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Original Study

Pathophysiology of Oropharyngeal Dysphagia Assessed by Videofluoroscopy in Patients with Dementia Taking Antipsychotics

Marta Miarons MS, BPharm [a,*], Pere Clavé MD, PhD [b,c], Robin Wijngaard BPharm [a], Omar Ortega PhD [b,c], Viridiana Arreola SLP, PhD [b], Weslania Nascimento SLP, PhD [b], Laia Rofes PhD [c]

[a] *Pharmacy Department, Hospital de Mataró, Mataró, Spain*
[b] *Gastrointestinal Physiology Laboratory, Hospital de Mataró, Universitat Autónoma de Barcelona, Mataró, Spain*
[c] *CIBERehd, Instituto de Salud Carlos III, Madrid, Spain*

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A B S T R A C T

Objectives: The objective of this study was to assess the pathophysiology of oropharyngeal dysphagia (OD) in patients with dementia, specifically in those taking antipsychotics (APs).
Design: A cross-sectional study was performed from January 2011 to May 2017 in a general hospital.
Setting and Participants: We included 114 patients with dementia, of which 39 (34.2%) were taking APs (82.5 ± 7.8 years, Barthel Index 52.28 ± 30.42) and 29 patients without dementia (82.4 ± 6.7 years, Barthel Index 77.71 ± 24.7) and OD confirmed by a videofluoroscopy.
Measures: Demographical and clinical factors as well as swallowing function of patients with dementia with OD were compared with older patients without dementia with OD. We also compared patients with dementia taking and not taking APs. Impaired efficacy during videofluoroscopy was defined as the presence of oral and/or pharyngeal residue, and impaired safety (unsafe swallow) was defined as aspiration or penetration. Receiver operating characteristic curves were drawn for laryngeal vestibule closure (LVC) time to predict unsafe swallow.
Results: 87.7% of patients with dementia presented impaired efficacy of swallow and 74.6% impaired safety [penetration-aspiration scale (PAS) 3.94 ± 1.94]. 86.2% of patients without dementia presented impaired efficacy and 44.8% impaired safety (PAS 2.21 ± 1.92). Time to LVC was significantly delayed in patients with dementia taking APs in comparison with patients without dementia (LVC 0.377 ± 0.093 vs 0.305 ± 0.026, $P = .003$). In contrast, there were no differences in the PAS and LVC time in patients with dementia taking and not taking APs (PAS 3.96 ± 0.26 vs 3.88 ± 0.22, LVC 0.398 ± 0.117 vs 0.376 ± 0.115, NS). LVC time ≥0.340 seconds predicted unsafe swallow in patients with dementia with an accuracy of 0.71.
Conclusions/Implications: Patients with dementia presented high prevalence and severity of videofluoroscopy signs of impaired efficacy and safety of swallow and a more severe impairment in airway protection mechanisms (higher PAS and LVC delay). Clinical practice should implement specific protocols to prevent OD and its complications in these patients. AP treatment did not significantly worsen swallowing impairments.

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Dysphagia, or swallowing disorder, can be a result of behavioral or sensory impairments, and problems with coordination, position, level of consciousness, and motor function (or a combination) and is common in patients with advanced dementia.[1,2] Oropharyngeal dysphagia (OD) is one of the most frequent causes of aspiration, and aspiration pneumonia has been reported to be one of the most common cause of death in people with dementia at advanced stages.[3,4]

The reported prevalence of dysphagia in persons with dementia ranges from 13% to 84%, depending on several factors such as the selection criteria. Prevalence of dysphagia is higher in more severe phases of the disease,[1,5–8] with 28% to 55% suffering from aspiration.[8–10] Mechanisms involved in swallowing difficulties vary with different types of dementia. In patients with Alzheimer's disease, deficits in the sensory aspects of swallowing tend to occur, leading to

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* Address correspondence to Marta Miarons, MS, BPharm, Pharmacy Department, Hospital de Mataró, Cirera Street s/n 08304 Mataró, Spain.
E-mail address: mmiarons@csdm.cat (M. Miarons).

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delayed oral transit time.[11,12] In patients with vascular dementia, the motor aspect of swallowing is affected, resulting in difficulty with bolus formation and mastication.[12] Sensory deficits, autonomic dysfunction, and fluctuation in cognition can lead to swallowing problems in patients with dementia with Lewy bodies and Parkinson disease dementia.[13]

OD has recently been recognized as a major geriatric syndrome[14,15] because of its high prevalence of multiple complications, risk factors, and precipitating diseases in older people.[16] Cognitive impairment or dementia is also recognized as a geriatric syndrome[17] and has been identified as a risk factor for aspiration pneumonia.[18]

In addition, given that approximately 50% of older people take more than 4 drugs[19] and that patients with dementia are usually older people, they are likely to take drugs that induce swallowing impairment.[19–21] Among them, antipsychotics (APs) (also known as neuroleptics) are frequently associated with the presence of swallowing disorders.[22] There are 2 main types of APs: typical (or first generation) APs, which act on the dopaminergic system, blocking dopamine type 2 receptors; and atypical (or second generation) APs, which have lower affinity and occupancy of the dopaminergic receptors and a high degree of occupancy of the serotoninergic receptors 5-HT2A.[23] Both types of APs are widely used to reduce neuropsychiatric symptoms in patients with dementia, even though they are only recommended when other nonpharmacologic techniques, such as stimulation techniques, group therapy, and sensory interventions including music therapy, have been ineffective.[24] When blocking dopamine receptors, APs can produce both therapeutic and adverse effects, including extrapyramidal symptoms, a consequence of their action on the nigrostriatal pathway, and include acute dyskinesia and dystonic reactions, tardive dyskinesia, parkinsonism, akinesia, akathisia, and dysphagia. APs are usually prescribed for behavioral symptoms of dementia and also for other indications such as schizophrenia or psychosis, delusional disorders, and mood disorders, which can also worsen dysphagia.

