The period of hypotension following orthostatic challenge is prolonged in dementia with Lewy bodies

Running head: Orthostatic hypotension in DLB

M. Andersson, O. Hansson, MD, PhD, L. Minthon, MD, PhD, C.G. Ballard, MD, E. Londos, MD, PhD

From the Neuropsychiatric clinic, Malmö University Hospital, Malmö, Sweden (M. Andersson, O. Hansson, L. Minthon, E. Londos), Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Sweden (M. Andersson, O. Hansson, L. Minthon, E. Londos), Wolfson Centre for Age-Related Diseases, King's College, London, UK (C.G. Ballard).

Corresponding author:

Maria Andersson, Neuropsychiatric clinic, Malmö University Hospital, 20502 Malmö, Sweden

Phone: +46-40-335036, Fax: +46-40-335654, E-mail: Maria_A.Andersson@med.lu.se

Keywords: dementia, Lewy body disease, blood pressure, orthostatic hypotension.

Word count: 2113 words, abstract 238 words

The authors declare no conflicts of interests.

SUMMARY

Objectives: To determine whether orthostatic hypotension (OH) is more common in patients with dementia than in older people without cognitive impairment and to identify key differences in the profile of the orthostatic response and the pulse drive during orthostatic challenge between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

Methods: The orthostatic response was evaluated in 235 patients with AD, 52 patients with DLB and 62 elderly controls. The blood pressure and pulse rate were measured in supine position, immediately after standing up and after one, three, five and ten minutes of standing. OH was defined as a reduction of systolic blood pressure (SBP) of at least 20 mm Hg or a reduction of diastolic blood pressure (DBP) of at least 10 mm Hg.

Results: OH occurred in 69% of the DLB patients and in 42% of the AD patients, but only in 13% of the controls. ($p<0.001$ controls vs AD and controls vs DLB, $p=0.001$ AD vs DLB) The DLB patients had a greater drop in SBP than the other study groups during orthostatic challenge and had a more prolonged period of orthostasis. The pulse drive on orthostatic challenge was similar in between groups. However, in the DLB group it was not adequate to restore the blood pressure to supine values.

Conclusions: Patients with DLB react different to orthostatic challenge than patients with AD or controls, with important clinical implications for key disease symptoms and treatment.

INTRODUCTION

Worldwide, 25 million people suffer from dementia, the majority of whom have Alzheimer's disease (AD). It is a devastating illness, which results in a progressive decline in cognitive ability and functional capacity, causes immense distress to patients, their carers and families and has an enormous societal impact. Dementia with Lewy bodies (DLB) is often claimed to be the second most common cause of neurodegenerative dementia in older people after AD. A systematic review of six studies has found prevalence estimates for clinical DLB of up to 30.5% of all dementia cases.(Zaccai *et al.,* 2005) The central feature of DLB is progressive cognitive decline accompanied by fluctuating cognition, visual hallucinations and parkinsonism. Suggestive features are REM sleep behaviour disorder, severe neuroleptic sensitivity and low dopamine transporter uptake in basal ganglia. Some of the supportive features are falls, syncope, loss of consciousness, systematised delusions, hallucinations of other modalities, depression, autonomic failure and abnormal metaiodobenzyl guanidine (MIBG) myocardial scintigraphy.(McKeith *et al.,* 1996; McKeith *et al.,* 1999; McKeith *et al.,* 2005)

Orthostatic hypotension (OH) is a common problem amongst older people living in the community, with prevalence between 4% and 33% depending on the methodology used and differences in population characteristics. The frequency increases with age.(Mathias *et al.,* 1999b; Kenny *et al.,* 2002) A review published in 2005 focussing on the diagnosis of DLB, concluded that autonomic function, such as OH has not been adequately studied, although preliminary reports indicate that it is a major problem in these patients.(Geser *et al.,* 2005)

The effect of standing up on blood pressure and pulse reaction is important to clarify for several reasons. First, it might be used as an instrument to differentiate different types of

dementia from each other. This will have clinical implications as DLB patients show good responsiveness to cholinesterase inhibitors but extreme sensitivity to the side effects of neuroleptic drugs. It is also important since the course and prognosis may differ from other dementias.(Geser *et al.,* 2005) Second, it is important to recognise a low blood pressure in patients with dementia as many of the drugs used to treat dementia have blood pressure lowering properties and specific interventions may be necessary to improve related symptoms and reduce the risk of falls.

