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Pyloric distensibility in health and disease

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Pyloric distensibility

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ABSTRACT AND KEYWORDS

Until recently, gastric motility measurements in Humans were mostly limited to accommodation (using barostat or 3-dimensional imaging studies of gastric volume) and gastric emptying tests, the latter being the only one performed in routine clinical care. Accurate and easy to use techniques were lacking to assess pyloric function in health and disease. Recently, pyloric distensibility has been developed and validated to assess pyloric opening. Several studies confirmed that pyloric distensibility was decreased in gastroparesis and correlated with gastric emptying as well as gastroparesis symptoms. In addition, pyloric distensibility may predict outcome of endoscopic techniques targeting the pylorus, namely intra-pyloric botulinum toxin injection and gastric per-oral pyloromyotomy. Pyloric distensibility appears therefore to be a promising and useful new tool in the workup of gastroparesis patients.

Keywords

Compliance; Gastric emptying; Gastroparesis; Pyloromyotomy; Pylorus.

TEXT

Gastric physiology assessment in Humans has been focused for decades on accommodation testing (using barostat or 3-dimensional imaging studies, such as magnetic resonance imaging or single photon emission computed tomography) and gastric emptying studies. Accurate and easy-to-use techniques are lacking to assess pyloric function in health and disease. Recently, pyloric distensibility measurement has been developed and validated to assess pyloric functioning. Indeed, previously available techniques to assess pyloric function were imaging (dynamic contrast X-rays or ultrasound) and adapted antro-duodenal manometry using either sleeve catheter positioned into the pylorus or high-resolution manometry. These techniques are unfortunately mastered by only a few centers which limits their spread worldwide (1, 2). Gastric emptying tests only provide an indirect assessment of pyloric function, as gastric emptying depends also on antral peristaltic activity as well as gastric accommodation. This review details the principle of pyloric distensibility measurement and its usefulness in clinical practice in the diagnosis and management of altered gastric motility.

Pyloric distensibility measurement

The distensibility of a tissue is its ability to stretch and expand in response to an applied pressure. Distensibility applies to elastic tissues and especially ring-shaped sphincters. Low distensibility indicates resistance to distension and increased stiffness, whereas high distensibility reflects an “open” sphincter. There exist two other similar concepts that should not be misused: compliance, applying to hollow organs like the urinary bladder or the rectum,

and elasticity, which reflects the ease to stretch an entire sphincter and not just at its narrowest point like for distensibility.

The technology allowing the assessment of tissue distensibility is named FLIP for "Functional Luminal Imaging Probe" and relies on "impedance planimetry". A device has been marketed as the EndoFLIP™ imaging system, and was first used to assess lower esophageal sphincter distensibility (3), and later to assess the other sphincters of GI tract, including Oddi's sphincter (4), anal sphincter (5) and pylorus (6). Distensibility measurements were shown to be superior to pressure measurements in the diagnosis (5, 7) and prediction of response to treatment (8) at other sphincters.

The equipment is composed of a recording unit, also controlling volume injection by a syringe containing a proprietary conductive saline solution (9), and a probe composed of a 240 cm-long and 2.8 mm-wide plastic catheter with at its distal end a polyurethane bag. This balloon is cylindrical and infinitely compliant. The EndoFLIP™ bag is composed of a series of 17 impedance electrodes spaced 5 or 10 mm apart depending on the model and of one solid-state pressure transducer to determine intra-bag pressure. Pyloric pressure can be expressed as it is measured but can also be expressed relatively to antral pressure, which should be measured with the deflated balloon before or after probe positioning at the pylorus. The balloon is connected to a pump, allowing injections of 0 to 60 mL of solution (volume-controlled balloon distensions). Excitation electrodes are positioned at the ends of the balloon and generate the electric current (100 µA at a frequency of 5 kHz). The impedance electrodes can measure the voltages between each of them. Ohm's law states that the current (I) is proportional to the voltage (V) applied across the conductor and inversely proportional to the resistance of the conductor (R), with the formula $V = I \times R$. Planimetry, a branch of mathematics studying plane areas, enables to calculate the CSA at the 16 electrode intervals.

