OESOPHAGUS

Simultaneous recordings of oesophageal acid exposure with conventional pH monitoring and a wireless system (Bravo)

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Objectives: Oesophageal pH monitoring is a useful test for the diagnosis of gastro-oesophageal reflux disease (GORD) but has some limitations related to the nasopharyngeal electrode. Recently, a telemetric catheter free system (CFS) (Bravo; Medtronic) was developed. The aim of this study was to determine the concordance of data between the conventional pH measurement system (CPHMS) and the CFS Bravo.
Methods: Forty patients with symptoms suggestive of GORD underwent 24 hour oesophageal pH monitoring using the CPHMS with a nasopharyngeal electrode and the Bravo CFS simultaneously. The sensitive tips of both electrodes were positioned at the same level under fluoroscopy. In addition to automatic analysis, each reflux episode was checked visually and characterised.
Results: There was a significant correlation ($r = 0.87$, $p < 0.0001$) between the 24 hour oesophageal acid exposures recorded by the CPHMS and the CFS. Twenty four hour oesophageal acid exposure was significantly lower with the CFS than with the CPHMS (2.4 (0.4–8.7) v 3.6 (0.7–8.6); $p < 0.0001$). Consequently, with the CFS, the cut off level for the diagnosis of GORD, as calculated from the regression equation, was 2.9% (for the 4.2% cut off determined in controls with the CPHMS). After this adjustment, concordance of the diagnosis of GORD was 88% (kappa 0.760). Diagnosis of GORD was established in more patients with the CFS 48 hour results than with the 24 hour results.
Conclusions: Despite strong correlations between oesophageal acid exposure recorded with the two devices, the Bravo CFS significantly under recorded acid exposure compared with the CPHMS. Provided some correcting factors are used, the Bravo CFS can improve the sensitivity of pHmetry for the diagnosis of GORD by allowing more prolonged recordings.

O esophageal pH monitoring is a widely used test for the diagnosis of gastro-oesophageal reflux disease (GORD). The development more than 20 years ago of a portable data logger allowing prolonged ambulatory recordings largely contributed to its widespread diffusion. Although oesophageal pH monitoring cannot be regarded as a definitive gold standard for GORD diagnosis, it is indicated in several clinical situations defined by national or expert groups.[1–5] Ideally, the test must be performed in patients living in their usual environment and engaged in regular daily activities. There are however certain limitations to current pH monitoring techniques. It was recently shown that the test itself has significant effects on reflux provoking activities. In fact, pH testing appears to reduce the period of time spent being active, to induce changes in eating habits and, moreover, to reduce the frequency of GORD symptoms. In addition, patients report that pH testing frequently induces some unexpected side effects and that it bothers them most of the time.[6]

A new telemetric catheter free system (CFS) has been recently developed to monitor oesophageal pH. The device (Bravo pH Monitoring System; Medtronic, Minneapolis, Minnesota, USA) is temporarily implanted in the patient's oesophageal mucosa avoiding the inconvenience of wearing a nasopharyngeal electrode. Although the Bravo CFS appears to be effective in measuring oesophageal exposure,[7] no study has reported simultaneous monitoring of oesophageal pH using both systems (that is, the conventional pH measurement system (CPHMS) and the Bravo CFS). Such simultaneous monitoring is the only way to establish that the two

systems actually detect identical reflux events and produce an equivalent diagnostic yield for GORD.

Consequently, the aim of this study was to determine the concordance of data collected with the CPHMS and the Bravo CFS by simultaneously monitoring distal oesophageal pH using both systems in the same patients.

PATIENTS AND METHODS

Forty patients with symptoms suggestive of GORD and referred to the functional laboratory of four French academic centres for 24 hour pH monitoring were enrolled in this prospective study. All patients had undergone oesogastro-duodenoscopy in the preceding six months during which information on the Z line level and presence/absence of hiatal hernia was recorded. Patients were not included if they were known to have severe oesophageal motility disorders or if they had severe oesophagitis (Los Angeles grade C or above). Likewise, women who were pregnant or were not using reliable contraceptive methods were not included. The study protocol was approved by the local ethics committee (CCPPRB des Pays de Loire No 2), and informed consent was obtained from all patients.

