



Archived at the Flinders Academic Commons:

<http://dspace.flinders.edu.au/dspace/>

‘This is the peer reviewed version of the following article: Rommel N, Omari TI, Selleslagh M, Kritas S, Cock C, Rosan R, Rodriguez L, Nurko S. High- resolution manometry combined with impedance measurements discriminates the cause of dysphagia in children. *Eur J Pediatr*. 2015 Dec;174(12):1629-37.

which has been published in final form at

<http://dx.doi.org/10.1007/s00431-015-2582-9>

“The final publication is available at Springer via <http://dx.doi.org/10.1007/s00431-015-2582-9>”.

© Springer-Verlag Berlin Heidelberg 2015

1 **High- resolution manometry combined with impedance measurements discriminates the**
2 **cause of dysphagia in children.**

3

4 **Rommel N, Omari TI, Selleslagh M, Kritas S, Cock C, Rosan R, Rodriguez L, Nurko S.**

5

6 **Eur J Pediatr. 2015 Dec;174(12):1629-37.**

7

8 **Abbreviations**

9	AIM	Automated Impedance Manometry
10	EGJ	Esophago-Gastric Junction
11	EPT	Esophageal Pressure Topography
12	GERD	Gastro-Esophageal Reflux Disease
13	HRM	High Resolution Manometry
14	HRMI	High Resolution Manometry Impedance
15	IBP	Intrabolus pressure
16	IBP-slope	Intrabolus Pressure slope
17	ICD	Iso Contour Defect
18	IRP	Integrated Relaxation Pressure
19	NS	Not Significant
20	PFI	Pressure Flow Index
21	PNI	Pressure at Nadir Impedance
22	PP	Peak Pressure
23	TNIPP	Time from Nadir Impedance to Peak Pressure

24

25

26

27 What is already known about this subject:

- 28 • Pressure-flow analysis (PFA) can detect abnormalities in esophageal motility using
29 integrated analysis of bolus propulsion and bolus flow during swallowing.
- 30 • AIM analysis has recently been reported to be useful in identifying subtle pre-
31 operative esophageal dysfunction in adult patients who developed post-fundoplication
32 dysphagia as well as in patients with non-obstructive dysphagia.

33

34 What are the new findings:

- 35 • Pressure flow parameters can distinguish the cause of dysphagia in pediatric patients
- 36 • Combined high resolution manometry and impedance measurements with pressure-
37 flow analysis can differentiate pediatric patients with dysphagia symptoms in relation
38 to either weak peristalsis (poor bolus clearance) or over-pressurization (abnormal
39 bolus flow resistance).

40 How might it impact on clinical practice in the future?

- 41 • This study supports the use of a novel objective analysis method on recordings that are
42 readily used in pediatric clinical practise.
- 43 • The pressure flow approach allows discriminating esophageal dysfunction in relation
44 to dysphagia symptoms in children. This has not been achieved in children with
45 current analysis methods.
- 46 • The new findings of this study allow a dichotomous categorization of esophageal
47 function, which may help to guide the selection of the most optimal treatment such as
48 pharmacological or endoscopic therapy.

49

50 **ABSTRACT**

51
52 Pressure-flow analysis allows assessing esophageal bolus transport in relation to esophageal pressures.

53 This study aimed to characterize pressure-flow metrics in relation to dysphagia in pediatric patients.

54 We analysed esophageal pressure impedance recordings of 5ml liquid and viscous swallows from 35
55 children (17M, mean 10.5±0.8 yrs). Primary indication for referral was GERD (9), post-fundoplication

56 dysphagia (5), idiopathic dysphagia (16), trachea-esophageal fistula (2) and other (3). Peristaltic

57 function was assessed using the 20mmHg iso-contour defect and the timing between bolus pressure

58 and flow was assessed using the Pressure Flow Index, a metric elevated in relation to dysphagia.

59 Patients were stratified in relation to dysphagia and to peristaltic defect size. Dysphagia was

60 characterized by a weaker peristalsis for liquids and higher Pressure Flow Index for viscous. When

61 patients were stratified based on weak or normal peristalsis, dysphagia with weak peristalsis related to

62 a larger iso-contour defect size and dysphagia with normal peristalsis related to higher Pressure Flow

63 Index

64 *Conclusion:* Pressure-flow analysis enables differentiation of patients with dysphagia due to weak

65 peristalsis (poor bolus clearance) from abnormal bolus flow resistance (esophageal outflow-

66 obstruction). This new dichotomous categorization of esophageal function may help guide the

67 selection of optimal treatment such as pharmacological or endoscopic therapy.

