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Propagation patterns of jejunal motor activity measured by high-resolution water-perfused manometry

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Abstract

Background: The manometric diagnosis of severe intestinal dysmotility is performed at most institutions using catheters with 2–8 sensors 5–10 cm apart. The recent application of high-resolution manometry catheters with closely spaced sensors to other gut segments has been highly successful. The objective of the present study was to determine the feasibility of a jejunal high-resolution manometry method and to carry out a descriptive analysis of normal jejunal motor function.

Methods: A 36-channel high-resolution water-perfused manometry catheter (MMS-Laborie, Enschede, The Netherlands) was orally placed in the jejunum of 18 healthy subjects (10 men, eight women; 21–38 age range). Intestinal motility was recorded during 5 h, 3 during fasting, and 2 after a 450 kcal solid-liquid meal. Analysis of motility patterns was supported by computerized tools.

Key Results: All healthy subjects except one showed at least one complete migrating motor complex during the 3 h fasting period. Phase III activity lasted 5 ± 1 min and migrated aborally at a velocity of 7 ± 3 cm/min. High-resolution spatial analysis showed that during phase III each individual contraction propagated rapidly (75 ± 37 cm/min) over a 32 ± 10 cm segment of the jejunum. During phase II, most contractile activity corresponded to propagated contractile events which increased in frequency from early to late phase II (0.5 ± 0.9 vs 2.5 ± 1.3 events/10 min, respectively; $p < 0.001$). After meal ingestion, non-propagated activity increased, whereas propagated events were less frequent than during late phase II.

Conclusions & Inferences: Jejunal motility analysis with high-resolution manometry identifies propagated contractile patterns which are not apparent with conventional manometric catheters.

KEYWORDS
high-resolution intestinal manometry, intestinal motility, postprandial motility, propagated contractions

Alcala-Gonzalez and Malagelada share first authorship.

1 | INTRODUCTION

Intestinal manometry is the current gold standard test for the diagnosis of intestinal motility disorders, but still relies on the methodology developed 40 years ago using manometric catheters with few (2–8), widely spaced (5–10 cm) recording sites.[1,2]

High-resolution manometry involves multiple and closely spaced recording sites covering a relatively long segment of the gut.[3] This methodology is particularly useful for the analysis of propagation patterns of motor activity.[4] Indeed, high-resolution manometry has become the gold standard for the evaluation of esophageal motor function.[5] Interesting data have been produced by exploratory studies in the proximal intestine,[6–9] but unfortunately, the application of high-resolution manometry for the evaluation of jejunal motility has been limited by the lack of commercially available high-resolution catheters long enough to cover the jejunum. Motor activity of the digestive tract can be recorded using solid-state or water-perfused systems. Solid-state catheters incorporate intraluminal pressure sensors; these catheters may experience shifts in basal pressure during prolonged studies, as required for evaluation of jejunal activity, are relatively fragile considering the sharp bends of the small intestine, and furthermore, are expensive. With multilumen water-perfused catheters, intraluminal pressures are transmitted from intraluminal side holes via water-filled lines to external pressure transducers; perfusion catheters are more robust and considerably less expensive than solid state. The accuracy of the recordings depends on the balance between the compliance of the lines and the perfusion rate. We used a water-perfused system with a perfusion rate that provided accurate detection of pressure waves (phasic jejunal contractions) and a total water load manageable for the duration of the studies.

The aims of the present study were as follows: (a) to determine the feasibility of a high-resolution manometry method to evaluate the activity of the jejunum; and (b) to carry out a descriptive analysis of normal jejunal motor function with particular focus on two aspects: the organization of fasting phase III activity, and the differences between fasting phase II and the postprandial pattern. To these aims, we designed a high-resolution manometry technology to measure jejunal motility by means of a 36-channel perfusion catheter with 1-cm spaced side holes.

