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RESEARCH ARTICLE

Translational Physiology

Measuring autonomic influence on gastrointestinal contractility: development and preliminary validation of novel capsule-based indices

Mitali Mehta,[1] Zhan Zhao,[2] Asala Erekat,[1] Jack Semler,[3] Niyati Neupane,[1] Bridget R. Mueller,[1] Kaitlyn Coyle,[1] Gabriela Cedillo,[1] and Jessica Robinson-Papp[1]

[1]*Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, United States;* [2]*Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York, United States; and* [3]*Amherst, New York, United States*

Abstract

The migrating motor complex (MMC) is a key feature of fasting gastrointestinal (GI) motility, but its disruption in neuropathic conditions remains poorly characterized. Wireless motility capsules (WMCs) offer a noninvasive means of collecting motility data, facilitating study of larger cohorts. We aimed to develop WMC-derived metrics to identify neuropathic dysmotility and its associations with autonomic nervous system (ANS) function. We analyzed WMC data from 98 controls and 71 people living with human immunodeficiency virus (HIV; PWH) in whom autonomic neuropathy (AN) and delayed small bowel transit time (dSBTT) are common. We studied nine contractility metrics, including established and novel metrics targeting rhythmic bursts of sustained contractile activity. Autonomic function, summarized as Modified Composite Autonomic Severity Score (MCASS), was used to draw associations with contractility measures. All contractility metrics were higher in PWH compared with controls ($P \leq 0.01$ for all). Among PWH, those with AN showed the highest contractility, whereas those with dSBTT had the lowest. In controls, rhythmic bursts were more clustered, especially in the later portions of the small bowel recording, and had less variability in contraction amplitude and timing, potentially indicating greater organization. Overall, worse autonomic function was associated with higher contractility. WMC-derived metrics effectively capture fasting small bowel motility and may distinguish neuropathic patterns, which appear to progress from increased, disorganized contractility to decreased contractility as dSBTT develops. Future studies should validate these findings in other WMCs and populations to clarify their potential in advancing understanding of the pathophysiology of gut-brain-axis disorders.

NEW & NOTEWORTHY This study introduces novel WMC-derived contractility indices to quantify gastrointestinal motility, enabling noninvasive characterization of neuropathic dysmotility. In PWH, hypercontractility and disorganized rhythmic bursts were observed despite autonomic neuropathy and delayed transit, suggesting a spectrum in which inefficient high-amplitude contractions initially may preserve transit before progressive delay ensues. Leveraging raw pressure data from WMC technology, these indices are linkable to extrinsic autonomic biomarkers and may advance understanding of gut-brain axis disorder pathophysiology.

autonomic dysfunction; enteric nervous system (ENS); migrating motor complex (MMC); neuropathic dysmotility; wireless motility capsule (WMC)

INTRODUCTION

In between meals, a migrating motor complex (MMC) moves throughout the small intestine, sweeping along any remaining debris and preventing stasis of luminal contents (1, 2). The components of an intact MMC have been well documented in humans using catheter-based manometry (3). In general, one representative MMC cycle might last ~90 to 120 min; the majority of this time is either quiescence (*phase 1*) or infrequent/irregular contractions (*phase 2*), followed by ~10 min of regular high-amplitude contractions (*phase 3*) (4). In manometry recordings, *phase 3* can be observed as a burst of propagating contractions (~11–12 cycles per minute) migrating distally along the small bowel. The amplitude and propagation rate of *phase 3* contractions generally decrease as they approach the ileum, reflecting distinct regional variations in small bowel motility patterns (2, 5).

An intact gastrointestinal (GI) neuromuscular apparatus is essential for the coordinated functioning of an effective

Correspondence: M. Mehta (mitali.mehta@mssm.edu).
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MMC and forms a key part of the gut-brain-axis (GBA) (6, 7). This neuromuscular apparatus comprises longitudinal and circular muscle layers, the interstitial cells of Cajal (ICCs), the neurons of the enteric nervous system (ENS), and the neurons of the extrinsic autonomic nervous system (ANS). ICC, the pacemaker cells of the gut, sets the foundational contractility rhythms by generating electrical slow-wave activity, which is then modulated by the ENS. ENS neurons are diverse; ENS sensory, motor, and interneurons operate local reflex arcs, which allow GI contraction patterns to respond to local conditions (8). The ANS, through sympathetic and parasympathetic fibers, innervates the gut wall and modulates ENS activity via neurotransmitters, primarily norepinephrine (inhibitory) and acetylcholine (stimulatory), respectively (9). Sympathetic fibers may also exert direct effects on smooth muscle. Overall, parasympathetic input promotes, while sympathetic activity inhibits, GI contractility (9, 10).

Given this anatomical framework, disruption of the MMC is typically broadly attributed to neuropathic, and less commonly myopathic, etiologies. Characteristic manometric patterns have been described for both myopathic and neuropathic dysmotility (4). However, these findings are based on limited data, since the procedure of manometry is invasive and requires specialized expertise. Myopathy is rare and generally marked by hypomotility. In contrast, neuropathic changes are generally described as increased and/or disordered contractions including prolonged tonic rises in baseline pressure, abnormal propagation of *phase 3* activity, and extended high-frequency contractions and/or high-amplitude contractions (11). However, the data supporting these characterizations are limited, typically being derived from small studies and expert opinion.