68

69 **KEYWORDS**

70 Esophageal motility; high resolution manometry; impedance measurement; dysphagia

71

72

73

74

75

76

77

78 **INTRODUCTION**

79 Early satiety, perception of food getting stuck in the esophagus, gagging, pain, food refusal
80 and vomiting are common clinical symptoms of esophageal dysphagia in children. These
81 symptoms may be indicative of an underlying esophageal motility disorder potentially caused
82 by impaired esophageal propulsion or increased resistance to bolus flow at the esophago-
83 gastric junction (EGJ). Currently, high resolution manometry (HRM) is becoming the
84 standard investigation for diagnosis of esophageal dysmotility [5]. HRM recordings with
85 esophageal pressure topography (EPT) enables features of peristalsis, such as the pattern and
86 integrity of the contraction, as well as the extent of EGJ relaxation to be more easily
87 determined via objective metrics [20,10,4]. The clinical interpretation of EPT metrics for the
88 diagnosis of esophageal motility disorders is currently guided by the Chicago Classification
89 [2]. However the applicability of the Chicago Classification to the pediatric population
90 remains problematic as certain important metrics such as integrated relaxation pressure and distal
91 latency, are age and size dependent, and therefore, require adjustment in order to improve diagnostic
92 accuracy in children [23]. Furthermore, pediatric EPT data are limited due to clinical challenges
93 [22] and normative values are lacking due to ethical restrictions.

94 Despite the fact that the HRM technique allows identification of esophageal motility
95 disorders, the relationship between esophageal contractile patterns and bolus transport
96 disruption, leading to bolus hold up perception and symptoms, is far from clear, even in
97 adults. Symptoms of dysphagia poorly correlate with conventional manometric findings [6]
98 and the underlying cause of these symptoms still remains unclear in a large proportion of
99 dysphagia patients [6, 7, 9, 18].

100 The evidence that HRM based metrics are improving the predictability of bolus transit failure
101 is inconsistent [1], suggesting that manometry as a standalone technique may not be sensitive

102 enough to elucidate esophageal motility events underlying ineffective esophageal bolus
103 clearance and/or dysphagia. Therefore combining esophageal pressure patterns with bolus
104 flow measured by intraluminal impedance was proposed to assess bolus transport throughout
105 the esophageal lumen and across the EGJ [12, 13, 14]. Unfortunately, the combined
106 manometry-impedance measurements yielded little in terms of further diagnostic insights in
107 patients presenting with dysphagia [13, 14].

108

109 A novel analysis method combining pressure and impedance has been recently developed
110 [16]. Pressure-flow analysis (PFA) has been shown to detect pharyngeal bolus residue and
111 aspiration during deglutition [16] as well as esophageal bolus hold up in relation to dysphagia
112 in both adults [3, 11, 15, 17, 21] and to a limited extend in pediatric populations [8].

113

114 We hypothesize that PFA may be an adequate tool to differentiate the underlying motility
115 disorders causing esophageal dysphagia in a heterogeneous cohort of children presented with
116 dysphagia symptoms. Therefore, the purpose of this study was to characterize pressure-flow
117 metrics in relation to dysphagia symptoms in pediatric patients.

118

119

120 **METHODS**

121 Subjects

122 High resolution manometry impedance recordings from 35 children (17M, 18F, mean
123 10.5 ± 0.8 yrs SD) (Table 1) were retrospectively included. All studies were conducted at the
124 Centre for Motility and Functional Gastrointestinal Disorders at Boston Children's Hospital,
125 USA. The primary reasons for referral included gastroesophageal reflux disease (GERD;
126 $n=9$), post-fundoplication dysphagia ($n=5$), dysphagia of unknown etiology (idiopathic;

127 n=16), tracheo-esophageal fistula (n=2) and other (dysphagia after resection of
128 hemangioendothelioma; n=1, behavioral issues; n=1, chest pain; n=1). Patients with achalasia
129 were excluded from the present study. Access to patient files was approved by the Research
130 Ethics Committee, Boston Children's Hospital, USA (P00001287).

131

132 Study Protocol

133 Manometry-impedance data were acquired using a 3.2mm diameter solid state catheter
134 incorporating 36, 1cm spaced pressure sensors and 12 adjoining impedance segments spaced
135 at 2cm (Unisensor USA Inc, Portsmouth, NH).

136 Subjects were intubated after topical anaesthesia (2% lidocaine) was applied to the nose, and
137 the catheter was positioned with sensors straddling the upper esophageal sphincter (UES),
138 entire esophageal body and EGJ with at least 2 manometric sensors positioned in the stomach.
139 Pressure and impedance data were acquired at 20Hz (Solar GI, MMS, Netherlands) with the
140 patient sitting semi-supine. A maximum of 10 boluses of 5ml saline (0.9% NaCl) and 5ml
141 viscous bolus (Sandhill Scientific Inc) were administered orally via a syringe after a minimum
142 5-min accommodation period.