Key points

- High-resolution manometry provides a new insight into the propagation patterns of jejunal contractile events.
- The different phases of the fasting and postprandial periods are characterized by a specific balance of propagated and non-propagated contractile activity.
- High-resolution manometry enhances the evaluation of jejunal motility, but its clinical value remains to be established.

2 | MATERIALS AND METHODS

2.1 | Study design

Unicentric, prospective, pilot study in healthy subjects recording the jejunal motor activity during fasting and after a standard meal by high-resolution manometry. The study protocol was approved by the Ethics Committee of the University Hospital Vall d'Hebron, and all participants gave their written informed consent before enrollment. The study protocol was registered with the ClinicalTrials.gov (ID: NCT04764019). All co-authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Participants

Eighteen healthy, non-obese subjects without a history of gastrointestinal symptoms were recruited by public advertising. Exclusion criteria were chronic health conditions, use of medications (except sporadic use of NSAIDs and antihistaminics), alcohol abuse, and use of recreational drugs. Absence of current digestive symptoms was verified using a standard abdominal symptom questionnaire (no symptom >2 on a 0–10 scale). Psychological and eating disorders were excluded using the following tests: Hospital Anxiety and Depression scale, Dutch Eating Behavior Questionnaire (Emotional eating, External eating, Restrained eating), and Physical anhedonia scale.

2.3 | Manometric equipment

A customized 36-channel perfusion high-resolution catheter was designed to measure jejunal motility (Mui Scientific). The catheter was made of silicone and had an external diameter of 4.7 mm, 36 lumens of 0.4 mm for pressure recording and one central lumen of 1.5 mm for guidewire placement. The first two perfusion side holes (recording sites) were located 58 and 48 cm from the tip of the catheter to register antral and duodenal contractions; the following 34 side holes, starting at 38 cm from the tip, were separated by 1 cm (4–38 cm from the tip) to measure jejunal contractile activity. Radio-opaque markers were located before the first and third most proximal side holes to facilitate fluoroscopic localization. The tip of the catheter incorporated a small weight (three 5 × 2 mm tungsten pellets) to facilitate progression of the catheter through the stomach. The catheter was connected to a low-compliance manometric system (Solar GI HRM manometry system, MMS-Laborie), and each channel was perfused with distilled water. Antral and duodenal recording sites served for final positioning of the catheter after intubation under fluoroscopic control.

The standard perfusion rate of the equipment is 0.15 ml/min which implicates a total water load of 1620 ml during the study. To attempt a reduction of the water load, a series of preliminary studies were performed correlating the perfusion rate and the pressure rise in response to occlusion of the side holes. Perfusion rates of

0.075, 0.1125, and 0.15 ml/min were tested; with each perfusion rate, three series of five consecutive 20-s occlusions were performed. Compared to the 0.15 ml/min perfusion rate, the 0.075 and 0.1125 ml/min perfusion rates reduced pressures at 20-s occlusion by 49 ± 3 and 24 ± 1%, respectively; the same relation was observed at different occlusion times. Since lower flow rates impaired pressure recordings, we finally established 0.15 ml/min flow rate per channel to be used.

2.4 | Manometry procedure

Studies were conducted at the Vall d'Hebron GI Motility Unit in the morning, after an overnight fast. The manometric system was first calibrated by connecting the catheter to the perfusion pump and baseline values were adjusted. Then, the catheter, with a metallic guidewire in the central lumen to facilitate localization, was introduced transnasally and placed into the small bowel under fluoroscopic control. Subjects were then conducted to a quiet room where the manometric catheter was connected to the recording system. Fasting intestinal motor activity was measured for 3 h in supine position and then a 450 kcal solid-liquid test meal was ingested in bed with the trunk at an angle of 45° to the horizontal. After meal ingestion, the study was continued in supine position for a 2 -h postprandial recording period.

2.5 | Analysis of manometric recordings

Studies were analyzed both visually and using the MMS Database Software v9.5h (MMS-Laborie) by two physicians (CM and LA).

