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# Value of the 24 hour intraoesophageal pH monitoring in children

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**Abstract**

**Twenty four hour oesophageal intraluminal pH probe studies were performed in 114 children (range age: one month–12 years) referred for symptoms or signs compatible with gastro-oesophageal reflux. Forty five patients had reflux disease alone, 69 had evidence of oesophagitis which was assessed endoscopically and histologically. Recordings were also performed in 63 control patients. The occurrence of reflux was analysed for the total study period and particularly while awake, asleep, fasting, and during postcibal periods. Oesophageal acid exposure time and the number of reflux episodes lasting >five minutes during the total study period provided the best discrimination between patients and controls; however, 20% and 30% of all reflux patients had both normal (with 2 SD of control) acid exposure time and number of long lasting reflux episodes, respectively. Patients with oesophagitis had significantly more acid reflux than those with simple uncomplicated disease during postcibal, fasting, awake periods, but not during sleep; however, increasing severity of oesophagitis was not associated with increasing acid exposure. The ability of the intraluminal oesophageal pH test to discriminate patients with various degrees of reflux disease decreased if only postprandial pH variables were taken into account. We conclude that: (1) the 24 hour intraoesophageal pH monitoring may present false negative results that limit overall sensitivity of the test; (2) the presence of oesophagitis does not seem to be associated with increased oesophageal acid exposure during sleep; (3) limiting the pH recording to postprandial periods reduces the discriminatory power of the test.**

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Prolonged intraluminal oesophageal pH monitoring is currently regarded as the most accurate method to diagnose gastro-oesophageal reflux (GOR), particularly in patients presenting with atypical symptoms.[1 2] It has also proved useful in defining a temporal profile of reflux in individual subjects: thus the test allows the provision of a more rational approach to therapy.[3 4] Although important contributions have been made to assess the diagnostic value of the longterm pH monitoring in any age paediatric group, only few reports in children have attempted to correlate the pH pattern of reflux with the clinical severity of gastrooesophageal reflux disease and to determine the ability of the test to differentiate normal subjects from patients with various degrees of reflux disease.[5–7]

In the present stury we evaluated the value of the 24 hour intraoesophageal pH monitoring in defining the best indicators of gastrooesophageal reflux disease in children. Furthermore, we wished to assess the accuracy of the test both in discriminating children with gastro-oesophageal reflux disease from normal subjects and in distinguishing the disease spectrum of reflux patients.

## Methods

### PATIENTS

One hundred and fourteen consecutive patients, referred for symptoms suggestive of gastro-oesophageal reflux, were included in our investigation. All patients had a well documented history of recurrent vomiting or regurgitation; some had additional gastro-oesophageal reflux complications such as weight failure (45), haematemesis (17), chronic respiratory symptoms (19). Children in whom vomiting was particularly protracted and severe underwent *x*-ray examination of small bowel in order to exclude intestinal malrotation. Clinical entities mimicking gastro-oesophageal reflux, such as food intolerance, malabsorption, neurologic and metabolic disorders, renal and infectious diseases, were strictly excluded in all of them. The patients underwent 24 hour intraoesophageal pH monitoring and oesophagogastroduodenoscopy (with oesophageal biopsy) as part of their evaluation. Patients were divided in two groups based on endoscopic and microscopic appearance of oesophageal mucosa: 45 patients (age: 26·6 (42·07) months (mean (SD)); range: two months–10 years) were affected by gastro-oesophageal reflux disease alone (gastro-oesophageal reflux patients); 69 children (age: 41·3 (50·15) months) $p<0·05$ in comparison with gastro-oesophageal reflux disease alone patients; range: one month–12 years) had reflux oesophagitis (moderate in 39 cases, severe in 30 cases) (RO patients). Another 63 children (age: 24·02 (32·6) months; range: two months–12 years) carefully selected for absence of typical symptoms of gastro-oesophageal reflux, represented our control group (C patients). The main diagnoses in this group were recurrent functional abdominal pain (five), chronic functional constipation (nine), irritable bowel syndrome (11), feeding problems secondary to maternal anxiety or inexperience (19), previous history of apnoea (10), upper respiratory infections (nine). A flexible glass pH electrode (Microelectrodes Inc MI 506) was passed through the nose and positioned in the oesophageal lumen with its tip at the 87% of the nares-lower oesophageal sphincter distance as determined either by manometry or by calculation from the formula of Strobel.[8] In each patient position of the electrode

