Multiple Swallow Test for the Quantitative and Qualitative Evaluation of Esophageal Motility Disorders

Klaus Tatsch, Wilhelm Schroettle, and Carl-Martin Kirsch

Division of Nuclear Medicine, Department of Radiology, Klinikum Grosshadern, University of Munich, Germany

Esophageal motility was evaluated from the analysis of six consecutive swallows. A sum image was generated comprising the representative information of an entire study. Calculation of emptying rates and characterization of the bolus behavior was performed from the sum image and the single swallow data. In 86 patients investigated, liquid and solid-phase studies showed a remarkable variation of single swallow data in normals (relative variation coefficient for liquid: 10%, solid: 14%), which were even higher ($p < 0.001$) in patients with disorders (liquid: 31%, solid: 25%). As sum images compensate for this intra-individual variation, false-positive (liquid: 16%, solid: 25%) or negative single swallow findings (liquid: 36%, solid: 27%) are reduced. Qualitative analysis of condensed sum images provided characteristic image patterns representing different pathophysiologic aspects. Since the method introduced better discriminates between normal and pathologic function, it may enhance diagnostic accuracy.

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In 1972, Kazem (*1*) reported the use of a radiopharmaceutical and gamma camera to monitor swallowing. Since then, several scintigraphic techniques have been successfully established for the evaluation of esophageal motility (*2–9*) using quantitative parameters (*2,3,5,7*), functional imaging (*4,9*), or a combination and extension of these basic approaches (*6,8*). Usually these tests are performed with only one or two radiolabeled swallows. The findings of some previous studies, however, indicate that single swallows may show a considerable intra-individual variation (*10–12*). Thus, as suggested by Bartlett and coworkers (*13*), more than one swallow may be required to reliably diagnose or exclude esophageal motility disorders. To overcome this problem we developed protocols for acquisition and processing of multiple consecutive swallows, which permit a combined quantitative and qualitative evaluation of six swallows during a single investigation.

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For reprints contact: K. Tatsch MD, Division of Nuclear Medicine, Department of Radiology, Klinikum Grosshadern, University of Munich, Marchioninistr. 15, 8000 Munich 70, Germany.

MATERIALS AND METHODS

Patients

Esophageal scintigraphy was performed in 86 patients. Fifteen patients without evidence of esophageal disease according to their history and the results of clinical investigations were referred to as normal controls. Seventy-one patients suffered from diseases that are commonly associated with esophageal motility disorders: 19 patients with connective tissue disease (progressive systemic sclerosis, mixed connective tissue disease, dermatomyositis), 26 patients with insulin-dependent diabetes mellitus, 8 patients with gastroesophageal reflux, 5 patients with achalasia, and 13 patients with some other disorders as myasthenia gravis, esophageal spasm, anorexia nervosa, or dysphagia.

Esophageal Scintigraphy

Acquisition. The patients were studied in the supine position with a LFOV gamma camera connected to a commercially available computer system (Siemens MicroDelta). Esophageal transit studies were performed with six radiolabeled liquid and solid test boluses each. Data were recorded using a standardized dynamic acquisition protocol (240 frames; 0.8 sec/frame; byte mode; 64 × 64 matrix). The transit of liquid bolus was studied with water (10 ml per swallow, labeled with approximately 10 MBq of ^{99m}Tc-sulfur colloid each). Solid bolus investigations were performed with a baby paste prepared according to a standardized protocol: 20 g instant Alete Milch-Fertigbrei® were dissolved in 40 ml of water and administered in portions of 10 g per swallow, labeled with approximately 5 MBq of ^{99m}Tc-sulfur colloid each. Compared to the consistency of, for example, a compact gelatine bolus or cubes of chicken liver, the baby paste administered is more likely semi-solid in its nature. Its viscosity was adjusted in such a manner that it did not drop from the spoon. Normally a marked dispersion of the bolus during its esophageal passage cannot be observed.

