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Procedure for the semi-automatic detection of gastro-oesophageal reflux patterns in intraluminal impedance measurements in infants

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Abstract

The diagnosis of gastro-oesophageal reflux (GOR) is of great interest for paediatric gastroenterologists. pH monitoring is the commonly used procedure for GOR diagnosis but a major amount of postprandial GOR is missed due to the mostly non-acidic gastric contents in infants. The multiple intraluminal impedance technique is based on the recording of the impedance changes during bolus transport inside the oesophagus. It is the first method which allows the pH-independent, long-term registration of GOR. The use of the impedance technology in clinical practice has been limited so far by the time-consuming, visual evaluation of the impedance traces.

The new approach of a semi-automatic analysis of the impedance measurements allows the automated detection of reflux patterns. It is based on event marking and an optimised feature description of the impedance traces combined with a fuzzy system for pattern recognition. The classifier is developed and tested on 50 investigations in infants. Compared to the comprehensive, multiple visual evaluation the achieved precision is 75% sensitivity and 48% positive prediction. In comparison to a single visual evaluation the analysis of the automatically proposed patterns corresponds to a 96% reduction of the evaluation time with no loss of precision. Thus the applicability of the impedance technology is enhanced significantly. A combined measurement of pH and impedance gives evidence about the occurrence of GOR, its pH and the acidic exposure of the oesophagus. © 1999 IPEM. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Gastro-oesophageal reflux; GOR; Infant; Fuzzy system; Pattern recognition; ANFIS; Intraluminal electrical impedance; pH monitoring

1. Introduction

The recognition of gastro-oesophageal reflux (GOR), i.e. the regurgitation of gastric contents into the oesophagus, is of great interest for gastroenterologists. GOR eventually occurs in all individuals, it becomes pathological when it causes relevant symptoms. GOR may cause heartburn, oesophagitis and respiratory diseases. Known consequences of GOR in infants are irritability, failure to thrive and aspiration pneumonia. GOR may also provoke reflectory apnoea when the gastric contents rises up to the pharynx [1–3, 4, pp. 27–50]. In paediatrics GOR is considered to be one of the possible reasons for apparent life-threatening events (ALTE) and the sudden infant death syndrome (SIDS). Investigations show that 47% of the infants with ALTE suffered from GOR [5] and that about 10% of the victims of SIDS had apnoea caused by GOR [6–8].

pH monitoring, the intraluminal measurement of the pH value close to the lower oesophageal sphincter, is considered the 'gold standard' in the diagnosis of GOR in infants [9]. A pH below 4.0 inside the oesophagus is considered to be indicative of GOR according to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition [10] (ESPGHAN). However, the gastric contents in infants is neutralised by the milk formula for a period of one to two hours after each feeding [11]. Consequently a major amount of reflux episodes are concealed from pH monitoring, due to their non-acidity [12].

The recently developed procedure for the recording of gastrointestinal motility by means of multiple, intraluminal electrical impedance measurement is based on the

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registration of changes in the electrical impedance during the passage of a bolus [13]. Based on the fact that food, saliva and digestive enzymes are better electrical conductors than the muscular wall of the oesophagus and the surrounding tissues, a significant and specific change in the impedance traces can be observed for each propulsive or retrograde flow [14]. Recent studies verified the capabilities of the impedance technology to visualise oesophageal transport patterns such as swallows, liquid or gas reflux [15–17]. Consequently, the impedance method allows the detailed, long-term, pH-independent registration of GOR and shows a significantly higher sensitivity for the detection of GOR in infants compared to pH monitoring [12].

So far the analysis of the impedance traces has been a time consuming procedure. The physicians had to carry out a visual scoring to eliminate artefacts and to identify reflux episodes. For a detailed visual analysis of the impedance traces, consecutive frames of 10–15 s are presented to the physician. On average the physician has to analyse about 1800 frames for a 6-h measurement. The necessary evaluation time ranges from 4 to 8 h depending on the experience of the investigator.