Phases of the MMC were detected visually following standard criteria as follows: Phase III activity defined as regular contractile activity of more than 10 mmHg at a frequency of 10–12 contractions per minute during at least 2 min; Phase I activity, defined as the period of motor quiescence after phase III and followed by phase II; phase II was considered to begin when the first propagated contraction of more than 10 mmHg amplitude was detected after phase I, and to end when phase III activity began.

Baseline pressure was automatically determined every minute of recording using the 10th percentile level. Contractile events were predefined as an increase of pressure exceeding baseline pressure by more than 10 mmHg, lasting more than 2 s and <10 s. Computerized analysis was used to measure the number, frequency, and amplitude of phasic pressure waves (contractions) in fasting and fed periods. Artifacts, defined as simultaneous pressure rises occurring at all recording sites with similar amplitude and identical duration, were automatically excluded. Micturition episodes were identified during the recordings and also excluded from the measurements. Parameters in 10-min periods in the early and late phase II (just after phase I and before phase III, respectively) and early and late postprandial period (beginning and end of postprandial recording, respectively) were measured. In each channel, the area under the curve (AUC) was measured in the fasting and postprandial recording periods. The AUC was automatically calculated by the system integrating all pressure values above the 10^{th} percentile cut-off level every min and expressed as mmHg*min; hence, the area under the curve is a motility index accounting for the number and amplitude of contractions.

Propagated events were visually identified when the pressure contours of individual contractions overlapped between at least 10 consecutive sensors. Their velocity of propagation was measured as the length of propagation (distance between the first and last sensor detecting each propagated event) divided by the duration of propagation (time interval between the onset of the contraction at the first and last sensor). Non-propagated or shortly propagated irregular activity was measured by computerized analysis in the interim between propagated events during early phase II, late phase II, early postprandial, and late postprandial periods.

2.6 | Statistical analysis

Statistical analysis was performed with GraphPad Prism 9. Mean values (±SD) or median and 5th–95th percentile of the parameters measured were calculated. Normality of data distribution was evaluated by the Kolmogorov–Smirnov test. Comparisons of parametric, normally distributed data were made by Student's *t* test, paired tests for intragroup comparisons, and unpaired tests for intergroup comparisons; otherwise, the Wilcoxon signed-rank test was used for paired data within groups, and the Mann–Whitney *U* test for unpaired data between groups. Continuous variables were correlated using Pearson's *R*. One-way ANOVA was used for multiple comparisons; when the ANOVA was significant, post hoc comparisons were performed applying the Bonferroni multiple comparison correction procedure. Differences were considered significant at a p value <0.05.

3 | RESULTS

3.1 | Demographics and study flow

Eight women and 10 men, 21–38 years range with body mass index between 18.5 and 30 kg/m^2 participated in the study. Jejunal intubation was achieved in all participants in 86 ± 28 min. All participants tolerated the procedure, completed the study, and were included for analysis. Micturition episodes occurred 1–3 times per study (mean 1.8 ± 0.9).

3.2 | Fasting activity

In eight subjects two or more phase III fronts were observed, and in them, total duration of the MMC was 89 ± 38 min (range 44–155 min), including a phase of quiescence (phase I), a phase of intermittent, irregular activity (phase II) and a phase of continuous, rhythmic activity (phase III).