During data acquisition, a radiolabeled test bolus was offered to the patient being investigated every 30 sec. He or she was asked to ingest the bolus by a single deglutition and to avoid swallowing for the next 30 sec until the next bolus was offered. The investigation with liquid was always performed prior to the one with solid boluses.

Processing. From each dynamic study, a condensed image was created, showing the six consecutive swallows in a space-time matrix. The procedure of condensation was confined to a user-defined region of interest comprising the esophagus from the pharynx to the lower sphincter. By this technique, the processing of radioactive events from undesired areas (e.g., oral cavity,

stomach) is markedly reduced. The method and algorithms used for image condensation were described previously (*6,9,14*). The creation and display of condensed images is schematically shown in Figure 1.

The raw version of a condensed multiple swallow study was then used for further processing. The start of each single swallow was defined manually (under visual control) or automatically (by searching for a marked rise in the count rate of pixels forming the upper rows of the condensed image) (Fig. 2A). Single swallows of a whole series then were standardized with respect to the determined starting points as schematically shown in Figure 2B. By this procedure, six condensed images were established, consisting of 32 columns (= frames) each. The starting point of a swallow was always set to the sixth column of an image because the count rates of the first five columns are used to calculate the mean residual activity prior to a swallow (see equation for the calculation of esophageal emptying rates). Finally the six standardized single swallow images were arranged consecutively (Fig. 2C) and by addition a condensed sum image was created, comprising the representative information of a whole multiple swallow study (Fig. 2D).

For quantitative evaluation, time-activity curves were derived from the sum and all six single swallow images. The curves were generated by plotting the count rates of the 32 columns assembled in each image. The count rate of each column was obtained by addition of its single pixel data. With all curves a three-point smoothing was performed. Esophageal emptying rates were calculated 12 sec after the swallow was initiated and 10 sec after the esophageal count rate had reached its maximum. Since there was no remarkable difference between the two values, we confined our data presentation to one, the 10-sec value. Quantitative data were evaluated for each single swallow as well as the sum image, representing a mean emptying rate for the whole study. To take into account that in severe motility disorders the esophagus may not be cleared from residual activity between consecutive swallows, a background (i.e., residual activity) correction was performed with the following equation:

$$\text{esophageal emptying (\%)} = \frac{cts_{max} - cts_{10\ sec}}{cts_{max} - cts_{mra}} \times 100$$

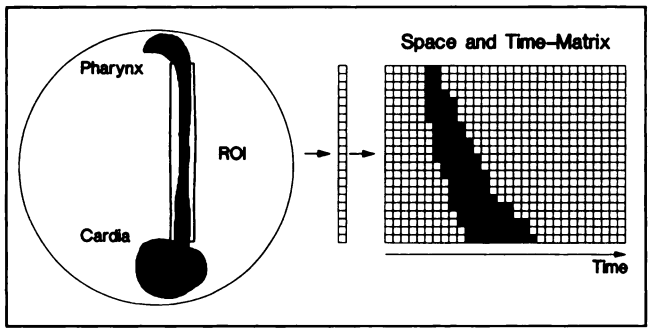

FIGURE 1. The figure schematically shows the generation and display of condensed images. In each consecutive frame of the study (n = 240), the information in an esophageal region of interest is compressed into a single column, displaying the distribution of the tracer from the pharynx to the cardia within a 0.8-sec interval. The columns obtained are consecutively arranged, thus generating a space and time matrix whose vertical and horizontal dimensions represent spatial and temporal activity changes, respectively.