was checked by fluoroscopy. The reference electrode was attached to the abdomen. Gastro-oesophageal reflux was defined whenever the distal oesophageal pH dropped to less than 4 for at least 20 seconds or if an additional decrease of at least 1 pH unit occurred during periods of pH less than 4. Before and at the end of each recording the system was standardised against buffer solutions at pH 4 and 7. If the pH drift exceeded 0·3 pH unit the tracing was discarded. The pH was recorded on a modified computer monitor (Proxima 'light', Sensormedics, Italy) and analysed on a printer or by an IBM personal computer. The following parameters were analysed from the tracings: (i) the percentage of time the oesophageal pH was less than 4 (% gastro-oesophageal reflux); (ii) the number of reflux episodes; (iii) the number of reflux episodes requiring >five minutes to clear (rise in intraluminal pH to >4); (iv) the mean duration of reflux (minutes) (total time pH <4/number or reflux episodes); (v) length of the longest episode (min). The pH variables were evaluated during: (i) entire recording period; (ii) wakefulness; (iii) sleep (wake time plus sleep time equals the entire time); (iv) first two postprandial hours (<2 pp h); (v) after the first two postprandial hours (>2 pp h) (early postprandial period plus fasting period equals entire time). Length of the longest episode was only calculated during the entire recording period. Studies were well tolerated by all patients: only few subjects required restraining during the first minutes of examination. Children were given the daily customary feeds in a volume determined by their appetite; they could move freely and maintained their usual daily activities. A nurse continuously observed the patients and marked on the pH recording apparatus the sleeping periods. The three groups of subjects did not significantly differ for the amount of time spent in either awake or sleep states.

TABLE I *Twenty-four hour intraoesophageal pH variables in children with gastro-oesophageal reflux (GOR) disease and in controls*

| *Cases (n)* | *Controls* 63 | *GORD disease alone* 45 | *GOR disease with oesophagitis* 69 |
|---|---|---|---|
| 1 Twenty-four hours | | | |
| Exposure acid time (% GOR) | 1·46 (1·01) | 6·4 (3·66) [85·42]* | 9·62 (9·32) [78·26]† |
| Episodes (n) | 10·96 (8·5) | 28·7 (15·9) [43·75]* | 34·74 (20·1) [57·9]* |
| Episodes >5′ (n) | 0·6 [0·9] | 3·9 (3·32) [70·83]* | 6·75 (6·96) [69·57]*† |
| Longest episode (min) | 6·29 (5·9) | 16·30 (10·70) [47·92]* | 31·59 (52·73) [47·83]*† |
| Mean duration (min) | 2·37 (2·24) | 8·52 (8·72) [16·67]* | 10·01 (11·33) [15·94]* |
| 2 First two postprandial hours | | | |
| Exposure acid time (% GOR) | 0·48 (0·63) | 2·52 (2·27)* | 3·88 (4·79)* |
| Episodes (n) | 4·36 (5·3) | 12·02 (11·76)* | 16·85 (13·47)* |
| Episodes >5′ (n) | 0·17 (0·45) | 1·51 (2·12)* | 2·83 (3·25)*† |
| Mean duration (min) | 1·32 (1·30) | 4·62 (7·64)* | 4·44 (7·01)* |
| 3 After first two postprandial hours | | | |
| Exposure acid time (% GOR) | 0·98 (0·8) | 3·99 (2·36)* | 5·71 (6·53)* |
| Episodes (n) | 6·63 (5·34) | 16·64 (8·28)* | 17·88 (10·93)* |
| Episodes >5′ (n) | 0·40 (0·80) | 2·41 (2·12)* | 3·93 (5·01)*† |
| Mean duration (min) | 2·22 (1·80) | 3·91 (3·06)† | 5·51 (8·06)* |
| 4 Awake | | | |
| Exposure acid time (% GOR) | 1·01 (0·80) | 2·98 (2·42)* | 6·25 (6·41)* |
| Episodes (n) | 8·70 (7·80) | 21·31 (15·61)* | 27·67 (19·11)* |
| Episodes >5′ (n) | 0·31 (0·67) | 1·69 (2·31) | 4·11 (4·64)*§ |
| Mean duration (min) | 2·02 (2·80) | 2·29 (1·83) | 3·76 (5·25) |
| 5 Asleep | | | |
| Exposure acid time (% GOR) | 0·44 (0·55) | 3·42 (3·91)* | 3·37 (5·19)* |
| Episodes (n) | 2·25 (2·36) | 7·81 (5·73)* | 7·39 (6·86)* |
| Episodes >5′ (n) | 0·30 (0·70) | 2·41 (2·61)* | 2·32 (3·41)* |
| Mean duration (min) | 2·04 (2·04) | 5·81 (5·32)* | 5·01 (5·04)* |

