Original Paper: Motility

Digestion

Digestion 1999;60:567–571

Received: October 7, 1998
Accepted: February 12, 1999

# Noninvasive $^{13}$C-Octanoic Acid Breath Test Shows Delayed Gastric Emptying in Patients with Amyotrophic Lateral Sclerosis

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**Key Words**
Amyotrophic lateral sclerosis · Gastric emptying · $^{13}$C-octanoic acid breath test · Autonomic involvement

**Abstract**
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive loss of motor neurons. However, ALS has been recognized to also involve non-motor systems. Subclinical involvement of the autonomic system in ALS has been described. The recently developed $^{13}$C-octanoic acid breath test allows the noninvasive measurement of gastric emptying. With this new technique we investigated 18 patients with ALS and 14 healthy volunteers. None of the patients had diabetes mellitus or other disorders known to cause autonomic dysfunction. The participants received a solid standard test meal labeled with $^{13}$C-octanoic acid. Breath samples were taken at 15-min intervals for 5 h and were analyzed for $^{13}CO_2$ by isotope selective nondispersive infrared spectrometry. Gastric emptying peak time ($t_{peak}$) and emptying half time (t½) were determined. All healthy volunteers displayed normal gastric emptying with a mean emptying t½ of 138 ± 34 (range 68–172) min. Gastric emptying was delayed (t½ > 160 min) in 15 of 18 patients with ALS. Emptying t½ in ALS patients was 218 ± 48 (range 126–278) min ($p < 0.001$). These results are compatible with autonomic involvement in patients with ALS, causing delayed gastric emptying of solids and encouraging the theory that ALS is a multisystem disease rather than a disease of the motor neurons only.

## Introduction

Amyotrophic lateral sclerosis (ALS) is the progressive degeneration of corticobulbar, corticospinal, brainstem and spinal cord motor neurons. Clinical manifestations comprise muscle weakness, muscle atrophy, hyperreflexia, spasticity and bulbar paresis. The disease rarely develops before the third decade and occurs sporadically in most instances. Familial occurrence with an autosomal dominant trait is observed in about 10% of cases. The sensory apparatus, the regulatory mechanisms for control and coordination of movement, as well as the intellect and thinking remain intact. There is consistent selectivity in

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0012–2823/99/0606–0567$17.50/0

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**Table 1.** Baseline characteristics of control group, ALS patients and subgroups

| | Control group (n = 14) | ALS total (n = 18) | Site of onset | | Bulbar involvement | |
|---|---|---|---|---|---|---|
| | | | bulbar (n = 9) | limb (n = 9) | none or mild (n = 6) | moderate or severe (n = 12) |
| M/F | 8/6 | 11/7 | 6/3 | 5/4 | 3/3 | 7/4 |
| Age, years | 59.2 ± 12.6 | 62.6 ± 8.7 | 63.5 ± 4.8 | 61.2 ± 12.0 | 62.3 ± 4.6 | 62.7 ± 10.4 |
| Disease duration, months | – | 22.4 ± 12.5 | 19.1 ± 7.8 | 26.8 ± 15.7 | 21.3 ± 14.6 | 29.6 ± 15.1 |
| Norris score | – | 66.4 ± 12.7 | 68.9 ± 5.8 | 63.2 ± 17.4 | 55.4 ± 16.1 | 72.5 ± 11.4 |

motor system involvement. The motor neurons required for ocular motility remain unaffected as do the parasympathetic neurons in the sacral spinal cord which innervate the sphincters of the bowel [1].

However, subclinical or clinical involvement of neuronal areas other than motor neurons has been described. Lowe [2], e.g., reported on characteristic pathological findings in the non-motor cortex and in many subcortical structures in long-term survivors. End-stage ALS patients may also present non-motor clinical symptoms such as emotional changes like involuntary laughing and crying or frontal lobe dementia. In the last years new techniques in measuring autonomic function showed involvement of autonomic cardial and sudomotor regulation in ALS [3–5].

Radioactive isotope methods are currently considered the gold standard for measurement of gastric emptying. The $^{13}CO_2$ isotope breath test has been developed as a nonradioactive alternative [6]. A test meal is labeled with the stable, nonradioactive isotope $^{13}C$. The principle of this test is based on the oxidation of the labeled short-chain fatty acid to $^{13}CO_2$ after emptying the labeled acid together with the test meal from the stomach. The $^{13}CO_2/^{12}CO_2$ ratio is analyzed by isotope selective nondispersive infrared spectrometry from exhaled air.

The aim of the present study was to investigate gastric emptying times in order to assess gastrointestinal autonomic function in patients with ALS.