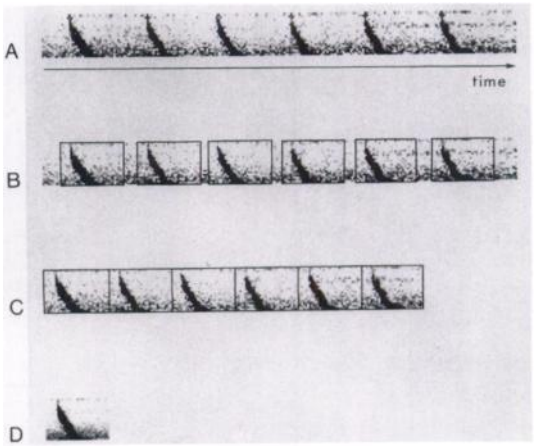

FIGURE 2. Generation of sum images from a multiple swallow study. (A) In the raw version of a condensed multiple swallow study, the starting point of each single swallow is marked manually or automatically (cursor = cross). (B) Single swallows are standardized with respect to their starting points. Six condensed images are created, consisting of 32 frames (= columns) each with the starting point set to the sixth frame. (C) Consecutive arrangement of the six standardized single swallow images. (D) Addition to a sum image which comprises the information of an entire multiple swallow study and is used for further quantitative and qualitative evaluation.

where

cts_{max} = maximal count rate observed in the columns of a condensed image.

$cts_{10\ sec}$ = count rate 10 sec after t_{max}.

cts_{mra} = mean residual activity calculated as mean count rate of the first five columns (= frames) prior to a swallow.

This approach explains that in particular cases the emptying rate of a single swallow may exceed the value of 100%, e.g., if residual activity from a preceding swallow will be cleared with the following one. In some cases of disturbed function, the 10-sec value could not be calculated because the maximum was not reached within 10 sec after the swallow was initiated.

Qualitative evaluation of esophageal function was performed by visual interpretation of the bolus behavior during its esophageal passage. Condensed sum images as well as the standardized single swallow images were analyzed with respect to the location of a disorder and the image patterns obtained (e.g., reflux, retrograde motion, cumulation, or oscillation of activity). The generation and processing of condensed images according to our protocol took approximately 5 min per study.

RESULTS

Sum Image Data in Normal Controls

In the 15 patients without esophageal abnormalities, the mean esophageal emptying rate derived from the sum image was 92% ± 6% s.d. for liquid and 93% ± 7% s.d. for solid bolus investigations. Based on these data, emptying rates of less than 80% (mean value − 2 s.d.) in the present study were defined as pathologic.

Count Rates

In standardized single swallow images of patients with normal function, maximal count rates between 140 and

