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Reproducibility of continuous 24 hour oesophageal pH monitoring in infants and children

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Abstract

The reproducibility of 24 hour oesophageal pH monitoring was studied in 30 infants and children including the proportions of the investigation time with a pH <4 (reflux index), the number of episodes with a pH <4 or lasting longer than five minutes, and the duration of the longest episode with a pH <4. Twenty four hour pH monitoring was performed using identical equipment on two consecutive days under similar conditions. Pearson correlation coefficients range from 0·88 to 0·98. The results obtained on two consecutive days were similar. The reflux index and the number of reflux episodes >five minutes were the most reproducible parameters. Despite the many patient related factors influencing pH data, the reproducibility of 24 hour pH monitoring data are satisfactory for routine clinical application.

Gastro-oesophageal reflux is occasionally experienced by most individuals. Occasional brief spurts of acid into the oesophagus are a normal phenomenon, in both adults and infants.[1-3] Nevertheless, measurement of the duration of exposure of the oesophageal mucosa to acid is an objective guide to reflux. Oesophageal pH monitoring is a valuable method to detect (acid) reflux. Johnson and DeMeester extended recording to 24 hours to 'allow observing gastro-oesophageal reflux patterns during one complete human circadian cycle'.[4] The aim of this study was to analyse the reproducibility of 24 hour pH monitoring.

Methods

PATIENTS

An oesophageal pH monitoring was performed in 30 infants and children, using a Memolog 2a-600 (Scan Detectronics). The system collected the data (1 pH every 7·5 seconds) until the memory was fully loaded. The readout of data was performed using an Apple IIe computer; the program was developed by our team. The following parameters were studied: the reflux index (% of the total investigation time with a pH <4), the number of episodes with a pH <4 and the number of episodes with a pH <4 lasting >five minutes in 24 hours, the duration of the longest episode with a pH <4. The pH electrode was a glass microelectode (MI 506, Microelectrodes Inc.) with a maximal outer body diameter of 1·6 mm and a cutaneous silver/silver chloride reference electrode. Before and after each study, the pH electrode was calibrated by the same person in buffers with pH 1·68 and 7·00; the exactness of the measured pH was controlled in pH 4·00. Calibration was repeated if a drift of more than 0·2 pH occurred with any buffer. The electrode was introduced transnasally, and located in the middle third of the oesophagus; the exact location was controlled by *x* ray examination. An adaptation period of about 30 minutes to the nasal probe was allowed before recording was started. All patients continued their normal feeding and activities. Events, including feeding and activities were carefully reported by the nursery staff and/or the parents ('activity report'). After 24 hour, data were read out and the investigation was repeated using the same equipment after recalibration. The electrode was situated at exactly the same location and the recording was repeated in similar circumstances: the 'activity-report' of the previous day was precisely repeated. After another 24 hours the second recording was stopped, data were read out, and the same parameters analysed.

The age of the patients varied from two weeks to eight years. Eleven (age six months-eight years; mean three years) were investigated because of 'classic' symptoms of gastro-oesophageal reflux (vomiting, regurgitation); 19 because of atypical manifestations: 15 were presented with apnoea, apparent life threatening event (age 0·5–6·0 months; mean 2·5 months), four were investigated because of chronic respiratory disease (age three-six years; mean 4·5 years). Written consent was obtained from the parents before the patients entered the study, as well as approval from the children themselves who were old enough to do so.

STATISTICAL ANALYSIS

Statistical analysis was performed for the four parameters regarding the group of data considered as normal, regarding the group with abnormal data, and regarding all 30 patients included in the study. Analysis consisted of drawing scatterplots and lines of equality, calculation of Pearson correlation coefficients. Graphs, relating differences of the data to the

TABLE *Pearson correlation coefficient*

	Pearson correlation coefficient (r)				
		Abnormal		*All*	
(*n*)	*Normal* 11	*19**	*18†*	*30**	*29†*
Reflux index	0·98	0·87	0·94	0·95	0·97
N ep pH<4	0·95	0·97	0·98	0·98	0·98
N ep >5 min pH<4	0·96	0·94	0·95	0·98	0·98
Long ep pH<4	0·97	0·91	0·93	0·95	0·96

The nearer the Pearson correlation coefficient (r) comes to 1, the better the correlation. Pearson correlation coefficient was calculated regarding all infants (*) or with the one infant with a pH oscillating around 4 dropped out (†) (methods different from the study design).