The current study aimed to determine whether 1: OH is more common in patients suffering from dementia than in older people without cognitive impairment, 2: the profile of the orthostatic response is different in DLB and AD, 3: the pulse drive during orthostatic measurement differs between DLB, AD and elderly controls.

METHODS

Study population

Two hundred and eighty seven patients (235 AD, 52 DLB) from the Malmö Alzheimer's study and 62 controls were assessed. All the patients attended the Neuropsychiatric Clinic, Malmö University Hospital, Malmö, Sweden and were evaluated with a detailed clinical investigation of cognitive function during 1999-2003. The complete investigation included anamnestic data, physical and neuropsychiatric examination, tests of cognitive function (Mini Mental State Examination (MMSE) (Folstein *et al.,* 1975) and Alzheimer's Disease Assessment Scale (ADAS) (Mohs *et al.,* 1983)), blood and cerebrospinal fluid (CSF) sampling, brain CT, regional cerebral blood flow (rCBF), EKG and blood pressure measurements. Only AD patients showing mild or moderate disease and with a complete

investigation were selected to participate in the study. All patients diagnosed with DLB during the study interval were included. More than 90% of the patients were living in the community, 7 of the AD patients and 3 of the DLB patients were living in nursing homes. The diagnosis was given prospectively using operationalized diagnostic criteria (NINCDS-ADRDA (McKhann *et al.,* 1984) for probable AD and DLB consensus criteria for probable DLB (McKeith *et al.,* 1996)).

The controls (n=62) were recruited through advertisements. Volunteers went through physical examination and cognitive testing. Inclusion criteria were absence of memory complaints or any other cognitive symptoms, preservation of general cognitive functioning and no active neurological or psychiatric disease. Individuals with other medical conditions that did not affect cognition where not excluded.

Blood pressure measurements

Orthostatic blood pressure was measured at the patient's first visit at the clinic. The measurement was performed in accordance to a standardised scheme using a validated digital sphygmomanometer (OMRON M5-1) over the brachial artery.(El Assaad *et al.,* 2003) The blood pressure and pulse rate were recorded after at least ten minutes rest in a supine position, immediately after standing up, and after one, three, five and ten minutes of standing. All subjects stood up by themselves without assistance. OH was defined as a reduction of SBP of at least 20 mm Hg or a reduction of DBP of at least 10 mm Hg. (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology) Some of the orthostatic measurements were incomplete (3% of the controls, 15% of the AD patients and 20% of the DLB patients). The most frequent reasons for not completing the measurement were apparatus failure, orthostatic symptoms, patients being unable to stand for ten minutes

and patients unwilling to participate. In the evaluation of OH both patients with complete and incomplete orthostatic measurements were included.

The study was approved by the ethics committee of Lund University.

Statistical analysis

Statistical analysis was performed with use of The Statistical Package for Social Sciences (SPSS) software version 12.0.1. To avoid bias with non-normally distributed variables non-parametric statistics (Kruskal-Wallis and Mann-Whitney U test) were used to detect significant group differences. Binary variables were compared using Chi-Square Tests.

