

# Dysphagia in Children with Esophageal Atresia: Current Diagnostic Options

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## Abstract

Dysphagia or swallowing disorder is very common (range, 15–52%) in patients with esophageal atresia. Children present with a wide range of symptoms. The most common diagnostic tools to evaluate esophageal dysphagia, such as upper barium study and manometry, aim to characterize anatomy and function of the esophageal body and the esophagogastric junction (EGJ). Using these technologies, a variety of pathological motor patterns have been identified in children with esophageal atresia. However, the most challenging part of diagnosing patients with esophageal dysphagia lies in the fact that these methods fail to link functional symptoms such as dysphagia with the esophageal motor disorders observed. A recent method, called pressure-flow analysis (PFA), uses simultaneously acquired impedance and manometry measurements, and applies an integrated analysis of these recordings to derive quantitative pressure-flow metrics. These pressure-flow metrics allow detection of the interplay between bolus flow, motor patterns, and symptomatology by combining data on bolus transit and bolus flow resistance. Based on a dichotomous categorization, flow resistance at the EGJ and ineffective esophageal bolus transit can be determined. This method has the potential to guide therapeutic decisions for esophageal dysmotility in pediatric patients with esophageal atresia.

## Keywords

- ▶ swallowing
- ▶ esophageal atresia
- ▶ children
- ▶ manometry
- ▶ impedance
- ▶ measurement

## Introduction

Esophageal atresia (EA) is a congenital anomaly occurring in 1 in 4,000 live births.<sup>1</sup> Patients with EA are at risk for respiratory and gastrointestinal morbidity. Overall survival rates are 90%, and approaching 100% when excluding preterm infants and infants with associated anomalies.<sup>1–4</sup> With low mortality, the focus has shifted to the morbidity in these survivors. In the first year of life not only respiratory problems are frequent (37%), but also digestive problems.<sup>5</sup> Many patients struggle with anastomotic stenosis (range, 22–37%), recurrent fistula (4%), gastroesophageal reflux requiring antireflux

surgery (12%), or dysphagia (range, 15–52%).<sup>5–7</sup> Dysphagia is the most common symptom in patients with EA of all ages and the incidence can vary, depending on the definition.<sup>5,6,8,9</sup> The incidence seems to be lower in young children than in children and adults.<sup>5–7</sup> Dysphagia is defined as a swallowing disorder caused by sensory–motor dysfunctions or structural pathology of the oral, pharyngeal, and/or esophageal phases of bolus transport to the stomach. Some patients may only display mild symptoms and need fluids to facilitate swallowing, others encounter some occasional swallowing difficulties, but other patients present with persistent dysphagia requiring alternative feeding.<sup>10</sup> Many adolescent and adult

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patients have adapted their eating habits by eating slowly, longer chewing on solid foods, drinking after having swallowed solid foods, and avoiding dry and hard solid foods. Children present with a wide spectrum of symptoms: early satiety, gagging, hypersalivation, food refusal, and vomiting.

The major cause of dysphagia in EA is dysmotility of the esophagus. The problem can become more severe when structural pathology (esophageal stricture or congenital esophageal stenosis) is superimposed on the underlying disordered motility. The clinical diagnostic methods routinely used to assess EA patients are a radiological barium study and manometry. Both aim to evaluate the anatomy and motor function of the esophagus and esophagogastric junction (EGJ).<sup>11,12</sup> In general, the most challenging part of diagnosing patients with dysphagia lies in the fact that these methods can fail to link symptoms of an underlying esophageal motor disorder. A recent method—called pressure-flow analysis (PFA)—combines simultaneously acquired impedance and manometry measurements and uses an integrated analysis of these recordings to derive quantitative pressure-flow metrics.<sup>13</sup> These pressure-flow metrics allow detection of the interplay between bolus flow, motor patterns, and symptomatology by combining data on bolus transit and bolus flow resistance. Symptoms of dysphagia and increased perception of bolus passage may be indicative of impaired esophageal propulsion or increased resistance to bolus flow at the EGJ.