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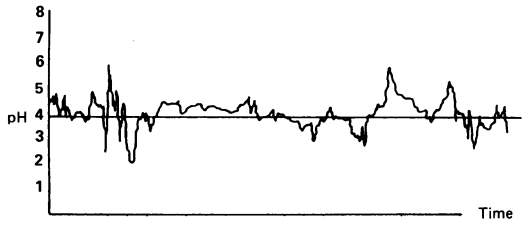

Figure 1: pH Tracing in one patient, oscillating around pH 4.

best estimation of the true value, allow the investigation of any relation between measurement error and the true value.[5] The limits of agreement are the 95% confidence interval of the differences between all pairs (day 1-day 2 results), and show the magnitude of the variability of the differences observed between corresponding observations.

Results

Data of the first pH monitoring were considered within 'normal ranges' (established in age matched asymptomatic infants[3] or asymptomatic adult volunteers)[6] in 11 patients (one of the group with clinic gastro-oesophageal reflux pathology, 10 of the group with atypical manifestations). Regarding 'normal/abnormal', all data were confirmed by the second monitoring.

One infant was dropped out as well as included for statistical analysis (Table). The pH tracing of this patient was very particular: pH oscillated during a major period of the investigation around four (Fig 1). The second tracing was comparable with the first; and to exclude technical failure, the second monitoring was performed using another Memolog and another microelectrode (so methodology applied in this infant differed from the study design). As pH was during prolonged periods around the cut off limit (pH 4), calculated parameters did not very well correlate despite the similar aspect of the tracings: reflux index: 18–34% (day 1-day 2), number of episodes with a pH <4: 77–104, number of reflux episodes lasting longer than five minutes: 13–17, duration of the longest episode (min): 53–87. Difference in mean pH between both registrations was only 0·12 pH. Because of the different methodology, one could argue to drop these data out for statistical evaluation. When included for statistical analysis, however, correlation coefficients do not significantly differ (Table).

The calculated Pearson correlation coefficients ranged from 0·88 to 0·98. Correlation coefficients were slightly higher in the group with normal data, compared with the group with pathologic data. Overall correlation coefficients