RESULTS

In this study on the reaction to orthostatic challenge we included 62 controls, 235 AD patients and 52 DLB patients. There was no significant difference in age or mean MMSE score between the AD and the DLB patients (table 1). [Insert table 1 about here] The use of medications known to influence the blood pressure was compared between the groups (table 2). The drugs were classified by the Anatomical Therapeutic Chemical classification system (ATC) recommended by the World Health Organization (WHO). (Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaboration Centre for Drug Statistics Methodology; 2001. http://www.whocc.no) The use of antidepressants was more prevalent among AD and DLB patients compared to the controls. The use of medication in the group "antipsychotics, anxiolytics and sedatives" also differed in between all three groups (table 2). [Insert table 2 about here] The blood pressure (BP) and pulse rate were analysed for all included patients as well as for the orthostatic patients only. To compare the different profiles of the orthostatic response, the mean drop in BP from supine rest at each measurement point (standing, 1 min, 3 min, 5 min and 10 min) was calculated. As shown in figure 1 the DLB

patients had a greater drop in SBP than the other study groups during orthostatic challenge. Moreover, they had a more prolonged period of orthostasis (figure 1). [Insert figure 1 about here] We found that OH occurred in 36 (69%) of the DLB patients, in 99 (42%) of the AD patients and in 8 (13%) of the controls. The differences were significant ($p<0.001$ AD vs. controls and DLB vs controls, $p=0.001$ AD vs DLB).

The profiles of the orthostatic patients (n=143) are illustrated in figure 2A and show that the DLB patients with OH have a larger and more prolonged drop of SBP, when compared to AD or controls with OH. The pulse drive on orthostatic challenge was similar in all groups (figure 2B). [Insert figure 2 about here]

To illustrate the duration of orthostasis in the different diagnostic groups, each patient's systolic blood pressure curve was analysed individually. Each measurement point (standing, 1 min, 3 min, 5 min, 10 min) was dichotomised as orthostatic or not orthostatic. The sum of all orthostatic values (0-5) in each individual was calculated. The minimum value zero is possible because OH was defined by both systolic and diastolic drop. The number of orthostatic measurement points was increased in the DLB group compared to both the control group and the AD group. (table 3) [Insert table 3 about here]

The use of antipsychotics, anxiolytics and sedatives differed between the two dementia groups. (table 2) To investigate the effect of these drugs on the orthostatic response the DLB and AD groups were divided in two groups respectively, one with the above mentioned medication and one without, and the profiles of the orthostatic responses were compared. (figure 3) There were no significant differences between the DLB patients taking the medication and the ones not taking the medication. The AD and DLB subjects taking the

medication differed significantly on all measurement points ($p<0.001$). The AD and DLB patients not taking the medication differed significantly on standing ($p=0.017$), after 1 min ($p=0.004$), after 3 min ($p=0.014$) and after 10 min ($p=0.009$) of standing. [Insert figure 3 about here]

DISCUSSION

In the largest study of OH in patients with DLB, we determined that DLB patients had a greater drop in blood pressure during orthostatic challenge over 10 minutes, than patients with AD or elderly controls. Furthermore we report an important new finding, demonstrating that DLB patients had a significantly more protracted period of orthostasis than AD patients. The pulse drive was similar in DLB and AD, but the rise in pulse rate was not adequate to restore the blood pressure to supine values in DLB patients. The study also confirmed a significantly higher prevalence of OH in patients suffering from dementia compared to older people without dementia.

The blood pressure measurements were standardised and detailed. It is important to test for OH during 10 minutes of standing since patients, and dementia patients in particular, may not manifest significant falls in blood pressure until after five minutes of standing or more.(Passant *et al.,* 1996) The measurements were carried out from approximately 8 am to 5 pm. There seem to be only minor natural blood pressure alterations during this time in healthy elderly men.(Bjorklund *et al.,* 2000) In patients suffering from OH the orthostatic reaction and its symptoms may be worse in the morning.(Mathias *et al.,* 1999a; Mathias *et al.,* 1999b) In this study 82% of the controls, 51% of the AD patients and 61% of the DLB patients had their orthostatic measurements carried out before noon. There were no significant differences in the

frequency of orthostatic reactions between the individuals in the same group regarding whether they had had their measurement carried out before or after noon (data not shown).