A literature review of the relationship between OD and APs[24] concluded that extrapyramidal symptoms-related dysphagia is a dangerous but potentially reversible side-effect in patients receiving APs. Another literature review showed that whereas some studies found a relationship between swallowing impairment and the use of APs, others did not.[25] Therefore, considering the absence of well-designed randomized controlled trials, and that it is difficult to differentiate whether the effect is due to the condition for which the AP is prescribed or from the AP itself, it is clear that more research is needed to evaluate the pathophysiology of OD in patients under antipsychotic treatment.

Hence, the objectives of this study were (1) to characterize the pathophysiology of OD using videofluoroscopy (VFS) in patients with OD and dementia, and (2) to determine if APs can further affect dysphagia, independently of the condition for which they are prescribed.

Methods

Patients

An observational, retrospective, cross-sectional study analyzed all inpatients with dementia 75 years or older who were discharged from any department of a general hospital, from January 2011 to May 2017, with a positive VFS performed after the discharge and defined as presence of signs of impaired efficacy (oral and/or pharyngeal residue) and/or safety of swallow (aspiration or penetration). Diagnosis of dementia was established according to the *International Classification Diseases, Ninth Edition* codes, in which codes for people with dementia are 290.x and 294.x.[26] All VFS parameters of patients with dementia were compared with patients without dementia; older inpatients with a diagnosis of OD were confirmed with VFS during their hospitalization. Exclusion criteria for both groups were patients with head and neck or esophageal cancer. The study protocol was approved by the ethics committee of the hospital and conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments.[27]

Data Collection

In accordance with clinical practice, an overall assessment was carried out by a multidisciplinary team on patients with dementia the day of admission and included (1) demographic data, (2) comorbidities carefully collected and later measured with the Charlson comorbidity index,[28] (3) frailty according to the Edmonton Frail Scale[29]; and (4) functional capacity analyzed with the Barthel index.[30] Other variables were measured after the inclusion of the patient in the study and using the clinical history including (5) cognition according to the global deterioration scale[31] and (6) antipsychotic and other drug exposure.[32]

In our hospital, we systematically use the volume-viscosity swallow test (V-VST)[33] for bedside clinical assessment of swallowing function of high-risk populations, such as older patients. The V-VST is an accurate bedside assessment method with good psychometric properties, good reliability, and a detailed and easy-to-perform protocol designed to protect patients' safety. It is capable to evaluate the safety and efficacy of swallowing and has a system to detect silent aspirations. For patients with a positive V-VST, we also perform a VFS study. In this study, we included patients with a positive VFS study who had signs of impaired efficacy (oral and/or pharyngeal residue) and/or safety of swallow (aspiration or penetration) during the VFS study.[16]

Videofluorscopic Signs of OD

VFS is the gold standard for studying the oral and pharyngeal mechanisms of dysphagia and for evaluating efficacy and safety of swallow in older patients.[33] All patients were imaged while seated, in a lateral projection that included the oral cavity, pharynx, larynx, and cervical esophagus.[34,35] VFS characteristics are described in Supplementary Material 1.

VFS signs of impaired safety of swallow or unsafe swallow are defined as any swallow showing a significant entrance of part of the bolus into the airway during the VFS and rated according to the penetration-aspiration scale (PAS). Unsafe swallow was predicted by measuring the time between glossopalatal junction opening and LVC.[36,37] Severity of aspiration or penetration was rated according to the PAS and according to whether they were followed by cough (silent aspirations) or not.[35,38] A video demonstration shows impaired swallowing safety (aspiration) associated with a delayed laryngeal vestibule closure time (LVC) (Video 1).

Oropharyngeal Physiology

Measurements of oropharyngeal swallow response were obtained during the swallowing of 5 mL-nectar boluses in patients with dementia and patients without dementia. all patients swallowed this bolus and it is highly sensitive to physiological measures of swallowing impairment. LVC time and upper esophageal sphincter opening (UESO) times were measured. LVC time is the time interval in ms from glossopalatal junction (GPJ) opening to LVC and is considered to be the main physiological parameter in assessing impaired airway protection, which leads to aspiration in neurologic patients and older people.[37]

Antipsychotic Exposure and Other Drug Exposure

We examined the computerized medication prescription log for the use of antipsychotic medications during the 15 days before the VFS. Antipsychotic medications were defined as those classified by the third level of the Anatomical and Therapeutic Classification (ATC) code N05A: APs.[32] In addition to the presence/absence of APs, we also converted the total daily exposure dose into chlorpromazine equivalence units (CEUs) using established scales.[39]

In addition, we categorized each AP according to its high, medium, or low capacity to induce extrapyramidal symptoms and identified whether the AP was typical or atypical.[42] Finally, we examined the computerized medication prescription log in the 15 days before the VFS for other drugs that might affect swallowing function,[41] available at Supplementary Material 2.

Data Analysis and Statistical Methods

Categorical variables were described as percentages and quantitative parameters as mean ± standard deviation. For the study of association of the categorical variables, the χ^2 test or the Fisher test was used, and for continuous variables, the Mann–Whitney U test or the *t* test were used. We also performed a multivariate analysis to assess the association between antipsychotic exposition and PAS and oral and/or pharyngeal residue adjusting for the possible confounding factors.

For our primary aim, we compared VFS parameters in patients with dementia to patients without dementia. For the second aim, we compared VFS parameters in patients taking and not taking APs. The size of the sample of normal study participants was determined based on power calculations.

Receiver operating characteristic (ROC) curves were drawn for laryngeal vestibule closure (LVC) time to determine the LVC cut-off of time at 5-mL nectar that would identify patients with impaired safety of swallow (PAS ≥ 3). The diagnostic accuracy of LVC cut-off time is the area under the ROC curve. We also compared the ROC curves of patients with and without dementia to further assess the mechanisms of unsafe swallow in these patients. To draw ROC curves, the impairment of the safety of swallow was measured using VFS, which as expressed above is one of the gold standard instrumental diagnostic method to evaluate OD.[33] *P* values of <.05 was considered statistically significant. Statistical analyses were performed with the SPSS v 15.0 (SPSS Inc, Chicago, IL).