Oesophageal pH was simultaneously monitored for 24 hours with two systems, a CPHMS (Mark III or Digitrapper pH; Medtronic, Stockholm, Sweden) with a transnasal antimony catheter and the Bravo CFS.

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Abbreviations: GORD, gastro-oesophageal reflux disease; CFS, catheter free system; CPHMS, conventional pH measurement system; SAP, symptom analysis probability

Characteristics of the CFS pH capsule and recorder have been described previously.[7] Briefly, the pH capsule is oblong in shape and contains an antimony pH electrode and a reference electrode at its distal tip. In addition, the capsule contains an internal battery and a transmitter entirely encapsulated in epoxy. The pH capsule sends a data signal to an external receiver via radiofrequency telemetry. pH data are recorded at six second sampling intervals (frequency 0.16 Hz).

Before each procedure the pH capsule was activated and calibrated with its receiver in pH buffer solutions of pH 7.01 and pH 1.07 (Medtronic A/S, Skovlunde, Denmark) at room temperature (22–23°C). After an overnight fast, the prepackaged assembly, incorporating both the delivery system and the capsule itself, was passed either through the nostril (after local anaesthesia) or through the mouth, according to the choice of the investigator and preference of the patient. The pH electrode of the Bravo capsule was fixed 5 cm above the Z line previously located by endoscopy. In order to maintain the position, the vacuum pump was connected to apply suction to the wall of the capsule. Successful capture of oesophageal mucosa was assumed when the vacuum gauge on the pump stabilised at a value ≥510 mm Hg for 30 seconds. The activation nob on the handle was then turned clockwise 90° and re-extended, which had the effect of releasing the pH capsule from its attachment point on the delivery system. The delivery system was then removed.

The CPHMS has been described in detail elsewhere.[8] Briefly, a combined single use antimony pH electrode (ref 9012P-2031; Medtronics, Maastricht, the Netherlands) connected to the portable data logger was calibrated before insertion using standard buffer solutions of pH 7.01 and 1.07 at room temperature. A recording was taken every four seconds (frequency 0.25 Hz). Following light local anaesthesia (2% xylocaine spray), the pH probe was inserted via the nostril and placed at the same level as the capsule pH. The tip of the transnasal catheter was adjusted if needed to the same level as the CFS under systematic fluoroscopic control. Simultaneous recordings were then started.

Recording protocol
During the first 24 hours of recording, subjects remained ambulant in the clinic or at home. Meals were not standardised for energy composition. However, patients were instructed to have lunch (between 12am and 2pm) and dinner (between 7pm and 9pm) at the same time for the two consecutive days of recordings. They were also asked to go to bed in the evening no later than 11pm. Oesophageal pH was first recorded for 24 hours with both devices.

At the end of the first 24 hours, the antimony electrode was removed whereas the Bravo CFS recording was continued for a second 24 hour period. All patients were then discharged to their home for the second 24 hour period of recording (Bravo pH recording only).

During the 48 hours of recording, patients indicated on a diary card the presence of any symptoms as well as the time being upright or supine. In addition, at the end of the two 24 hour periods, they completed questionnaire to indicate whether or not they had unusual discomfort, dysphagia for solids, dysphagia for liquids, sleep disorders, throat discomfort, or thoracic discomfort. Finally, patients were requested to complete a diary card daily from day 3 to day 14 to indicate whether they perceived dysphagia for solids, dysphagia for liquids, sleep disturbances, or thoracic discomfort. Fourteen days after the recording, patients attended the clinic's outpatient unit for a fluoroscopic test to verify the absence of the capsule.