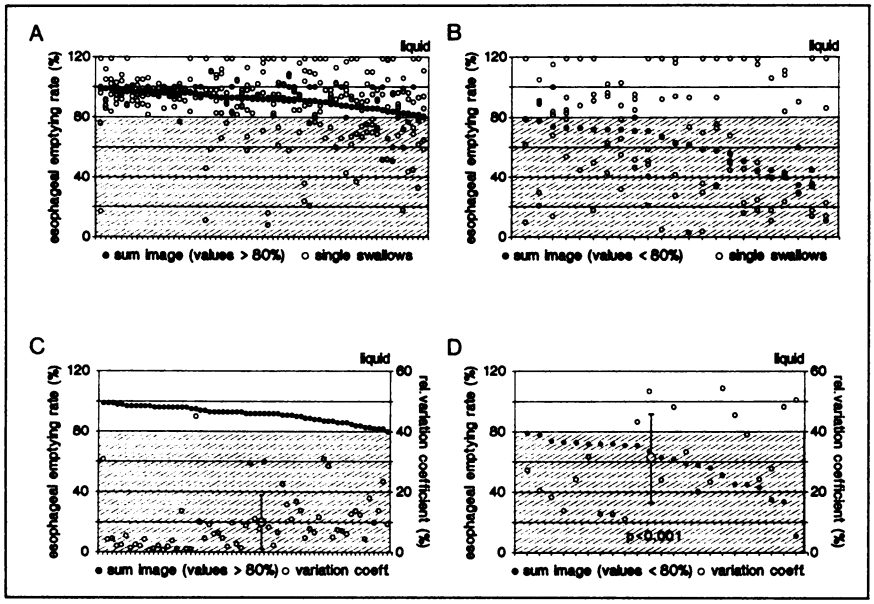

FIGURE 3. Sum image and single swallow data of the liquid-phase investigations. Esophageal emptying rates calculated for the sum image are plotted in descending order. Each mark on the ordinate represents one patient. The corresponding single swallow data to a sum image are shown in the same column. For esophageal emptying rates >100%, see explanations in the text. In normal function (defined by sum image values >80%) (A) as well as in patients with disorders (<80%) (B), single swallow data show a remarkable intra-individual variation. The relative variation coefficient calculated for the single swallow data of each patient show a significantly higher variation in patients with dysfunction (D) compared to those with normal emptying (C).

200 counts/frame (= column) and minimal rates of 10–30 counts/frame were obtained. In sum images of normal function, count rates of maximal 800–1200 cts/frame and minimal 80–180 cts/frame were observed. In patients with delayed emptying, the count rates/frame were higher compared to normals and varied considerably in dependence of the severity of the disorder (count rates of maximal 1200 cts/frame and minimal 500 cts/frame in single swallow images, and maximal 4000 cts/frame and minimal 2500 cts/frame in sum images, respectively).

Quantitative Evaluation

The sum image and single swallow data of the investigations with liquid and solid test boluses are summarized in Figures 3 and 4. In these figures, the esophageal emptying rates derived from the sum images are plotted in descending order. Each dot represents the value obtained for one patient. The single swallow data corresponding to a particular sum image are shown in the same column. Figures 3A and 4A comprise the findings for liquid and solid bolus studies in patients with normal sum image data (emptying rates >80%), Figures 3B and 4B summarize the results in patients with sum image data in the pathologic range (emptying rates <80%).

The findings in both liquid and solid bolus investigations show that single swallow data considerably differ from that obtained for the corresponding sum image. Patients with normal emptying in sum images showed a considerable number of pathologic single swallow data (liquid: 16%; solid: 25%). Normal single swallows were frequently observed in patients with a pathologic emptying rate in the sum image as well (liquid: 36%; solid: 27%).

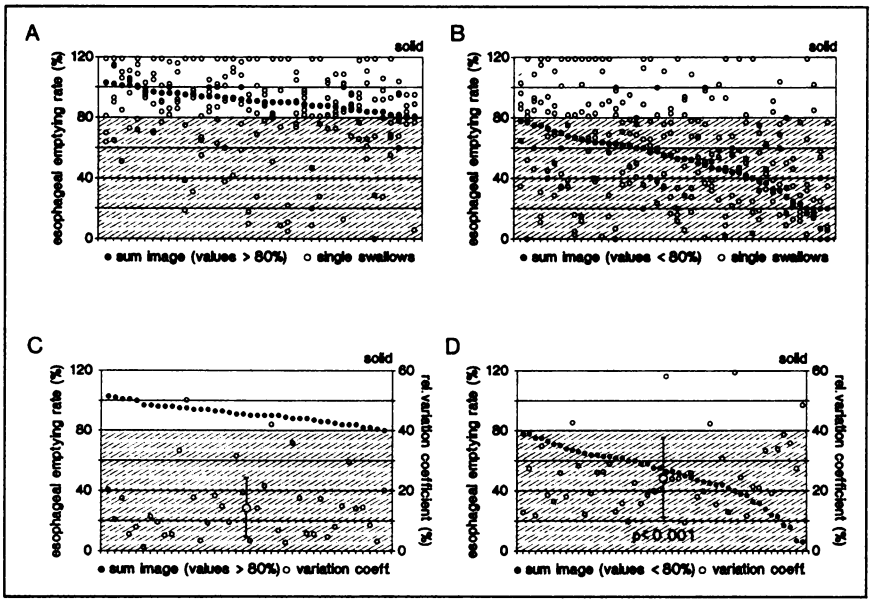

FIGURE 4. Sum image and single swallow data of the solid bolus investigations. Similar to the findings in liquid bolus studies (Fig. 3) single swallow data considerably differed from the corresponding sum image value (A,B). Again the intra-individual variation between the single swallows was more pronounced in patients with dysfunction (B,D) compared to those with normal emptying (A,C).