143

144 Dysphagia assessment

145 Patient clinical notes were reviewed to collect data on underlying conditions, dysphagia
146 symptoms and past therapies. Patients were classified as positive for dysphagia if perception
147 of bolus hold up during deglutition of a solid bolus was reported by the patient or
148 parent/caregiver during the pre-consultation leading to the manometric assessment.

149

150 Data analysis

151 Pressure flow analysis metrics were objectively derived from the raw pressure-impedance
152 data using using AIMplot, a purpose designed analysis software (Copyright T Omari,

153 MATLAB version 2009b, The MathWorks Inc, Natick, MA, USA). Analysis was performed
154 blinded to final diagnosis. The AIM analysis method is illustrated in Figure 1. AIMplot
155 derived parameters have been described previously (17-22). The following pressure-flow
156 variables were derived:

- 157 a) Peak Pressure (PP, mmHg): marker for esophageal contractile strength.
- 158 b) Pressure at Nadir Impedance (PNI, mmHg): intrabolus distension pressure during bolus
159 transport.
- 160 a) Intrabolus Pressure (IBP, mmHg): marker for obstruction.
- 161 b) IBP slope (IBP slope, mmHg/sec): marker for the degree of pressurisation needed to
162 propel the bolus onward.
- 163 c) Time from Nadir Impedance to Peak Pressure (TNIPP, sec): time interval between
164 nadir impedance (identifying the centre of bolus) and peak esophageal pressure: marker
165 marker of how far ahead of the peristaltic wave the bolus moving.
- 166 d) Pressure Flow Index (PFI) reflects the relationship between intrabolus pressure and
167 bolus flow timing in the esophagus. The PFI is calculated using the formula $PFI = (IBP$
168 $* IBP\ slope)/(TNIPP)$ and is a predictive measure elevated in relation to dysphagia (17-
169 18). PFI serves as global measure of pressure-flow.

170 Pressure-flow metrics were derived for the whole length of the esophagus as well as the most
171 distal part of the esophagus (from transition zone to EGJ). The peristaltic integrity was also
172 assessed on the HRM plot using the 20mmHg iso-contour defect (ICD) (5).

173 This PFA analysis was performed in a heterogenous group of 30 children presenting with
174 esophageal dysphagia without underlying anatomic and congenital malformations. Pressure-
175 flow metrics derived from 25 healthy controls aged 20-50yrs with no dysphagia (7M; mean
176 age 36.1 ± 2.2 yrs) was used as a control reference range (10th -90th percentile; collated at the

177 Gastroenterology Unit, WCH, North Adelaide, Australia and the Intestinal Procedures Unit,
178 RGH, Daw Park, Australia).

179

180 Statistical analysis

181 All statistical analyses were performed using SigmaPlot 11.0 (Systat Software Inc.,
182 Chicago,IL, USA). Patients were stratified with or without dysphagia depending on the
183 presence of symptoms of dysphagia on solids as obtained from the clinical notes.
184 Furthermore, patients were stratified as having weak or normal peristalsis depending on the
185 peristaltic defect size on HRM (weak peristalsis = ICD >2 cm) [24]. AIM parameters were
186 averaged for all liquid and viscous swallows prior to all analysis. Data are expressed as mean
187 \pm SEM or Median [IQR]. Grouped data comparisons were done using One Way Analysis of
188 Variance (Bonferroni *post-hoc*) or one Way Analysis of Variance on the Ranks (Dunn's *post-*
189 *hoc*).

190

191 **RESULTS**

192 **1. Pressure-flow metrics relation to reported symptoms of dysphagia on solids.**

193 In 35 patients, a total of 658 swallows were analysed comprising 343 liquid and 315 semisolid
194 boluses (Table 2).

195 Out of 25 patients reporting dysphagia (Table 1), all had reported dysphagia to solids.
196 Although, pressure-flow metrics for the whole oesophagus did not discriminate children
197 reporting dysphagia, PFI in the distal esophagus was significantly increased for viscous
198 boluses. Furthermore, a larger ICD for liquid boluses was also found in patients reporting
199 dysphagia to solids. Data are shown in Table 2.

200

201 **2. Pressure-flow metrics according to underlying pathology**

202 This analysis was performed in the 30 children without underlying anatomic and congenital
203 malformations. All patients were clinically presented with symptoms of dysphagia: 9 had
204 GERD, 5 were investigated post fundoplication and 16 presented with idiopathic dysphagia.
205 Table 3 summarises the ICD and pressure-flow metrics for liquid and viscous boluses
206 between these three diagnostic groups. For liquid boluses, the TNIPP in post-fundoplication
207 patients was significantly shorter compared to the GERD patients who had not undergone
208 anti-reflux surgery. For viscous boluses, an overall trend for higher PNI was seen within the
209 post-fundoplication group, although statistical significance was not reached ($p=0.06$).