Results

Demographic and Clinical Inventory Scores

We included 114 consecutive patients with dementia (82.5 ± 7.8 years, 57.0% woman) and 29 patients without dementia (83.5 ± 7.5 years, 65.7% woman). Patients' sociodemographic and clinical characteristics are described in Table 1. Briefly, sociodemographic and clinical characteristics were similar in patients with dementia and patients without dementia, except for the former having a lower Barthel index (52.28 ± 30.42 vs 77.71 ± 24.74, respectively, $P < .001$), higher score in the global deterioration scale (3.57 ± 1.72 vs 1.34 ± 0.87, $P < .001$) and a higher prevalence of cerebrovascular diseases (N = 49, 43% vs N = 1, 2.9%, $P = .003$). APs and other drug exposure in patients with dementia are described in Table 2. Briefly, 34.2% (N = 39) of patients with dementia were receiving APs and atypical APs were the most frequently AP used. Table 3 compares sociodemographic and clinical characteristics of patients with dementia taking APs and those without AP exposure. Briefly, sociodemographic and clinical characteristics were similar in both groups, including the dose, the type of antipsychotic (typical or atypical) and its capacity to induce extrapyramidal symptoms, except for the global deterioration scale (4.16 ± 1.61 and 3.28 ± 1.70, respectively, $P = .009$). The median antipsychotic exposure was 136.23 ± 146.89 CEU (range, 2.5-833.3 CEU), equivalent to a daily dose of 2.5 mg haloperidol.[40] Antidepressants, anxiolytics, and angiotensin-converting enzyme

Table 1
Demographic Characteristics of Patients with Dementia and Patients without Dementia Included in the Study

Demographic and Clinical Characteristics	Patients with Dementia (N = 114)	Patients without Dementia (N = 35)	*P* Value	OR (95% CI)
Age (years)	82.5 ± 7.8	83.7 ± 7.5	.744	1.02 (0.96–1.07)
Women	65 (57.0%)	65.7%	.434	1.25 (0.55–2.86)
Comorbidities				
Cerebrovascular disease (stroke)*	49 (43.0%)	1 (2.9%)	**<.001**	20.30 (2.68–154.05)
Heart failure	17 (14.9%)	9 (25.7%)	.211	1.11 (0.05–0.27)
Hypertension	38 (33.3%)	12 (34.3%)	.911	0.63 (0.39–9.36)
Ischemic cardiopathy	23 (20.2%)	9 (25.7%)	.487	0.70 (0.28–1.75)
Chronic pneumopathy	42 (36.8%)	11 (31.4%)	.687	1.37 (0.58–3.25)
Oncology/hematology disease	17 (14.9%)	5 (14.3%)	1.000	1.71 (0.47–6.21)
Hepatic disease	5 (4.4%)	0 (0%)	.592	NA
Renal impairment	21 (18.4%)	9 (25.7%)	.345	1.01 (0.37–2.75)
Diabetes mellitus	36 (31.6%)	12 (34.3%)	.837	0.65 (0.28–1.49)
Functional capacity				
Barthel index*	52.28 ± 30.42	77.71 ± 24.74	**<.001**	4.39 (1.44–13.40)
Barthel index ≤40*	47 (41.2%)	5 (14.3%)	**.004**	4.21 (1.60–10.52)
Barthel index >40	67 (58.8%)	30 (85.7%)		
Charlson index	5.47 ± 0.96 (2-7)	5.77 ± 1.77 (2-7)	.628	1.04 (0.92–1.11)
Global deterioration scale*	3.57 ± 1.72 (1-7)	1.34 ± 0.87	**<.001**	10.75 (1.81–88.67)
Frailty				
Not frail	31 (27.2%)	12 (34.3%)		0.72 (0.32–1.68)
Vulnerable/mild frailty	54 (47.4%)	13 (37.1%)	.729	2.25 (1.01–5.03)
Moderate/severe frailty	29 (25.4%)	10 (28.6%)		0.51 (0.20–1.31)
Type of dementia				
Vascular dementia	17 (14.9%)	0 (0%)	NA	NA
Degenerative dementia	23 (20.2%)	0 (0%)	NA	NA
Mixed dementia	14 (12.3%)	0 (0%)	NA	NA
Cognitive impairment	60 (52.6%)	4 (11.4%)	NA	NA

Note. Bold values are statistically significant $P < .05$.
N, number of patients; *NA*, not available; *OR*, odds ratio.

Table 2
Antipsychotic and Other Drug Exposure in Patients with Dementia

Drug Exposure	Patients with Dementia (N = 114)
Antipsychotic exposure	
One or more	39 (34.2%)
Typical antipsychotic	3 (2.6%)
Atypical antipsychotic	34 (29.8%)
Both	2 (1.8%)
Chlorpromazine equivalence units <100	25 (19.5%)
Chlorpromazine equivalence units ≥100	20 (15.6%)
Chlorpromazine equivalent dose	136.34 ± 146.88 (2.5–833.3)
Capacity to induce extrapyramidal symptoms	
High	4 (3.5%)
Moderate	17 (14.9%)
Low	18 (15.5%)
Other drug exposure (ATC code)	
A10B Oral antidiabetics	17 (14.9%)
C07A Beta blocking agents	24 (21.0%)
C08C Calcium channel blockers	8 (7.0%)
C09A, C09B Angiotensin-converting enzyme inhibitors and combinations	30 (26.3%)
C09C, C09D Angiotensin II antagonists and combinations	14 (12.3%)
N03A Antiepileptics	13 (11.4%)
N04A Anticholinergic agents	1 (0.8%)
N04B Dopaminergic agents	17 (14.9%)
N05B Anxiolytics	33 (28.9%)
N05C Hypnotics and sedatives	23 (20.2%)
N06A Antidepressants	65 (57.0%)
N06B Psychostimulants, agents used for attention deficit hyperactivity disorder and nootropics	1 (0.9%)
N06C Psycholeptics and psychoanaleptics in combination	1 (0.9%)
N06D Drugs against dementia	17 (14.9%)

n, number of patients.

inhibitors and combinations were the most frequent drugs used by patients with dementia. In contrast, oral antidiabetics, anxiolytics, and antidepressants were the most frequent drugs used by patients without dementia.

