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Effects of the frame acquisition rate on the sensitivity of gastro-oesophageal reflux scintigraphy

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Objective: To compare the sensitivity of gastro-oesophageal reflux (GOR) scintigraphy at 5-s and 60-s frame acquisition rates.

Methods: GOR scintigraphy of 50 subjects (1 month–20 years old, mean 42 months) were analysed concurrently using 5-s and 60-s acquisition frames. Reflux episodes were graded as low if activity was detected in the distal half of the oesophagus and high if activity was detected in its upper half or in the oral cavity. For comparison purposes, detected GOR in any number of 5-s frames corresponding to one 60-s frame was counted as one episode.

Results: A total of 679 episodes of GOR to the upper oesophagus were counted using a 5-s acquisition technique. Only 183 of such episodes were detected on 60-s acquisition images. To the lower oesophagus, a total of 1749 GOR episodes were detected using a 5-s

acquisition technique and only 1045 episodes using 60-s acquisition frames (these also included the high-level GOR on 5-s frames counted as low level on 60-s acquisition frames). 10 patients had high-level GOR episodes that were detected only using a 5-s acquisition technique, leading to a different diagnosis in these patients. No correlation between the number of reflux episodes and the gastric emptying rates was noted.

Conclusion: The 5-s frame acquisition technique is more sensitive than the 60-s frame acquisition technique for detecting both high- and low-level GOR.

Advances in knowledge: Brief GOR episodes with a relatively low number of radioactive counts are frequently indistinguishable from intense background activity on 60-s acquisition frames.

Gastro-oesophageal reflux (GOR) scintigraphy is a non-invasive and sensitive method for detecting GOR in symptomatic subjects. In addition to identifying repetitive reflux episodes, GOR scintigraphy quantifies refluxate levels, duration and frequency, measures gastric emptying and evaluates for possible lung aspiration. Although the method was introduced in the early 1970s, until now, there has been no single universally accepted protocol for this study [1]. Most comparative studies for reflux quantification related GOR scintigraphy to pH monitoring of the oesophagus, which has been considered as the gold standard for measurement of acid reflux. For example, Orenstein et al [2] showed that scintigraphy detected refluxate in the oesophagus half of the time that the pH probe did at the 60-s framing rate, and only a quarter of the time at the 10-s framing rate. The authors also reported that the 60-s framing rate showed more agreement between scintigraphy and the pH probe than the 10-s framing rate in documenting reflux duration.

However, recent data obtained by multichannel intraluminal impedance and manometry provide new details related to GOR. Thus, based on different impedance patterns, the reflux episodes can be classified as containing gas, liquid or both, while the GOR content can be classified as acid (pH drops from >4.0 to <4.0), minor acid (pH remains >4.0 but drops >1 pH unit), non-acid reflux (pH remains >4.0 and does not drop >1 pH unit) and acid re-reflux (occurs while intra-oesophageal pH is already <4.0) [3]. It has been shown that, although conventional pH monitoring can quantify oesophageal acid exposure and evaluate the association between symptoms and acid reflux, it cannot reliably detect reflux episodes with pH >4 [4]. In detecting weakly acidic reflux, pH alone had a sensitivity of only 28%, whereas 83% of weakly acidic reflux episodes detected by pH were not associated with multichannel intraluminal impedance-detected reflux [5]. In their recent studies, Lee et al [6] reported that 43% of GOR was acid reflux and 57% was non-acid, Xiao et al [7] showed that more than half (52.4%) of the reflux episodes were mixed, 37.2% were liquid and 10.4% were gas, whereas Kline et al [8] reported that 57% of patients with negative endoscopy and negative 24-h pH testing received a diagnosis unachievable with standard pH testing. Moreover, the non-acid reflux increased at post-prandial time ($p < 0.001$) [6], and this is likely to affect even more the percentage of

reflux episodes detected by a GOR scintigraphy scan done immediately after the ingestion of milk.

