abbreviations:** DLB, Dementia with Lewy bodies; AD, Alzheimer's disease; ADvasc, Alzheimer's disease with vascular components; NC, Normal controls; MMSE, Mini Mental State Examination; NS, not significant. SD; standard deviation.



deviation [SD]) differed significantly ( $P < 0.001$ ) between the group with no OH ( $25.2 \pm 4.8$ ) and the group with combined systolic and diastolic OH ( $22.0 \pm 4.8$ ). There was one normal control with an MMSE of 24; notably, this was the oldest person, who was 94 years old.

Previous diagnoses of hypertension and hypotension were equally prevalent in the different diagnostic groups. Only 2% to 4% had a previous diagnosis of OH (Table 1).

Some orthostatic measurements were incomplete (3.2% of the controls, 15.3% of the AD patients, and 17.3% of the DLB patients). Of these, 74% were missing the last 10-minute measurement point only.

Ninety of the 203 individuals (44%) had OH according to the criteria. The prevalence of OH differed significantly among the diagnostic groups and is described in Table 2. OH was most common in the DLB (69%) and the ADvasc (50%) groups. Among the 90 individuals with OH, 40% were pure systolic OH, 11% diastolic OH, and 49% mixed systolic and diastolic OH. The pattern of OH (systolic, diastolic or both) differed significantly ( $P < 0.001$ ) among the 4 diagnostic groups.

A combination of systolic and diastolic OH was the most common type of OH both in DLB (67%) and ADvasc (48%) groups, while systolic OH was the most common type in AD (63%) as well as in normal controls (63%). Diastolic OH was

observed in the ADvasc group (22%) but not seen at all in normal controls (Table 2).

Among the 90 orthostatic subjects, 87 (97%) had their orthostatic drop within 5 minutes of standing. There was no difference between the diagnostic groups regarding what measurement point the OH drop appeared (Fig. 1).

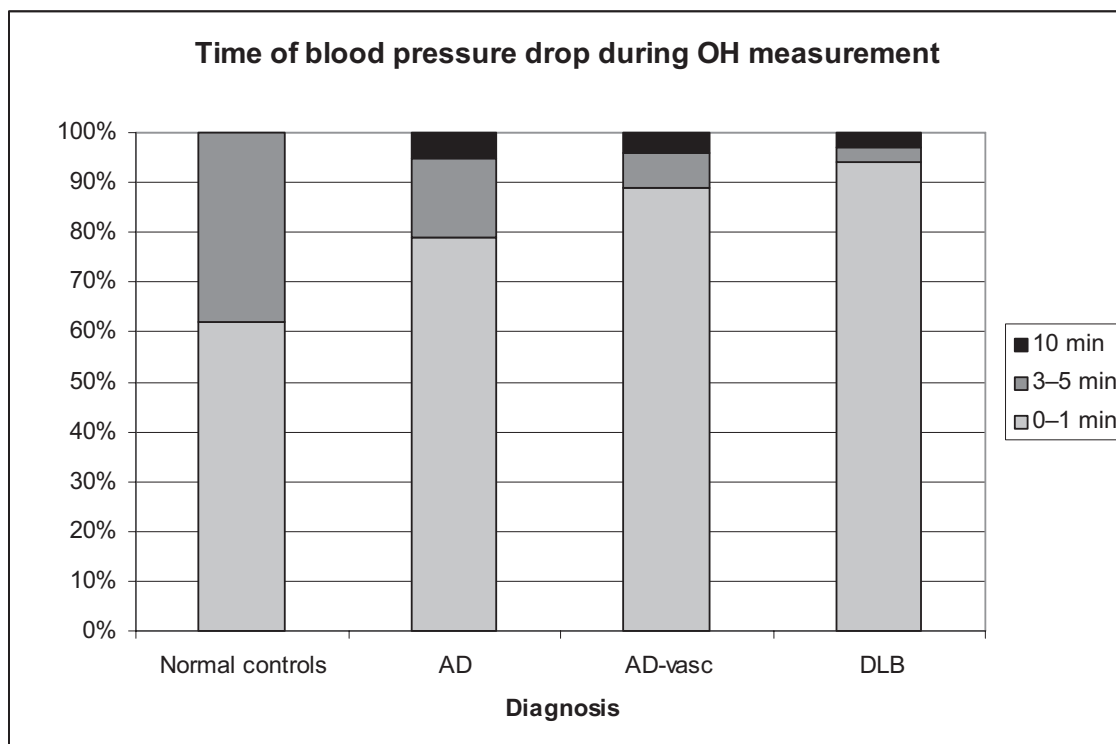
Excluding the 81 patients with antihypertensive medication, the prevalence of orthostatic hypotension changed from 13% to 8% in normal controls, from 38% to 43% in AD, remained unchanged at 50% in ADvasc, and changed from 70% to 74% in DLB.