Indeed, the resistance depends on the length (l), cross-sectional area (CSA) and resistivity of the conductor (ρ), with the formula $R = \rho l/CSA$, the CSA being the only unknown parameter. The diameter is calculated as the square root of $4CSA/\pi$ and the distensibility index by dividing the CSA (in cm^2) by the simultaneous intra-balloon pressure (in mmHg), which can be directly measured by the pressure transducer located inside the balloon. There are two models of probes commercialized depending on the length of the bag: 8 cm-long (EF-325N) or 16 cm-long (EF-322N), the most used at the pylorus level for anatomic issues being the 8 cm probe. At the pylorus, impedance planimetry is used to measure the CSA of the pyloric sphincter and to calculate its distensibility with the help of pyloric pressure. The pressure of the pylorus can also be determined at the same time. All FLIP metrics are listed in Table 1 and some recordings are shown in Figure 1.

There is a lack of standardization of study protocols (10). Subjects are usually asked to fast for at least 8 hours before EndoFLIP™ is performed (11, 12). In fact, no post-prandial assessment of pyloric distensibility has been performed until now with the technique, due to technical issues (6). Indeed, EndoFLIP™ positioning and measurements are most of the time performed during upper gastrointestinal endoscopy under general anesthesia, which requires fasting. Other alternatives may involve probe positioning under videofluoroscopy, which again requires fasting. Last, it remains unknown whether the transpyloric flow of gastric content, including triturated food, may impair distensibility measurement. Endoscopic positioning involves probe insertion through a large-channel therapeutic endoscope (12), transorally (13) or even transnasally (12), running parallel to an endoscope (14) or not. The easiest method seems to pass the probe through the biopsy channel of a therapeutic endoscope. The position of the catheter through the pylorus can be checked using endoscopic view or fluoroscopic control (6). Once in place, the balloon can be filled with different volumes (10, 20, 30, 40, 50 and 60 mL), usually using a stepwise protocol (6, 11, 15).

Volumes of 40 cc or 50 cc are usually considered as the best to visualize the contour of the pyloric sphincter, especially compared to small volumes of distension (12). Whether anesthetics influence pyloric distensibility is currently unknown. Studies performed at the eso-gastric junction level suggest that anesthetics have an impact on lower esophageal sphincter distensibility. At the pylorus level, studies have been conducted either in anesthetized patients, mostly using propofol (9, 11, 15, 16), or even in non-anesthetized patients using videofluoroscopic positioning (6). Preliminary data suggest that the influence of anesthetics is modest although this remains to be confirmed by systematic and comparative studies. Agonists of mu-opioid receptor, e.g. fentanyl, alter neuronal inhibition at the pylorus (17) but no study assessed their influence on pyloric distensibility. Therefore, their use during EndoFLIP^{TM} measurements at the pylorus should be avoided until studies clarifying their impact on pyloric function are available.

The technique can be used whenever an upper gastrointestinal endoscopy is not contra-indicated, except in case of active bleeding. To avoid variation in pyloric parameters due to peristaltic contractions, values should be recorded when pyloric pressure and CSA are stable for at least 5 seconds. Distensibility is best assessed when the intra-bag pressure is at its maximum, with a recommended cut-off > 15 mmHg (18). The correct position of the probe should be verified before performing the measures, either under endoscopic or fluoroscopic control. Furthermore, real-time measurements enable to recognize the distinctive shape of the pylorus, looking like a narrow segment with decreased CSA. The blood sugar level does not modify the results in the diabetic subject but its effect in healthy volunteers is unknown (19). The influence on the results of factors like general anesthesia, drugs taken by the patient, passing the pylorus with the endoscope or inflating the stomach before the measurements is unknown. Figures 2 and 3 show the correct positioning of the probe at the pylorus in fluoroscopy and endoscopic view respectively.