### Etiology of Esophageal Dysfunction

The etiology of esophageal dysmotility is still debated, with motility disorders mainly being stratified as primary, secondary, or tertiary. A primary dysmotility disorder relates to either the abnormal development of the esophageal muscle or to the innervation of the esophagus.<sup>14</sup> Abnormal preoperative esophageal motility<sup>15</sup> and abnormal gastric motility<sup>16</sup> have been described in newborns with EA as well as in patients with tracheoesophageal fistula without atresia.<sup>17</sup> In terms of innervation, histopathological data support the role of abnormal intrinsic and extrinsic innervation of the esophagus. Neuronal abnormalities of the esophagus have been described in the EA.<sup>18–20</sup> These abnormalities could, at least partially, explain the abnormal esophageal motor patterns observed in EA. Not only intrinsic but also extrinsic neuronal defects are seen. In neonates with EA, the distal end of the proximal esophageal segment had hypoganglionosis and immature ganglion cells in the myenteric plexus.<sup>18</sup> Qi et al demonstrated extrinsic neuronal defects in an Adriamycin (Farmiblastima; Tedec-Meiji Farma S. A., Madrid, Spain)-induced rat model.<sup>20</sup> The course and branching pattern of the vagal nerve to the lower esophagus was affected in these animals. Finally, the interstitial cells of Cajal seem to play a role as well. They are considered the intestinal pacemaker underlying rhythmicity and help to propagate intestinal peristalsis. These cell counts are reduced in the esophagus of patients with EA.<sup>21</sup>

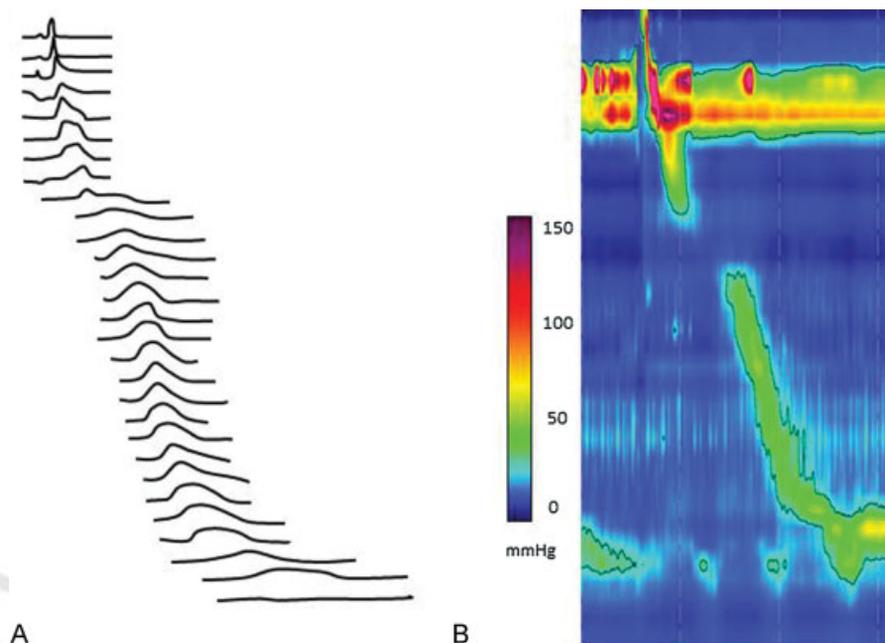
On the other hand, esophageal dysmotility can be secondary, caused by external factors such as surgery and gastroesophageal reflux.<sup>22,23</sup> During surgery, extensive

mobilization can cause myoneural damage and worsen esophageal motility.<sup>23</sup> Shono et al described the pre- and postoperative esophageal motor patterns in a patient with EA and found that the postoperative manometry was more disturbed compared with the initial study.<sup>24</sup> Finally, tertiary motor dysfunction can occur when esophageal dysmotility relates to structural pathology, such as stricture formation at the level of the anastomosis, congenital esophageal stenosis, or stricture as the result of acid gastroesophageal reflux disease.<sup>25,26</sup>

Irrespective of the pathogenesis of the esophageal motor dysfunction, the immediate clinical management and care of the EA patient starts with an adequate assessment of the esophageal motor patterns which may explain the clinical symptoms. The next section will discuss the currently available modalities to assess motor function in patient with EA.