**Regression analysis.** Using logistic regression analysis with OH as the dependent variable, we found that 71.5% of the individuals were correctly classified. AD exhibited a 3 times increased risk for OH in comparison with controls, ADvasc, a 5 times increased risk, and DLB, a 12 times increased risk. When presence of any kind of diastolic OH was the dependent variable, 67% of the patients were correctly classified, and ADvasc had a 5 times and DLB a 3 times increased risk for the diastolic component compared with controls. When any kind of systolic OH was used as the dependent variable the model was not significant. None of the other variables investigated were significantly influencing OH, such as gender, age, cardiovascular disease, and arrhythmias

**Table 2.** Blood pressure, pulse rate and type of orthostatic hypotension in the different diagnostic groups.

	DLB (N = 51–52)	AD (N = 49–53)	ADvasc (N = 53–57)	NC (N = 62)	p VALUE
<b>Blood pressure (mmHg)</b>					
Supine SBP/DBP (m ± SD)	150 ± 21/81 ± 10	149 ± 20/83 ± 12	147 ± 24/85 ± 11	141 ± 18/80 ± 8	DLB vs AD p = ns DLB vs ADvasc p = ns AD vs ADvasc p = ns
Standing SBP/DBP (m ± SD)	123 ± 29/73 ± 16	141 ± 23/85 ± 16	136 ± 24/79 ± 13	141 ± 21/84 ± 10	DLB vs AD p = 0.001/<0.001 DLB vs ADvasc p = 0.019/0.035 AD vs ADvasc p = ns/0.05
<b>Pulse rate (bpm)</b>					
Difference supine – standing (m ± SD, median, min-max)	7,2 ± 7,4 6 (–12 to 28)	9,3 ± 9,9 9 (–26 to 35)	10,1 ± 10,8 9 (–17 to 42)	8,9 ± 8,5 8 (–23 to 40)	NS NS
OH, systolic and/or diastolic, N (%)	36 (69%)	19 (38%)	27 (50%)	8 (13%)	DLB vs AD p = 0.001, DLB vs ADvasc p = 0.006, AD vs ADvasc p = ns, NC vs AD p = 0.002, NC vs ADvasc p < 0.001, NC vs DLB p < 0.001
Systolic OH, N (%)	11 (31%)	12 (63%)	8 (30%)	5 (63%)	p < 0.001
Diastolic OH, N (%)	1 (3%)	3 (16%)	6 (22%)	0	p < 0.001
Systolic and diastolic OH N (%)	24 (67%)	4 (21%)	13 (48%)	3 (38%)	p < 0.001
OR immediately standing –1 min N (%)	34 (94%)	15 (79%)	24 (89%)	5 (62%)	ns
OR 3–5 min N N(%)	1 (3%)	3 (16%)	2 (7%)	3 (38%)	ns
OR 10 min N (%)	1 (3%)	1 (5%)	1 (4%)	0	ns

**Abbreviations:** DLB, Dementia with Lewy bodies; AD, Alzheimer's disease; ADvasc, Alzheimer's disease with vascular components; NC, Normal control; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; OH, Orthostatic hypotension; OR, Orthostatic reaction; NS, not significant.



**Figure 1.** Timepoint during the 10 minute orthostatic blood pressure test when the blood pressure drop ( $\geq 20$  mmHg systolic or  $\geq 10$  mmHg diastolic) occurs in the different diagnostic groups.

or medications such as antihypertensive, nonsteroidal anti-inflammatory (NSAIDs), acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics.

### Discussion

This OH study reports that patients with DLB were more likely to have both a systolic and a diastolic component in OH compared with AD, with and without minor vascular components, and that the distribution between the 2 components differed significantly among the dementia diagnoses. This could indicate that the combined systolic and diastolic OH represents a more profoundly disturbed autonomic dysfunction, probably attributed to  $\alpha$ -synucleinopathy both in the central (brainstem) and in the peripheral (sympathetic ganglia) autonomic nervous system.<sup>29</sup> Interestingly, also patients with AD with vascular components exhibited a pattern with more combined OH equivalent to that of DLB patients, though it was less pronounced. The reason for this is unknown, but one speculation could be in alignment with the suggestion that additional pathological components, such as combined AD and vascular events in dementia, worsens the outcome.<sup>30,31</sup> On the other hand, pure vascular dementia was previously shown to have a lower incidence of autonomic dysfunction.<sup>5</sup>