The aim of the semi-automatic procedure is the realisation of a high sensitivity for the detection of GOR and the reduction of the evaluation time. The presentation of a reduced set of frames, which are scored as reflux patterns by the pattern recognition system, will enable the physician to execute an accelerated evaluation of the investigations.

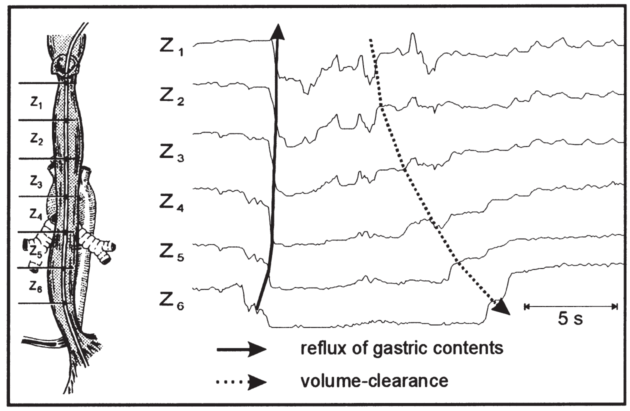

Fig. 1. Example of a GOR recorded by intra-oesophageal impedance measurement ($Z_1 - Z_6$: impedance channels 1–6, Z_1 proximal, Z_6 distal).

2. Methods and materials

The study is based on investigations in 50 infants (32 males, 18 females), median age 72 days, range 6–220 days. All patients showed clinical evidence of GOR or respiratory problems such as aspiration pneumonia, wheezing or recurrent coughing. The protocol for the recording had been approved by the Ethics Committee of the Medical Faculty of the Aachen University of Technology, Germany. All measurements were performed after informed consent had been obtained from the parents.

2.1. Measuring technique

For the measurement a flexible catheter with an outer diameter of 1.8 mm was used. The catheter was equipped with seven electrodes formed by metallic cylinders, separated by a distance of 1.5 cm (Fig. 1). The impedance was derived bipolarly between adjacent electrodes. Thus, the movement of oesophageal content was registered by six differential impedance measurements over a length of 9 cm. For additional data the catheter was provided with a pH antimony electrode in between the fifth and sixth impedance electrodes, so that monopolar pH monitoring could be carried out simultaneously. The external reference electrode for the pH monitoring was placed on the abdomen.

The catheter was introduced nasally, so that the pH electrode resided 3 cm above the gastro-oesophageal junction. This position was confirmed by fluoroscopy. All signals were recorded with a sampling rate of 50 Hz. The mean duration of the measurement procedure was 6 h. All patterns were recorded with the help of a computer-based system for data acquisition (PIAS 8, Helmholtz-Institute, Germany) using the software package MOT (Helmholtz-Institute, Germany).

The measurement principle of the multiple, intraluminal impedance procedure implies that the registration of propulsive and retrograde flow inside the oesophagus is possible. However, it has to be taken into account that the mean value and the amplitude of the impedance signal depend on the conductivity of the gastric contents, the surrounding tissues and the position of the catheter. As these parameters vary during an investigation, only short-time changes of the impedance signals are considered for the detection of GOR. According to these restrictions the main criterion for the distinction between GOR and other registered events has to be based on the transport direction [13]. Furthermore, an automated evaluation should be independent of the duration of GOR, which varies depending on the pathophysiological condition of the patient.

2.2. Visual evaluation of GOR

The typical pattern of a GOR is shown in Fig. 1. An empty oesophagus is characterised by a high impedance value in each channel. In correspondence with the reflux of gastric contents into the oesophagus the impedance in the channels decreases and remains on a low level as long as the measuring segment is filled with gastric contents. The transport velocity can be detected by the time delay between the adjacent channels. The maximum height reached by the gastric contents during GOR can be derived from the number of channels showing the typical impedance decrease. The physiological process of oesophageal reflux-clearance is performed by a contraction wave running from proximal to distal, propelling the gastric contents back into the stomach (Fig. 1). After the volume-clearance in the segment, the recorded impedance in the corresponding channel returns to the initial value.