Values as mean (SD); the number in square brackets represents the percent in that group with values > SD from controls. *p<0·01 *v* controls; †p<0·05 *v* controls; ‡p<0·05 *v* GOR disease alone patients; §p<0·01 *v* GOR disease alone patients.

All patients underwent oesophagogastroduodenoscopy according to a technique published elsewhere.[9] At least two biopsy specimens were taken from the oesophageal mucosa, above the distal 20% of the oesophagus. The biopsies were taken from macroscopically abnormal mucosa or from endoscopically normal appearing mucosa. Diagnosis and grading of oesophagitis were based upon endoscopic and/or histologic criteria. Both endoscopic oedema and oerythema were not considered reliable markers of oesophagitis: in these cases biopsy evidence of oesophagitis was required. Endoscopic lesions such as erosions or ulcerations were judged to be definite findings of oesophagitis. Oesophagitis was histologically graded as moderate if intraepithelial eosinophils or ≥20 intraepithelial neutrophils per high power field were seen; as severe if there was also evidence of mucosal ulceration (acute inflammation with superficial erosions and/or complete ulcerations of the mucosa).[10] Histological features such as basal cell hyperplasia and extension of papillae could not be always evaluated in mucosal specimens and, therefore, were not included among the histological criteria for oesophagitis. Written informed consent was obtained from parents of each patient and the diagnostic protocol was approved by the Ethical Committee of our Faculty.

### STATISTICAL ANALYSIS

The unpaired *t* test and the stepwise discriminating analysis were used for statistical analysis.

## Results

Analysis of pH recordings is reported in Table I. The controls were divided in three groups according to different ages (0–6 months; >6–24 months; >24 months): results of the pH recordings for the three groups are shown in Table II. The percentage time spent with pH below 4 and the number of reflux episodes lasting >five minutes were the variables most consistently abnormal both in gastro-oesophageal reflux patients and reflux oesophagitis patients. However, 14·6% of gastro-oesophageal reflux patients and 21·74% of reflux oesophagitis patients had a normal acid exposure time (below 2 SD from the control mean); whereas 29·17% of gastro-oesophageal reflux patients and 30·43% of reflux oesophagitis patients had a number of gastro-oesophageal reflux episodes requiring five minutes or longer to clear below 2 SD from the control mean. Patients with oesophagitis differed significantly (p<0·01) from gastro-oesophageal reflux patients both for the acid exposure time (% gastro-oesophageal reflux) and gastro-oesophageal reflux episodes >five minutes during the total monitoring and awake periods; furthermore, the number of episodes >five minutes was significantly (p<0·01) higher in reflux oesophagitis than gastro-oesophageal reflux patients both during and after the first two postprandial hours. The two groups of patients did not differ in any single variable during sleep. Increasing severity of oesophagitis was not associated with higher acid exposure (Table III).