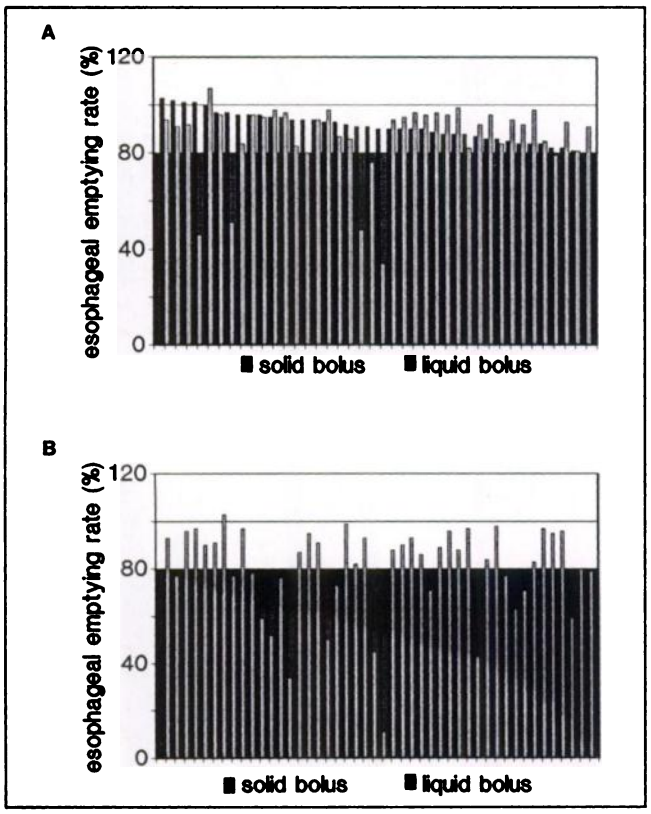

FIGURE 5. By comparing the sum image data of the solid with those of the liquid-phase study in the same patient, a tolerable agreement (concordant findings in 85%) was obtained in patients with normal emptying (>80%) (A). In pathologic solid bolus studies (B), the corresponding test result for liquid differed considerably showing regular emptying in 59% of the cases.

As a parameter for the intra-individual variation of swallowing, the relative variation coefficient was calculated for the single swallow data of each patient and plotted in Figure 3C-D (liquid bolus) and 4C-D (solid bolus). In patients with normal findings in the sum image, the mean variation coefficient was 10% ± 9% for studies with liquid (Fig. 3C) and 14% ± 11% for solid bolus investigations (Fig. 4C). In studies with pathologic results in the sum image, the relative variation coefficient of the single swallow data was 31% ± 14% for liquid (Fig. 3D) and 25% ± 12% for solid bolus investigations (Fig. 4D). These values are significantly higher ($p < 0.001$; Student's t-test) compared to those in patients with normal findings in the sum image.

Figure 5 compares the sum image data of the solid with the liquid bolus test in the same subject. Patients with a normal solid bolus study showed concordant findings with liquid (emptying rates >80%) in 85% of the cases (Fig. 5A). In pathologic solid bolus studies, however, the corresponding test results for liquid were considerably different, showing frequently (59%) normal emptying rates (Fig. 5B).

Qualitative Evaluation

As shown by representative examples in Figure 6 and 7, the condensed sum image provides excellent information about the bolus behavior during its esophageal passage. In a condensed sum image, motility disorders appear in proportion to the extent, location, and frequency of their manifestation during the multiple swallow investigation. Thus, the sum image accentuates the predominant finding obtained in a series of swallows and delivers characteristic image patterns which represent different pathophysiologic aspects of dysfunction as shown by some examples (Figs. 6 and 7). Besides the typical pattern of normal bolus transit (Fig. 6A) episodes of gastroesophageal reflux, retrograde bolus motion (Fig. 6B), activity cumulation in hypo- or aperistalsis (Fig. 6C), oscillatory bolus movements as in esophageal spasm (Fig. 6D), or the characteristic main location of a disorder (Fig. 6E) are reliably identified. Furthermore, the condensed sum image not only provides representative and properly weighted information in pronounced dysfunction, but also in minor disorders (Fig. 7A) and particularly in normal variation of swallowing (Fig. 7B), such as aberrant swallows or some pitfalls as extra swallows or deglutitive inhibition.