The analysis of an investigation is carried out as a visual examination of the impedance patterns. A sliding frame is moved along the data-stream and the signals are evaluated according to the following criteria derived from the measurement principle:

- The GOR has to start with a decrease of the impedance in the distal impedance channel.
- The reflux pattern has to be detected at least in the two most distal impedance channels.
- The decrease in impedance can be observed in higher situated channels corresponding to the height reached by the gastric contents.

The task for the physician consists of distinguishing reflux patterns from swallows or artefacts due to patient movement. To achieve a high rate of detected GOR a thorough evaluation of the impedance signals is carried out by up to five specialists. All refluxes detected by different specialists are combined and considered as reference for the evaluation of the semi-automatic procedure for detection of GOR. 2076 reflux episodes were detected and their volume-clearances were determined. The analysis of the mean pH measured during these episodes showed 210 GOR with pH≤4; 1769 GOR with 4<pH<6.8; 66 GOR with pH≥6.8; the pH of 31 reflux episodes was not determined due to technical reasons.

2.3. Automated detection of GOR

The proposed pattern recognition algorithm is outlined in Fig. 2. First a pre-processing is carried out, which allows the detection of phases with transport activity inside the oesophagus. These periods, called 'episodes of interest' are described by a set of features which allows the characterisation of the direction of transport and the shape of the signal. To distinguish between reflux episodes and other events, a fuzzy classifier is defined. The fuzzy system is optimised using a Neuro-Fuzzy approach based on adaptive network-based fuzzy inference systems (ANFIS) [18,19].

In the following discussion the term 'reflux' is used to describe episodes which correspond to a GOR detected by the visual analysis; the term 'event' is used for all other alarms detected by the algorithm, such as swallows, belches and artefacts due to movements.

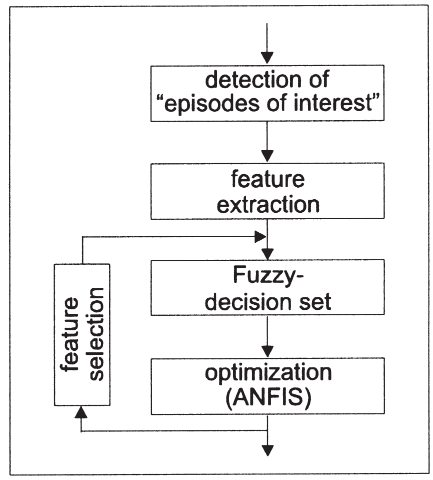

Fig. 2. Block diagram for the detection of GOR in intraluminal impedance measurements.

2.3.1. Marking of 'episodes of interest'

Before transforming the measured impedance signals into a feature representation, the signals are scanned for periods of oesophageal transport (Fig. 2). Corresponding to the measurement principle each transport is related to a drop in impedance. Consequently, a pre-processing which separates refluxes and events from phases without activity inside the oesophagus may reduce the computing time considerably.

In accordance with the given requests for GOR in the impedance traces each reflux must be observed in the most distal impedance channel in the oesophagus so that the application of the pre-processing is limited to this channel.

The method introduced relies on a differentiating filter algorithm applied to the impedance signal (Fig. 3). First the impedance signal is low pass filtered by a discrete butterworth filter with a cut-off frequency of 1.3 Hz and a filter order of 10. A differentiation with a time gap of ΔT=3 s is realised to detected steep as well as moderate gradients of drops in impedance. Afterwards a moving average filter is implemented (n=150) and the local minimum is detected. This local extreme value finally corresponds to the maximum rate of change of the original impedance signal. The degrees of freedom as the time delay for the differentiation, the cut-off frequency and the order of the applied filters are adapted in the sense of a maximum sensitivity related to the detection of reflux patterns.