The wireless motility capsule (WMC) offers an alternative, scalable method for assessing GI pressure patterns, with advantages in tolerability and ease of administration over traditional manometry. However, a significant challenge in using the WMC to characterize normal or disordered small intestinal pressure waves is that the capsule is not stationary. The WMC may be propelled by GI contractions and carried by some pressure waves, while potentially being bypassed by others, thus complicating the interpretation of underlying motility patterns.

The primary aim of this study was to develop novel metrics from WMC-derived pressure data to define normal fasting small intestinal motility and distinguish it from neuropathic dysmotility. We further sought to evaluate whether these metrics correlate with objective measures of extrinsic ANS influence, in its sympathetic and parasympathetic branches. To do so, we performed a secondary analysis of previously collected WMC data from 98 healthy asymptomatic individuals (with no significant GI comorbidities) and 71 people living with human immunodeficiency virus (HIV; PWH) enrolled in previous studies. HIV infection is known to cause direct ENS injury (12) and is also frequently associated with dysfunction of the extrinsic ANS, a condition known as HIV-associated autonomic neuropathy (HIV-AN) (13). We have previously shown that PWH commonly exhibit delayed small bowel transit time (dSBTT) (14), and therefore, PWH represent an ideal population for studying neuropathic GI dysmotility.

METHODS

Study Population and Testing Procedures

For the current analysis, data were compiled from 168 participants who underwent standardized WMC assessment in three prior studies. Data for healthy controls ($n = 98$) were sourced from two prior studies coauthored by J.S. (15, 16), whereas data from PWH ($n = 71$) were obtained from a single cross-sectional study (14). All procedures were performed in accordance with protocols approved by the appropriate Institutional Review Board (IRB) and all participants provided written informed consent. Recruitment methods, eligibility criteria, and testing procedures have been detailed in prior work (14).

A standardized WMC testing procedure was used across studies as previously described (14, 17). After ingestion, the WMC (Medtronic) travels through the GI tract, continuously recording intraluminal pressure data at a 2 Hz sampling rate during the first 24 h, and one reading per second thereafter (18, 19). These data are transmitted to a receiver that the participant must keep within 3 ft, typically on a lanyard around their neck during waking hours and at bedside at night. The data were initially downloaded using a proprietary software MotiliGI (v. 3.1, Medronic Inc.) for transit time analysis. Subsequently, another proprietary software, gastrointestinal motility software (GIMS, v. 3.0) data viewer, was used to isolate and extract pressure recordings from the small bowel of each participant as a CSV file.

The PWH cohort also underwent a noninvasive standardized battery of autonomic function tests (AFTs) from WR Medical Electronics to assess the extrinsic ANS. The testing protocol assesses the integrity of autonomic reflexes including an evoked sweat (sudomotor) response (Q-Sweat), heart rate response to deep breathing, the Valsalva maneuver, and tilt table testing (20). Data from these assessments were used to calculate two validated scores: Composite Autonomic Severity Score (CASS) and Modified Composite Autonomic Severity Score (MCASS). A CASS score of $\geq$3 was used to define extrinsic autonomic neuropathy (AN) to maintain consistency with prior work in HIV (21), although higher CASS scores (e.g., $\geq$5) have been associated with symptomatic autonomic failure (20). HIV-AN is typically less severe. We historically adopted a cutoff of 3 to distinguish normal from abnormal findings to increase specificity in PWH, who often present with complex medical comorbidities. The MCASS and its three subscores (cardiovagal, sudomotor, and adrenergic) were used for correlative analyses, given their broader range of values (21). The cardiovagal subscore reflects parasympathetic dysfunction, the sudomotor subscore reflects cholinergic sympathetic innervation of the skin, and the adrenergic subscore reflects cardiovascular sympathetic dysfunction. In addition, we calculated adrenergic (i.e., sympathetic) baroreflex sensitivity (BRSA), because we have previously shown that there may be sympathetic overactivity in early AN and CASS and MCASS only capture hypoactivity (22, 23).

Based on these testing procedures, it would have been possible to create four subgroups of PWH: +/− delayed small bowel transit time (dSBTT), +/− AN. However, due to relatively small numbers, we chose to create three groups: dSBTT ($n = 16$); normal SBTT with AN ($n = 24$); and normal

SBTT without AN ($n = 30$). Such grouping also had a physiological rationale in that the presence of dSBTT implies dysfunction of the GI neuromuscular apparatus (regardless of the presence or absence of extrinsic AN).