210

211 **3. The relationship between peristaltic integrity and oesophageal bolus** 212 **pressurisation**

213 Patients were further stratified based on the presence of normal or weak peristalsis as
214 indicated by the ICD size (12). Patients with a history of dysphagia to solids displayed
215 significantly larger peristaltic breaks for both liquids and viscous boluses (Figure 2). Bolus
216 pressurisation, as indicated by PFI, was increased in patients with dysphagia to solids (Table
217 2), however, when stratified on peristaltic capacity (normal vs. weak) no differences were
218 found (Figure 3). This finding is illustrated by a clinical case of a post fundoplication patient
219 in Figure 4. In a two year old girl with post- fundoplication dysphagia, standard EPT metrics
220 yielded normal findings for esophageal peristaltic integrity (ICD <2cm) and EGJ pressure
221 (IRP4s = 3mmHg). However, pressure-flow analysis metrics demonstrated that the patient
222 exhibited a highly elevated PFI suggesting high flow resistance during swallowing (liquid PFI
223 = 344 and viscous PFI = 1447). Careful review of the manometric tracing, revealed frequent
224 episodes where the initiation of a pharyngeal swallow failed to inhibit the progression of
225 esophageal primary peristaltic wave and thus, suggesting an impaired deglutitive inhibition in
226 this patient._

227

228 **4. Esophageal motility profile of pediatric patients with history of dysphagia to**
229 **solids**

230 Pediatric patients were stratified into using a dichotomous motility matrix based on PFI and
231 ICD (Figure 5). Patients without a history of dysphagia were situated within the range of
232 young adult healthy controls (10th – 90th percentile) whereas patients with a history of
233 dysphagia were located outside the range.

234

235

236

237

238

239 **DISCUSSION**

240 Dysphagia in children is still a very poorly understood clinical phenomenon. Symptoms of
241 vomiting, perception of food being stuck in the esophagus, early satiety and food refusal
242 suggest a link to failed esophageal bolus transport, however in a significant group of these
243 children no clear abnormal motility patterns can be seen either by standard or HRM
244 manometry. Esophageal motility disorders are typically assessed with intraluminal
245 manometry which does not provide any direct information about esophageal bolus transit. In
246 adults, the benefit of combined pressure-impedance recordings has shown to be limited [13,
247 14] but this may be due to the fact that in these studies pressure and impedance measurements
248 were analysed separately [19]. To date, no pediatric studies are available studying the
249 diagnostic yield of combining HRM and impedance measurements. The current study used a
250 new automated method to analyse HRM-impedance recordings in a combined fashion to fully
251 characterize pressure-flow patterns in the esophageal body of pediatric patients with

252 dysphagia. Pressure-flow analysis has been previously used to describe the interactions
253 between esophageal bolus movement and pressure patterns during liquid and semisolid
254 boluses in adults with dysphagia [17-21]) [3, 11, 15, 17, 21] and it has been shown that PFA
255 can give insights into the potential pathophysiology of dysphagia.

256 Overall we found that esophageal bolus pressurisation (as indicated by the PFI) differentiates
257 children with and without a history of dysphagia irrespective of their peristaltic function. The
258 combination of HRM and pressure-flow analysis allows the differentiation of patients in
259 relation to weak esophageal peristalsis (large ICD) and/or abnormal bolus flow resistance
260 (high PFI). Moreover, in post-fundoplication patients the timing of esophageal motor response
261 and bolus movement differ.

262 According to the Chicago Classification (CC) criteria, the current gold standard for the
263 diagnostic interpretation of high resolution manometry recordings in adults, poor esophageal
264 contractility is defined based on the length of the peristaltic defect break size. Break size is
265 calculated as the largest continuous break in the 20mmHg isobaric contour [2]. In our patients
266 the break size was larger in children with dysphagia compared to patients without dysphagia
267 when swallowing liquids suggesting that this reduced segmental contractility of the esophagus
268 would lead to inadequate bolus transport and thus symptoms of dysphagia. However, the
269 optimal ICD length criteria used to predict bolus transport failure and to explain symptoms of
270 dysphagia in pediatric patients is still under discussion [1]. Due to the lack of age appropriate
271 normative criteria, complementary additional information may be needed to support a CC
272 motility disorder diagnosis [23]. Pressure-flow analysis may provide such evidence. For
273 example, the PFI is a global measure of esophageal function, which takes into account the
274 level of bolus pressurisation and pattern of flow. In the current study, the PFI differentiated
275 children with and without dysphagia irrespective of their peristaltic integrity. Hence, when a
276 primary motor disorder pattern is determined through application of the CC algorithm, the PFI

277 may determine if these findings may be driving symptom perception and therefore are of
278 clinical relevance.