A restricted set of 'episodes of interest' at $T=T_{alarm}$ results from this procedure. All episodes are characterised by a decrease in the impedance in the most distal impedance channel. However, the detected episodes are marked regardless of the direction of transport, because they are based on the information given by a single impedance channel. For a more precise description of

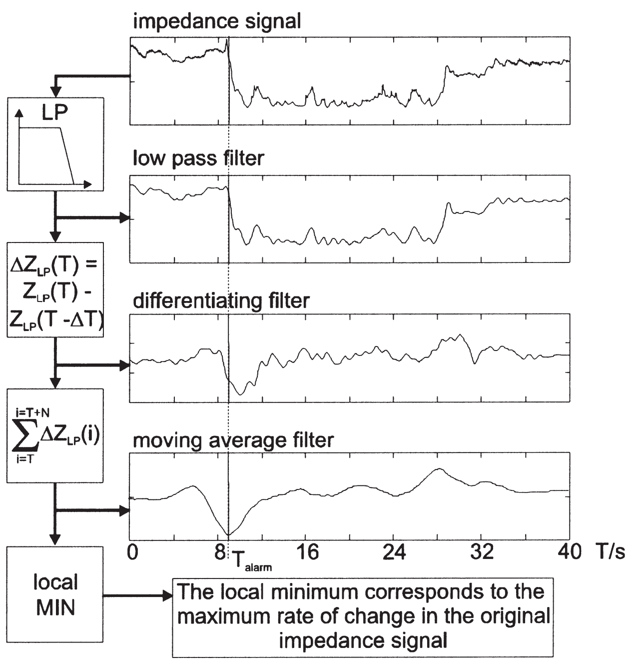

Fig. 3. Filter design for the marking of 'episodes of interest'.

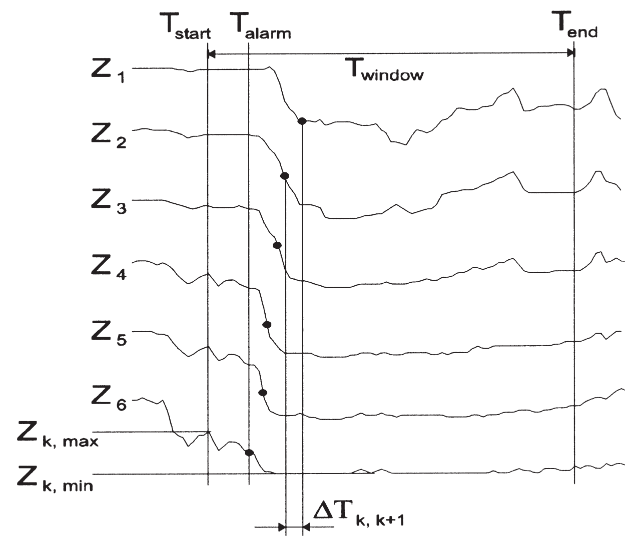

Fig. 4. Parameters to detect the typical characteristics of GOR measured by intraluminal impedance measurement.

these episodes of interest a feature representation is developed.

2.3.2. Feature extraction

The feature set tries to reproduce the criteria on which a manual scoring of the multiple, intraluminal impedance traces is based, and to transform them into different features (Fig. 2). All features are calculated in the vicinity of the alarm belonging to each episode of interest (T_{alarm}). The time window is defined by $T_{\mathrm{alarm}}-T_{\mathrm{start}}\leq T_{\mathrm{alarm}}\leq T_{\mathrm{alarm}}+T_{\mathrm{end}}$, the extreme values for each channel ($Z_{k,\mathrm{min}}$, $Z_{k,\mathrm{max}}$, with k = number of the impedance channel) are determined in the defined time window (Fig. 4). For a reflux pattern it is expected that the maximum impedance is detected before the minimum, thus impedance channels which do not meet this criterion were ignored for the calculation of the features.

The implemented features can be divided into two groups containing deterministic and statistical information. The definition of GOR is based on the direction of transport from distal to proximal. Consequently a set of features describing the time delay of the drop in impedance between adjacent channels is calculated ($\Delta T_{k,\,k+1}$, Fig. 4). This subset is calculated by means of the detection of the time for a 50% impedance decrease for each channel (features X_1-X_5; T_{start}=0.5 s; T_{end}=4.5 s).