In order to study the ability of the test in

TABLE II *Twenty-four hour intraoesophageal pH variables in 63 controls with different ages*

| *Age groups* | *0–6 months* | *>6 months–2 years* | *>2 years* |
|---|---|---|---|
| Cases (n) | 24 | 28 | 11 |
| Exposure acid time (% GOR) | 1·74 (1·14) | 1·29 (0·92) | 1·33 (0·7) |
| Episodes (n) | 10·08 (7·5) | 11·96 (9·2) | 10·36 (8·3) |
| Episodes >5′ (n) | 1·0 (1·11) | 0·46 (0·77) | 0·27 (0·6) |
| Longest episode (min) | 8·5 (8·07) | 5·03 (3·42) | 4·35 (2·22) |
| Mean duration (min) | 2·45 (2·25) | 1·40 (0·45) | 3·22 (3·38) |

No statistical differences among the three groups for each variable. Values as mean (SD).

distinguishing the disease spectrum of reflux patients a step-wise discriminating analysis was carried out. Discriminating capacity of the 24 hour intraoesophageal pH monitoring was calculated as percentage of correct classification into the different subgroups of patients taken into consideration (Table IV). The pH test showed the highest discriminating power when gastro-oesophageal reflux patients and controls were compared (90·32% of patients 'correctly classified'), whereas when all patients (gastro-oesophageal reflux patients and reflux oesophagitis patients) or the reflux oesophagitis patients were compared with controls the discriminating capacity of the test was slightly lower (85% and 84% of patients 'correctly classified', respectively). Even lower degrees of discriminating power were seen when we attempted to compare patients with gastro-oesophageal reflux disease alone and those with oesophagitis and patients with different degrees of oesophagitis. The discriminating ability of the test was clearly diminuished if we only analysed the variables of the first two postprandial hours.

## Discussion

This study showed that the prolonged intraoesophageal pH monitoring may present false negative results that could limit its diagnostic accuracy. Our results indicate that a negative 24 hour intraoesophageal pH monitoring in children with symptoms suggesting gastro-oesophageal reflux and with normal endoscopy (and biopsy) might not exclude gastro-oesophageal reflux as cause of their symptomatology provided that other entities mimicking gastro-oesophageal reflux have been excluded. In our patients with normal oesophageal pH monitoring, diagnosis of gastro-oesophageal reflux disease was also supported by the fact that clinical remission was obtained from postural therapy, thickening of feedings and administration of prokinetic drugs. In addition, severity of symptoms in this group of patients was similar to that of patients with positive pH test and with oesophagitis. On the other hand, since oesophagitis is considered a reliable marker of reflux disease, its presence will clearly support a diagnosis of gastro-oesophageal reflux even in spite of a normal prolonged pHmetry. Several factors can explain a negative pH monitoring in subjects with gastro-oesophageal reflux disease. First, episodes of alkaline or 'hypoacid' gastro-oesophageal reflux might be overlooked using the standard routine pH measurement, because identification of such episodes would require simultaneous recordings of both intra-oesophageal and intragastric pH. This seems to be critical because intraoesophageal pH values >7 may indicate swallowed saliva and episodes of pH drop (even of ≥1 pH U) that did not fall below the threshold value of 4 were not considered by our analysis method as true reflux episodes. Whether oesophageal bile reflux plays a role in the pathophysiology of gastrooesophageal reflux disease has not clearly proved up to now.[11–13] Second, increased flow of saliva occurring after nasogastric probe positioning can decrease the exposure acid time of the oesophagus by neutralising the acidity of the refluxed content.[14] A third possible explanation for a negative pH result in patients with gastro-oesophageal reflux disease lies in the variability of the prolonged intraoesophageal pH monitoring which in a series of adult patients had been reported to have a reproducibility ranging from 34 to 61%.[15]