279 The variety of underlying medical pathologies that present with dysphagia is vast. In our
280 pediatric population underlying primary diagnoses were also heterogeneous; yet three major
281 underlying diagnostic groups could be identified i.e. GERD, post fundoplication patients and
282 a group of patients with undefined aetiology excluding the previous two categories. The data
283 (Table 2) show that the timing of esophageal motor responses to bolus movement is different
284 in pediatric post fundoplication patients compared to the other diagnostic subgroups of
285 patients with dysphagia. In post fundoplication patients, a shorter time was observed between
286 the point when the oesophagus is most distended (nadir impedance) and the bolus peak
287 pressure, indicating a more pressurised bolus travelling through the oesophagus in closer
288 proximity to the peristaltic wave front. This may be EGJ outflow related rather than being the
289 consequence of poor esophageal contractility.

290 To further explore the relationship between peristaltic integrity (size of the segmental defect
291 expressing bolus clearance) and esophageal luminal resistance to bolus flow (PFI), we
292 dichotomously stratified the current pediatric patient cohort. Our data show that the
293 combination of EPT and pressure-flow analysis can also differentiate pediatric patients with
294 dysphagia with symptoms in relation to either weak peristalsis (poor bolus clearance) or to
295 abnormal bolus flow resistance (high intra-bolus pressure relative to flow). This is an
296 important finding, which may guide the need for pharmacological or endoscopic therapies.

297 This study has limitations. We studied children with heterogeneous causes of dysphagia
298 retrospectively based on the clinical reporting of symptoms of dysphagia on solids and used
299 young adults as controls, as currently no paediatric normal values exist. Future prospective
300 studies assessing perception of bolus hold up in pediatric patients are needed to rule out
301 whether the proposed parameters also link with detection of bolus hold up and symptom

302 generation during swallowing. The fact that subtle bolus flow differences are detected by
303 pressure-flow metrics in this heterogeneous group of pediatric patients is in our view
304 promising, especially in relation to the post fundoplication patients. Our measurements are
305 also more objective, and not subject to individual interpretability, making our findings more
306 robust. We recognise that the cause of symptoms may differ with specific entities of
307 dysphagia pathology such as, for example, non-obstructive dysphagia. Studies investigating
308 more specific subgroups of children with dysphagia are ongoing.

309

310 In conclusion, we combined high resolution manometry impedance recordings to objectively
311 derive pressure-flow variables which reveal subtle abnormalities of esophageal function that
312 link with the dysphagia symptoms of pediatric patients. Pediatric dysphagia patients have an
313 increased PFI in the distal esophagus. Dichotomous categorization of dysphagia patients
314 based on either esophageal peristaltic integrity or PFI may help guide the selection of optimal
315 therapy being either treatment of weak peristalsis (hypocontractile esophagus) or treatment of
316 the EGJ obstruction. Pressure-flow analysis is a promising tool for the clinical interpretation
317 of esophageal motility and further optimization of medical interventions.

318

319

320

321

322

323

324 **REFERENCES**

- 325 1. Bogte A, Bredenoord A, Oors J, et al. Relationship between esophageal contraction
326 patterns and clearance of swallowed liquid and solid boluses in healthy controls and
327 patients with dysphagia. *Neurogastroenterol Mot* 2012;24:e364-e372.
- 328 2. Bredenoord AJ, Fox M, Kahrilas PJ, et al. and the International high resolution
329 manometry Working Group. Chicago classification criteria of esophageal motility
330 disorders defined in high resolution esophageal pressure topography.
331 *Neurogastroenterol Mot* 2012; 24(Suppl.1):57-65.
- 332 3. Chen, C.-L., Yi, C.-H., Liu, T.-T., Hsu, C.-S. & Omari, T. I. Characterization of
333 esophageal pressure-flow abnormalities in patients with non-obstructive dysphagia
334 and normal manometry findings. *J Gastroenterol Hepatol* 2013; 28, 946–53.
- 335 4. Ghosh SK, Pandolfino JE, Zhang Q et al. Quantifying esophageal peristalsis with
336 high-resolution manometry: a study of 75 asymptomatic volunteers. *Am J Physiol*
337 *Gastrointest Liver Physiol* 2006;290:G988–97.
- 338 5. Gyawali CP, et al. Evaluation of esophageal motor function in clinical practice.
339 *Neurogastroenterol Motil* 2013;25:99-133.
- 340 6. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association
341 technical review on the clinical use of esophageal manometry. *Gastroenterology*
342 1994;107:1865-84.
- 343 7. Lazarescu G, Karamanolis G, Aprile L, De Oliviera R, Dantas R, Sifrim D. Perception
344 of dysphagia: lack of correlation with objective measurements of esophageal function.
345 *Neurogastroenterol Motil* 2010; 22, 1292–e337.
- 346 8. Loots C, van Herwaarden MY, Benninga MA, VanderZee DC, van Wijk MP, Omari
347 TI. Gastroesophageal reflux, esophageal function, gastric emptying, and the