Characteristics of OD in Patients with Dementia Referred for the VFS

Aspiration or penetration into the LV during the pharyngeal phase (PAS ≥ 3) was observed in 85 (74.6%) patients with dementia, and mean PAS was 3.94 ± 1.94. Aspiration into the airway during swallow response was observed in 35 (30.7%) patients. Moreover, 11 (9.7%) patients had silent (level 8) aspirations. The prevalence of patients with dementia with oral and/or pharyngeal residue was 87.8% (N = 100).

Table 3
Characteristics of Patients with Dementia Regarding Antipsychotic Exposure

Patients (N = 114)	APs (N = 39, 34.2%)	No APs (N = 75, 65.8%)	*P* Value
Age	83.0 ± 6.3	82.5 ± 7.8	.773
Woman	23 (59%)	42 (56.0%)	.843
Barthel index	46.4 ± 31.0	55.5 ± 29.5	.130
Charlson index	5.52 ± 0.78	5.43 ± 1.04	.713
Global deterioration scale*	4.16 ± 1.61	3.28 ± 1.70	**.009**
Deglutition parameters			
PAS	3.99 ± 0.26	3.90 ± 0.22	.684
PAS ≥3	31 (79.5%)	49 (65.3%)	.121
Oral and/or pharyngeal residue	35 (89.7%)	65 (86.7%)	.769
LVC	0.392 ± 0.117	0.371 ± 0.115	.753
UESO*	0.326 ± 0.099	0.279 ± 0.102	**.036**

N, number of patients.
*$P < .05$.

Overall duration of swallow response was 1.095 ± 0.020 seconds and the reconfiguration phase to a digestive pathway was severely delayed, as time to LVC was 0.377 ± 0.093 seconds and time to UESO was 0.295 ± 0.101 seconds. Time to LVC in patients with dementia with aspiration or penetration was significantly longer than that in patients with dementia with safe swallow (0.398 ± 0.107 vs 0.322 ± 0.114, $P = .032$). Time to UESO in patients with dementia with aspiration or penetration was also significantly longer than in patients with dementia with safe swallow (0.308 ± 0.106 vs 0.265 ± 0.087, $P = .041$).

Supplementary Tables 1 and 2 show the characteristics of patients with dementia according to whether or not they presented safety of swallow impairments (aspiration or penetration into the LV, PAS ≥3) or impaired efficacy (oral and/or pharyngeal residue). Briefly, clinical scores were similar for patients with dementia with impaired safety and efficacy, but time to UESO and LVC was significantly longer in patients with impaired safety. We found a significant association between the chronic use of beta blocking agents (ATC code C07A) and safe swallow ($P = .006$). We also found a significant association between the use of dopaminergic agents (ATC code: N04A) and a more efficacious swallow ($P = .038$) and the use of antidepressants (ATC code N06A) and impaired efficacy of swallow ($P = .040$).

Effect of antipsychotic agents

Differences between patients with dementia taking APs and patients with dementia without taking APs regarding PAS ≥3 were not statistically significant after adjusting for the possible confounding variables (age, sex, and the global deterioration scale), nor regarding oral and/or pharyngeal residue (Table 3). Figure 1 shows the time of main events of the oropharyngeal swallow response during 5 mL-nectar swallows in patients with dementia taking APs, patients with dementia without taking Aps, and patients without dementia. Time to LVC was similar between patients with dementia taking APs and patients with dementia without taking APs. In contrast, the time to UESO was significantly longer in patients with dementia taking APs than in patients with dementia without taking APs (0.326 ± 0.099 vs 0.279 ± 0.102, $P = .036$).

Characteristics of Oropharyngeal Dysphagia in Older Patients without Dementia Referred for the VFS

The prevalence of patients with oral and/or pharyngeal residue was 86.2% (N = 25). Penetration into the LV during the pharyngeal phase (PAS ≥ 3) was observed in 13 (44.8%) patients and mean PAS was 2.21 ± 1.92. Aspiration into the airway during swallow response was observed in 4 (13.7%) patients, $P = .018$ vs patients with dementia. Moreover, 2 (6.9%) patients had silent (level 8) aspirations, $P = .030$ vs patients with dementia.

Overall duration of swallow response was 1.047 ± 0.020 seconds, significantly shorter than in patients with dementia ($P = .040$). The reconfiguration phase to a digestive pathway was also delayed in patients with dementia compared with patients without dementia, as time to LVC in patients with dementia was significantly longer than in patients without dementia (0.377 ± 0.093 vs 0.312 ± 0.022, $P = .033$). Time to UESO in patients with dementia was also significantly longer in comparison with patients without dementia (0.295 ± 0.101 vs 0.238 ± 0.079, $P = .029$).

ROC Curves

We used ROC curves to detect the optimal cut-off value of LVC time to predict unsafe swallow in patients with dementia and patients without dementia during 5 mL-nectar bolus swallows (Figures 2 and 3). Figure 2 shows ROC curves in patients with dementia (patients with dementia taking APs and patients with dementia without taking APs)