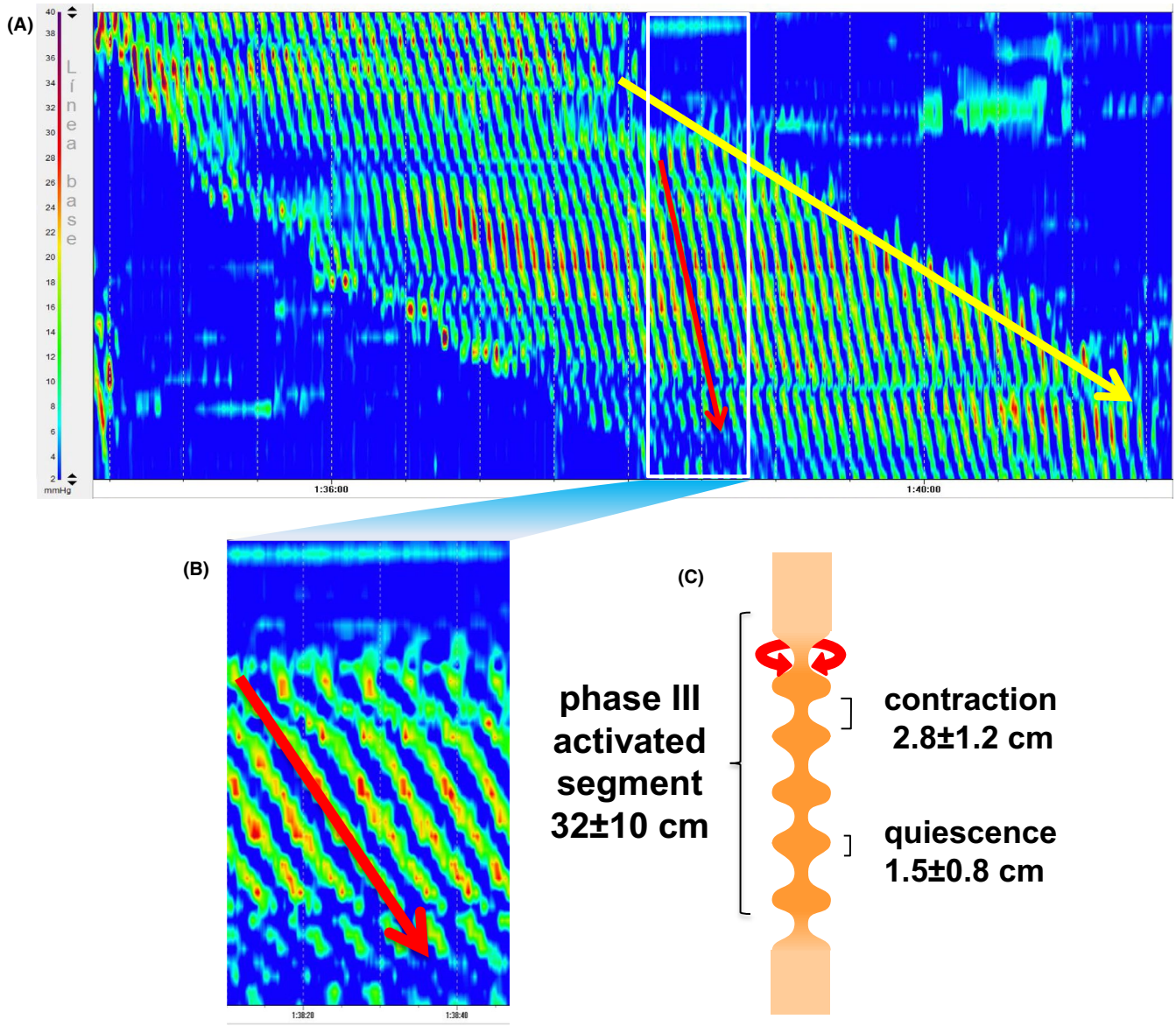

FIGURE 1 Jejunal phase III activity. (A) Example of high-resolution manometry (7 min recording) showing phase III activity. (B) Expanded tracing. (C) Schematic representation of jejunal segment activated during phase III. Note, migration of phase III activity front at 7 ± 3 cm/min (yellow arrow) and propagation of individual contractions at 75 ± 37 cm/min (red arrow) from top to bottom of the entire activated segment