- 348 relationship to dysphagia before and after antireflux surgery in children. *J Pediatr.*
349 2013;162(3):566-573.
- 350 9. Lundquist A, Olsson R, Ekberg O. Clinical and radiological evaluation reveals high
351 prevalence of abnormalities in young adults with dysphagia. *Dysphagia* 1998;13:202-
352 207.
- 353 10. Massey BT, Dodds WJ, Hogan WJ, et al. Abnormal esophageal motility. An analysis
354 of concurrent radiographic and manometric findings. *Gastroenterology* 1991;101:344-
355 54.
- 356 11. Myers JC, Nguyen NQ, Jamieson GG, et al. Susceptibility to dysphagia after
357 fundoplication revealed by novel automated impedance manometry analysis.
358 *Neurogastroenterol Mot* 2012;24(9):812-e393.
- 359 12. Nguyen NQ, Rigda R, Tippett M, et al. Assessment of oesophageal motor function
360 using combined perfusion manometry and multi-channel intra-luminal impedance
361 measurement in normal subjects. *Neurogastroenterol Motil* 2005;17:458-65.
- 362 13. Nguyen, N. Q., Tippett, M., Smout, A. J. P. M. & Holloway, R. H. Relationship
363 between pressure wave amplitude and esophageal bolus clearance assessed by
364 combined manometry and multichannel intraluminal impedance measurement. *Am. J.*
365 *Gastroenterol.* 2006;101, 2476-84.
- 366 14. Nguyen, N. Q., Ching, K., Tippett, M., Smout, a J. P. M. & Holloway, R. H. Impact of
367 nadir lower oesophageal sphincter pressure on bolus clearance assessed by combined
368 manometry and multi-channel intra-luminal impedance measurement.
369 *Neurogastroenterol Motil* 2010; 22, 50-5.
- 370 15. Nguyen NQ, Holloway RH, Smout AJ, Omari TI. Automated impedance-manometry
371 analysis detects esophageal motor dysfunction in patients who have non-obstructive
372 dysphagia with normal manometry. *Neurogastroenterol Motil.* 2013;25(3):238-45.

- 373 16. Omari TI, Dejaeger E, van Beckevoort D et al. A method to objectively assess
374 swallow function in adults with suspected aspiration. *Gastroenterology*
375 2011;140:1454-63.
- 376 17. Omari TI, Wauters L, Rommel N, Kritas S, Myers JC. Oesophageal pressure-flow
377 metrics in relation to bolus volume, bolus consistency, and bolus perception. *United*
378 *European Gastroenterol J.* 2013;1(4):249-58.
- 379 18. Omari T, Tack J, Rommel N. Impedance as an adjunct to manometric testing: What it
380 has failed to do and what it may tell us in the future. *Eur J Gastroenterol*, 2014
381 Oct;2(5):355-66.
- 382 19. Ott DJ, Richter JE, Chen YM et al. Esophageal radiography and manometry:
383 correlation in 172 patients with dysphagia. *Am J Gastroentgenol* 1987;149:307-11.
- 384 20. Pandolfino JE, Ghosh SK, Zhang Q, et al. Quantifying EGJ morphology and
385 relaxation with high-resolution manometry; a study of 75 asymptomatic volunteers.
386 *Am J Gastrointest Liver Physiol* 2006;290:G1033–40.
- 387 21. Rommel, N., Van Oudenhove, L., Tack, J. & Omari, T. I. Automated impedance
388 manometry analysis as a method to assess esophageal function. *Neurogastroenterol*
389 *Motil* 2014; 1–10.
- 390 22. Rommel N, Selleslagh M, Haesendonck N, Hellemans M, Kritas S, Omari T, Hoffman
391 I, Tack J. Clinical challenges of esophageal high resolution manometry in pediatrics:
392 acquisition and analysis. *Gastroenterology*, 2014, 146: 5, Suppl 1, S419.
- 393 23. Singendonck M et al. Applying the Chicago classification criteria of esophageal
394 motility to a pediatric cohort: effects of patient age and size. *Neurogastroenterol Motil.*
395 2014;26(9):1333-41.

396 24. Roman S, Lin Z, Kwiatek MA, Pandolfino JE, Kahrilas PJ. Weak
397 peristalsis in esophageal pressure topography: classification and association with
398 Dysphagia. *Am J Gastroenterol* 2011;106: 349–56.
399

400 **FIGURE LEGENDS**

401

402 **Figure 1**

403 **A.** An esophageal pressure topography plot showing pressures associated with a 5ml viscous
404 bolus swallow. Five space-time landmarks define the region of interest (ROI) for calculations
405 (i. the time of onset of swallow; ii. the time of proximal peak pressure; iii. the proximal
406 margin of the esophageal pressure wave sequence; iv. the position of the transition zone; v.
407 distal margin of the esophageal pressure wave sequence).