The second type of features is based on the statistical characteristics of the investigated time window, this type of information is essential to distinguish refluxes from artefacts due to movement or breathing. Different features describing the shape of the impedance traces in the vicinity of the alarm are developed:

- To give an estimate of the impedance change in the oesophagus during the given alarm the ratio of the amplitude change to the local maximum amplitude is calculated (feature X_6; T_{start}=0.5 s; T_{end}=4.5 s; Fig. 4).

$$X_6=\sum_{k=1}^{6}\frac{Z_{k,\mathrm{max}}-Z_{k,\mathrm{min}}}{Z_{k,\mathrm{min}}}$$

- To obtain information on the distribution of the amplitudes inside the considered time window the histograms before and after the given alarm are calculated. Two features derived from these histograms (Hist) are extracted (features X_7, X_8; T_{start}=3 s; T_{end}=15 s). Each histogram is divided into 20 containers, and to summarise the information given by the histogram each container is linearly weighted. Only the three distal impedance channels are considered due to the limited height reached by some GOR.

$$X_7=\sum_{k=4}^{6}\left\{\sum_{i=1}^{20} i\cdot\left[\mathrm{Hist}_i\left(\frac{Z_k-Z_{k,\mathrm{min}}}{Z_{k,\mathrm{max}}-Z_{k,\mathrm{min}}}\right)\right]_{T=T_{\mathrm{alarm}}-T_{\mathrm{start}}}^{T=T_{\mathrm{alarm}}}\right\}$$

$$X_8=\sum_{k=4}^{6}\left\{\sum_{i=1}^{20}(20-i)\cdot\left[\mathrm{Hist}_i\left(\frac{Z_k-Z_{k,\mathrm{min}}}{Z_{k,\mathrm{max}}-Z_{k,\mathrm{min}}}\right)\right]_{T=T_{\mathrm{alarm}}}^{T=T_{\mathrm{alarm}}+T_{\mathrm{end}}}\right\}$$

- Further statistical information is drawn from the mean value (features X_9-X_{14}; T_{start}=0.5 s; T_{end}=4.5 s) and the standard deviation (features $X_{15}-X_{21}$;T_{start}=0.5 s; T_{end}=4.5 s) in each channel inside the window considered.

2.3.3. Fuzzy decision set

Introduced in 1965 by Zadeh [20], fuzzy sets today are a commonly used tool in pattern recognition. The advantages of fuzzy sets as linguistic variables and the intuitive definition of decision rules suggest their use for reflux detection. Especially in view of the extremely unfavourable ratio of refluxes to events of approximately 1:30, the introduction of expert knowledge instead of a fully automatic training for the design of the pattern recognition system appears advisable.

For each examined feature combination a fuzzy set was defined, using a Sugeno-type fuzzy inference system and Gaussian membership functions [21].

2.3.4. *Optimisation using ANFIS*

To optimise the membership functions and the output of the fuzzy set a Neuro-Fuzzy algorithm was used. The approach of an adaptive network-based fuzzy inference system combines the advantages of fuzzy sets and neural networks. Recently it was shown that neural networks and fuzzy sets can be described by a common framework [18,22,23]. This allows the representation of the fuzzy set as a neural network which can be trained by the application of the back-propagation algorithm and the least-squared method [19]. The defined fuzzy set has been trained using ANFIS as a tool for the automatic optimisation of the used fuzzy classifier.

2.3.5. *Feature selection*

The objective of the feature selection is the determination of a reduced set of features which allows the classification of the episodes of interest into refluxes and false alarms.

The sensitivity, the percentage of detected GOR and the positive prediction, together with the percentage of correctly given alarms, are chosen as indicators to measure the quality of the pattern recognition system. To give a visual representation of the achieved accuracy a Relative Operating Characteristic (ROC) and the crossplot of positive prediction and sensitivity are generated (Fig. 5).