DISCUSSION

Recent investigations suggest that intra-subject variation between repetitive swallows may be significant (*2,3*). Aberrant swallows in normal controls (*10–12,15*) may compromise the distinction of normal from pathologic findings, especially if the latter are mild. Furthermore, poor reproducibility of esophageal transit studies has been reported for both normal controls as well as patients with motility disorders (*13*). To improve esophageal scintigraphy Klein et al. (*16*) suggested the development of protocols for multiple swallow studies. These authors further stated that such repetitive investigations are routine in esophageal manometry and would appear indicated in esophageal scintigraphy.

We have developed a scintigraphic approach which fulfills the demands for a multiple swallow test. The acquisition and processing protocols permit combined quantitative and qualitative evaluation of multiple consecutive swallows during a single investigation using a sum image derived from continuously recorded single swallow data. As suggested by Bartlett et al. (*13*) and confirmed by our own experience, the analysis of six swallows provides sufficient data to establish an accurate diagnosis. An evaluation of more swallows (e.g., eight to twelve) as described by us previously (*17,18*) did not result in noteworthy additional information. To investigate the intra-individual variability in a multiple swallow study, we evaluated quantitative parameters for the sum image and each single swallow. Single swallow data have shown to vary considerably in both liquid as well as solid bolus studies. In subjects with regular emptying in the sum image, 16% (liquid) and 25% (solid) of the single swallow data were outside of the normal range. This potential for false-positive results may effectively be overcome using sum image data from repetitive swallows. In patients with mo-