## Subjects and Methods

The baseline characteristics of the healthy volunteers and the ALS patients and subgroups are given in table 1. 18 patients (7 women and 11 men; mean age 62.6 ± 8.7, range 38–74 years) participated in the study. The diagnosis of ALS was based on conventional clinical criteria [1]. Patients with further neurological diseases or systemic diseases known to cause autonomic dysfunction like diabetes mellitus were excluded. None of the patients had gastrointestinal diseases or gastrointestinal surgery. No case of familial ALS was included in the study. 14 healthy, age-matched volunteers served as a control group (mean age 59.2 ± 12.6, range 32–68 years). None of the patients or volunteers took antibiotics or any medication known to influence intestinal transit times. The study protocol was approved by the Ethics Committee of the University of Munich and written informed consent was obtained from all patients.

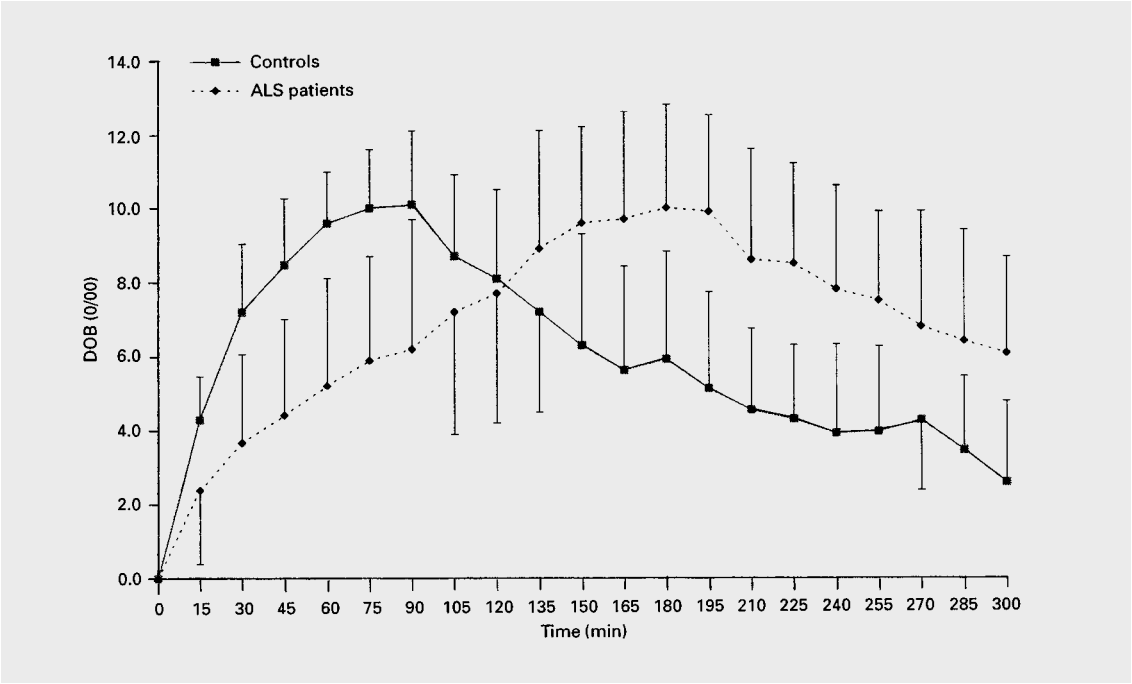
According to the site of disease onset 2 groups of patients were differentiated. Bulbar-onset disease was defined as initial symptoms in the bulbar region, and limb-onset disease as initial symtoms in the limbs, even if there was bulbar involvement at the time of enrollment [7]. Further, patients were divided into subgroups depending on the degree of bulbar involvement at the time of measurement. According to a bulbar involvement score [8] 2 groups were differentiated, 1 with no or mild bulbar impairment (score 0–7), and the other with moderate to marked impairment (score 8–15). The disease duration (in months), the total score of the Norris scale [9], and upper motor neuron involvement [8] were correlated with gastric emptying half time ($t_{1/2}$) and peak time ($t_{peak}$).

*Test Meal and $^{13}C$-Octanoic Acid Breath Test Technique*

In both groups, patients and controls, gastric emptying tests were performed in the sitting position at 9 a.m. after an overnight fast. The patients received a solid standard test meal consisting of 1 scrambled egg, labeled with 100 mg $^{13}C$-octanoic acid, 12 g rye breat, 15 g butter, 20 g jam, 25 g cheese spread and 200 ml tea (caloric content 586 kcal, 12% protein, 42% fat, 46% carbohydrates). Octanoic acid has been used as a tracer molecule because it is poorly absorbed in the stomach, but rapidly absorbed and metabolized in the duodenum [10]. Breath samples were taken baseline and thereafter at 15-min intervals for 5 h and were analyzed for $^{13}CO_2$ by isotope selective nondispersive infrared spectrometry (Wagner Analysentechnik, Worpswede, Germany). Using a nonlinear regression method, gastric emptying $t_{1/2}$ were determined. In addition, the time of maximum $^{13}CO_2$ excretion (peak of the gastric emptying curve, $t_{peak}$) has been determined. The mathematical model used to analyze the results is described in full detail by Ghoos et al. [6]. The parameters were computed as suggested by Ghoos et al. [6]: emptying $t_{1/2} = (1/k) \cdot \ln(1 - 2^{-(1/\beta)}) - 66$, and $t_{peak} = (1/k) \cdot \ln(b) - 66$.