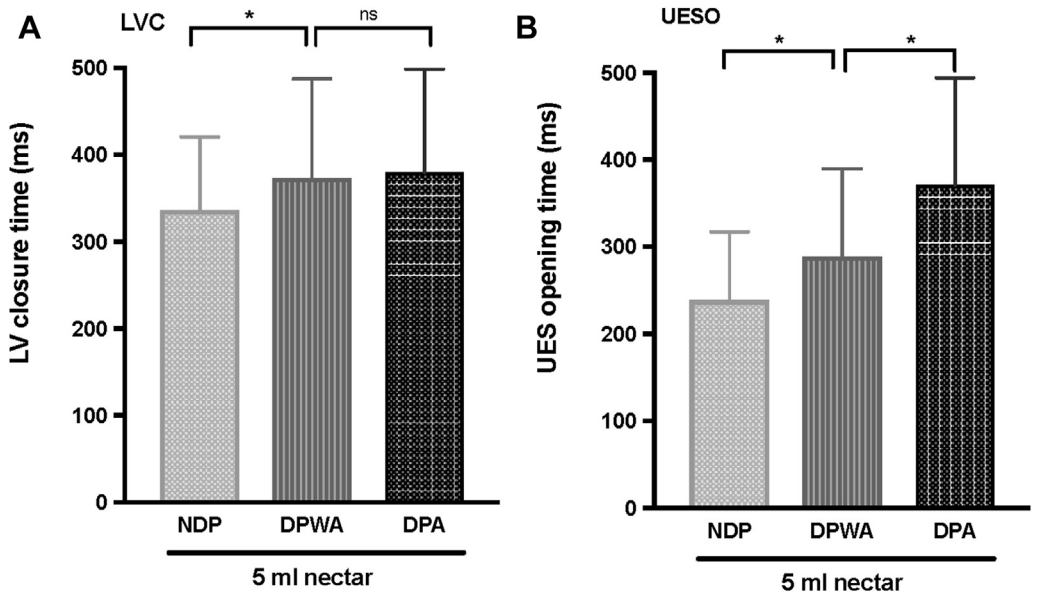

Fig. 1. Timing of main events of the oropharyngeal swallow response during 5-mL nectar swallows in patients without dementia (NDP), patients with dementia without taking APs (DPWA), and patients with dementia taking APs (DPA) and according to the safety and efficacy of swallow. (A) LVC in NDP, DPWA and DPA; (B) UESO. *$P < .05$, ns: nonsignificant.

and patients without dementia. Figure 3 compares ROC curves in patients with dementia taking APs and patients with dementia without taking APs. We have found that a cut-off time for LVC ≥0.340 seconds predicts unsafe swallow (PAS≥ 3) in patients with dementia and patients without dementia with good diagnostic accuracy regardless of whether or not they were on APs. The area under the curve (AUC) was 0.71 [95% confidence interval (CI); 0.60–0.82, $P = .006$] in patients with dementia and 0.64 (95% CI; 0.43–0.84, $P = .821$) in patients without dementia. Among patients with dementia, the AUC was 0.67 (95% CI; 0.53–0.80, $P = .070$) in patients with dementia without taking APs, and 0.82 in patients with dementia taking APs (95% CI; 0.66–0.98, $P = .021$).

Discussion

As far as we know, this study is the first one that characterizes the biomechanics of swallowing function using VFS in older patients with dementia and compares it in patients taking and not taking APs. This is an important development as, regardless of the stage of the disease, OD puts patients with dementia at high risk of malnutrition and aspiration pneumonia, which is a major contributing factor to mortality.[3,43–45] Our study shows high prevalence and severity of VFS signs of impaired efficacy and safety in patients with dementia in comparison with older patients without dementia with OD. Patients with dementia presented a more severe impairment in airway protection mechanisms (PAS and LVC delay) than patients without dementia. Impaired swallowing safety in patients with dementia is caused by specific impairment in swallow response including delayed timing of airway protection mechanisms, and LVC time ≥340 ms predicts unsafe swallow in patients with dementia with good diagnostic accuracy. In our study, AP treatment did not cause further swallowing impairments in older patients with dementia.

Our cohort of patients with dementia presented similar sociodemographic and clinical characteristics as patients without dementia, except for having a lower Barthel index[30] and a higher score

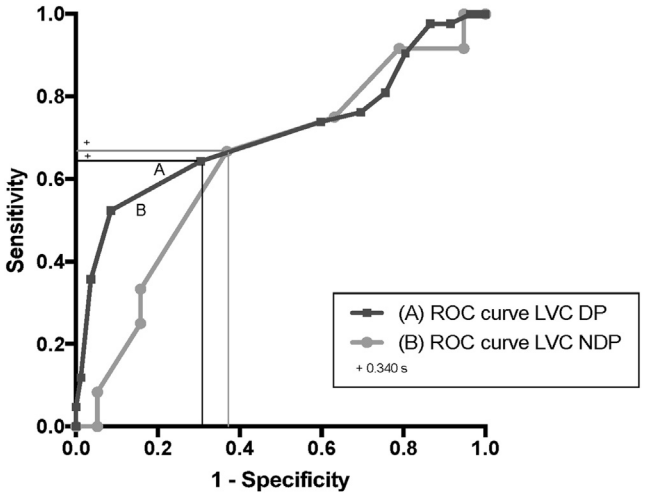

Fig. 2. ROC showing sensitivity/specificity of the LVC time at 5-mL nectar for unsafe swallow (penetrations and/or aspirations) in (A) patients with dementia (DP) and (B) patients without dementia (NDP).

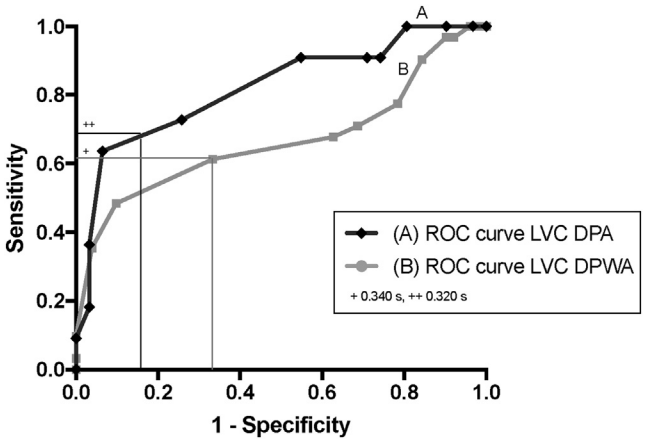

Fig. 3. ROC showing sensitivity/specificity of the LVC time at 5 mL nectar for unsafe swallow (penetrations and/or aspirations) in (A) patients with dementia taking APs (DPA) and (B) patients with dementia without taking APs (DPWA).

in the global deterioration scale.[31] We found that swallow response was severely impaired in patients with dementia compared with patients without dementia as time from GPJ opening to LVC was significantly delayed. However, we did not find significant differences regarding efficacy of swallow. Our results agree with previous studies performed on patients with dementia. In the prospective study by Horner et al,[8] in patients with Alzheimer's disease, global VFS examination score was significantly more impaired in severe dementia. Langmore et al[7] showed frontotemporal dementia patients had an increased food leakage time compared with healthy control patients when evaluated using fiberoptic endoscopic evaluation of swallowing.