Analysis of pH monitoring data
Recorded data obtained from the CFS as well as from the CPHMS were transferred to a desktop computer and processed with a dedicated software Polygram Net (Medtronics). Patients were considered to have had episodes of reflux when pH was less than 4 for at least six seconds; episodes were considered to have ended when pH reached 5. For each 24 hour period (CPHMS and CFS day 1 and CFS day 2), the following parameters were determined: per cent of total time pH <4, upright time pH <4, night time pH <4. In addition, the total number of reflux episodes, number of reflux episodes longer than five minutes, and the mean duration of reflux episodes were determined.

One of the authors (RT) read all pH curves by displaying the two tracings (CFS and CPHMS) on the computer screen in order to analyse each reflux episode (duration and lowest pH reached) and determine whether it was recorded by both devices or only by one. A reflux episode was defined as simultaneous only if both tracings had at least one contemporary segment at pH <4.

Statistical analysis
As values of pH monitoring are not always normally distributed, non-parametric tests were used when requested for comparison of parameters of oesophageal acid exposure; otherwise, a paired t test and ANOVA analysis were applied. Concordance of diagnostic yield was calculated by dividing the number of patients having the same diagnostic conclusion with both methods by the total number of patients. The diagnosis of GORD was established according to the upper limit of normal values of 24 hour oesophageal acid exposure. The cut off level of the CFS measured acid exposure was calculated from the regression equation by using the cut off level determined in healthy controls by the CPHMS.[8]

Symptom analysis was performed for both recordings using the symptom analysis probability (SAP) method, as previously described.[9]

RESULTS
Attachment, safety, and tolerance
Forty patients were included (mean age 50 (14) years; 21 males). Thirty nine of the 40 patients had heartburn (n = 7), regurgitation (n = 6), or both symptoms (n = 26). Fourteen patients had a hiatus hernia (mean height 2.7 (1.1) cm). Thirty six patients had no oesophagitis and four had oesophagitis Los Angeles grade A.

The CFS was successfully attached in 36/40 patients. In four patients the capsule was not attached. For one patient the capsule was not ingested because of a dysfunction of the capsule (and no capsule was available for immediate substitution). In two patients, placement failure was due to poor tolerance with vomiting, and in one patient to failure of detachment from the delivery system. The capsule was introduced through the nostril in 12 patients and through

Table 1 Prevalence of symptoms in patients during the first 24 hour period (day 1) of simultaneous recordings with the catheter free system (Bravo) and the conventional pH measurement system (Synectics), and the second 24 hour period (day 2) recording with only the catheter free system

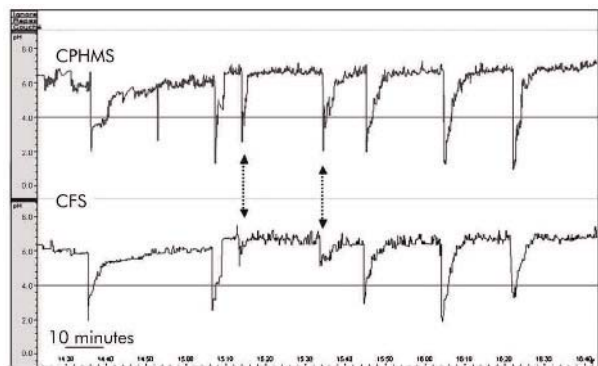|	Day 1 (%)	Day 2 (%)	p Value*
Sleep disorders	68	15	<0.0001
Dysphagia for solids	74	60	NS
Dysphagia for liquids	51	20	0.006
Thoracic discomfort	68	57	NS
Saliva swallowing discomfort	51	29	0.05

*χ^2 test.

Figure 1 Simultaneous recordings of oesophageal pH using the conventional pH measurement system (CPHMS) with an antimony transnasal electrode (upper trace) and the Bravo catheter free system (CFS) (lower trace). Arrows indicate pH events detected by both devices but recorded by only one. On the Bravo CFS trace, although the decrease in pH appears (arrows), it does not reach the pH 4 threshold.

the mouth in 27. No serious adverse event occurred. Only minor adverse events were reported during the introduction procedure (epistaxis n = 1, dizzy spell n = 1).