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146 **Pyloric distensibility contribution to pyloric physiology understanding**

147 Fasting pyloric pressure has been shown to be about 5 mmHg above the antral
148 pressure using antro-duodenal manometric recording in healthy subjects (2, 6). Meals increase
149 pyloric pressure only by 3 mmHg in those subjects, which is the lowest sphincter pressure
150 along the GI tract (2). Even if there are no data regarding the correlation between pyloric
151 pressures measured by manometric probes and EndoFLIP^{TM} in healthy subjects, Snape et al.
152 showed that there was a correlation between both measures in patients with nausea and
153 vomiting (9). However, pyloric pressure measured either by manometry or the EndoFLIP^{TM}
154 system is not different between subjects with or without delayed gastric emptying (6, 9).
155 Therefore, pyloric diameter and distensibility may appear as complementary with pressure
156 measure to assess pyloric function. Two groups investigated pyloric distensibility and
157 pressure in healthy subjects using EndoFLIP^{TM}, one from France (6) and the other from India
158 (11). The French study in 21 healthy non anesthetized volunteers showed fasting pyloric
159 pressure to be 9.7 ± 4.4 mmHg and fasting pyloric distensibility to be 25.2 ± 2.4 mm²/mmHg,
160 both at 40 mL of bag inflation (6, 16, 20). The Indian study in 20 non anesthetized /
161 anesthetized healthy subjects showed fasting pyloric pressure to be 23.6 ± 15.3 mmHg and
162 fasting pyloric distensibility to be 8.4 ± 4.7 mm²/mmHg (11). Pyloric distensibility was
163 therefore lower in the Indian study, which raises the possibility of ethnical/racial or
164 anesthetic-induced differences. In the French study, the lower 90% percentile of pyloric
165 distensibility was set at 10, which was further used to define altered vs normal values, in
166 particular to study gastroparetic patients (16). However, confirmatory studies involving other
167 populations are needed before using this threshold in routine care. The comparison of both
168 healthy volunteers' cohorts is detailed in Table 2. Both studies identified that the pylorus was

more distensible than the lower esophageal sphincter, with a distensibility index of 2-4 mm^2/mmHg at 20 and 30 mL of balloon inflation respectively (21). This may rely on the fact that the pylorus is not affected by the crural diaphragm, which may increase stiffness at its level.

Fasting pyloric distensibility is negatively correlated with gastric half-emptying time (6, 9, 12, 22). Gender, age, height, weight and body mass index did not seem to affect pyloric distensibility in healthy subjects (11). There are currently no data regarding the impact of blood glucose on pyloric distensibility in healthy subjects. One report pointed out however in diabetic patients that no correlation was observed between pyloric distensibility and acute hyperglycemia nor chronic hyperglycemic states as measured by glycated hemoglobin (23).

Pyloric distensibility as a diagnostic tool in gastroparesis

Most of the recent studies focused on the usefulness of pyloric distensibility assessment in gastroparesis workup. Gastroparesis is defined by delayed gastric emptying without mechanical obstruction of the stomach, associated with symptoms, including postprandial fullness, early satiation, epigastric pain, nausea and/or vomiting. In the United Kingdom, gastroparesis prevalence in the general population was estimated at 0.014% (24). A cost of 4000 to 9000 US$ / patient / year is estimated in this disease (25). The etiology of gastroparesis is dominated by diabetes which is found in nearly 30-40% of patients, but also includes less frequently neurodegenerative disease, gastro-intestinal infection, systemic sclerosis or gastric surgery. However, gastroparesis remains idiopathic in nearly 40% to 50% of cases (24).

Mearin et al. first reported pyloric dysfunction in gastroparesis a few decades ago (26) and defined pylorospasm as mean basal pyloric pressure >10 mmHg using perfused catheters. However, no correlation between pyloric pressure and gastric emptying was reported (12). More recently, distensibility measurement was reported to be more sensitive in evaluating pyloric function than basal and peak pressures, since patients with severely delayed gastric emptying had a significantly decreased distensibility of the pylorus even if pressures were similar to those of patients who had nausea/vomiting with normal gastric emptying (9).