We found that the overall duration of swallow response in patients with dementia was significantly prolonged. Impaired safety was specifically related to delayed LVC in accordance with previous studies[16,43] and a delay in the UESO time was associated with residue in patients with dementia, which is caused by the interruption of the vagally mediated contraction of the cricopharyngeal muscle, anterior hyoid movement, and intrabolus pressure cause by tongue thrust.[46,47] Studies in healthy people over 80 years of age found that older age was associated with a prolonged swallow response and an increase in the presence of oropharyngeal residue in comparison with younger people,[48–51] but in patients with dementia, there is also a slow synaptic conduction in the central nervous system and an impaired function of peripheral afferents to the swallowing center caused by the neurodegenerative disease.[49]

Regarding medication, we found that time to UESO was significantly longer in patients with dementia taking APs than in patients with dementia without taking APs (Table 3), so the oral motor response had been altered although not to the extent of impairing safety or efficacy of swallow. Some earlier studies showed impairment in swallow function with the use of AP treatment but the evidence is scarce.[24] Wada et al[52] showed that APs used in Alzheimer's disease patients increased the latency of swallow response and the risk for aspiration pneumonia ($P < .003$). Rudolph et al[53] studied patients exposed to APs and found that mean dysphagia severity rating scale score was worse in the group who received APs ($P < .01$). However, Fioravanti et al[54] studied 47 older patients living in a nursing home and found no statistical differences between patients taking and not taking APs with regard to prevalence of altered voice, coughing, altered chewing, anterior leakage, multiple swallowing, and altered elevation of the larynx. Shinagawa et al[13] studied 29 outpatients with dementia with Lewy bodies and 33 with Alzheimer's disease. The use of APs did not affect any items of an eating/swallowing questionnaire. Our findings suggest that in patients with dementia, the report of impairment in swallowing function could be mainly due as a result of the aging process and the illness itself, even though APs could have a minimum deleterious contribution in worsening the swallow response of these patients.

We also found a statistically significant association between beta blocking agents and safe swallow. An observational study performed on 966 older patients found that beta-blockers might have a protective effect on the swallowing function, but the mechanism responsible is not obvious.[39] Beta blocking agents have been shown to increase substance P levels in guinea-pigs,[55] which can enhance swallowing function.[56] Dopaminergic agents such as levodopa have also been associated with an increase in efficacy of swallow in our study. Fuh et al[57] found that levodopa improved the swallowing function in more than one-half of the patients studied, possibly because of the reduction of bradykinesia and rigidity of the tongue. Monte et al[58] also suggested a role for levodopa in the oral phase of deglutition. Finally, we found that antidepressants were related to impaired efficacy of swallow. It has been suggested that some antidepressants with anticholinergic actions can produce xerostomia, contributing to impaired oropharyngeal bolus transport.[59]

We did not find other possible risk factors for efficacy and/or safety of swallow in patients with dementia, not even the Barthel index, the global deterioration scale, the frail phenotype, or the prevalence of cerebrovascular diseases, even though some studies have.[43,60,61]

This study has some strengths, but also some limitations: (1) this was a retrospective cross-sectional study performed at a single site, which limits the number of patients included and our ability to find differences in the risk factors of OD or other secondary variables, such as comorbidities; (2) although we matched for age, sex, and global deterioration scale to compare swallowing between patients taking and not taking APs, there were other potential confounding variables that may have interfered with the relationship of antipsychotic medications and swallowing; and (3) our cohort of patients with dementia had sociodemographic characteristics that limit their comparison with patients without dementia, which have better functional capacity and lower global deterioration scale. Despite these limitations, there is enough evidence for clinicians to consider patients with dementia at high risk of swallowing problems in comparison with patients without dementia.

Finally, a major contribution of the present investigation is that we have created a ROC curve to find an optimal cut-off time to LVC to discriminate safe from unsafe swallow of patients with dementia taking APs and patients with dementia without taking APs and to compare it with patients without dementia. In our study, ROC curves (with high AUC values) showed LVC could discriminate patients with unsafe swallow. According to these results, we selected $\geq$0.340 seconds as the best LVC cut-off time to detect the presence of unsafe swallow in patients with dementia and patients without dementia. In a previous study performed on stroke patients,[40] the best LVC cut-off time to detect the presence of unsafe swallow was also $\geq$0.340 seconds, so a cut-off time of 0.340 seconds could be the best cut-off time to detect the presence of unsafe swallow in several phenotypes of dysphagia patients.

Conclusions

In conclusion, we demonstrated that patients with dementia with clinical signs of OD present a high prevalence of videofluoroscopic signs of impaired safety and efficacy of swallow. Clinical practice should implement specific protocols to prevent OD and its complications in these patients. We have characterized a specific pattern of impairment of the safety of swallow associated with a delayed swallow response (LVC time) in patients with dementia, and we found a threshold of >0.340 seconds of LVC to be the main predictor of unsafe swallow. Finally, in our study, the use of APs did not further cause significant swallowing impairments in our patients with dementia and OD.