Overall tolerance was good and no patient requested stopping the study. Sleep disorders, dysphagia for liquids, and saliva swallowing discomfort were reported significantly more often during the first 24 hours (CFS and CPHMS together) than on the second day (table 1). Dysphagia for solids and thoracic discomfort were frequently reported by patients (74% and 68%, respectively). Although slightly less frequent on the second day, these symptoms were still present in a number of patients (table 1). In addition, from day 3 to day 14, daily monitored symptoms tended to decrease but both dysphagia for solids and thoracic discomfort were present for several days (26% and 19% at day 7, respectively) and disappeared more slowly than dysphagia for liquids and sleep disorders (9% and 13% at day 7, respectively). The CFS capsule had disappeared in all of the patients at the 14 day fluoroscopic examination.

Oesophageal acid exposure monitored by CFS and CPHMS (first 24 hour period)

Double recordings were obtained in 33 of 36 patients. In one patient both recordings spontaneously stopped (unidentified cause) after seven hours. In two patients the Bravo capsule was considered to be detached from the oesophagus after three and four hours of oesophageal recording, as the pH for CFS suddenly became acidic (pH<2) and then continuously

remained so. Correct positioning of both probes was fluoroscopically checked in 30 of these 33 patients. In some patients adjustment of the antimony catheter (not exceeding 2 cm) was needed to ensure the same recording level for both probes.

For the first 24 hour period, visual analysis of the recordings for the 33 patients identified 1388 reflux episodes. The two devices recorded 563 episodes simultaneously whereas 724 episodes were recorded by the CPHMS but not by the CFS (figs 1, 2). Reflux episodes that were only detected by the CPHMS were significantly shorter (56 (134) s) than those detected by the two devices (236 (506) s; p<0.0001). The mean pH of reflux episodes that were only detected by the CPHMS was significantly higher (2.58 (0.98) U pH) than those detected by the two devices (2.19 (0.90) U pH; p<0.0001). There were 101 reflux episodes detected only by the CFS. These episodes were characterised by a rather long duration (217 (780) s) and were less acidic (mean pH 2.95 (0.77) U pH; p<0.001) than those detected by the CPHMS only or by the two devices. Lack of signal recorded by the CFS accounted for only 10 of the 724 episodes only recorded by the CPHMS whereas lack of signal recorded by the CPHMS accounted for 18 of the 101 episodes only recorded by the CFS. Regarding episodes recorded by both devices, mean duration was not significantly different between the CFS and CPHMS (246 (420) v 236 (496) s, respectively) whereas the mean minimal pH of reflux episodes was significantly higher with the CFS than with the CPHMS (2.85 (0.77) v 2.19 (0.88) U pH, respectively; p<0.0001).

Oesophageal acid exposures recorded by both devices during the initial 24 h period are given in table 2. pH parameters recorded using the CPHMS were significantly higher than those recorded by the CFS for all analysed periods (total, upright, and supine).