3.2.1 | Phase III

Phase III activity fronts were observed 1–3 times per subject in all subjects but one (total 25 phase III fronts in 17 subjects; mean 1.5 ± 0.7 fronts/subject). Based on the antral recording site, it was detected that 75% of the phase III activity fronts originated in the antrum. The duration of phase III activity (5 ± 1 min; range 2–8 min) was longer at the distal recording sites (mean of 5.2 ± 1.5 min over the 10 proximal sites vs 5.6 ± 1.6 min over the 10 distal sites; $p = 0.029$). Phase III fronts migrated from the most proximal recording sites in caudad direction at a mean velocity of 6.6 ± 2.8 cm/min and the velocity decreased distally (mean of 7.9 ± 3.7 min over the 10 proximal sites, and 6.0 ± 3.0 min over the 10 distal sites; $p = 0.008$). The length of the jejunal segment simultaneously generating phase III activity, calculated by the function: length (cm) = migration velocity (cm/min) × duration (min), was 32 ± 10 cm (range 11–37 cm; Figure 1). In 12 phases III, the length of the activated segment exceeded the 33 cm recording span; in the other 13 phases III, the activated segment was entirely visible and in them, the length of the segment directly measured by the number of recording sites activated, exhibited a close correlation with the length calculated by the mathematical function ($R = 0.856$; $p < 0.001$).

Jejunal phase III activity was characterized by continuous phasic activity at a rhythm of 11 ± 1 contractions/min (Table 1), and the frequency was similar at the proximal and distal recording sites. At each recording site, the individual contractions had an average duration of 3.4 ± 0.5 s and were simultaneously recorded over several contiguous recording sites covering an extension of 2.8 ± 1.2 cm of intestine. Contractions were separated by a gap of 2.1 ± 0.3 s and the length of the quiescent jejunal sections between contractions

TABLE 1 Jejunal motility normal range values in the fasting and postprandial periods

	Mean ± SD	5th–95th percentile
Phase I		
Frequency, contractions/min	0.4 ± 0.1	0.2–0.6
Contraction amplitude, mmHg	14.5 ± 3.4	12.0–18.9
AUC, mmHg*min	94 ± 5	67–123
Phase II		
Early phase II		
Frequency, contractions/min	0.9 ± 0.4	0.3–1.8
Contraction amplitude, mmHg	14.1 ± 6.8	5.7–23.2
AUC, mmHg*min	121 ± 43	83–197
Late phase II		
Frequency, contractions/min	2.1 ± 0.5	1.3–3.0
Contraction amplitude, mmHg	20.7 ± 3.2	16.2–26.4
AUC, mmHg*min	178 ± 38	129–243
Phase III		
Frequency, contractions/min	11.0 ± 0.8	10.2–12.0
Contraction amplitude, mmHg	24.0 ± 3.6	17.3–29.3
AUC, mmHg*min	548 ± 101	405–733
Postprandial period		
Early postprandial		
Frequency, contractions/min	3.9 ± 1.5	2.1–7.9
Contraction amplitude, mmHg	22.4 ± 2.8	18.2–29.3
AUC, mmHg*min	270 ± 105	182–449
Late postprandial		
Frequency, contractions/min	3.4 ± 1.1	1.8–5.9
Contraction amplitude, mmHg	20.7 ± 3.0	16.8–27.2
AUC, mmHg*min	233 ± 75	165–374

was 1.5 ± 0.8 cm. Hence, the area of jejunum activated during phase III (32 ± 10 cm), generated 7.8 ± 3.0 contracted sections of intestine of 2.8 cm separated by corresponding 1.5 cm sections of non-contracted intestine (Figure 1). High-resolution analysis also showed that the individual contractions conforming phase III propagated over the entire segment of activated intestine (from top to bottom), traveling rapidly at 75 ± 37 cm/min. The propagation velocity of the individual contractions correlated with the migration velocity of the phase III activity front, that is, when the phase III migrated faster, the propagation velocity of the individual contractions was quicker ($R = 0.76$, $p < 0.001$).