The control group was healthier than the dementia groups regarding cardiac disease and the use of antidepressants and other psychoactive drugs. Importantly, the only significant difference between the AD and the DLB group concerned the use of antipsychotics, anxiolytics and sedatives. The difference in medication between the dementia groups is not likely to alone explain the differences in blood pressure reaction to orthostatic challenge, since the difference in systolic drop between the AD and the DLB patients taking the medication was highly significant as well as the difference in systolic drop between the AD and DLB patients not taking the medication. There was no significant difference in systolic drop between the DLB patients with and without the medication, although the medication seemed to aggravate the OH in DLB. This is important to be aware of in the clinic, in order to avoid worsening of OH in these patients. The diagnosis of probable DLB was given using the 1996 DLB consensus criteria which do not include autonomic dysfunction as a supportive feature.(McKeith *et al.,* 1996)

It has been shown that AD, fronto-temporal dementia and vascular dementia patients have normal pulse reactions during orthostatic testing.(Passant *et al.,* 1997) Our results show that this is also true for DLB. This indicates that the heart is normally activated but not enough, since the DLB patients stay orthostatic, and the failure might also be in the sympathetic activation of the vasculature. In a neuropathological study from 2005 Benarroch *et al* suggests that OH in DLB and Parkinson's disease may be due to degeneration of sympathetic ganglion neurones.(Benarroch *et al.,* 2005) A new method to distinguish DLB from AD is [^{123}I]MIBG myocardial scintigraphy, which has shown reduced uptake of norepinephrine precursors in

cardiac sympathetic terminals in DLB compared to AD.(Watanabe *et al.*, 2001; Yoshita *et al.*, 2001) The results further underscore the postganglionic pattern of involvement of the autonomic nervous system in DLB.

Dysautonomia, including OH, has been highlighted as a supportive feature for the diagnosis of DLB in the new consensus criteria, but was not given a more prominent place in diagnosis because of the paucity of empirical data.(McKeith *et al.,* 2005) This study shows that the profile of the orthostatic reaction is different between dementia groups. DLB has the greatest drop in blood pressure and most longstanding reaction to orthostatic challenge. This may have clinical implications for treatment as well as for understanding the neurophysiological properties of the disease. Further studies are needed to determine if OH can play a more important role in the diagnosis of DLB.

ACKNOWLEDGEMENTS

Carina Wattmo for statistical advice. AnnaCarin Björkman and Cecilia Dahl for administration of patient material. Sassa Persson for technical information on blood pressure measurement instruments.

FUNDING

The study was supported by the Alzheimer Foundation, Sweden.

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TABLES

Table 1, demographic data

	Controls (n=62)	AD (n=235)	DLB (n=52)
Median age (years)	73	76*	77†
Age range	60-94	52-87	54-89
Women, n	41 (66%)	161 (69%)‡	23 (44%) §
Mean MMSE score ± SD	29±1	21±5‖	22±5¶

*p=0.017 AD vs controls, †p=0.009 DLB vs controls, ‡p=0.002 AD vs DLB, §p=0.031 DLB vs controls, ‖p<0.001 AD vs controls, ¶p<0.001 DLB vs controls.

Table 2, medication and medical history

	Controls (n=62)	AD (n=235)	DLB (n=52)
Antidepressants, n	3 (5%)	98 (42%)*	26 (51%)†
Antipsych/Anx/Sed‡, n	1 (2%)	74 (32%) §‖	28 (55%) ¶
Antihypertensives/cardiac therapy, n	23 (37%)	79 (34%)	19 (37%)
Cardiac disease**, n	8 (13%)	64 (27%)††	18 (35%)‡‡
Hypertension, n	12 (21%)	56 (24%)	18 (35%)
Arteriosclerosis§§, n	10 (17%)	53 (23%)	14 (27%)

*p<0.001 AD vs controls, †p<0.001 DLB vs controls, ‡Antipsychotics, Anxiolytics, Sedatives/Hypnotics, §p<0.001 AD vs controls, ‖p=0.003 AD vs DLB, ¶p<0.001 DLB vs controls, **Atrial fibrillation, AV-block I, Congestive heart failure, ††p=0.03 AD vs controls, ‡‡p=0.011 DLB vs controls, §§Myocardial infarction, Coronary artery disease, Peripheral artery disease.

Table 3. Sum of orthostatic measurement points. Systolic values.