It is of interest that oesophageal acid exposure

TABLE III *Twenty-four hour intraoesophageal pH variables in children with moderate reflux oesophagitis and in children with severe reflux oesophagitis*

| *Cases (n)* | *Moderate oesophagitis 39* | *Severe oesophagitis 30* |
|---|---|---|
| Age (months) (mean SD) | 33·19 (45·32) | 48·57 (53·21) |
| 1 24 hours | | |
| Exposure acid time (% GOR) | 10·15 (11·37) | 8·06 (6·36) |
| Episodes (n) | 30·02 (22·37) | 34·59 (18·19) |
| Episodes >5′ (n) | 5·46 (5·1) | 7·27 (8·26) |
| Longest episode (min) | 36·59 (69·01) | 23·38 (21·75) |
| Mean duration (min) | 9·48 (11·56) | 9·76 (10·66) |
| 2 First 2 postprandial hours | | |
| Exposure acid time (% GOR) | 3·97 (6·02) | 3·37 (2·87) |
| Episodes (n) | 14·27 (14·23) | 17·76 (12·47) |
| Episodes >5′ (n) | 2·32 (3·31) | 3·11 (3·09) |
| Mean duration (min) | 3·27 (2·9) | 5·29 (9·12) |
| 3 After 2 postprandial hours | | |
| Exposure acid time (% GOR) | 6·15 (7·12) | 4·66 (5·61) |
| Episodes (n) | 17·75 (11·17) | 16·84 (10·92) |
| Episodes >5′ (n) | 3·13 (3·37) | 4·27 (6·16) |
| Mean duration (min) | 6·21 (9·2) | 4·51 (16·7) |
| 4 Awake | | |
| Exposure acid time (% GOR) | 6·18 (7·14) | 5·71 (5·4) |
| Episodes (n) | 24·73 (20·58) | 28·54 (17·2) |
| Episodes >5′ (n) | 3·32 (3·74) | 4·46 (5·24) |
| Mean duration (min) | 3·42 (4·03) | 3·84 (6·03) |
| 5 Asleep | | |
| Exposure acid time (% GOR) | 3·96 (6·37) | 2·35 (3·21) |
| Episodes (n) | 7·57 (7·65) | 6·35 (5·92) |
| Episodes >5′ (n) | 2·13 (3·02) | 2·22 (3·65) |
| Mean duration (min) | 5·43 (5·56) | 4·23 (4·24) |

Values as mean (SD). No statistical differences between the two groups for each variable.

TABLE IV *Discriminant function analysis of the 24 hour intraoesophageal pH monitoring*

| *Patient groups compared* | *pH variables in the analysis* | *Wilk's lambda* | *Percent of grouped cases correctly classified** |
|---|---|---|---|
| Controls/all patients† | Episodes for 24 hours | 0·795 | |
| | 24 hour mean duration | 0·698 | |
| | Asleep mean duration | 0·655 | 84·85 (69·5) |
| | % postprandial GOR | 0·636 | |
| | Episodes >5′/24 hours | 0·582 | |
| Controls/patients with GOR disease alone | % postprandial GOR | 0·569 | |
| | 24 hour mean duration | 0·490 | 90·32 (70·00) |
| | Postprandial mean duration | 0·421 | |
| | Postprandial episodes >5′ | 0·326 | |
| Controls/patients with oesophagitis | Episodes for 24 hours | 0·747 | |
| | 24 hour mean duration | 0·643 | |
| | Asleep mean duration | 0·623 | 83·81 (75·24) |
| | % postprandial GOR | 0·597 | |
| | 24 hour longest episode | 0·584 | |
| GOR disease alone/oesophagitis | % awake GOR | 0·912 | |
| | 24 hour longest episode | 0·884 | 65·79 (55·61) |
| | Age | 0·848 | |
| Moderate oesophagitis/severe oesophagitis | % asleep GOR | 0·974 | |
| | Episodes >5′/24 hours | 0·931 | 59·46 (54·48) |
| | Age | 0·879 | |

*In brackets: discriminant analysis performed by means of the pH variables of the first two postprandial hours. GOR=gastrooesophageal reflux. RO=reflux oesophagitis.