3.2.2 | Phase II

The mean duration of phase II was 72 ± 36 min (31–137 min range). Contractile activity was irregular, but, a consistent increase over time from early to late phase II was observed in all subjects (AUC 121 ± 43 vs 178 ± 38 mmHg*min, respectively; $p < 0.001$; Table 1).

Most contractile activity during phase II corresponded to propagated contractile events which increased in frequency from early to late phase II (0.5 ± 0.9 vs 2.5 ± 1.3 events/10 min, respectively; $p < 0.001$). Most events (79%) initiated at the proximal recording sites and propagated at 80 ± 33 cm/min throughout the 34 jejunal recording sites, the rest originated at different levels and migrated over 22 ± 5 cm (Figure 2). Retrograde propagation was exceptional (2 ± 4% of events per subject). The number of contractions in these propagated events ranged between 1 and 5, similarly in early and late phase II ($p = 0.176$). Single-contraction events (34%) propagated faster than multiple contraction events (106 ± 32 vs 68 ± 25 cm/min, respectively; $p < 0.001$). The proportion of single vs multiple contraction events and their velocity of propagation did not change from early to late the phase II. No rhythm in the sequence of propagated events was detected.

In-between these propagated events, contractile activity was scarce and corresponded to phasic, low-amplitude, non-propagated, or shortly propagated contractions (Figure 3); to note, the number of contractions in these interim periods corresponded to a relatively small proportion (26 ± 13%) of the total contractions during phase II, including propagated events.

3.2.3 | Phase I

Phase I lasted 12 ± 5 min (range 5–21 min) and was characterized by practically absent contractile activity (0.4 ± 0.1 contractions/min; Table 1).

3.3 | Postprandial activity

After meal ingestion, intestinal contractility increased and remained stable in frequency and amplitude throughout the 2-h postprandial recording period (AUC 270 ± 105 mmHg*min in the early vs 233 ± 75 in the late postprandial period; $p = 0.094$). The AUC of the postprandial period was consistently higher than during fasting phase II ($p < 0.001$ vs both early and late phase II; Table 1).

The increase in contractile activity was due to an increase in non-propagated or shortly propagated irregular activity which was more intense than during phase II (3.1 ± 1.6 vs 1.1 ± 0.4 contractions/min; $p < 0.001$; Figure 2).

By contrast, propagated events were less frequent than during late phase II (Figure 3). The proportion of single-contraction propagated events was reduced compared to phase II (16% vs 34%; $p = 0.001$) and remained stable throughout the postprandial period. No rhythm in the sequence of these propagated events was detected.

3.4 | Effect of sex and body weight

No significant differences were found when comparing motility parameters between men and women, except the velocity of phase III