	Controls (n=62)	AD (n=235)	DLB (n=52)	Controls with OH (n=8)	AD with OH (n=99)	DLB with OH (n=36)
Median	0	0*†	2‡	1.5	2.0§	4.0‖
Range	0-4	0-5	0-5	1-4	0-5	0-5

*p=0.001 AD vs controls, †p<0.001 AD vs DLB, ‡p<0.001 DLB vs controls, §p<0.001 AD vs DLB, ‖p=0.042 DLB vs controls.

FIGURES

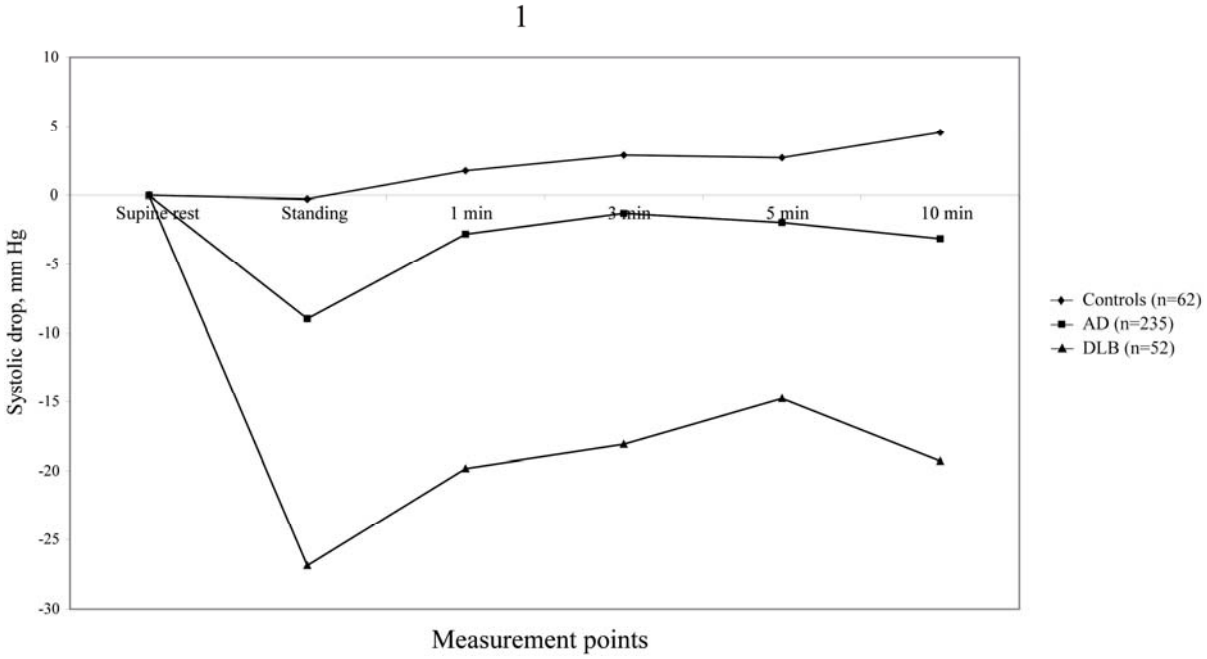

Figure 1. All included subjects (n=349). The mean BP after 10 minutes of rest in supine position was 141±18/80±8 mm Hg (mean SBP±SD/mean DBP±SD) for the controls, 147±23/83±12 mm Hg for the AD patients and 150±21/81±10 mm Hg for the DLB patients. The mean difference in systolic blood pressure from supine rest is shown. Differences were significant between AD and DLB on all measurement points ($p<0.001$), between DLB and controls on all measurement points ($p<0.001$) and between AD and controls on standing ($p<0.001$), 5 min ($p=0.048$) and 10 min ($p=0.003$).