### Current Diagnostic Methods to Investigate Dysphagia in EA

Diagnostic tools used to investigate dysphagia aim to describe esophageal anatomy as well as function. Radiological esophagograms or upper gastrointestinal studies allow visualization of dysfunction due to structural abnormalities in the esophagus such as strictures. Recently, an esophageal anastomotic stricture index has been proposed for the diagnosis of strictures in EA.<sup>27</sup> Although esophageal function has been assessed using radiological dynamic studies, manometry has been the diagnostic tool of choice to diagnose esophageal motor disorders. Over the last decade, high-resolution manometry (HRM) has gained acceptance as a diagnostic tool offering new perspectives in identifying motility patterns. The clinical applicability of esophageal manometry has been revolutionized through the improved reliability of the equipment, increased resolution of sensors (low resolution includes 8–10 sensors, high resolution includes 25–36 sensors), the transition from perfused to solid state sensors, and smaller catheter diameter.<sup>28</sup> Moreover, these technological advances allowed visualization of pressure recordings not only as line tracings, but also as “Clouse” plots of esophageal pressure topography (EPT) (→Fig. 1). Based on the EPT metrics, derived from these plots, different patterns of motor function are recognized more easily and classified into a diagnostic algorithm called “the Chicago classification,” which provides normative values and guidelines for evaluating esophageal motor function.<sup>29</sup> The Chicago classification differentiates four categories of esophageal motor dysfunction: (1) Disorders of EGJ outflow obstruction (including achalasia); (2) major disorders of peristalsis (including distal esophageal spasm, Jackhammer esophagus, and absent contractility); (3) minor disorders of peristalsis (including ineffective motility and fragmented peristalsis); and (4) normal motor function. When applying the Chicago classification in a pediatric population, adjustments for age and size cutoffs are needed as shorter esophageal length and smaller esophagogastric function diameter influence the metrics.<sup>30</sup> Therefore, age and size



**Fig. 1** Esophageal high-resolution manometry tracing of a normal liquid swallow, presented as a line plot (A) and as a color (Clouse) line plot (B). The color panel indicates the corresponding pressure values.

adjustments of the diagnostic criteria used are needed, specifically for the integrated relaxation pressure reflecting deglutitive EGJ relaxation (IRP4) and for distal latency.<sup>30</sup>

Three recent studies used HRM in patients with EA.<sup>11,31,32</sup> First, Lemoine et al described three patterns of disturbed motor function in children using EPT metrics derived from the Chicago classification: aperistalsis (38%), pressurization (15%), and various types of distal contractions (47%).<sup>11</sup> Interestingly, the esophageal peristalsis was affected in all children, even in the asymptomatic children. These three observed abnormal motor patterns were observed, suggesting that the symptoms were not associated with the altered motor patterns. Second, van Wijk et al showed HRM patterns of normal peristalsis in the proximal esophagus and absent esophageal propagation distally in 6/20 patients.<sup>31</sup> In the remaining 14 patients, any normal peristaltic waves were recorded. However, the lower esophageal sphincter relaxation remained complete in the majority (84%) of swallows. Third, Pedersen et al using HRM showed absence of peristalsis in the majority (83%) of included patients, while only 4% of the patients were able to induce esophageal propagation.<sup>32</sup> No correlation could be found between symptoms and frequency of propagating swallows.

### Role of Impedance

In clinical practice, the interpretation of these HRM motor patterns has been impeded by the lack of a clear correlation of motor patterning with symptoms. Potential reasons may relate to the ignorance of the role of bolus flow in symptom generation. Therefore, it was suggested to not only evaluate pressure, but also its relation to bolus flow in an objective way using impedance monitoring. Impedance monitoring is a

technology mostly used in the assessment of gastroesophageal reflux disease as well as bolus transit in children with EA as an alternative for combined manometry and radiology.<sup>33–35</sup> Impedance measurement has now been incorporated into commercially available manometric diagnostic systems and the simultaneous recording is widely available—called HRM impedance.<sup>13</sup> Combining the above described diagnostic tools was believed to allow assessment of the interplay between structural and functional capacity of the esophagus, but largely failed to provide the expected diagnostic gain and to allow defining a relation with clinical symptoms.<sup>11,12</sup> This may potentially relate to a lack of sensitivity of the used technologies, a lack of an integrated analysis method of manometry and impedance recordings, and the fact that normal clearance can also be achieved with abnormal motility patterns.<sup>31</sup>

### Pressure-Flow Analysis to Investigate Dysphagia

Recently, PFA has been developed to allow for integrated analysis of simultaneously recorded esophageal motility and bolus flow. This method aims to provide additional physiological insights by directly integrating impedance measurements, defining bolus flow, with pressure measurements, defining the forces that drive flow. The PFA was first validated for pharyngeal dysphagia in adults<sup>36,37</sup> and subsequently applied for the evaluation of esophageal dysphagia.<sup>38</sup>