408 **B.** Derivation of the AIM analysis pressure flow metrics in an impedance–manometry line
409 plot. Guided by the timing of landmarks Nadir Impedance (NI) and Peak pressure (PP), the
410 AIM metrics are measured along the pressure-impedance array using an automated software
411 algorithm.

412

413 **Figure 2**

414 Isocontour defect data stratified in relation to either normal or weak peristalsis. Weak
415 peristalsis is defined by the presence of an isocontour 20mmHg defect size larger than 2cm on
416 the pressure topography plot. Data of dysphagic patients are presented in black, non
417 dysphagic patient data in grey. Data were analysed using ANOVA, p-values from significant
418 post-hoc tests (Dunn’s method corrected for multiple comparisons) are presented, *p<0.05.

419

420 **Figure 3**

421 Pressure flow index data stratified in relation to either normal or weak peristalsis. Weak
422 peristalsis is defined by the presence of an isocontour 20mmHg defect size larger than 2cm on
423 the pressure topography plot. Data of dysphagic patients are presented in black, non

424 dysphagic patient data in grey. Data were analysed using ANOVA, p-values from significant
425 post-hoc tests (Dunn's method corrected for multiple comparisons) are presented, *p<0.05.

426

427 **Figure 4**

428 Recordings in a two year old girl who developed dysphagia to solids follow fundoplication for
429 GERD. A. shows example swallows in standard esophageal pressure topography (EFT)
430 format and B-C show AIM pressure-flow metrics. The panels show **A.** Four consecutive bolus
431 swallows demonstrating repeated failure of secondary swallows to inhibit peristalsis. **B.** An
432 esophageal pressure topography plot showing pressures associated with a 5ml viscous bolus
433 swallow. Five space-time landmarks define the region of interest (ROI) for calculations (i. the
434 time of onset of swallow; ii. the time of proximal peak pressure; iii. the proximal margin of
435 the esophageal pressure wave sequence; iv. the position of the transition zone; v. distal margin
436 of the esophageal pressure wave sequence). **C.** Bolus trajectory pathway defined using
437 TNIPP. This identifies bolus passage (NI) relative to the esophageal pressure wave (PP).

438

439 **Figure 5**

440 Dichotomous presentation of the relation between oesophageal integrity (ICD) and
441 oesophageal luminal resistance (PFI) in 35 children with and without dysphagia. The figure
442 presents a categorisation of esophageal pressure-flow profiles in 35 pediatric patients with
443 dysphagia based upon pressure flow index (PFI) and isocontour defect (ICD). This
444 categorisation enables a separation of patients who have predominantly abnormal bolus
445 clearance (large ICD) and/or those with abnormal flow resistance (high PFI). Mean data for
446 viscous boluses from patients with and without dysphagia are presented.

447

448 **TABLE LEGENDS**

449

450 **Table 1**

451 Patient characteristics. Data are expressed as percentage or as Mean±Standard Deviation (SD)
452 or Median with interquartile ranges (IQR).

453

454 **Table 2**

455 Pressure-flow metrics (AIM parameters) in relation to the presence of dysphagia to solids in
456 25 pediatric patients for liquid boluses (n=35) and viscous boluses (n=31). Data presented as
457 mean±SEM or median [IQR] and are compared using a One Way ANOVA, *p<0.05.

458

459 **Table 3**

460 Pressure flow metrics (AIM parameters) for liquid and viscous boluses in relation to
461 underlying pathology. Data are presented as mean±SEM or median [IQR] and compared
462 using a One Way ANOVA (*p<0.05 using a Bonferroni *post-hoc*).

463

Table 1. Patient characteristics (N= 35)

Age	Mean±SD (years)	10.5 ± 0.8,
	Median IQR	10.54 [1.96-19.64]
Male		17 (49%)
Weight	Mean±SD (kg)	54.7 ± 23.1
Height	Mean±SD (cm)	155.37 ± 20.9

Reason for referral

Idiopathic dysphagia (unknown aetiology)	16 (40%)
Gastroesophageal reflux disease	9 (27%)
Patient post-resection of hemangio- endothelioma	1 (3%)
Patient with Behavioural issues	1 (3%)
Chest pain	1 (3%)

Investigations for dysphagia performed post-surgery	7 (24%)
• Tracheoesophageal fistula	2
• Post-Nissen fundoplication	5