Three studies in gastroparetic patients (6, 12, 14) found a mean fasting pyloric distensibility of 16.9, 12.4, and 10.7 mm^2/mmHg respectively. Consequently, decreased pyloric distensibility was found in 38.5% to 54.2% of patients in idiopathic or diabetic gastroparesis cohorts (6, 16) but did not discriminate patients with diabetic or idiopathic gastroparesis (12, 14, 23).

Correlation between gastric emptying, symptoms and quality of life in gastroparesis remains debated (27-29). In contrast, all studies showed that pyloric distensibility was negatively correlated with dyspeptic gastroparetic symptoms, including postprandial fullness (6, 12), early satiety (6, 12), nausea (6, 9), vomiting (22) and retching (22). Furthermore, pyloric distensibility was also negatively correlated with quality of life in gastroparesis: the more decreased the distensibility the poorer the quality of life (6, 12). In one study, pyloric distensibility was better than gastric emptying test to correlate with symptoms, especially with vomiting (30). However, all those studies are retrospective and at risk for biases. Larger, prospective, well-designed studies are needed to confirm those results.

In gastroparesis, fasting pyloric distensibility was found to be negatively correlated with gastric emptying rate (6, 9, 12, 22) while patients with impaired pyloric distensibility had slower gastric emptying than those with normal distensibility. Another study assessed pyloric

distensibility in patients with chronic nausea and/or vomiting associated or not with delayed gastric emptying (9). In this study, pyloric distensibility, but not pyloric pressure, was decreased in patients with severely delayed gastric emptying compared to those with normal emptying.

Pyloric distensibility has also been shown to be impaired in diabetic gastroparesis, with a comparable frequency (nearly 40%) compared to idiopathic gastroparesis (23), suggesting that it is not a feature of diabetes *per se*. This is reinforced by the fact that altered pyloric distensibility was not associated with macro- and micro-angiopathy, in particular peripheral neuropathy, in the disease (23). Only one study assessed specifically pyloric distensibility in patients suspected of post-surgical gastroparesis (20). In this study involving 18 patients with antireflux surgery, 9 patients with esophagectomy, and 16 patients with sleeve gastrectomy, altered pyloric distensibility was found to be decreased in 61.1% of patients with antireflux surgery and 75.0% of patients with esophagectomy. However, sleeve gastrectomy was not associated with altered pyloric distensibility since a lesion of the vagus nerve or involvement of the distal antrum are not expected with this procedure.

Pyloric distensibility as a predictive tool for pyloric-targeted therapies for gastroparesis

Gastroparesis remains a therapeutic challenge (31). Different techniques targeting the pylorus have been recently developed to accelerate gastric emptying with the hope to improve symptoms. These include balloon dilation at the pylorus, pyloric botulinum toxin injections, transpyloric stenting (32), surgical pyloromyotomy (principally laparoscopic Heineke–Mikulicz pyloroplasty (33)) and more recently endoscopic pyloromyotomy (G-POEM for gastric per-oral endoscopic myotomy). Unfortunately, while initial cohort studies were promising, especially with pyloric botulinum toxin injections (34), further randomized

controlled trials suggested that such techniques were not effective in an overall gastroparetic patient population (35, 36). The development of pyloric distensibility measurement may allow to better select patients who will have the greatest benefit from these therapeutic interventions (37).

Decreased pyloric distensibility before treatments may predict favorable outcomes after pyloric dilation (6, 15), botulinum toxin injections (16, 22) and G-POEM (13, 14). It may also predict normalization of gastric emptying following botulinum toxin injections in gastroparetics (16). Following intrapyloric botulinum toxin A injections, overall dyspeptic symptom severity improved (16), more specifically postprandial fullness and bloating (16) and early satiety and nausea (22), in patients with altered pyloric distensibility at baseline. The risk of bias linked to the retrospective nature of these studies makes it necessary to carry out prospective randomized trials designed to validate the strategy of patient selection based on EndoFLIP^{TM} results.