There was a strong and highly significant correlation (r = 0.87, p<0.0001) between the 24 hour oesophageal acid exposure recorded by the CPHMS and by the CFS (fig 3). Similar correlation values were observed for the upright (r = 0.86, p<0.0001) as well as the supine (r = 0.88, p<0.0001) periods for oesophageal acid exposures recorded by the CPHMS and by the CFS. As the regression line equation did not correspond to the identity line, we calculated the upper limit of normal for the CFS measured oesophageal acid exposure. Using the cut off level of 4.2% determined in healthy controls by the CPHMS (see methods), the cut off level of the CFS for the diagnosis of GORD, as calculated from the regression equation, was 2.9%. Using these cut off levels, oesophageal acid exposure was abnormal in 14 patients with the CPHMS and in 13 patients with the CFS whereas 11 patients were diagnosed with reflux disease
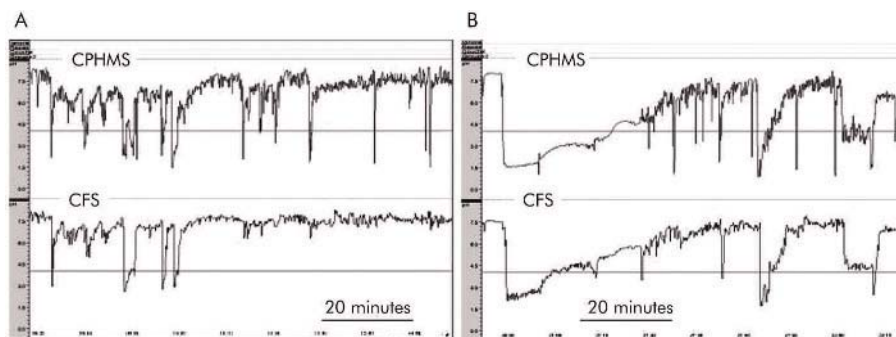

Figure 2 Simultaneous recordings of oesophageal pH using a conventional pH measurement system (CPHMS) with an antimony transnasal electrode (upper trace) and the Bravo catheter free system (CFS) (lower trace). (A) Several short reflux events observed on the upper trace do not appear on the lower trace. (B) Reflux events recorded by the Bravo catheter free system appear shorter for the time pH <4, and some reflux events reach the pH 4 threshold with the antimony transnasal electrode but not with the Bravo electrode.

Table 2 Oesophageal acid exposure measured during 24 hours of simultaneous recordings in 33 patients with the Bravo catheter free system and the conventional pH measurement system (CPHMS)

	Bravo	CPHMS	p Value*
pH <4, total time	2.4 (0.4–8.7)	3.6 (0.7–8.6)	0.0001
pH <4, upright time	3.4 (0.6–11.4)	4.7 (0.7–13.4)	0.0003
pH <4, supine time	0.2 (0.0–3.8)	0.4 (0.0–7.9)	0.0176
No of reflux events	23 (4–41)	40 (7–84)	0.0001
No of reflux events>5 min	2 (1–11)	2 (1–10)	0.82

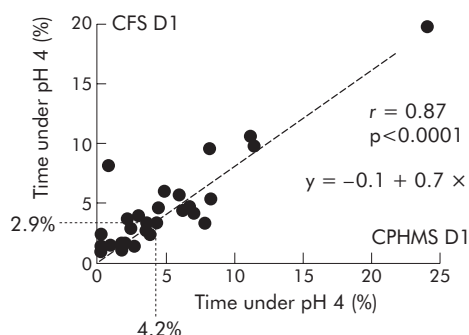Results are median (10th–90th percentiles).
*Wilcoxon test.

Figure 3 Values for 24 hour (D1) oesophageal acid exposure recorded simultaneously using both a conventional pH measurement system (CPHMS) with an antimony transnasal electrode and the Bravo catheter free system (CFS). Correlation line is indicated showing the trend for slightly lower values with the Bravo CFS measurements.
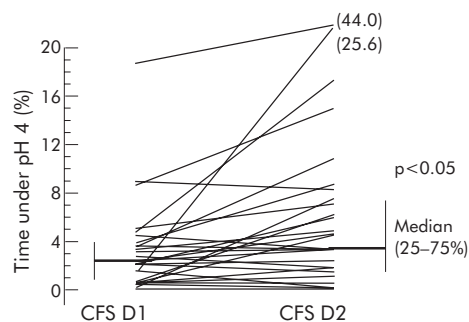

Figure 4 Individual values for 24 hour oesophageal acid exposure recorded on two consecutive days (D) using the Bravo catheter free system (CFS) in 30 patients with symptoms of gastro-oesophageal reflux disease.

with the two methods. After this adjustment, the concordance of the diagnosis of GORD was 88% (kappa 0.760). By omitting the two patients at the extremes of the data set, the correlation between the acid exposure values recorded by the CPHMS and by the CFS was stronger ($r = 0.95$, p<0.0001) than the previous one ($r = 0.87$). As a result, the slope of the regression line slightly increased from 0.71 to 0.77.