METHODS AND MATERIALS

Patients and imaging

GOR scintigraphies of 50 subjects (1 month–20 years old, mean 42 months) were analysed concurrently using 5-s and 60-s acquisition frames after the study was approved by the institutional review board. All patients had clinical suspicion for GOR, presenting with such conditions as feeding difficulties, recurrent cough, suspected aspiration, chronic lung infection, chronic sinusitis, recurrent vomiting or failure to thrive. A large proportion of them were underweight. All GOR scintigraphies were requested by their treating physician. No patients underwent prior fundoplication or any surgical intervention for GOR correction. The scintigraphy was performed after fasting for at least 6 h, generally overnight. A liquid meal consisting of formula, milk or orange juice containing between 200 μCi (7.4 MBq) and 1 mCi (37 MBq) of $^{99\text{m}}\text{Tc}$ sulphur colloid was administered orally or via a nasogastric tube. The dose of the radiopharmaceutical was calculated as $15 \mu\text{Ci kg}^{-1}$ (0.55 MBq kg^{-1}) and the volume of the liquid meal as 300 ml per 1.73 m^2 of total body surface area or approximately equal to that used for regular feeds. The radiopharmaceutical was mixed in about half of the liquid and administered first. The second half of the liquid meal was free of tracer and used to clear any remaining radioactivity from the oesophagus. With subjects in the prone position, serial 5-s images of the oesophagus and stomach were obtained for 60 min with the gamma camera detector under the imaging table. A low-energy, high-sensitivity collimator was used with a photopeak window for $^{99\text{m}}\text{Tc}$ (140 keV, 20% window). Radioactive markers were placed for anatomic reference over the sternal notch and the right shoulder. Anterior and posterior static images of the thorax were obtained at the end of the study to assess for aspiration of gastric contents. Regions of interest were drawn around the oesophagus and stomach, and the gastric residual was calculated at the end of the study after 60 min of imaging.

Scintigraphy scoring

All scans were reprocessed retrospectively at 5-s and 60-s acquisition frame rates. GOR episodes were assessed by viewing computer-enhanced images and evaluating the spikes of activity extending into the

oesophageal region. The level of their proximal extent was graded by visual assessment, the radioactive marker over the sternal notch serving as a reference point. All GOR episodes were counted individually by visual assessment of every frame to exclude possible errors related to automatic counting of activity within displaced portions of the stomach. The dynamic acquisition was also reviewed in the cine mode to identify movements of the body, which can simulate reflux spikes. Reflux episodes were graded as low if activity was detected in the distal half of the oesophagus and high if activity was detected in its upper half or the oral cavity. The number of reflux episodes detected by the two methods of scintigraphy acquisition was recorded and compared. For comparison purposes, recorded GOR in any number of 5-s frames corresponding to one 60-s frame was counted as one episode (Figure 1). Correlation of the number of GOR episodes with the patient's age and gastric residual at the end of the study was also performed.

Statistical analysis

Following GOR scintigraphy acquisition at 5-s and 60-s frame rates, all data were analysed using SPSS® v. 16.0 (SPSS Inc., Chicago, IL), StatsDirect v. 2.7.9 (StatsDirect Ltd, Altrincham, UK) and Microsoft Office Excel 2003 (Redmond, WA). Continuous variables were expressed as the mean $\pm$ standard error of the mean and tested for normal distribution. A paired *t*-test was used to compare the number of reflux episodes detected by the two methods if they followed a normal distribution; otherwise, a non-parametric test (paired Wilcoxon-signed rank test) was used. A *p*-value of <0.05 was considered to be significant. Linear regression analysis and correlation coefficient calculations were performed to assess the correlation between GOR

episodes and the patient's age as well as gastric residual at the end of the study. The agreement between the two methods of frame acquisition was evaluated using Bland–Altman agreement analysis [9], whereas the correlation between the number of GOR episodes recorded by each method was estimated using linear regression analysis.