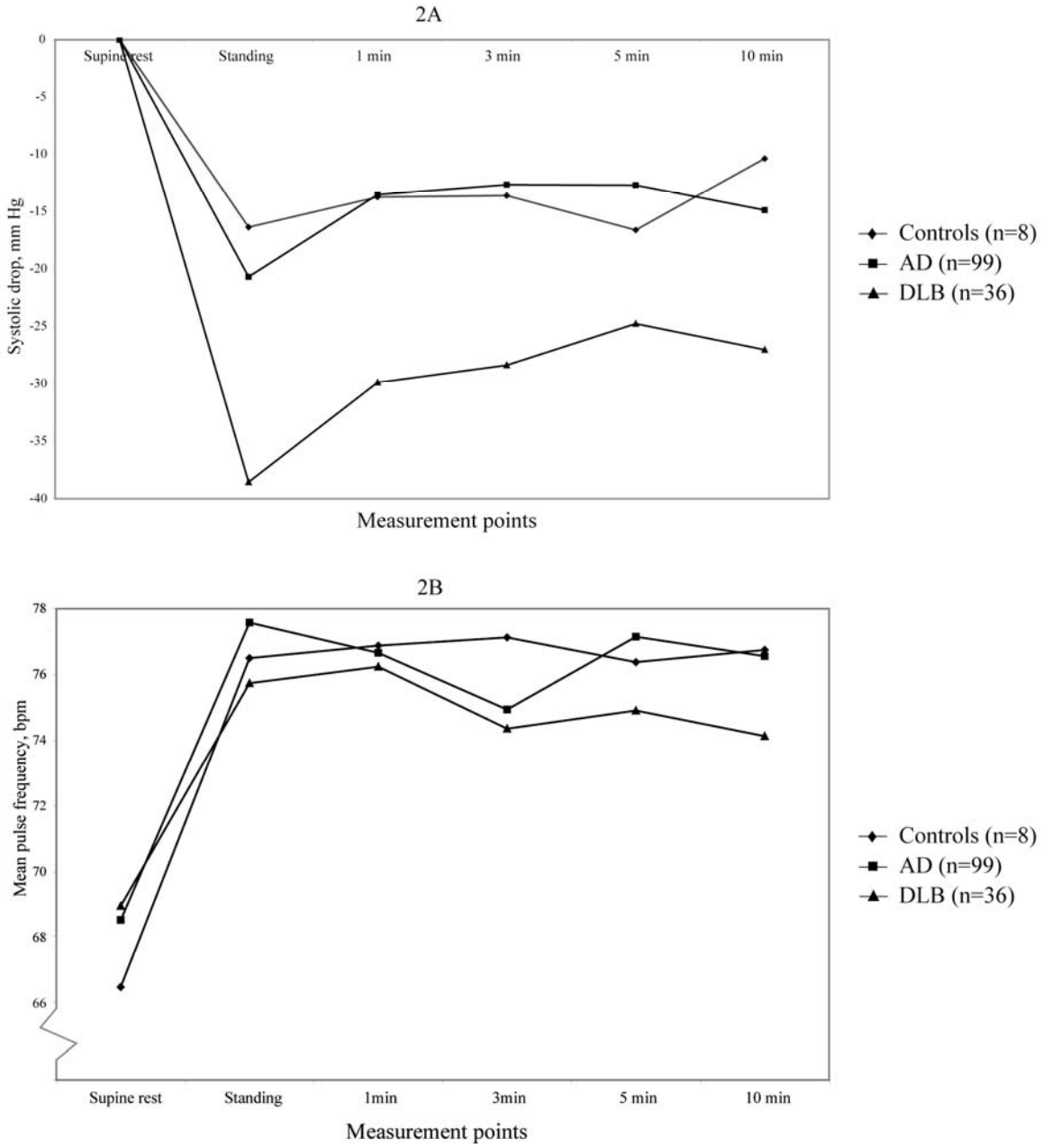

Figure 2. Orthostatic subjects (n=143). (A) The mean BP after 10 minutes of rest in supine position was 143±16/81±7 mm Hg (mean SBP±SD/mean DBP±SD) for the controls, 154±25/86±13 mm Hg for the AD patients and 151±22/81±10 mm Hg for the DLB patients. The mean difference in systolic blood pressure from supine rest is shown. Differences were significant between AD and DLB on standing ($p<0.001$), 1 min ($p<0.001$), 3 min ($p<0.001$), 5 min ($p=0.002$) and 10 min ($p=0.004$). Differences were significant between DLB and controls on standing ($p=0.001$), 1 min ($p=0.016$) and 10 min ($p=0.042$) (B) Pulse frequencies on

orthostatic challenge. The rise in heart frequency does not result in an adequate blood pressure response in the DLB group.