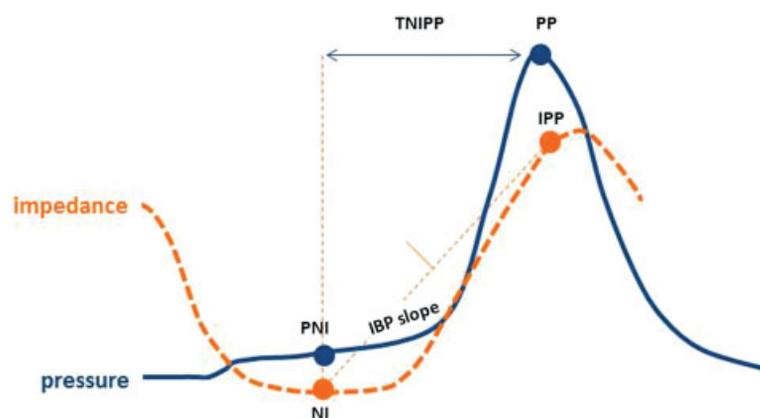
PFA can be performed using automated impedance AIM-plot analysis, a purpose designed MATLAB-based software.<sup>39</sup> This software automatically derives nine esophageal pressure-flow variables in the distal esophagus.

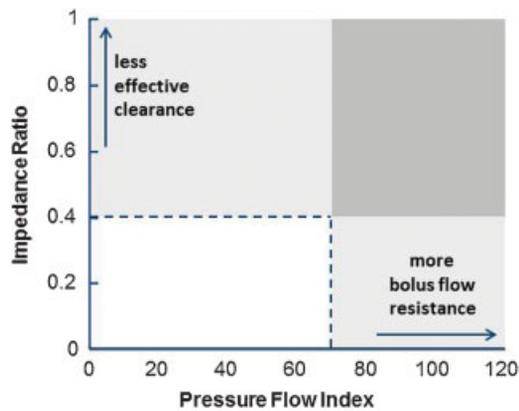
**Table 1** Description of the pressure flow metrics relevant to esophageal function testing and the corresponding abbreviations, units, and interpretation

Pressure flow metric	Abbreviations	Units	Interpretation
Nadir impedance	NI	Ohms	Bolus presence
Peak pressure	PP	mm Hg	Pressure recorded at maximum contractile tension
Impedance at peak pressure	IPP	Ohms	Bolus presence at time of maximum contractile tension
Impedance ratio: nadir impedance to impedance at peak pressure ratio	IR		Marker for incomplete bolus transit
Pressure at nadir impedance	PNI	mm Hg	Intrabolus pressure recorded when the esophageal lumen is maximally filled by the bolus
Intrabolus pressure	IBP	mm Hg	Intrabolus pressure recorded during luminal emptying
Intrabolus pressure slope	IBP slope	mm Hg	Rate of change in intrabolus pressure recorded during luminal emptying
Time from nadir impedance to peak pressure	TNIPP	s	Time interval from maximally full lumen to maximal contractile tension
Pressure flow index	$PFI (IBP \times \text{distal IBP-slope}) / (TNIPP) \text{ ratio}$		Relationship between peristaltic strength and flow resistance in the distal esophagus

The PFA metrics are described in ▶Table 1 and illustrated in ▶Fig. 2. These PFA metrics have been found valuable in the evaluation of postfundoplication dysphagia<sup>41</sup> and of non-obstructive dysphagia<sup>42</sup> and allow discriminating patients with dysphagia from patients without dysphagia.<sup>38</sup> Apart from the pressure-flow metrics, the pressure-flow index

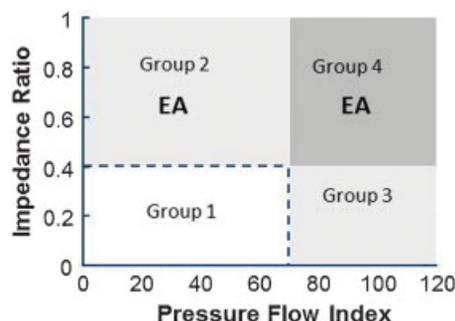
(PFI), a composite measure of bolus pressurization relative to flow, and the impedance ratio (IR), a measure of the degree of bolus clearance failure, can be calculated. A further extension of this PFA paradigm, beyond examination of individual metrics in isolation, is called the pressure-flow matrix<sup>41</sup>: this matrix visually presents the combination of PFI with the IR,

**Fig. 2** Pressure-flow analysis metrics indicated on a combined pressure and impedance line plot.<sup>40</sup> IBP, intrabolus pressure slope; IPP, impedance at peak pressure; IR, impedance ratio; NI, nadir impedance; PNI, pressure at nadir impedance; PP, peak pressure; TNIPP, time from NI to PP.