The design of the pattern recognition system proceeds as an iterative algorithm (Fig. 2). The transport direction is considered as the main characteristic to distinguish reflux episodes from events. Therefore, a fuzzy decision set based on the five features (X_1-X_5) describing the time delay between adjacent channels for a physical transport is chosen as first iteration.

To add further features a bottom-up strategy is chosen. Each remaining feature (X_6-X_{21}) is separately integrated to the fuzzy decision set and tested with regard to the achieved improvement concerning the accuracy of the classifier. The feature which yields the highest improvement is selected. Additional features are integrated until the addition of further features does not result in a more precise classification.

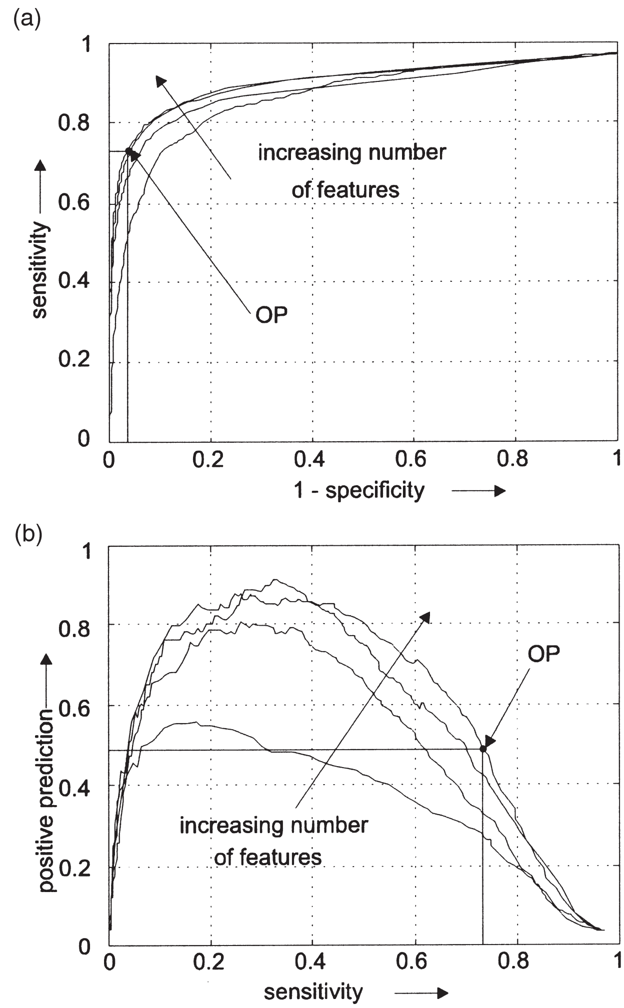

Fig. 5. (a) Relative Operating Characteristic (ROC) of the fuzzy pattern recognition system; (b) crossplot of positive prediction and sensitivity; OP: operating point (all data are calculated as mean per patient).

3. Results

Both procedures, the visual analysis and the automated detection of GOR, are evaluated on the cumulative data of 50 infants, all presented results represent the mean values for a single patient.

A 6-h measurement contains 42 reflux episodes on the average detected by the combined multiple visual evaluation of the impedance traces by different experts. In comparison a single visual evaluation of the approx. 1800 frames of 10–15 s each, identifies only 30–75% of these episodes, the positive prediction ranges from 30 to 90%. The quality of the result differs considerably depending on the experience and the concentration of the expert.

The procedure for the semi-automatic detection of GOR consists of two steps. Firstly, 'episodes of interest' are defined to detect oesophageal transport. The precision achieved for GOR detection is 96.5% sensitivity

Table 1
Result of the marking of 'episodes of interest' (mean per patient)

No. of refluxes (after multiple visual evaluation)	42
No. of refluxes (after detection of 'episodes of interest')	40.5
No. of events (after detection of 'episodes of interest')	1203
Total no. of 'episodes of interest'	1243.5
Sensitivity	96.6%
Positive prediction	3.3%

and 3.3% positive prediction (Table 1). Due to the large number of false alarms (n=1203) a visual evaluation would still require a large amount of time so that in a second step an enhanced automation of the pattern recognition process is mandatory.