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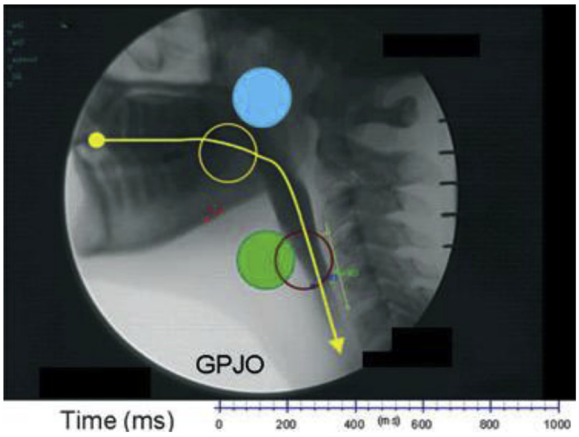
Appendix

Supplementary Material 1. Videofluoroscopy characteristics and measures/interpretations

In our study, videofluoroscopic recordings were obtained by using a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands), and images were recorded at 25 frames/seconds (Panasonic AG DVX-100B; Matsushita Electric Industrial Co, Ltd, Osaka, Japan). Swallow parameters were analyzed by software (Swallowing Observer; Image & Physiology SL, Barcelona, Spain) developed to capture and digitize the swallowing sequences, to assess the VFS signs, and measure the oropharyngeal swallow response.

Videofluoroscopic recordings and interpretations were made by a trained speech-language therapist. All patients were imaged seated, in lateral projection including the oral cavity, pharynx, larynx, and cervical esophagus.[16,27] During VFS, measurements of oropharyngeal swallow response were obtained during 5-mL nectar swallows of radiopaque bolus: Oropharyngeal reconfiguration, timing of the closing of the laryngeal vestibule, and the opening of the upper esophageal sphincter were measured and all temporal measurements were referenced to glossopalatal junction opening as time 0 (Supplementary Fig. E1).



Supplementary Fig. E1. Oropharyngeal swallow response: timing of LVC and UESO were measured and all temporal measurements were referenced to glossopalatal junction opening as time 0.[27]

The VFS study shows the dynamic signs of oropharyngeal swallow dysfunction. VFS signs of impaired efficacy of swallow are the presence of oral and/or pharyngeal residue (vallecular and/or pyriform sinus residue). VFS signs of impaired safety of swallow are aspiration or penetration, detected according to accepted definitions. Severity of aspiration or penetration was rated according to the PAS by Rosenbek et al.[38] as detailed above and according to whether they were followed by cough or not (silent aspirations).

Supplementary Material 2. Drugs that might affect swallowing function

Oral antidiabetics (third level ATC code A10B), beta blocking agents (C07A), selective calcium channel blockers with mainly vascular effects (C08C), angiotensin-converting enzyme inhibitors and combinations (C09A, C09B), agents acting on the renin-angiotensin system (C09C, C09D), antiepileptics (N03A), anticholinergic agents (N04A), dopaminergic agents (N04B), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), psychostimulants used for attention- deficit hyperactivity disorder and nootropics (N06B), psycholeptics and psychoanaleptics in combination (N06C), and drugs for dementia (N06D).[39]

web 4C/FPO

Supplementary Table 1
Characteristics of Patients with Dementia Regarding PAS

Patients (N = 114)	PAS ≥ 3 (N = 85, 74.6%)	PAS <3 (N = 29, 25.4%)	*P* Value	OR (CI 95%)
Age, years	82.7 ± 7.8	82.1 ± 7.7	.419	1.01 (0.96–1.06)
Woman	47 (58.8%)	18 (52.9%)	.680	1.43 (0.68–2.98)
Comorbidities				
Chronic pneumopathy	27 (33.8%)	15 (44.1%)	.299	0.68 (0.32–1.45)
Diabetes mellitus	22 (27.5%)	14 (41.2%)	.187	0.59 (0.28–1.25)
Ischemic cardiopathy	15 (18.8%)	8 (23.5%)	.613	0.81 (0.32–2.04)
Cerebrovascular disease (stroke)	38 (47.5%)	11 (32.4%)	.153	1.93 (0.90–4.16)
Heart failure	11 (13.8%)	6 (17.6%)	.578	0.65 (0.24–1.76)
Oncology/hematology disease	13 (16.3%)	4 (11.8%)	.775	1.76 (0.60–5.19)
Hepatic disease	3 (3.8%)	2 (5.9%)	.634	0.75 (0.12–4.67)
Heart failure	11 (12.9%)	8 (18.6%)	.435	0.65 (0.24–1.76)
Renal impairment	14 (17.5%)	7 (20.6%)	.793	0.55 (0.23–1.32)
Parkinson disease	6 (7.1%)	5 (11.6%)	.507	0.59 (0.17–2.03)
Functional capacity				
Barthel index	50.82 ± 3.42	57.06 ± 4.12	.102	0.99 (0.98–1.01)
Barthel index ≤40	37 (46.3%)	10 (29.4%)	.185	1.76 (0.82–3.78)
Charlson index	5.48 ± 0.98	5.39 ± 0.90	.469	1.12 (0.76–1.64)
Global deterioration scale	3.73 ± 1.71	3.12 ± 0.89	.214	1.15 (0.93–1.43)
1*	9 (11.3%)	10 (29.4%)		1
2	14 (17.5%)	2 (5.9%)		0.42 (0.07–2.60)
3	13 (16.3%)	7 (20.6%)		2.22 (0.19–26.63)
4	12 (5.0%)	7 (20.6%)	.125	0.42 (0.07–2.46)
5	15 (18.8%)	3 (8.8%)		0.38 (0.06–2.22)
6	16 (18.8%)	5 (11.6%)		1.06 (0.13–8.31)
7	1 (1.3%)	0 (0%)		NA
Frailty				
Not frail	21 (24.7%)	10 (34.4%)		1
Vulnerable/mild frailty	38 (44.7%)	16 (55.2%)	.180	1.38 (0.55–3.46)
Moderate/severe frailty	25 (29.4%)	4 (11.8%)		3.03 (0.91–10.11)
Type of dementia				
Cognitive impairment*	42 (52.5%)	18 (52.9%)		1
Vascular dementia	13 (16.3%)	4 (11.8%)	.267	0.80 (0.30–2.11)
Degenerative dementia	13 (16.3%)	10 (34.5%)		1.53 (0.45–5.29)
Mixed dementia	12 (15.0%)	5 (5.9%)		1.96 (0.41–3.51)
Swallowing parameters				
LVC† (s)	0.398 ± 0.107	0.322 ± 0.114	**.011**	NA‡
UESO† (s)	0.308 ± 0.106	0.265 ± 0.087	**.037**	NA‡
Antipsychotic exposure				
One or more	31 (38.8%)	8 (27.5%)	.201	1.94 (0.86–4.36)
Typical antipsychotic	2 (2.4%)	1 (3.4%)	1.000	1.13 (0.10–12.27)
Atypical antipsychotic	29 (34.1%)	7 (24.1%)	1.000	0.89 (0.08–9.69)
Both	2 (2.4%)	0 (0%)	1.000	NA
Chlorpromazine equivalence units ≥100	12 (37.5%)	5 (71.4%)	.205	1.00 (0.99–1.01)
Capacity to induce extrapyramidal symptoms				
High*	4 (5.0%)	0 (0%)		1
Moderate	13 (16.3%)	4 (11.8%)	.181	1.50 (0.35–6.42)
Low	15 (18.8%)	3 (8.8%)		NA
Other drug exposure (only statistically significant)				
C07A Beta blocking agents†	12 (15.0%)	11 (37.9%)	**.006**	**0.28 (0.12–0.66)**