RESULTS

Total number of gastro-oesophageal reflux episodes

All patients had reflux episodes that were detected by both techniques. A total of 2428 GOR episodes were detected using a 5-s acquisition technique and a total of 1228 GOR episodes were detected using a 60-s acquisition technique. The difference was statistically significant with $p < 0.001$. The total number of GOR episodes recorded by each method of frame acquisition in individual patients is shown in Figure 2. In our cohort, we were not able to find a relevant correlation between the total number of GOR episodes and the patient's age ($r = 0.17$ for 5-s frame acquisition and $r = 0.07$ for 60-s frame acquisition). However, the patients included in this study were preselected by their referring physician based on their symptoms, having a very high pre-test probability and not reflecting the true incidence of GOR among different age groups in the general population. Counterintuitively, no correlation was found between the total number of GOR episodes and gastric residual ($r = -0.07$ for 5-s frame acquisition and $r = -0.15$ for 60-s frame acquisition). The Bland–Altman plot showed a good agreement between the two methods (all values except one fell within the 95% limits of agreement; Figure 3b). The regression analysis revealed a linear correlation coefficient of 0.68 (Figure 3a),

Figure 1. Any number of gastro-oesophageal reflux episodes detected in the twelve 5-s frames corresponding to one 60-s frame counted as one episode.

Figure 2. Total number of gastro-oesophageal reflux (GOR) episodes as well as the number of high- and low-level GOR episode detected using 5-s and 60-s acquisition techniques in individual patients.

showing a moderate relationship between the total number of GOR episodes detected by two methods.

High-grade gastro-oesophageal reflux

The number of detected GOR episodes to the upper oesophagus was higher in most patients when the acquisition was performed at 5 s per frame than when it was performed at 60 s per frame (Figure 2). Overall, a total of 679 episodes of GOR to the upper oesophagus were detected using a 5-s acquisition technique. Only 183 of these episodes were labelled as being high-level GOR on 60-s acquisition frames (Figure 4), the difference being significant with $p < 0.001$. The average number of episodes of high-grade GOR per scan detected in different age groups is shown in Table 1. Linear regression analysis showed a low negative correlation between the number of high-grade GOR episodes and the patient's age ($r = -0.20$ for 5-s frame acquisition and $r = -0.33$ for 60-s frame acquisition; Figure 5a). There was a negligible relationship between the number of high-grade GOR episodes and gastric residual at 60 min ($r = -0.16$ for 5-s frame acquisition and $r = -0.10$ for 60-s frame acquisition; Figure 5b). 10 patients (representing 20% of our study population) had high-level GOR episodes that were detected only using a 5-s acquisition technique, leading to a different diagnosis in these subjects. Examples of such episodes are illustrated in Figure 6.

Low-grade gastro-oesophageal reflux

Overall, a total of 1749 episodes of GOR to the distal oesophagus were detected using a 5-s acquisition technique (Figure 4). Only 1045 of such episodes were detected on 60-s acquisition frames (these included also the high-level GOR episodes on 5-s frames counted as low level on 60-s frames). The difference proved statistically significant with $p < 0.001$. Although the total number of recorded GOR episodes to the distal oesophagus was much higher when a 5-s acquisition technique was used, individual cases with a higher number of low GOR episodes detected on 60-s frame acquisition were also encountered (Figure 2). This occurred when a significant number of GOR episodes were labelled as high level on 5-s frames but low level on 60-s frames.

The average number of low-grade GOR episodes recorded in different age groups is provided in Table 1. No linear correlation was found between the number of low-grade GOR episodes and the patient's age or between the number of reflux episodes and gastric residual at 60 min ($r < 0.20$ for both methods of frame acquisition).

DISCUSSION

The higher number of reflux episodes to both the lower and upper oesophagus detected by the 5-s frame

Figure 3. Linear regression analysis (a) and Bland-Altman agreement plot (b) for the total number of gastro-oesophageal reflux episodes detected by the two methods of frame acquisition.

acquisition indicates a higher sensitivity of this technique than the 60-s frame acquisition technique. At first, it might seem counterintuitive that a reflux episode seen on a 5-s frame is subsequently “wiped out” and is not visualised on a 60-s frame in conditions when the counts continue to add up. This is more likely to occur with brief GOR episodes (less than 5 s) and a relatively low number of radioactive counts. Although such episodes can be spotted clearly on 5-s acquisition frames, the activity subsequently becomes indistinguishable from intense scattered activity that progressively accumulates, thus resetting the background

level. In the current study, this led to missing the presence of high-grade episodes in 20% of scans and to a different diagnosis in these subjects. There was no distinct relationship between the total number of GOR episodes and the patient’s age; however, the subjects included in this study were preselected by their treating physician based on their clinical symptoms and did not reflect the incidence of GOR in the general population.