Day to day variability in oesophageal acid exposure and analysis of symptoms (comparison of acid exposure between the two consecutive days)

Among the 30 patients investigated on day 2, oesophageal acid exposure was higher on day 2 than on day 1 in 21 cases. Oesophageal acid exposure recorded by the CFS (n = 30) was significantly higher on day 2 than on day 1 (3.3% (1.4–7.5) v 2.4% (0.7–3.9), respectively; p<0.04) (fig 4). Likewise, the number of reflux episodes longer than five minutes tended to be higher on day 2 than on day 1 (4 (2–8) v 2 (1–5); p = 0.07). The number of reflux episodes was not different between the two consecutive days (23 (13–36) v 23 (10–32) for day 2 and day 1, respectively). However, using the cut off value for oesophageal acid exposure as previously determined (2.9%), there were more patients than on day 1 (13/33) that would have been diagnosed as GORD patients (18/30) although the difference did not reach statistical significance. There was a statistically significant correlation between the 24 hour oesophageal acid exposure values recorded by the CPHMS on day 1 and the CFS on day 2 ($r = 0.79$, n = 30).

Symptom association probability was available for 31 patients. The number of patients with a positive SAP (>95%) was not significantly different between recordings performed by the CFS (7/31) and the CPHMS (9/31) on day 1. However, the mean SAP tended to be higher with the CPHMS (62 (38)%) compared with the CFS (57 (40)%; p = 0.075, paired *t* test). On day 2, 4/31 patients had a positive SAP. Finally, nine of 31 patients had a positive SAP when 48 hour CFS monitoring was considered.

DISCUSSION

This study allowed us to document the characteristic features of reflux episodes by analysing simultaneous recordings using the newly developed Bravo CFS and the CPHMS with an antimony transnasal electrode. The results showed that despite strong correlations between oesophageal acid exposure recorded by the two devices, the Bravo CFS significantly under recorded acid exposure compared with the CPHMS.

A previous study has shown that electrode placement is easy and successful in the majority of subjects.[7] In our study, the rate of success was slightly lower due to difficulties in attaching the capsule to the oesophageal mucosa in some

patients. Our study was conducted in several centres and may reflect more real conditions of use by new investigators. In our opinion, although the attachment procedure is easy to learn, some practice is needed to adequately release the capsule from the delivery system. Overall tolerance was good. Comparing the first (capsule and pH probe) and the second (capsule only) day, there was a real improvement in symptoms, suggesting better tolerance of the CFS than the CPHMS.[10] However, for some patients, the capsule appeared to induce some specific symptoms. Although the design of our study does not allow specific determination of the role of the capsule in the symptoms reported by patients, several days of symptoms such as dysphagia and thoracic discomfort were frequently reported.[10]

Our data demonstrate strong correlations between parameters of pHmetry recorded by the two systems. However, they clearly show that measured oesophageal acid exposure was significantly lower with the CFS than with the CPHMS, even after deletion of the two patients at the extremes of the data set. This lower oesophageal acid exposure must be considered with regard to the smaller number of reflux events recorded with the CFS. Visual analysis of the tracings often showed that short reflux events could not be detected by the CFS, as illustrated in figs 1 and 2. The characteristic features of reflux events not detected by the CFS confirmed this visual assessment: mean duration of these undetected reflux events (as measured by the CPHMS) was shorter than one minute. This duration included the time needed to reach the pH 5 threshold defining the end of a reflux episode. On some occasions, lack of detection was related to the less profound

decrease in pH recorded by the CFS: pH fell below 4 with the CPHMS but not with the CFS (figs 1, 2). Some of these discrepancies could be explained by the different response characteristics of the two electrodes. The sampling frequency of the Bravo CFS electrode was lower than that of the CPHMS electrode (0.16 v 0.25 Hz), and the CFS capsule had a longer response time, possibly explaining detection differences. In contrast, it is unlikely that a higher position of the CFS capsule compared with the CPHMS electrode could be the cause of the differences as the position of the electrodes was checked and eventually adjusted in all but three patients. This was an essential step in our study, as the radioscopic examination frequently revealed differences of up to 2 cm between the levels of the two electrodes.