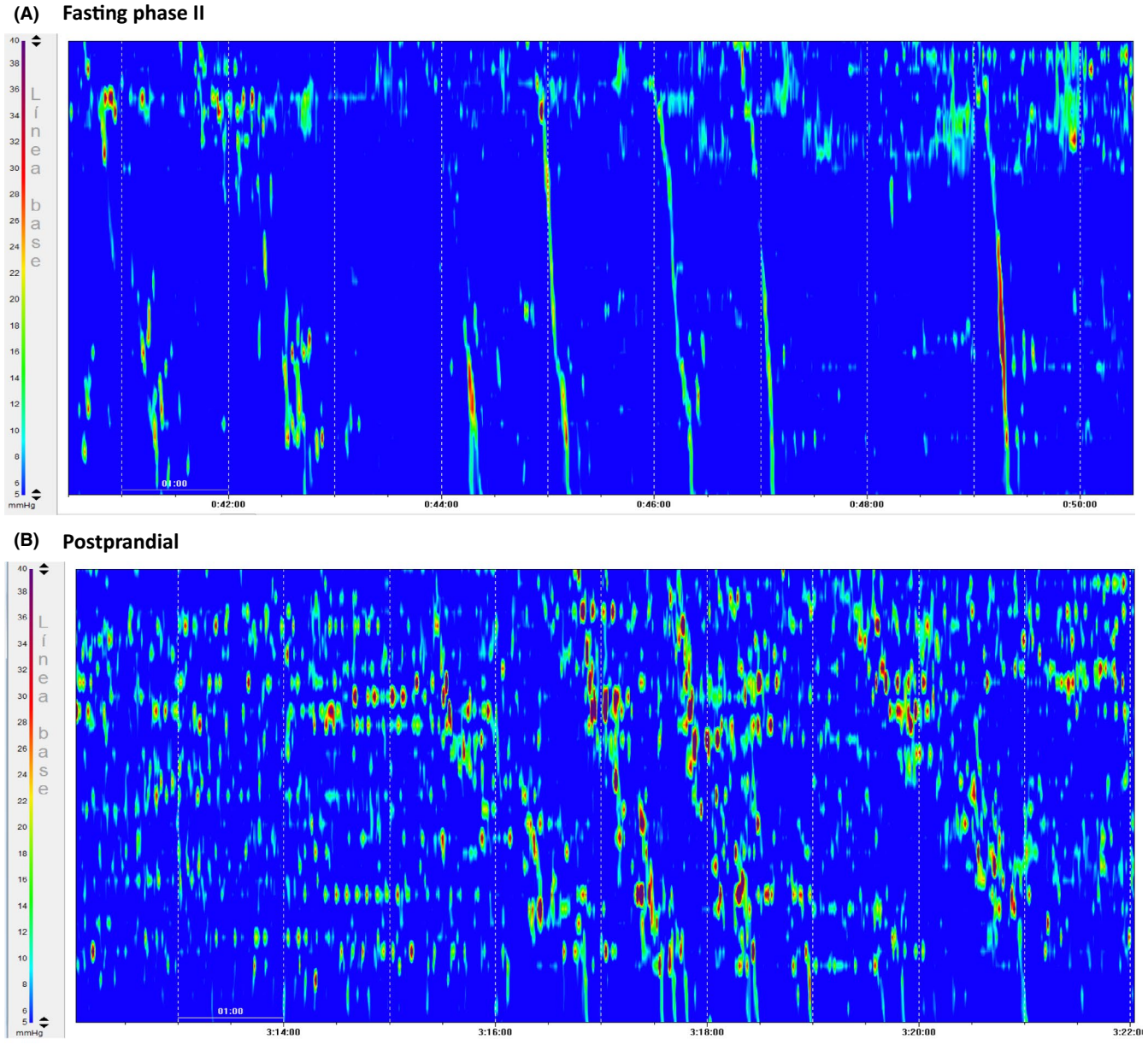

FIGURE 2 Fasting late phase II and postprandial high-resolution manometry recordings (10 min) in the same subject. Note, different contribution of propagated and non-propagated activity with increased non-propagated activity and reduced propagated events in the postprandial period as compared to fasting phase II

migration, which was slower in women (5.6 ± 1.8 vs 8.9 ± 3.6 cm/min, $p = 0.017$). No correlations between body mass index and the motility parameters measured were detected.

4 | DISCUSSION

Our study shows that high-resolution manometry identifies two distinct motor components in the jejunum: non-propagated and propagated activity. Two aspects should be highlighted in this regard: the organization of fasting phase III fronts, and the striking differences between fasting phase II activity and the postprandial pattern.