N, number of patients; *NA*, not available; *OR*, odds ratio.
*Reference category
†$P < .05$ and bold values $P < .05$.
‡Values are too small for precise OR.

Supplementary Table 2
Characteristics of Patients with Dementia Regarding the Presence of Oral and/or Pharyngeal Residue

Patients (N = 114)	Oral and/or Pharyngeal Residue (N = 100, 87.7%)	No Oral and/or Pharyngeal Residue (N = 14, 12.3%)	*P* Value	OR (95% CI)
Age, years	82.2 ± 8.1	84.6 ± 6.0	.432	0.96 (0.90–1.03)
Woman	62 (56.9%)	8 (42.1%)	.355	1.81 (0.68–4.86)
Comorbidities				
Chronic pneumopathy	36 (36.0%)	6 (42.9%)	.768	0.74 (0.27–1.99)
Diabetes mellitus	30 (30.0%)	6 (42.9%)	.365	0.74 (0.27–1.99)
Ischemic cardiopathy	19 (19.0%)	4 (28.6%)	.477	0.84 (0.25–2.81)
Cerebrovascular disease (stroke)	45 (45.0%)	4 (28.6%)	.388	2.37 (0.80–7.05)
Heart failure	15 (15.0%)	2 (14.3%)	1.000	0.92 (0.24–3.51)
Oncology/hematology disease	15 (15.0%)	2 (14.0%)	.937	1.06 (0.28–4.00)
Hepatic disease	5 (5.0%)	0 (0%)	1.000	NA
Heart failure	16 (14.7%)	3 (15.8%)	1.000	0.92 (0.24–3.51)
Renal impairment	20 (20.0%)	1 (7.1%)	.461	1.00 (0.30–3.31)
Parkinson disease	7 (6.4%)	4 (21.2%)	.060	0.26 (0.07–0.10)
Functional capacity				
Barthel index	51.36 ± 31.12	52.38 ± 24.36	.896	0.99 (0.98–1.02)
Barthel index ≤40	41 (41.0%)	5 (35.7%)	.431	1.25 (0.46–3.43)
Charlson index	5.48 ± 0.98	5.50 ± 0.76	.371	0.98 (0.84–1.12)
Global deterioration scale	3.58 ± 1.73	3.61 ± 1.60		0.96 (0.72–1.28)
1*	17 (17.0%)	2 (14.3%)		1
2	14 (14.0%)	2 (14.3%)		0.42 (0.07–2.60)
3	19 (19.0%)	1 (7.1%)		2.22 (0.19–26.63)
4	17 (17.0%)	2 (14.3%)	.789	0.42 (0.07–2.46)
5	16 (16.0%)	5 (35.7%)		0.38 (0.06–2.22)
6	16 (16.0%)	2 (14.3%)		1.06 (0.13–8.31)
7	1 (1.0%)	0 (0%)		NA
Frailty				
Not frail	27 (27.0%)	4 (21.2%)		1
Vulnerable/mild frailty	46 (46.0%)	8 (42.1%)	.935	1.00 (0.27–3.71)
Moderate/severe frailty	29 (29.0%)	2 (14.3%)		1.28 (0.26–6.30)
Type of dementia				
Cognitive impairment*	56 (56.0%)	4 (28.6%)		1
Vascular dementia	15 (15.0%)	2 (14.3%)	.177	0.31 (0.10–0.97)
Degenerative dementia	16 (16.0%)	7 (50.0%)		0.93 (0.18–4.89)
Mixed dementia	13 (13.0%)	1 (7.1%)		1.20 (0.23–6.17)
Swallowing parameters				
LVC (s)	0.381 ± 0.111	0.370 ± 0.281	.200	NA†
UESO (s)	0.301 ± 0.106	0.274 ± 0.087	.679	NA†
Antipsychotic exposure				
One or more	35 (35.0%)	4 (28.3%)	.850	0.92 (0.33–2.52)
Typical antipsychotic	3 (3.0%)	0 (0%)	.524	NA
Atypical antipsychotic	32 (32.0%)	4 (28.3%)	.542	1.87 (0.16–21.74)
Both	2 (2.0%)	0 (0%)	1.000	NA
Chlorpromazine equivalence units ≥100	15 (15.0%)	2 (50.0%)	1.000	1.87 (0.16–2.74)
Capacity to induce extrapyramidal symptoms				
Low*	16 (16.0%)	2 (14.3%)		1
Moderate	15 (15.0%)	2 (14.3%)	.882	2.65 (0.45–15.69)
High	4 (4.0%)	0 (0%)		NA
Other drug exposure (only statistically significant)				
N04B Dopaminergic agents‡	13 (13.0%)	5 (35.7%)	**.038**	0.29 (0.10–0.91)
N06A Antidepressants‡	61 (61.0%)	4 (29.6%)	**.040**	3.91 (1.15–13.34)

N, number of patients; *NA*, not available; *OR*, odds ratio.
*Reference category.
†Values are too small for precise OR
‡$P < .05$ and bold values $P < .05$.