Pyloric dilation (6) and G-POEM (14, 38, 39) all increase pyloric distensibility while pyloric pressure remains unchanged. Therefore, pyloric distensibility measurement during the procedure may also offer the opportunity to check if the intervention, and more specifically endoscopic or surgical myotomy, is successful (39). Indeed, changes in EndoFLIP^{TM} measurements (CSA and pyloric distensibility) immediately after G-POEM better predict 1-year clinical success compared to measurements at 3 months (13). Jacques et al. showed that a post-procedural pyloric distensibility over 9.2 mm²/mmHg (50 mL of balloon inflation) after G-POEM was associated with clinical success at 3 months (72.2% sensitivity and 100% specificity) (14). Likewise, Malik et al. showed that increased CSA following G-POEM was also associated with clinical response at 3 months (40). Last, Vosoughi et al. confirmed that pyloric CSA following G-POEM was the best independent predictor of 1-year clinical success with a cutoff value > 154 mm² at 40 mL of bag distension (sensitivity of 71% and a

specificity of 91%) (13). The same study also showed that post-G-POEM pyloric CSA was associated with improvement in gastric emptying at 1 year (13). Interestingly, pyloric distensibility may also guide a second procedure if the first one is unsuccessful. In patients refractory to pyloromyotomy, lower pre-dilation pyloric distensibility, which suggests ineffective myotomy, could predict a favorable outcome of pyloric dilatation (15).

Dynamic changes of the pyloric activity due to phasic pyloric contractions can also be assessed with EndoFLIP^{TM} (38). Watts et al. showed that G-POEM increased the maximal diameter and the distensibility of the pylorus, suggesting that the procedure improves pyloric opening (38). However, the number of phasic contractions of the pylorus remained unchanged after G-POEM compared to baseline recordings (38).

Research perspectives

Several issues remain to be investigated regarding the clinical use of pyloric distensibility measurement in routine care. First, the influence of technical factors, including general anesthesia or stomach inflation, on pyloric distensibility have to be investigated in order to optimize standardized protocol. Ideally, post-prandial measurement, although technically challenging, should enable us to better understand pyloric physiology and to determine relevant measures in order to explore symptoms that typically occur post-prandially. Last, the usefulness of pyloric distensibility measurement to predict patients' outcome should be ascertained using randomized controlled trials, which may rehabilitate and/or boost the use of pyloric-targeted therapies.

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FW and GG drafted the manuscript and provided critical revision of the manuscript for important intellectual content.

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Conflicts of interest

No competing interests declared.

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FIGURE LEGENDS

Figure 1. Representative recordings of fasting pyloric distensibility in a healthy subject (HV) and a patient with diabetic gastroparesis (GP). Measurements were made with the EndoFLIP^{TM} balloon inflated at 40 mL. The distensibility index was 29.5 mm²/mmHg and 7.8 mm²/mmHg in HV and GP patients respectively, whereas intra-bag pressures are noted below the recordings.

447 **Figure 2.** Fluoroscopic view of the EndoFLIP^{TM} probe with its catheter and the balloon
448 correctly positioned at the pylorus.

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451 **Figure 3.** Endoscopic view of the EndoFLIP^{TM} probe with its catheter and the balloon
452 correctly positioned at the pylorus. Courtesy of Dr Romain Legros, Limoges University
453 Hospital.