**Fig. 3** Pressure-flow matrix: Pressure flow index versus impedance ratio (Chen et al 2013).<sup>43</sup> This matrix visually presents the combination of PFI with the impedance ratio, aiming to dichotomously separate out patients with dysphagia who have predominantly abnormal bolus clearance and/or those with abnormal bolus resistance at the EGJ. The pressure-flow matrix (→Fig. 3) shows on the horizontal axis, bolus data of patients with normal and abnormal flow resistance, and on the vertical axis bolus data of patients with normal and abnormal bolus clearance. Depending on combined value of these two metrics, the predominant pressure flow pattern becomes clear. It is expected that control subjects will have a low-pressure flow index and low impedance ratio and these are indicated by the dotted line. EGJ, esophagogastric junction.

aiming to dichotomously separate out patients with dysphagia who have predominantly abnormal bolus clearance and/or those with abnormal bolus resistance at the EGJ.<sup>13,43</sup> The pressure-flow matrix (→Fig. 3) shows bolus data of patients with normal and abnormal flow resistance on the horizontal axis, and bolus data of patients with normal and abnormal bolus clearance on the vertical axis. Depending on the combined value of these two metrics, the predominant pressure-flow pattern becomes clear. It is expected that control patients will have a low PFI and a low IR



**Fig. 4** Pressure-flow matrix: Pressure presenting the flow index versus impedance ratio model. The four quadrants of the matrix indicated the following groups: Group 1, patients with normal effective transit and normal flow resistance across the EGJ; group 2, ineffective transit and normal bolus flow resistance across the EGJ; group 3, effective transit but increased bolus flow resistance across the EGJ; group 4, ineffective transit and increased bolus flow resistance across the EGJ. Patients with esophageal atresia are hypothesized to present in groups 2 and 4, but further research is needed to consolidate this hypothesis. EGJ, esophagogastric junction.

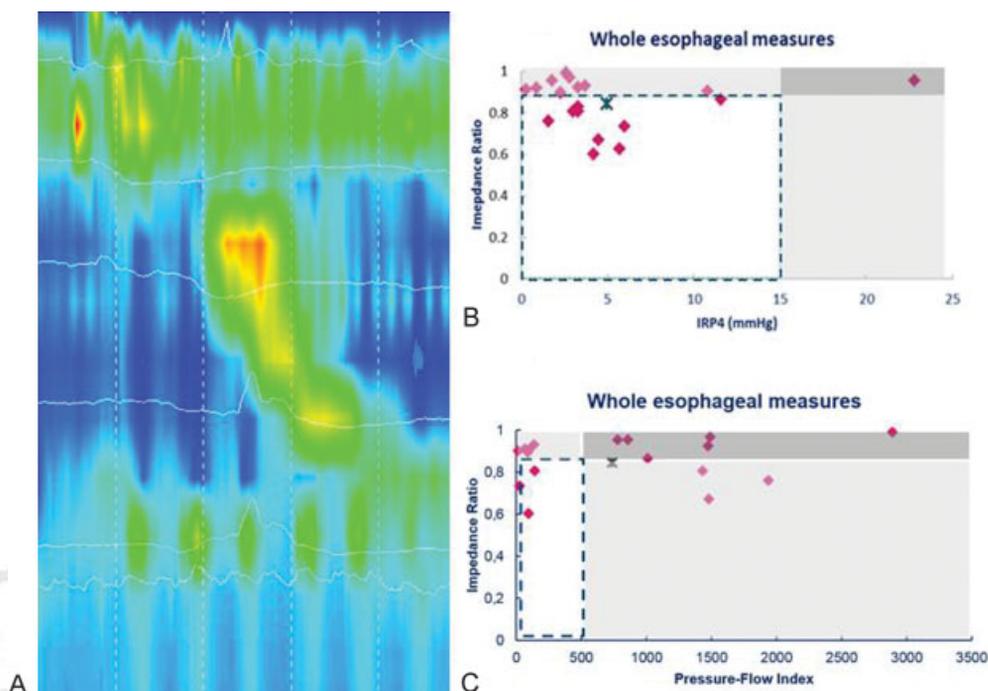
(→Figs. 3 and 4). The four quadrants of the matrix indicated the following groups (see →Fig. 4): Group 1, patients with normal effective transit and normal flow resistance across the EGJ; group 2, ineffective transit and normal bolus flow resistance across the EGJ; group 3, effective transit, but increased bolus flow resistance across the EGJ; group 4, ineffective transit and increased bolus flow resistance across the EGJ. When applying this matrix to patients with EA, it can be hypothesized that they will mainly present in groups 2 and 4 due to the poor clearance capacity of the affected esophagus, but further research is needed to consolidate this hypothesis.