In AD patients and elderly without dementia, the systolic OH component was more common. There was a corresponding initial increase in heart rate in all patient groups, but in the DLB patients the heart rate was not sufficient to

restore blood pressure. The inability to increase heart rate sufficiently could be an expression of the sympathetic nervous system affection earlier shown in metaiodobenzylguanidine (MIBG) studies.<sup>32,33</sup> Interestingly MIBG patterns differed between AD and DLB in the same way as the OH patterns in this study, with AD and normal controls with similar patterns and DLB and Parkinson's disease with pathological patterns. Inefficient pulse frequency response is one of the reasons why it is important to be concerned about OH in DLB. It is possibly a factor to consider in the choice of medications such as beta blockers. Another reason is that the type of OH did affect cognitive ability measured by MMSE, so that a more profound OH (both systolic and diastolic) resulted in significantly lower scores compared with no OH. Other studies have shown that OH may lead to deficiencies in visual memory and perception and thereby contribute to the cognitive pattern in Parkinson's disease dementia, which in many aspects is considered to be very similar to DLB.<sup>34,35</sup> This may signal that treatment of OH needs to be investigated as a possible cognitive treatment strategy in these patients.

One advantage of the study was that the blood pressure measurements were performed in a standardized manner during the visit to the clinic. Those who could not stand by themselves were excluded, which probably means an underreporting of orthostatic blood pressure. In order to detect OH, repeated measurements have been suggested<sup>36</sup>; however, within the 10-minute orthostatic measurement in our study, 93% had their orthostatic drop within 3 minutes and 97%





within 5 minutes of standing up, which means that just for the OH diagnosis it seems as if 3 minutes of standing is sufficient. In a study of subjects referred to an autonomic and nerve laboratory, only 61% of those with OH were discovered within the 10-minute test.<sup>22</sup> This lower figure probably reflects the patient population and was supported by the finding that younger subjects tended to be more prone to delayed OH. The orthostatic tests at our clinic are routinely carried out during 10 minutes, which earlier have allowed us to show a pattern of a prolonged OH in DLB patients.<sup>21</sup> Because of the patient's medical conditions in a geriatric population, measurements during 10 minutes of standing might not be possible to be carried out in all patients, which is why we also wanted to find additional patterns of OH characteristic of the different types of dementia.

One disadvantage of the study is that we still do not know how representative the 10-minute OH test is for blood pressure during the whole day and night, which needs to be further investigated, for example, using 24-hour blood pressure measurements. Furthermore, in this routine clinic setting, tests to differentiate the underlying cause of OH were not performed. A large proportion of patients received antihypertensive medication. However, excluding these patients did not change the prevalence of OH in the diagnostic groups, indicating that this is unlikely to be the solitary explanation for the orthostatic condition. Another weakness is that only very few diagnoses, 5 DLB patients, were confirmed by neuropathology.

The number of people with dementia is steadily increasing, and due to demographic trends, aging is rapidly proceeding in the developing world. DLB is increasingly recognized with concomitant risk for falls because of impaired mobility and balance. DLB patients also have a decrease in quality of life and loss of independence<sup>14</sup> and less empowerment and shared decision making. In the absence of curative treatment, additional factors such as OH are important to find and treat to optimize the clinical status of these patients. We need routines for OH measurements in the elderly group of patients and awareness of the importance of different OH patterns such as systolic and diastolic OH separately and in combination.

In conclusion, this is to our knowledge the first study to analyze the distribution of both diastolic and systolic OH in different types of dementias. We found special patterns in the different diagnostic groups with more combined systolic and diastolic OH in the DLB group compared with AD. This might suggest a more complex OH than in patients with AD or elderly controls. These findings could be used to support the clinical dementia diagnosis, both from a treatment and prognostic standpoint. This can also support the autonomic symptoms, especially orthostatic hypotension, to become a more important criterion in the DLB diagnosis.

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### Author Contributions

Analyzed the data: MEBL, EYL. Wrote the first draft of the manuscript: MEBL. Contributed to the writing of the manuscript: MEBL, VSL, CASW, EYL. Agree with manuscript results and conclusions: MEBL, VSL, LBM, CASW, EYL. Jointly developed the structure and arguments for the paper: MEBL, VSL, CASW, EYL. Made critical revisions and approved final version: MEBL, VSL, LBM, CASW, EYL. All authors reviewed and approved of the final manuscript.

### DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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