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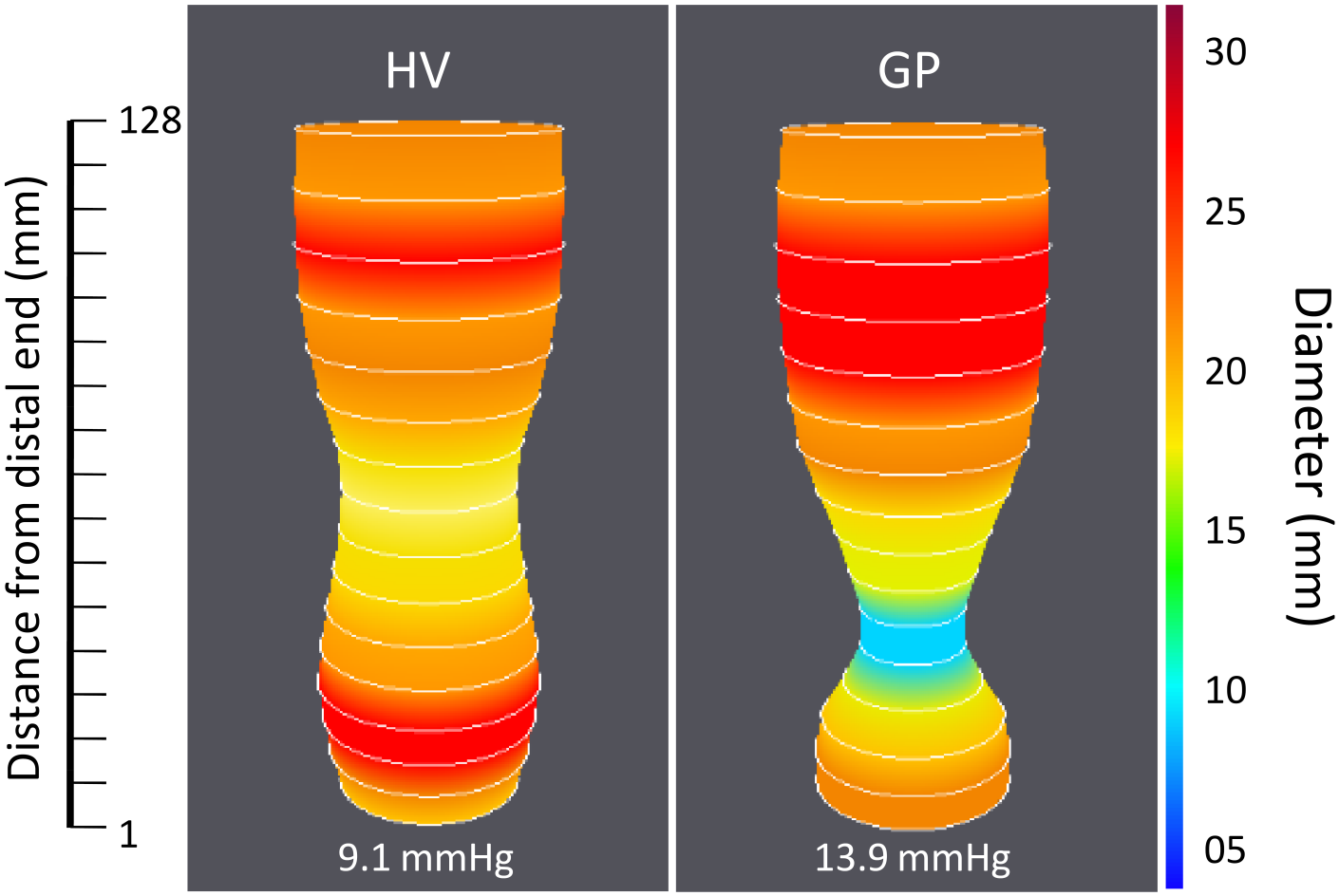