*Statistical Analysis*

Data are given as mean ± 1 SE. The results of the groups and subgroups were analyzed and compared by the Mann-Whitney U test, simple linear regression and correlation. p values of $< 0.05$ were considered significant.

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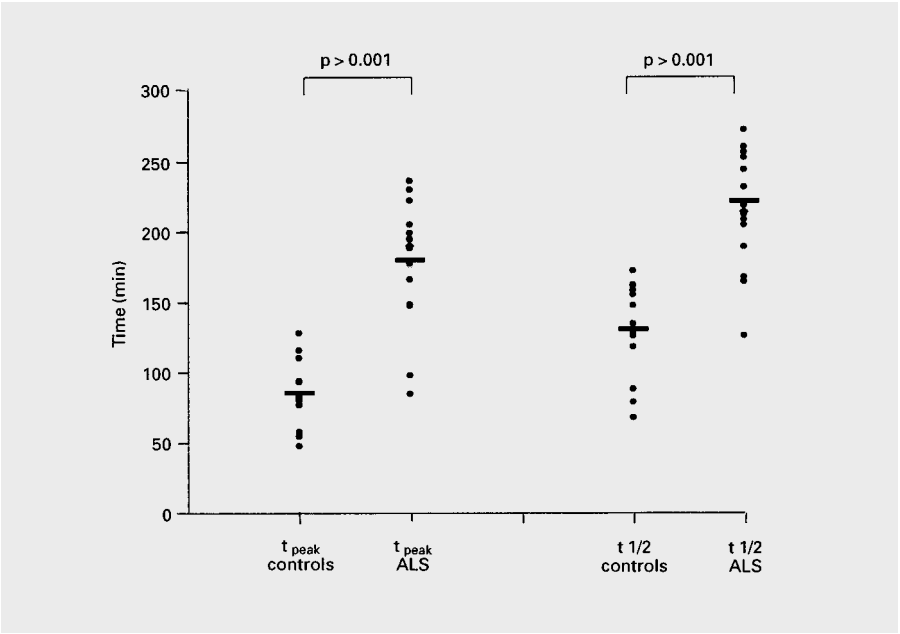


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**Fig. 1.** $^{13}CO_2$ enrichment in breath (mean ± SD) over time (min) after receiving the test meal in healthy volunteers and in ALS patients. DOB = Delta over base.

**Fig. 2.** Gastric emptying half time (t½) and peak time ($t_{peak}$) in healthy controls (n = 14) and in ALS patients (n = 18).

## Results

All participants consumed their test meal within a maximum of 16 min (range, patients 8–16 min; control group 6–12 min). In healthy volunteers $^{13}CO_2$ excretion resulted in a rapid peak with a peak maximum ($t_{peak}$) at 87 ± 23 (range 48–128) min, followed by an exponential decay (fig. 1, 2). Curve fitting of the averaged data by non-linear regression led to a mean t½ of 138 ± 34 min in this group (range 68–172 min; fig. 1, 2). In ALS patients, the $^{13}CO_2$ excretion $t_{peak}$ was 186 ± 39 (range 85–236) min ($p < 0.001$ compared to controls) and gastric emptying t½ was 218 ± 41 (range 126–272) min ($p < 0.001$ compared to controls; fig. 1, 2). The gastric emptying times, t½ and

**Table 2.** Gastric emptying half time (t½) and peak time ($t_{peak}$) of ALS patients, subgroups and control group

| | Control group (n = 14) | ALS total (n = 18) | Site of onset | | Bulbar involvement | |
|---|---|---|---|---|---|---|
| | | | bulbar (n = 9) | limb (n = 6) | none or mild (n = 6) | moderate or severe (n = 12) |
| t½, min | 138 ± 34 | 218 ± 41 | 226 ± 29 | 212 ± 33 | 208 ± 34 | 232 ± 40 |
| $t_{peak}$, min | 87 ± 23 | 186 ± 39 | 193 ± 35 | 176 ± 24 | 183 ± 28 | 188 ± 39 |
| | $p < 0.001$ | | n.s. | | n.s. | |

$t_{peak}$, were not significantly correlated with bulbar involvement or upper motor neuron involvement. The mean duration of the disease was 22.4 ± 12.5 (range 6–48) months. Gastric emptying times did not correlate with the duration of the disease. The ALS group showed a mean Norris score of 66.4 ± 12.7 (range 85–39) without correlation to the gastric emptying times. There was also no correlation between gastric emptying delay and upper motor neuron involvement. Eight patients described symptoms compatible with gastroparesis (fullness after food intake or nausea). However, a correlation with delayed gastric emptying times could not be demonstrated. In the ALS subgroup with moderate or marked bulbar symptoms, t½ was more delayed compared to the subgroup with no or just mild bulbar symptoms, although subgroup analysis did not reveal statistical significance (table 2). Differentiating ALS patients into 2 subgroups, 1 with bulbar onset disease and 1 with limb onset disease, showed that t½ and $t_{peak}$ were more delayed in the group with bulbar onset, but did not result in significant differences (table 2).