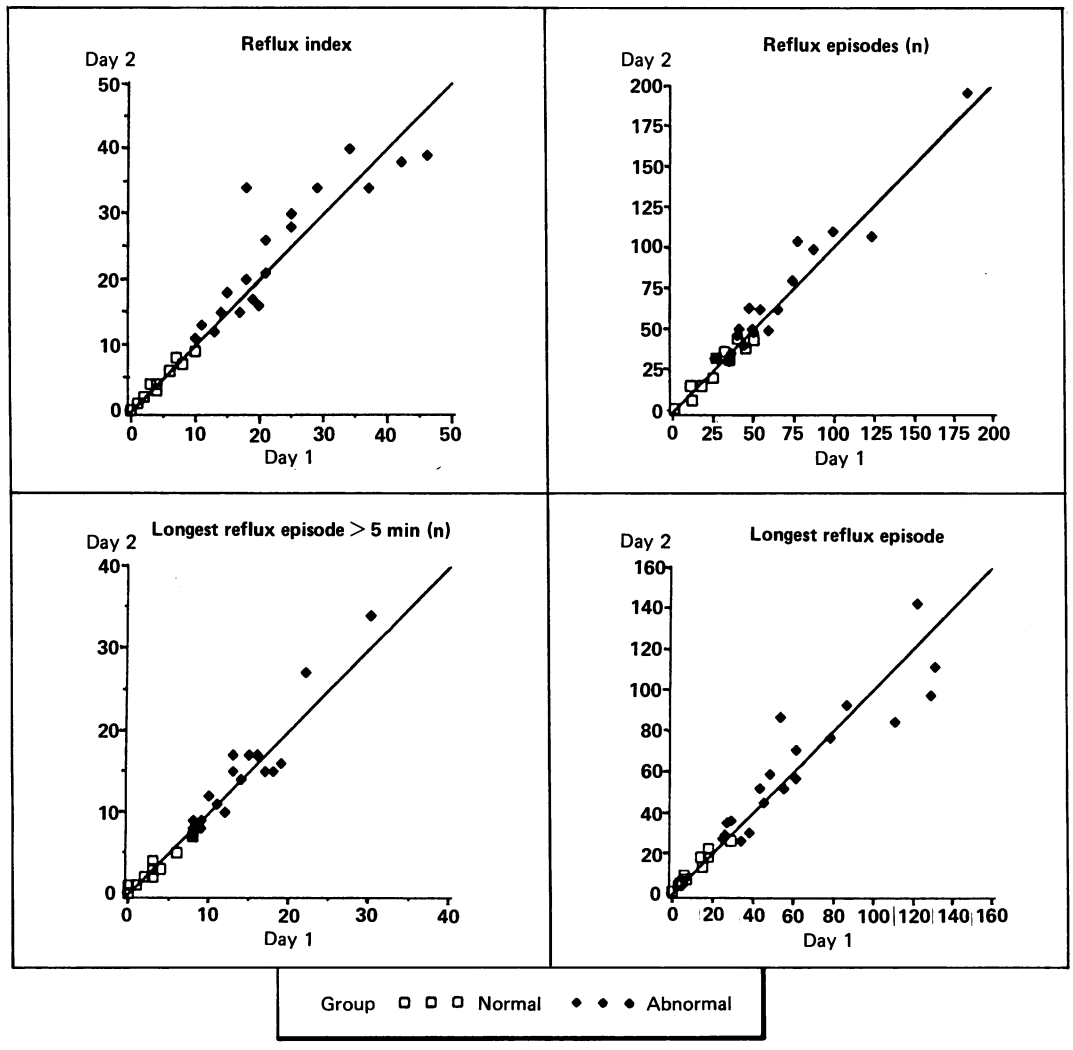

Figure 2: Reproducibility of pH monitoring data. Scatterplots and lines of equality of day 1 and day 2 data for the four parameters studied: reflux index, number of episodes with a pH<4, those lasting longer than five minutes, the duration of the longest episode.