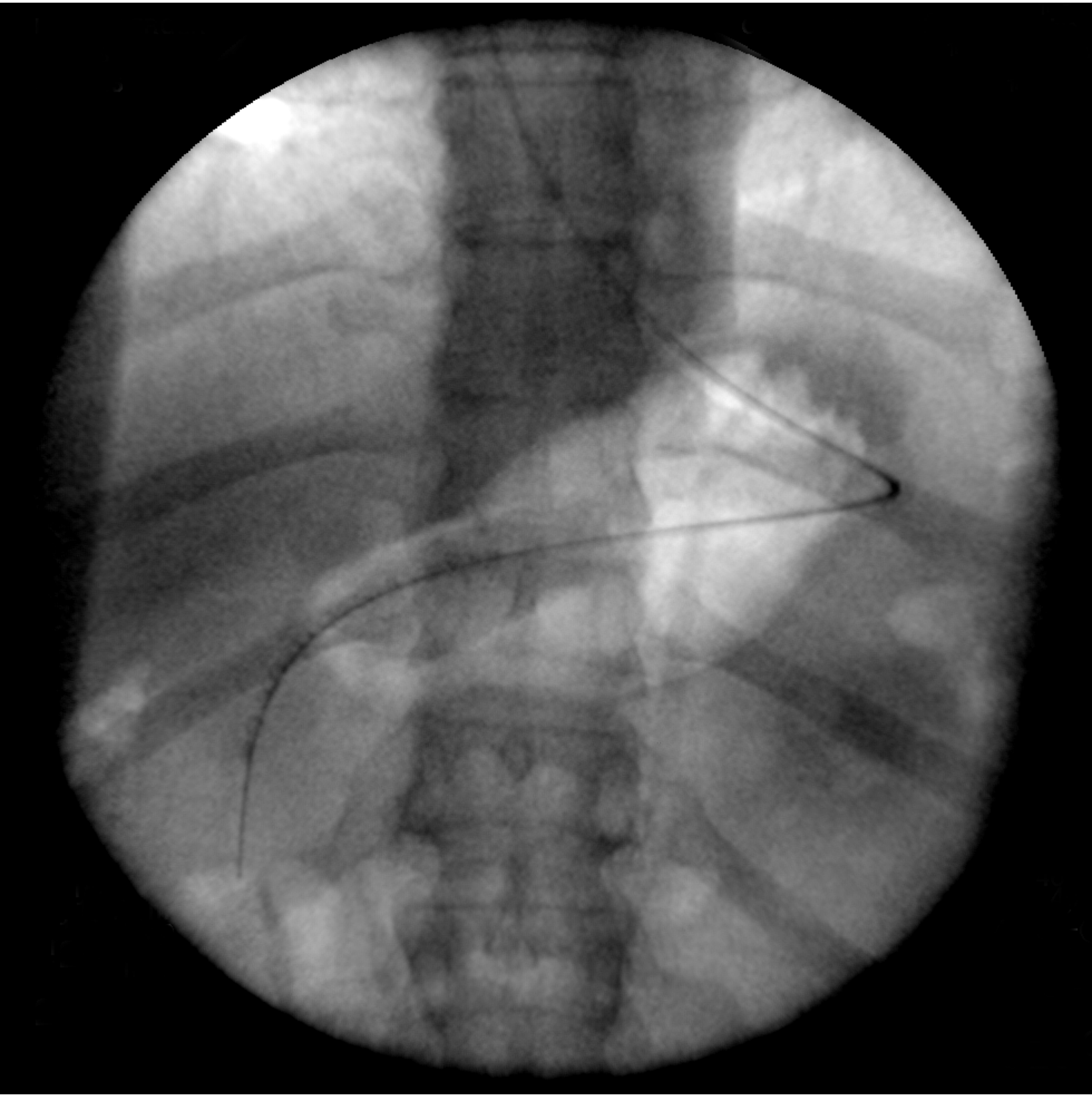

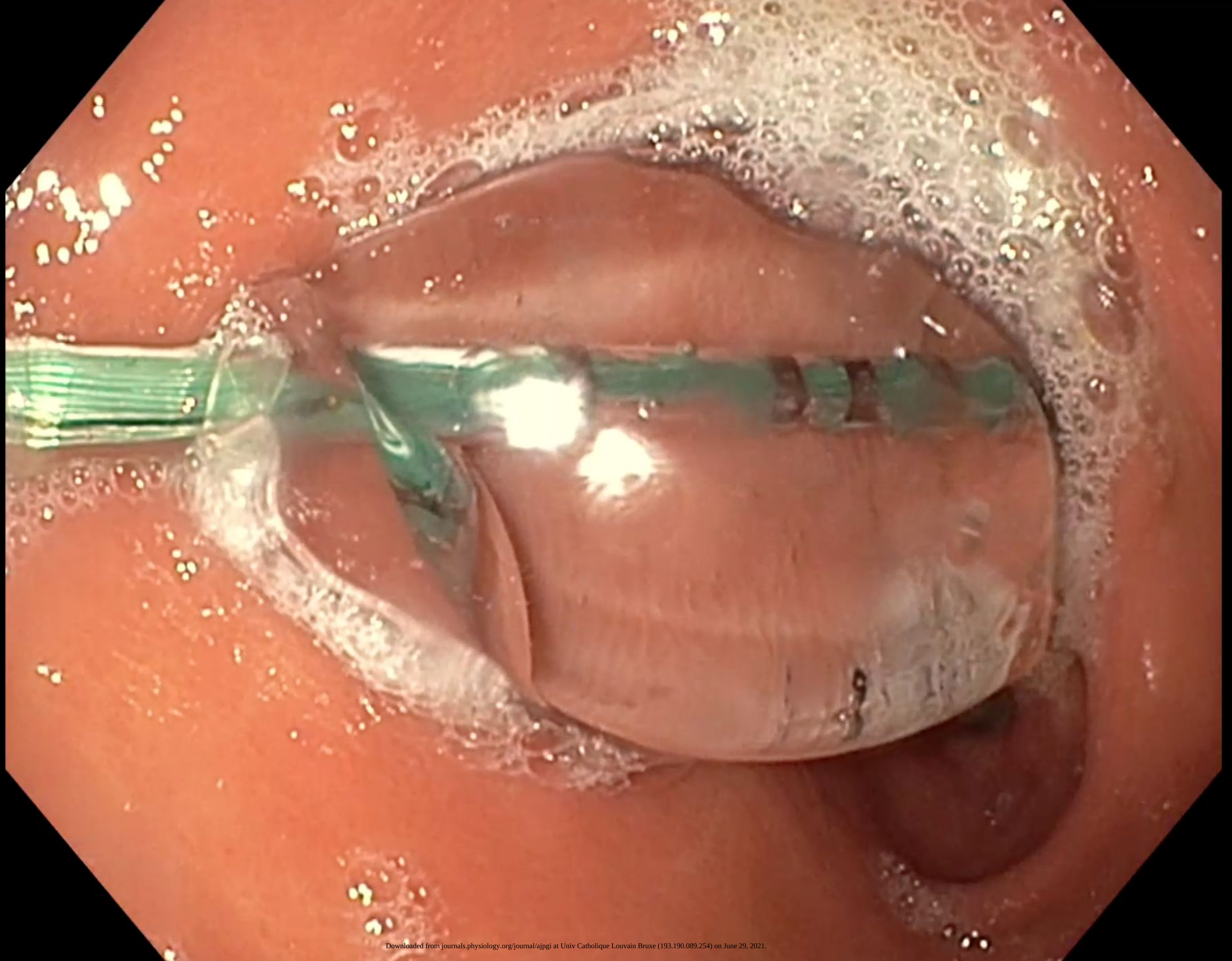

Table 1. FLIP metrics

Metrics	Abbreviation	Unit
Balloon distension volume	-	mL
Diameter	-	mm
Cross-sectional area	CSA	mm^2
Intra-bag pressure	-	mmHg
(Pyloric-)Distensibility Index	(P-)DI	mm^2/mmHg
FLIP: Functional Lumen Imaging Probe		

Table 2. Comparison of the two cohorts of healthy subjects assessed by EndoFLIP^{TM} at the pylorus

	French cohort (15)	**Indian cohort** (20)
Number, n	21	20
Male, n (%)	8 (38.1)	10 (50.0)
Mean age, years (range)	43.0 (29-58)	34.4 (18-54)
Diameter, mm	16.1 ± 2.1	13.0 ± 3.4
Pyloric pressure, mmHg*	9.7 ± 4.4	23.6 ± 15.3
CSA, mm²*	244.4 ± 48.4	141.7 ± 75.0
P-DI, mm²/mmHg*	25.2 ± 11.0	8.42 ± 4.7

CSA: Cross-Sectional Area, n: number, P-DI: Pyloric distensibility index

* Values are expressed as means ± standard deviation and correspond to a balloon inflation of 40 mL