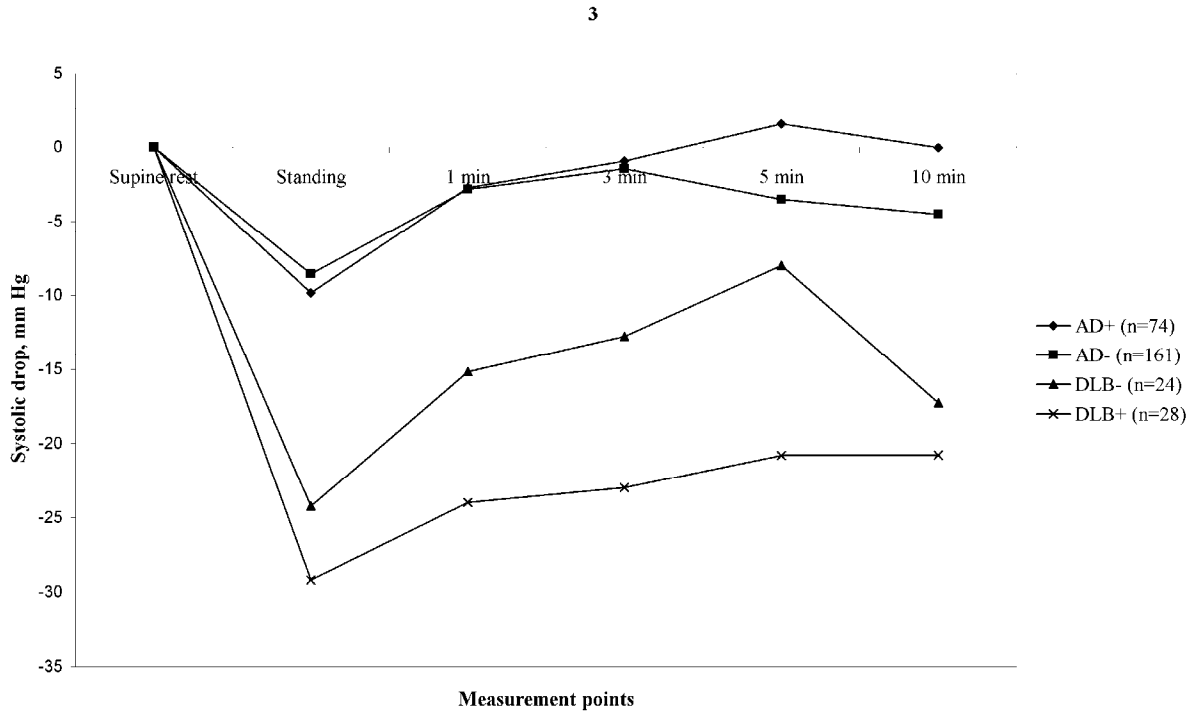

Figure 3. AD+ (AD with antipsychotics, anxiolytics, sedatives), AD- (AD without antipsychotics, anxiolytics, sedatives), DLB- (DLB without antipsychotics, anxiolytics, sedatives), DLB+ (DLB with antipsychotics, anxiolytics, sedatives). All included subjects. The mean difference in systolic blood pressure from supine rest is shown. There were no significant differences between the DLB group with and the DLB group without medication. Differences were significant between the AD group with medication and the DLB group with medication on all measurement points ($p<0.001$). Differences were significant between the AD group without medication and the DLB group without medication on standing ($p=0.017$), 1 min ($p=0.004$), 3 min ($p=0.014$) and 10 min ($p=0.009$).