The use of this dichotomized PFA approach in clinical practice is illustrated in →Fig. 5 in the case of a 2-month-old postoperative boy with type A EA with dysphagia. Standard EPT metrics yielded that the majority of the swallows were normal in terms of esophageal peristaltic integrity (isocontour defect < 2 cm) and EGJ function (IRP4s = 3 mm Hg) (→Fig. 5A, B). However, PFA metrics (→Fig. 5C) demonstrated that in the majority of the swallows both the IR and the PFI were highly elevated, the latter suggesting a high flow resistance during deglutition, not detected by HRM as a standalone technique. This highly elevated PFI may link to the abnormal bolus flow and thereby correspond with the patient's symptoms. The increased IR indicates poor bolus clearance during swallowing.

The presented PFA analysis may also provide valuable information on postsurgical outcome in EA patients, who not only often suffer from dysphagia but also from gastroesophageal reflux. For that reason, many patients are undergoing a fundoplication at the lower esophageal sphincter. Performing a fundoplication on a weak or absent peristaltic esophagus is debatable. The patient might postoperatively present with less reflux, but with more dysphagia.<sup>44</sup> PFA may be useful to predict preoperatively which children might develop (more) dysphagia postoperatively, as was the case in adults.<sup>39</sup> In this study by Meyers et al, a greater and faster compression of a viscous bolus with less bolus flow time was related to postoperative dysphagia symptoms. The authors concluded that susceptibility to postfundoplication dysphagia is related to a preexisting subclinical variation of esophageal function. As patients with EA are particularly vulnerable for abnormal esophageal motor function, preoperative evaluation is essential.

## Conclusion

At the moment, the clinical diagnosis of dysphagia in patients with EA relies heavily on clinical symptoms, radiologic, and a low-resolution manometric evaluation. The state of the art diagnosis involves high-resolution manometry supplemented with impedance measurements to assess the interplay between esophageal motor function and bolus clearance. Using a novel PFA method as an integrated analysis method of manometric and impedance measurements may be clinically useful to differentiate patients with impaired EGJ relaxation from patients with bolus outflow disorders. Pressure-flow matrix categorizing the quantitative PFA measures is



**Fig. 5** (A) High resolution manometry impedance color plot of a liquid swallow in a 2-month-old postoperative patient with type A esophageal atresia. In panels B and C, all liquid swallows of the recorded study in this patient are presented according to the PFA matrix paradigm. Panel B represents the impedance ratio versus the integrated relaxation pressure IRP4, a manometric parameter to describe relaxation of the esophagogastric junction during swallowing. The panel shows that many of the swallows look normal in terms of deglutitive relaxation as well as bolus clearance. Panel C shows the impedance ratio versus PFI matrix for the same swallows as evaluated in panel B. The PFI is however increased in the majority of the swallows and thereby reveals that these are abnormal in terms bolus transit and clearance. This example illustrates how PFA allows a more differentiating diagnosis than (high resolution) manometric assessment alone. IRP4, integrated relaxation pressure reflecting deglutitive EGJ relaxation; PFA, pressure-flow analysis; PFI, pressure-flow index.

potentially an objective platform to make more rational therapeutic decisions on whether to pharmacologically improve bolus clearance or to reduce the EGJ flow resistance in symptomatic patients with EA. In addition, PFA can help to predict postoperative dysphagia in patients undergoing fundoplication for severe GER.

#### Conflict of Interest

None.

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