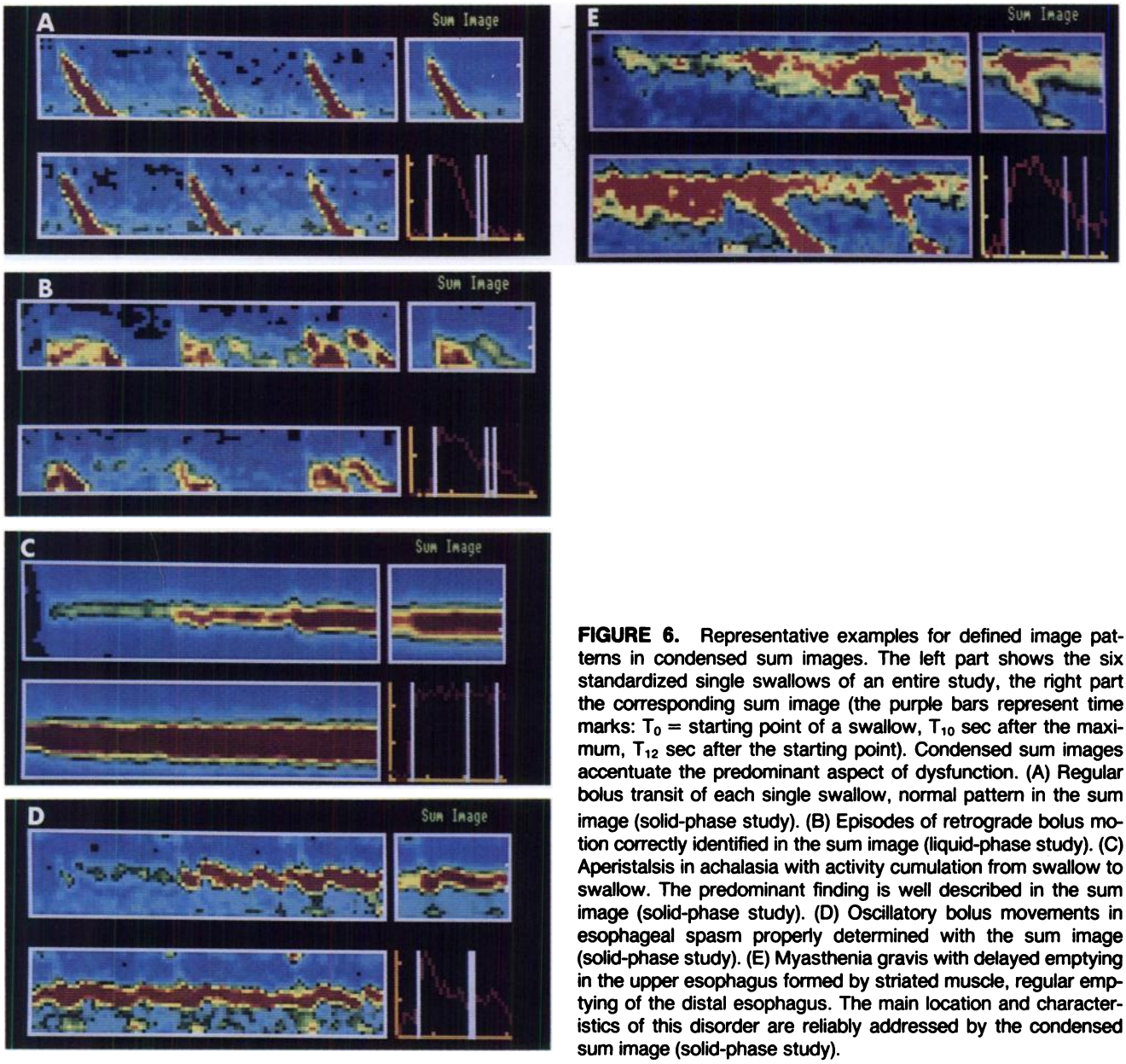

FIGURE 6. Representative examples for defined image patterns in condensed sum images. The left part shows the six standardized single swallows of an entire study, the right part the corresponding sum image (the purple bars represent time marks: T_0 = starting point of a swallow, T_{10} sec after the maximum, T_{12} sec after the starting point). Condensed sum images accentuate the predominant aspect of dysfunction. (A) Regular bolus transit of each single swallow, normal pattern in the sum image (solid-phase study). (B) Episodes of retrograde bolus motion correctly identified in the sum image (liquid-phase study). (C) Aperistalsis in achalasia with activity cumulation from swallow to swallow. The predominant finding is well described in the sum image (solid-phase study). (D) Oscillatory bolus movements in esophageal spasm properly determined with the sum image (solid-phase study). (E) Myasthenia gravis with delayed emptying in the upper esophagus formed by striated muscle, regular emptying of the distal esophagus. The main location and characteristics of this disorder are reliably addressed by the condensed sum image (solid-phase study).

tility disorders sum image data also help to discriminate between normal and pathologic findings. Normal single swallows were found at the mild end of the spectrum and also in severe abnormalities (liquid: 36%, solid: 27%) which may appear to be regular emptying. Thus, our findings confirm the intra-individual variation of swallowing and underline the fact that multiple swallow protocols are a useful approach to overcome it.

In studies with delayed emptying, the relative variation coefficients for single swallow data were significantly ($p < 0.001$) higher compared to those in normal function. These findings suggest that in patients with swallowing disorders single swallow data are even less reliable to establish a correct diagnosis or obtain the appropriate extent of functional impairment.