The intragastric volume could theoretically play a role in the pathogenesis of GOR; however, there are conflicting reports in the literature about the relationship

Figure 4. Total number of low- and high-grade gastro-oesophageal reflux episodes detected by 5-s and 60-s frame acquisition techniques.

of GOR and the gastric emptying rate [10]. In a study correlating gastric emptying and oesophageal pH impedance, Emerenziani et al [11] showed that the slower the emptying, the higher the pH and proximal extent of the refluxate. On the other hand, studies evaluating the intragastric distribution of food in patients with GOR disease and dyspepsia showed a significant negative correlation between the proximal gastric retention and the number of acidic reflux episodes, whereas total gastric emptying was similar in patients and controls [12]. In addition, the acquisition period is not well defined for the GOR studies, further complicating the interpretation. In our study, we were not able to find a direct association between the number of reflux episodes detected by either the technique of frame acquisition or the gastric emptying rate, regardless of age and refluxate level. These findings are consistent with prior reports showing no association between GOR and gastric emptying [10,13–16], suggesting that delayed gastric

emptying is not a major factor in the pathophysiology of GOR.

Since the number of 5-s frames ($n=720$ for 60 min of acquisition) is much higher than the number of 60-s frames ($n=60$), the time required to interpret the results may need to be taken into consideration, especially in a busy clinical setting. The frames can be easily scrolled for interpretation, and the physician has the option to choose the number of consecutive frames displayed simultaneously on the viewing monitor (this may vary depending on the reading workstation). Viewing all 5-s frames ($n=720$) can slightly increase the scan interpretation time (usually by 1–2 min) compared with viewing all 60-s frames ($n=60$). However, our results suggest that this minimal increase in scan interpretation time is justified by the additional information obtained in a large proportion of subjects. Specifying all individual frames with GOR may prove more time-consuming, but the option can be considered in selected cases (for example, for detecting subtle interval changes following therapy).

Study limitations

The protocol for GOR scintigraphy is not well defined, and other frame acquisition times such as 10, 15 or 30 s may also be used by different institutions. Such protocols have not been included in the current study and may require further investigation before standard recommendations are established. It is also known that changes in posture may affect GOR. Repeating the scan in a different body position or changing the patient's posture during scintigraphy acquisition could not be performed in this retrospective study but may represent an area of interest for further research. Differences in refluxate composition such as refluxate pH or gastric acid secretion may also need further attention.

Table 1. Gastric residual at 60 min and the average number of reflux episodes per scan detected in different age groups by the two methods of frame acquisition^a

Age group	Residual at 1 h (%)	High-grade GOR episodes		Low-grade GOR episodes	
		5-s frames	60-s frames	5-s frames	60-s frames
<1 year	50.6±4.4	18.9±2.6	6.3±1.6	34.1±2.1	22.6±2.5
1–10 years	58.4±4.0	11.9±2.4	2.8±0.7	35.2±1.7	20.5±1.6
≥11 years	49.1±13.6	11.3±4.0	0.8±0.8	35.5±4.8	19.5±2.7

GOR, gastro-oesophageal reflux.

^aValues are means±standard error of the means.

Figure 5. Linear regression plots showing the relationship between the number of high-grade gastro-oesophageal reflux episodes and the patient's age (a) as well as gastric residual (b).

CONCLUSIONS

Overall, the study has shown that the 5-s frame acquisition technique is a more sensitive method for detecting both high-grade and low-grade GOR than the 60-s frame acquisition technique. Inherently, the 60-s frame acquisition does not allow precise evaluation of the duration of brief GOR episodes at subminute intervals. In addition, brief GOR episodes with a relatively

low number of radioactive counts are frequently missed on 60-s acquisition frames, the activity being indistinguishable from intense background activity on these frames. Consequently, our results support the 5-s frame acquisition technique as a standard method for GOR scintigraphy acquisition. There was no correlation between the number of reflux episodes and the rate of gastric emptying.

Figure 6. Examples of high-level gastro-oesophageal reflux detected on 5-s frames (a) but not seen on 60-s frames (b).

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