† GOR and RO patients.

in control infants aged below six months did not significantly differ from that detected in older children, despite increased incidence of regurgitation that usually occurs in small infants.[16 17] This could be because of a greater intake of milk during the first months of life and consequent gastric neutralisation. This might result in underestimation of weakly acid reflux episodes.

Children with reflux disease (either alone or with oesophagitis) were clearly differentiated from controls during both fasting and fed periods. It has been previously suggested that patients with gastro-oesophageal reflux disease are easily separated from normal subjects by reflux occurring in the late postcibal period[16] or in the first two postcibal hours.[17] It is very difficult comparing pH recordings from different laboratories, however, as prolonged pH monitoring in children has been performed according to different methods and the infants investigated differed in severity of disease.

Development of oesophagitis was associated with increased acid exposure of the oesophagus. The number of reflux episodes lasting more than five minutes was the most significant variable that differentiated patients with oesophagitis from those with simple gastro-oesophageal reflux disease. The five minute value is currently regarded as the most accurate variable in predicting the occurence of oesophagitis because it reflects the mechanisms of oesophageal acid clearing.[3 19] A surprising finding relates to the fact that reflux during sleep was not implicated in the occurrence of oesophagitis. It is commonly assumed that reflux occurring during sleep can be more dangerous to the oesophagus than the awake acid exposure as acid clearing is usually impaired during sleep.[20] There is not, however, unanimity on the role of sleep reflux in causing oesophagitis. Recent reports on adults have produced strong evidence that oesophagitis is not associated with increased acid reflux during sleep.[21 22] It is also reported that appropriate acid clearing can be generated during sleep if an arousal response from sleep occurs:[23] it has been suggested that during periods of intra-oesophageal acid exposure, oesophageal afferent stimuli can induce swallowing with consequent peristaltic activity and that oesophageal motor activity is not compromised when subjects are sleeping.[23] We would like to speculate that our patients with oesophagitis had an intact arousal acid clearing mechanism resulting in an efficient clearing.

Although patients with oesophagitis had higher values of oesophageal acid exposure than children with simple gastro-oesophageal reflux disease, increased degree of oesophagitis was not associated with increased acid exposure. This observation gives new strength to the concept that factors other than acidity, such as decreased tissue resistance and prevalence of bilious and pancreatic secretions in the refluxate, may be involved in the pathogenesis of oesophagitis and could be responsible of higher degrees of oesophageal injury.[24]

It is still debated whether shorter pH tests would diagnose abnormal degrees of reflux.[2 25] Diagnostic sensitivity of short time recordings has been found to be accurate in some reports.[4 21 26 27] On the other hand short pH metric tests proved to be less reliable in the experience of other authors[19 28] particularly when they are limited to the postprandial period. This is not surprising mainly because it is commonly believed that reflux occurring after meals can be a physiological event.[3 4 28] On the other hand, if one assumes, as most do, that milk or formula feeding can neutralise gastric acidity, reflux of non-acid gastric content might not be detected by pH test, particularly in infants.[4 10] We found that discriminating power of the pH test decreased when analysis of the tracings included only the first two postprandial hours. In our opinion even if short periods of daytime recording might be attractive, prolonged pH monitoring would seem to be advantageous in identifying the temporal pattern of gastro-oesophageal reflux, in order to plan a more rational therapeutic approach; furthermore it seems particularly useful when gastro-oesophageal reflux is suspected in children with unexplained or atypical symptoms.

The results of this study were presented previously in abstract form at the XX Annual Meeting of the European Society for Paediatric Gastroenterology and Nutrition, Lisbon, June 24–26, 1987.

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