The muscle cells within the intestinal wall generate continuous rhythmic oscillations (8–12 cycles/min) of their membrane potential called slow waves. When membrane depolarization of the slow wave overcomes a certain threshold, spiking activity triggers phasic contractions of the smooth muscle. Intestinal motor function is orchestrated by the interstitial cells of Cajal, also called pacemaker cells, which are electrically coupled to the smooth muscle cells through gap junctions forming an extensive electrical syncytium that controls the propagation of contractions.[10,11] Our data show that during phase III a relatively long segment of jejunum becomes activated; the rhythm, propagation length, and velocity of the individual contractions during phase III indicate that every

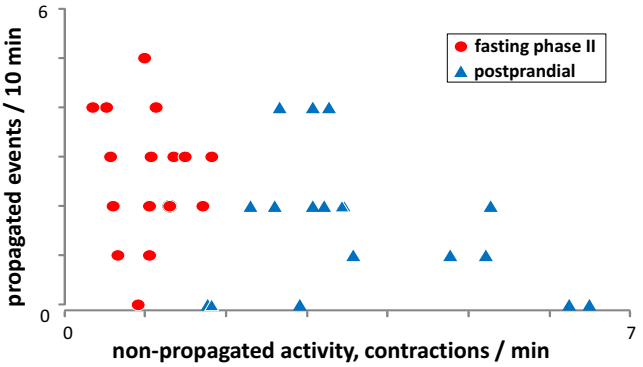

FIGURE 3 Individual data correlating propagated events and non-propagated activity. Note, discrimination between fasting late phase II and postprandial activity by high-resolution manometry

slow wave reaches the depolarization threshold and generates propagated contractions running from top to bottom of the activated segment.

In contrast to the uniformity of propagated activity during phase III, high-resolution manometry identified during phase II continuous non-propagated activity with interspersed propagated events. Propagated events were characterized by fronts of 1–5 powerful contractions rapidly propagating over long segments of the jejunum, and accounted for the major part of the activity, while non-propagated activity was relatively scarce and weak. High-resolution manometry after meal ingestion identified a distinctly different postprandial motor pattern, in which non-propagated (or shortly propagated) contractile activity became more prominent, with more frequent and stronger contractions, while propagated events decreased.

Classical studies in dogs correlating intestinal motor patterns with flow of contents help to interpret our results.[12–14] Indeed, flow of contents was maximal during fasting phase III, with peristaltic contractions squeezing the activated segment of jejunum, but still quite active during phase II, supporting the concept of the housekeeper role of fasting activity, which is concordant with the predominant propagated activity detected by our study during fasting.[15,16] Conceivably, the prominent non-propagated or shortly propagated activity in the postprandial period is related to mixing and stirring of contents, while sparse propagated events contributed to spreading of chime recruiting more distal areas of the intestine in the digestive process.[17]

Our study shows that small bowel high-resolution manometry is feasible. The superiority of multiple, closely spaced sensors in the evaluation of propagated activity has been previously described both in the small bowel and colonic studies.[18–20] The catheter designed was custom-made, but the rest of the perfusion manometry equipment is standard. Intubation was uneventful in all participants and the test was well tolerated.

Technical limitations in the acquisition process have to be acknowledged. The elasticity of the wall and the length of the silicon catheter increases the compliance of the line. By a series of preliminary studies, we determined the perfusion rate to be used, but still the system damps the recording of pressure peaks. Comparisons with conventional low-compliance or solid-state equipments can be figured out based on phase III activity, which is decreased by approximately 2–5 mmHg by our system.[21–23] During the 5 h recording, a relatively high water load flows from the perfused channels into the intestine, calling for bladder emptying during the study. The span covered by the catheter (33 cm) was too short to measure the length of the jejunal segment simultaneously generating phase III: 50% of phases III exceeded 33 cm and a formula had to be used to estimate the phase III span. Furthermore, the acquisition of multiple data requires automated analysis. With the current tools, we focused on relatively long-distance propagated activity, but the analytical paradigms can be further developed and upgraded for a more precise definition of non-propagated and shortly propagated activity.

The relevance of high-resolution manometry for the clinical evaluation of small bowel motor function in patients with suspected dysmotility remains to be established, but the sensitivity of the technique in the detection of propagation patterns of contractile activity may prove valuable for diagnostic purposes.

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CONFLICT OF INTEREST

No conflicts of interest.

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