Comparing the sum image data of the solid with the liquid tracer study in the same subject, we observed a tolerable agreement (concordant findings in 85%) in patients with normal emptying. Patients with disorders, however, often showed discrepant findings: In 59% of pathologic solid bolus studies, for example, the emptying of liquid was still normal. This observation indicates increased sensitivity of solid compared with liquid bolus investigations. As the results of solid bolus studies better correlated with clinical findings as well, there also is evidence for improvement in specificity. We are aware of the problems concerning the use of solid test meals (e.g., constant preparation to obtain reproducible consistency, possibility of bolus dispersion depending on its preparation and composition, comparison with other investigations using different medium for solid phase tests, etc.). Nevertheless our findings suggest that multiple swallow tests performed with solid tracers may be helpful to further enhance diagnostic accuracy, since we have found that

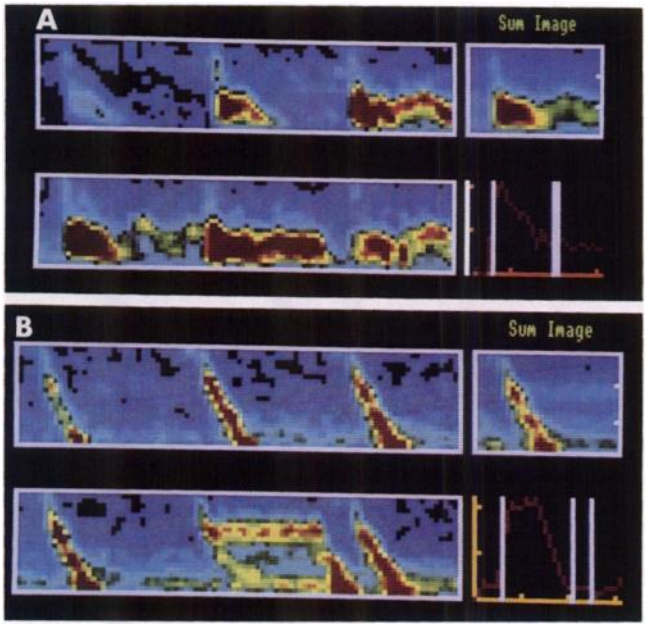

FIGURE 7. Value of condensed sum images in identifying minor disorders and normal variations of swallowing. (A) Mild esophageal dysfunction in a patient with progressive systemic sclerosis, showing delayed emptying in the distal esophagus in some single swallows only. Representative finding of the entire study in the condensed sum image (liquid-phase study). (B) A single aberrant swallow in a series of normal ones as an example for normal variation of swallowing. The condensed sum image properly puts the single aberrant swallow into perspective (solid-phase study).

swallowing disorders are adequately characterized by the use of solid boluses, we do not maintain the necessity to perform both liquid and solid bolus studies in each patient any longer.

The advantages of condensed imaging techniques to characterize precisely the fate of a labeled test bolus passing the esophagus have been previously shown (*6,8,9,12,14*). The particular benefit of our approach is that condensed images generated from repetitive swallows also take the intra-individual variation into account. These sum images encompass the single swallow findings of an entire study proportional to their appearance, thus providing patterns that more precisely identify the predominant aspect of dysfunction. This helps not only to distinguish various disorders but also to classify correctly normal function despite the presence of, for example, single aberrant swallows (Fig. 7B) or diagnostic pitfalls such as extra swallows or deglutitive inhibition. The diagnostic approach may reduce potential false results as described for single swallow tests by Blackwell et al. (*19*). Mughal and coworkers (*20*) found only a poor sensitivity (44%) and specificity (71%) for scintigraphy performed with a single swallow test compared with manometry analyzing at least ten wet swallows. As our data suggest, the two methods would have shown a better agreement, if performed with a corresponding number of swallows each.

In conclusion, we have elaborated a method to process multiple consecutive swallows for combined quantitative and qualitative evaluation of esophageal motility disorders. Sum image data that encompass the information of an entire study helps to compensate the intra-subject variation of swallowing in both liquid- and solid-phase investigations. Since this helps to better discriminate between normal and pathologic findings, our approach may enhance diagnostic accuracy in the evaluation of the spectrum of normal esophageal motility and that of its disorders.

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