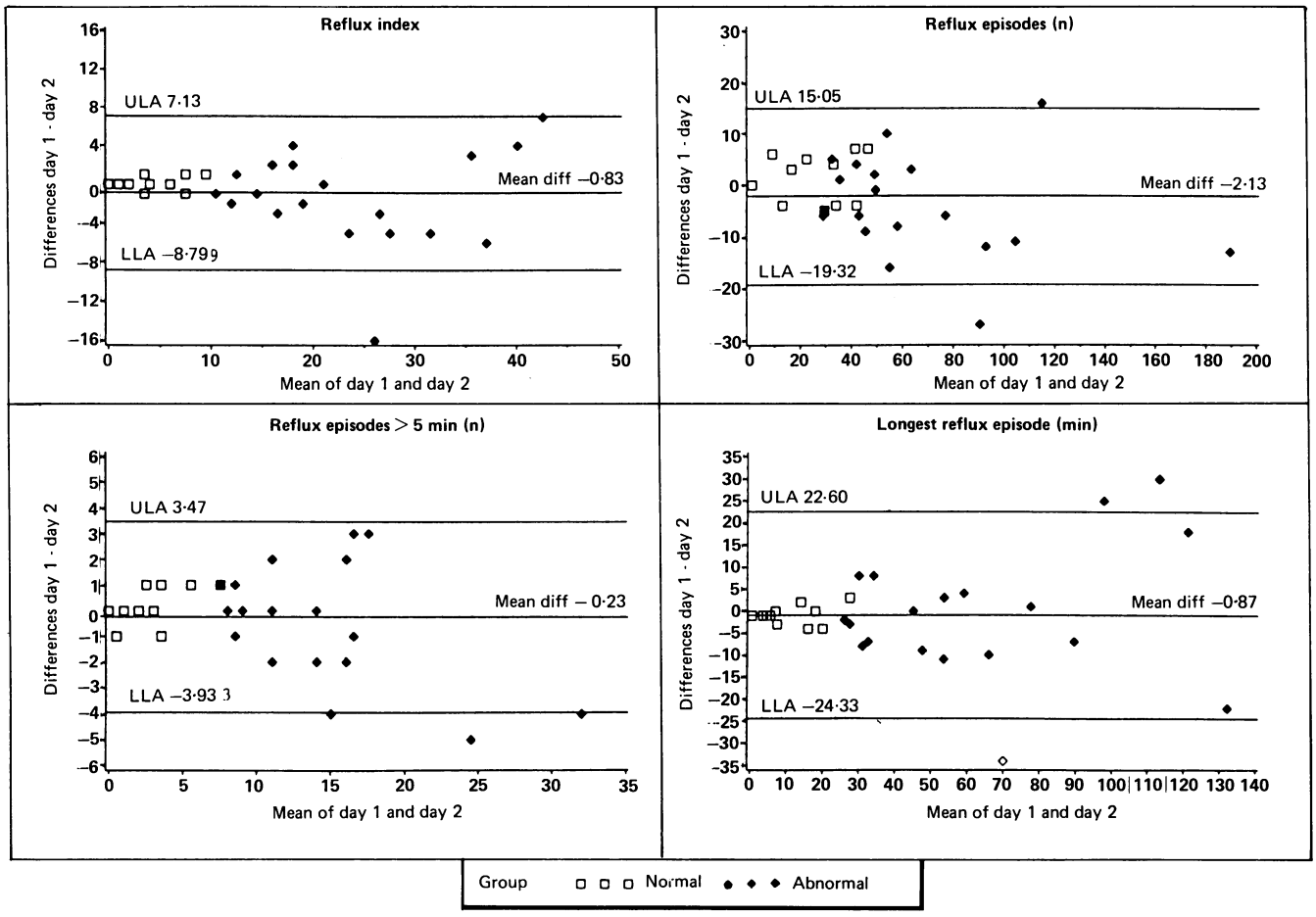

Figure 3: Reproducibility of pH monitoring data. Limits of agreement of the data of day 1 and day 2. Mean diff: mean difference of all pair-differences between day 1-day 2 data. ULA: upper limit of agreement; LLA: lower limit of agreement (the limits of agreement are the 95% confidence interval for differences between all pairs (day 1-day 2 results).

varied between 0·95 and 0·98. The lines of equality are shown in Figure 2.

If the investigation is perfectly reproducible, the 'mean difference' between both registrations should be zero as the same method was used.[5] The 'mean difference', as shown in Figure 4, was for all parameters slightly negative: this means that during the second registration there were fewer episodes with pH <4 detected. From this Figure it appears also very clearly that the more data were abnormal, the larger became the differences from the 'mean difference' that were observed between both recordings. Ninety five per cent of the differences are expected to be within the range of the 'mean difference' ±2 standard deviations (definition of a repeatability coefficient adapted by the British Standards Institution.[7] Regarding the reflux index and the number of episodes with pH <4 lasting >five minutes there was 1 difference out of the 95% confidence interval. Regarding the number of episodes with a pH <4, there were two; regarding the duration of the longest reflux episode there were three. The limits of agreement are small enough to be confident that data of day 1 and day 2 are reproducible.