Furthermore, the level of pH recording applied in the present study (that is, 5 cm above the squamocolumnar junction) was marginally lower than the usual standard position (that is, 5 cm proximal to the upper margin of the lower oesophageal sphincter).[7] It is very unlikely that this 1 cm difference could affect the results or that it could have affected the head to head comparison conducted at the same level for the two electrodes. As the signal from the CSF pH capsule cannot be captured if the patient is too far away from the receiver, missing data may also be to blame. However, this occurred rarely in our study, and accounted for only 10 of the 724 episodes recorded by the CPHMS alone. Conversely, the CFS detected a small number of reflux events which went undetected by the CPHMS. These reflux episodes undetected by conventional pH monitoring were characterised by a relatively long mean duration (217 s) and a rather high mean pH (2.95) in comparison with reflux events detected only by the CPHMS. These discordant results are difficult to explain but may be related in part to the inhomogeneous oesophageal content. The Bravo capsule was attached to the oesophageal wall whereas the antimony catheter remained free in the oesophageal lumen. Changes in body position or swallowing may also have temporarily modified the relative positions of the two electrodes.

Despite the strong correlation between oesophageal acid exposure recorded by the two systems, the CFS was less sensitive and consequently required the use of as yet undetermined normal values to interpret the recorded data. Applying a correcting factor calculated from the equation of the regression line, we were able to determine the theoretical upper level of normal values. After using this correction, our data showed the reliability of the CFS in terms of diagnostic yield as concordance between the two systems was 88%.

Our 48 hour monitorings revealed statistically significant differences for oesophageal acid exposure between the two consecutive 24 hour recordings. Various factors could account for higher acid exposure on the second day (fig 4) as monitoring conditions were clearly different from the first 24 hours. During the second 24 hour period, patients were in their more usual circumstances (withdrawal of the antimony catheter, home life). Measured under the specific conditions of our study, these variations are well in line with significant effects of conventional pH monitoring on reflux provoking activities.[6] These known limitations of conventional pH monitoring focus attention on the importance of developing new monitoring devices such as the CFS. Nevertheless, irrespective of the monitoring system used, normal values for acid exposure in healthy asymptomatic subjects will have to be determined in a large series in order to take into account variations induced both by the different characteristics of monitor responses to reflux events and by modifications in reflux provoking activities in patients with the CFS.

Finally, our data showed that 24 hour pH monitoring with the CPHMS was not more sensitive than with the CFS in terms of establishing a relationship between symptoms and occurrence of acid reflux. Symptom association probability was not significantly different between the CPHMS and the CFS (62 v 57%) on day 1, suggesting that the larger number of missed reflux events with the CFS is not of clinical relevance when studying the symptom reflux related relationship. In addition, as the CFS allows simultaneous monitoring of oesophageal pH and symptoms over a longer period (48 hours), the sensitivity of the device in detecting the symptom reflux related relationship is probably higher than[11] or, as seen from our results, at least equivalent to that of the CPHMS.

In conclusion, this work establishes the reliability of the Bravo CFS for measuring oesophageal acid exposure and diagnosing GORD. In addition, the potential advantages offered by this new device appear important not only for patient acceptance[7] but for prolonged monitoring under more physiologic conditions. In our opinion, unless systematic and reliable correcting factors can be validated to compare with the previously determined normal values for the CPHMS, normal values for these specific conditions (total ambulatory monitoring over 48 hours) need to be established.

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