## Discussion

In the last years subclinical or clinical involvement of non-motor areas in ALS has repeatedly been described. New techniques in measuring autonomic function revealed evidence of autonomic involvement, i.e. cardial and sudomotor regulation, in ALS. Performing autoregressive spectral analysis of heart rate variability, Pisano et al. [3] and Chida et al. [11] demonstrated a vagal-sympathetic imbalance in patients with ALS. These cardial alterations were not related to clinical features or to the duration of the disease. Prolonged sympathetic skin response latencies in patients with ALS were reported by Dettmers et al. [12] with absent sympathetic skin responses in one or both legs in 40% of ALS patients. Provicialli et al. [5] evaluated skin abnormalities in patients with skin biopsies and suggested autonomic involvement in ALS during the early stages of the disease.

Gastric emptying patterns have not yet been assessed in ALS. The $^{13}$C-octanoic acid breath test is a valid and well-reproducible method to measure gastric emptying [13–15]. It has been shown that gastric emptying measured by breath tests correlated well with scintigraphic studies [6, 13, 16]. Breath sample collection for the $^{13}CO_2$ breath test does not inconvenience patients and can be performed even in patients with advanced disease. The patient does not need to stay in the same position for several hours as is required for scintigraphic measurements. Only a small amount of air from the last phase of exhaling blown into a special bag is necessary for data aquisition. After careful instructions, most patients were able to collect the breath samples themselves on the appropriate time schedule. Only patients with advanced paresis in the upper limbs needed help. Because $^{13}CO_2$ measurements do not need to be done immediately, the breath samples can be mailed to an analytical laboratory.

Gastric emptying is a complex process governed by multiple factors. The consistence and the caloric density of the meal are as important as the neural regulation and motor activity of the stomach. Solid and liquid phases of a meal are emptied in different patterns from the stomach. In pathological conditions, such as autonomic gastroparesis, gastric emptying of solids is delayed first [17, 18]. However, the majority of patients with gastric transit disorders have delayed emptying of both liquids and solid food [13]. Measuring gastric emptying of solids is more sensitive for the detection of delayed gastric transit than measuring the emptying of liquids. Furthermore, reproducibility is better using solid test meals than liquids [19].

Diabetic patients with autonomic gastroparesis often do not complain of gastrointestinal symptoms. Due to the lack of specific complaints autonomic gastrointestinal dis-

turbances in diabetes mellitus are certainly underestimated [20, 21]. We have evaluated gastrointestinal symptoms in the ALS patients, but there was no correlation with delayed gastric emptying. However, gastrointestinal complaints reported by ALS patients, like constipation, diffuse abdominal pain and a feeling of fullness, may further support the theory of gastrointestinal autonomic involvement in ALS.

All patients could chew and swallow the test meal within normal time limits (16 min). Thus, esophageal transit did not seem to affect gastric emptying. None of the patients or volunteers took medication known to influence intestinal transit. 10 patients were treated with riluzole (50 mg twice daily). Riluzole, an inhibitor of glutamate release, is the first drug to be approved in the United States for the treatment of ALS. These patients had no side effects from this medication. However, 6 patients who were not treated with riluzole exhibited markedly delayed gastric empyting as well.

In summary, the noninvasive $^{13}C$ octanoic acid breath test is a feasible diagnostic tool to assess delayed gastric emptying in patients with ALS. Whether delayed gastric emptying in patients with ALS has to be interpreted as autonomic involvement in the context of a subclinical non-motor involvement remains to be elucidated by further studies involving a larger number of patients. Considering ALS as a multisystem disease rather than simply a disease of motor neurons may have major implications for research into pathogenesis. Delayed gastric emptying in ALS patients might be of clinical relevance since symptoms related to disturbed gastrointestinal transit may further reduce food intake and may be improved in part by prokinetic drugs. This technique may also be helpful to assess therapeutic estimates and the course of the disease.

## Acknowledgements

We would like to thank Mrs. Hotz, Mrs. Petrovitsch, S. Werner and M. Schlosshauer for brilliant technical assistance, and Dr. T. Salvin for reviewing the paper. This work was supported by the Friedrich Baur Foundation.

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