The results achieved with the optimised fuzzy model for pattern recognition are calculated using cross-validation [24]. The available data are divided into a test and a learning set containing 25 patients each. A classifier is trained on each of the two data sets and tested on the other. The classification result represents the mean value for both systems (Table 2). The final set-up of the fuzzy classifier consists of eight features (X_1-X_5, X_6, X_7, X_{10}) as input values. The addition of further features does not improve the classification result on the test set.

The operating point is chosen corresponding to the maximum sensitivity of 75% achieved by a single evaluation of a human expert. A sensitivity of 75% (±17) comes along with a positive prediction of 48% (±16) [Fig. 5(b)]. This corresponds to a specificity of 97% [± 3.5; Fig. 5(a)] for the pattern recognition system (Table 2). Compared to the visual analysis, the evaluation of the 1800 frames can be replaced by the analysis of 65.5 frames in the average. 31.5 of these frames contain reflux patterns. This means a reduction of 96% of frames to evaluate without a loss of sensitivity compared to the single visual evaluation.

4. Discussion

The fuzzy classifier represents only one pattern recognition approach out of a wide variety of classification algorithms. However, the tasks resulting from the properties of the classification problem correspond to the characteristics of the chosen classifier. These properties firstly consist in an unfavourable ratio of reflux episodes to events as result of the detection of the episodes of interest. Secondly, the features of both classes overlap caused by the disturbance of the impedance signals during movement. The proposed approach corresponds to these requests by the introduction of a priori knowledge derived from the distribution of each feature. Consequently, the iterative learning process starts from a convenient initial configuration speeding up the convergence of the learning process to an optimal or near-optimal point [25].

The comparison of the results from reflux detection achieved by impedance measurement and by pH monitoring shows significant differences. As shown in earlier studies [12] the impedance measurement allows the detection of GOR independent of its pH. The evaluation of the simultaneously recorded pH signal shows that only 16.1% of all detected reflux episodes had a minimum pH<4.0. The analysis of the pH-signal according to the standard protocol [10] led to a sensitivity of 50.3% and a positive prediction of 52.6% for the detection of acid reflux episodes. That corresponds to a sensitivity of 8.1% for the overall detection of reflux episodes. This demonstrates that pH monitoring provides insufficient information about the overall occurrence of GOR in infants. However, it yields good results in the diagnosis of GOR especially in combination with additional parameters as the 'oscillatory index' or the 'area under pH 4.0' [26,27].

These results emphasise that the detection and consequently the diagnosis of GOR in infants could be significantly improved by the use of a combined measurement procedure as proposed by Skopnik [12]. The combination of impedance measurement and pH monitoring can be realised without additional patient strain by using a combined catheter carrying impedance electrodes and an integrated pH sensor. The combined measurement provides information about the occurrence of GOR independent of its pH and about the acidic exposure of the oesophagus.

The visual evaluation of the long-term intraluminal impedance measurements is extremely time-consuming. The distinction of reflux episodes from artefacts, such as periods of crying or movements, requires a high level of concentration and knowledge. Our results indicate that the chosen approach of a fuzzy classifier combined with an automatic learning algorithm (ANFIS) represents a robust and suitable method for the detection of GOR in infants. Consequently, the long-term applicability of the multiple, intraluminal impedance measurement is no longer impeded by the time-consuming visual analysis. The adaptation of the procedure presented to other measurement applications, e.g. the measurement of GOR in adults, is possible. The different steps of the auto-

Table 2
Result of the pattern recognition system based on eight features after optimisation for a selected sensitivity of 75% (mean per patient)

Classified/true	Reflux patterns	Events
Reflux patterns	31.5	9
Events	34	1169

mated GOR-detection need to be adjusted but the general set-up could be maintained.

Nevertheless, it remains to be seen whether the reflux episodes detected by a semi-automatic procedure lead to the same diagnostic conclusions as the results found by a visual scoring.

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