466 TABLE 2

467

	5ml Liquid Bolus		5ml Viscous Bolus	
	No Dysphagia N= 10	Dysphagia N= 25	No Dysphagia N= 9	Dysphagia N= 23
Whole Esophagus				
PP mmHg	58±6	49±4	59±9	54±5
PNI mmHg	4±1	2±0	5±1	6±1
IBP mmHg	6±1	5±1	9 [4-11]	8 [6-11]
IBP slope mmHg/s	6 [2-9]	7 [5-11]	10 [8-11]	9 [7-14]
TNIPP sec	3.3±0.2	3.4±0.1	2.7±0.2	2.6±0.2
PFI	50 [9-102]	59 [25-125]	100 [63- 169]	67 [49-160]
ICD cm	2 [1-3]	4 [2-8]*	2 [0-3]	3 [1-9]
Distal Esophagus				
PP mmHg	62±7	50±5	60±10	55±6
PNI mmHg	4±1	3±0	6 [2-10]	6 [4 -8]
IBP mmHg	5 [3-7]	5 [3-6]	7±2	9±1
IBP slope mmHg/s	4 [2-8]	4 [3-7]	5 [4-7]	6 [4-13]
TNIPP sec	3.8±0.2	3.8±0.2	2.9±0.2	2.9±0.2
PFI	43 [16-99]	26 [9-126]	32 [13-67]	61 [25-139]*

468

469

470 TABLE 3

LIQUID SWALLOWS	GERD N = 9	Post Fundo Dysphagia N = 5	Idiopathic Dysphagia N = 16	ANOVA
Whole Esophagus				
ICD cm	4±1	2±1	5±1	0.217
PP mmHg	47 [36, 71]	54 [45, 83]	43 [36, 63]	0.372
PNI mmHg	2±1	3±1	3±1	0.947
IBP mmHg	5±1	5±2	5±1	0.886
IBP slope mmHg/s	5 [3, 7]	10 [4, 20]	7 [5, 9]	0.317
TNIPP sec	3.7±0.2	2.8±0.3*	3.3±0.2	0.039*
PFI	60 [23, 71]	102 [14, 238]	55 [23, 140]	0.917
Distal Esophagus				
PP mmHg	45 [39, 76]	55 [47, 90]	42 [31, 67]	0.362
PNI mmHg	3±0	4±1	3±1	0.431
IBP mmHg	4±1	6±2	5±1	0.625
IBP slope mmHg/s	4 [2, 6]	7 [1, 20]	4 [3, 5]	0.656
TNIPP sec	4.2±0.2	2.4±0.2	3.8±0.2	0.054
PFI	55 [4, 74]	129 [14, 250]	22 [9, 66]	0.435

471
472
473
474

*p<0.05 versus GERD as tested by ANOVA (Bonferroni *post-hoc*)

VISCOUS SWALLOWS	GERD N = 8	Post Fundo Dysphagia N = 5	Idiopathic Dysphagia N = 15	ANOVA
Whole Esophagus				
ICD cm	3±1	1±0	5±1	0.112
PP mmHg	62±11	68±8	51±6	0.386
PNI mmHg	4±1	8±2	7±4	0.139
IBP mmHg	7±1	12±3	10±2	0.094
IBP slope mmHg/s	10 [8, 14]	10 [6, 33]	10 [7, 14]	0.771
TNIPP sec	2.9±0.3	2.5±0.4	2.6±0.2	0.639
PFI	102 [69, 151]	65 [44, 787]	67 [50, 232]	0.947
Distal Esophagus				
PP mmHg	64±12	71±8	52±6	0.331
PNI mmHg	4±1	10±2	6±1	0.065
IBP mmHg	7 [2, 11]	14 [4, 20]	8 [5, 10]	0.347
IBP slope mmHg/s	5 [4, 12]	4 [3, 30]	6 [4, 10]	0.956
TNIPP sec	3.1±1.0	2.8±1.2	2.9±0.8	0.731
PFI	32 [15, 97]	38 [16, 779]	61 [25, 117]	0.418

475
476

477 **List of individual contributions**

478

479 **Nathalie Rommel** Roles: study concept and design, analysis and interpretation of data;
480 drafting of the manuscript; critical revision of the manuscript; statistical analysis; study
481 supervision.

482 **Taher I. Omari** Roles: study concept and design; analysis and interpretation of data; drafting
483 of the manuscript; critical revision; study supervision.

484 **Margot Selleslagh** Roles: analysis of data, critical revision of the manuscript.

485 **Stamatiki Kritas** Roles: analysis of data, critical revision of the manuscript.

486 **Charles Cock** Roles: critical revision of the manuscript.

487 **Rachel Rosan** Roles: Data acquisition and critical revision of the manuscript.

488 **Leonel Rodriguez** Roles: Data acquisition and critical revision of the manuscript.

489 **Samuel Nurko** Roles: study concept and design; acquisition, analysis and interpretation of
490 data; critical revision; study supervision.

491

492

493 **Conflict of Interest**

494 T Omari and N Rommel have AIM technology patent to disclose. None of the other authors

495 have any conflict of interest to disclose.

496

497