Discussion

During the past decade a significant increase in the understanding of gastro-oesophageal reflux has occurred. This has mainly been because of function studies performed on the lower oesophageal sphincter using pressure studies and pH monitoring.[8] Extended pH monitoring is probably the most accurate study for evaluating gastro-oesophageal reflux.[8] 'Normal' physiologic incidence of gastro-oesophageal reflux has been established in asymptomatic infants[3] and adults.[6] Normal ranges in the group of infants younger than one year are significantly higher compared with physiologic incidence in children older than one year, who do not differ significantly from the normal ranges in adults.

The results of continuous pH monitoring are subject to wide variation depending upon the conditions under which the study is performed. DeMeester *et al*[9] showed different reflux patterns in adults according to position, as well in asymptomatic volunteers as in patients ('upright' and 'supine' refluxers). In young asymptomatic infants, physiologic reflux is more frequently detected in supine, right and left side than in the prone position.[10] There is an increased occurrence of physiologic reflux episodes during awake periods, or periods of physical activity.[11] Normal infants, just as asymptomatic adults, rarely reflux during sleep.[11,12] Feeding will alter the incidence of (acid) gastro-oesophageal reflux. In young infants, feeding consists mainly of milk, a neutralising product of the acid gastric content. The number of (acid) gastro-oesophageal reflux episodes will be dependent on the number of feedings, and, in the postcibal

periods, on the volume and composition of the feedings.[13 14] During postcibal periods acid gastro-oesophageal reflux will be detected more frequently if an infant is fed with a 'low fat' formula.[14] Drugs may influence gastro-oesophageal reflux incidence; xanthines (theophylline, caffeine) are drugs that increase gastric acid secretion, and decrease lower oesophageal sphincter pressure. Therefore these drugs (or foods containing their derivatives – for example, coffee), can induce a gastro-oesophageal reflux pathology.[15 16] The number of registered reflux episodes will be dependent on the total duration of the investigation. Because most of these factors change during the first year of life, the incidence of 'normal physiologic' gastro-oesophageal reflux will be age dependent in the very young group.[3] Once a child is over one year old, daily life becomes more and more comparable with adult life (as well for feeding as the sleep pattern), and the incidence of reflux becomes more constant and comparable.

It is obvious that pH data are not only influenced by patient related factors, but also by technical factors. The nearer the pH electrode is located to the lower oesophageal sphincter, the more reflux episodes that will be registered.[17] For all the above reasons, it was rather fortunately that regarding 'normal/abnormal' all data were confirmed by the second monitoring.

The question of reproducibility of pH data, given all these variables, has not been thoroughly discussed previously.[18] Reproducibility is, however, an important aspect of a biomedical test. Boesby performed 10 12 hour registrations in one normal eupeptic volunteer with quite reproducible results (variation coefficient pH <4: 0·94).[19] Bontempo published results on duplicated recordings within five days in 20 subjects with reflux symptoms, showing a correlation in 16 of them.[20] Our results reveal that reproducibility is very high in normal recordings, and a little lesser – although still very good – in abnormal tracings, if feeding and activities are controlled.

Data scatterplots and lines of equality were for the four parameters excellent; the Pearson correlation coefficient was as well. The use of this coefficient, however, has been shown to be possibly misleading in some cases.[5] Therefore another graphical technique, based on simple calculations was performed ('precision of estimated limits of agreement')[5]. As the limits of agreement revealed clinically irrelevant differences, variability of the differences was within normal ranges. Therefore the method of 24 hour pH monitoring can be postulated as reproducible. Applying this technique, the number of episodes with a pH <4 appeared to be less reproducible than the other parameters, despite the higher Pearson correlation coefficient.

The relativity of whatever parameter analysis is illustrated by the one registration with a pH oscillating around the cut-off limit (pH 4). Because minimal differences in registered pH (mean difference 0·12 pH), parameters analysed were quite different, however without a significant influence on the statistical analysis.

Our results suggest, given the high reproducibility of 24 pH monitoring data, the latter is a sufficient long period to obtain reliable results.

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