WMC Data Preprocessing

The WMC fails to transmit data whenever the participant is out of range (typically further than three feet) from the receiver. Thus, to ensure data quality we prescreened all data files to exclude those with excessive gaps. We found no prior literature to guide this process and so developed our own criteria. Files were retained only if they contained at least 60 min of valid small bowel pressure data (not necessarily continuous) to provide sufficient sampling of pressure data. Previous WMC (SmartPill) studies (24, 25) required 80%–90% data completeness over the entire transit period to avoid participant exclusion. We chose a much more inclusive approach, so our results would be maximally generalizable to real-world settings. In addition, we further required at least one continuous period of at least 5 min during which at least 20 contractions were observed. A contraction was defined as a pressure event consisting of one or more peaks exceeding 10 mmHg, ending when the signal returned below 10 mmHg (26). We required this because some of our metrics were designed to quantify features of rhythmicity. The 5-min window was selected based on prior literature, showing that *phase 3* MMC bursts typically last 5–10 min; choosing the shorter time frame minimized participant exclusion (27). All preprocessing steps (and subsequent analyses) were performed using custom-developed R scripts (28).

WMC Contractility Metrics

We calculated two standard contractility metrics that have been previously described, sum of the amplitudes and motility index (MI) (29–31), as well as several novel metrics (Table 1).

Conceptually, these metrics were grouped into three categories. The total contractility metrics (sum of amplitudes and MI) are commonly used and aim to quantify the overall contractile activity experienced by the WMC during its passage through the small bowel. Sum of amplitudes is especially sensitive to missing data. Thus, for this metric only we implemented an imputation procedure to address more limited missing data in participant files, which had passed the initial screening process. Missing values were estimated using mean imputation, calculated as a rolling average from the 1-min contraction window before and after each gap.

Time-adjusted contractility metrics (contractions per hour, high-amplitude contractions per hour, and the fraction of time spent rapidly contracting) were more novel and sought to reflect, in various ways, the vigorousness of contractility observed by the WMC adjusting for differences in SBTT.

The rhythmicity-based metrics were the most conceptually novel. Our goal in developing them was to identify and quantify periods of high rhythmicity, under the premise that they might represent *phase 3* of the MMC and might be particularly susceptible to changes related to dysfunction of the GI neuromuscular apparatus. Taking a cue from the cardiac autonomic literature, we also aimed to investigate the

Table 1. *WMC contractility metrics*

Motility Metric	Definition	Purpose/Construct Being Measured
Total contractility metrics		
Sum of the amplitudes	Cumulative sum of all pressure readings after imputation of missing data	Total pressure propelling the WMC through the small bowel
MI	Comprehensive measure of motility combining contraction frequency and amplitudes	Overall contractility of small bowel
Time-adjusted contractility metrics		
Contractions per hour	Total number of contractions divided by SBTT in hours	Overall contractility, adjusting for SBTT differences
High-amplitude contractions per hour	Total number of high-amplitude contractions divided by SBTT in hours. High amplitude defined as >26.7 mmHg based on prior literature (30, 32).	Overall high amplitude contractility adjusting for SBTT differences
Fraction of time spent rapidly contracting	Total number of minutes with ≥10 contractions per minute divided by SBTT in minutes. It reflects the proportion of SBTT characterized by high frequency contractility (33).	Overall high frequency contractility adjusting for SBTT differences
Rhythmic bursts metrics		
Rhythmic bursts *1*) Slow rhythmic bursts *2*) Medium rhythmic bursts *3*) Fast rhythmic bursts	5-min nonoverlapping bursts of elevated contraction frequency containing at least 20 contractions (4/min) further divided into: *1*) Slow: 20–29 (~4–6/min) *2*) Medium: 30–39 (~6–8/min) *3*) Fast: ≥ 40 (~8/min or greater)	Periods of rhythmicity potentially reflective of *phase 3* MMC
Rhythmic bursts per hour	Total number of all non-overlapping rhythmic bursts divided by the duration of recorded small bowel pressure data in hours	Quantify periods of rhythmicity potentially indicative of MMC *phase 3*
RMSSDa	Median of the root mean square of successive differences in peak amplitudes across all rhythmic bursts	Variability in contraction strength during rhythmic bursts
RMSSDt	Median of the root mean square of successive differences in time between peak amplitudes, reported separately for slow, medium, and fast rhythmic bursts	Variability in timing of contractions during rhythmic bursts

MI, motility index; MMC, migrating motor complex; RMSSDt, root mean square of successive differences for time; RMSSDa, root mean square of successive differences for amplitude; SBTT, small bowel transit time; WMC, wireless motility capsule.

variability in contractions during segments of high rhythmicity as a potential indicator of autonomic influence. We defined "rhythmic bursts" as 5-min nonoverlapping periods in which at least 20 contractions were observed (i.e., 4 per minute) (Fig. 1). The 5-min window was chosen because the typical *phase 3* duration is 5–10 min. Longer durations would have reduced the number of analyzable rhythmic bursts, and shorter durations would have limited the validity of the variability assessments described in RESULTS. These rhythmic bursts were further categorized into fast, medium, or slow, corresponding to on average approximately ≥8, 6–8, or 4–6 contractions per minute (CPM), respectively (see also Table 1). Although *phase 3* of the MMC has a well-defined frequency of 11–12 CPM, we implemented these more inclusive thresholds to capture rhythmicity across a broader range while also accounting for WMC limitations (e.g., sensor mobility) (30) and known lower distal frequencies as reported in manometry studies. This approach enabled a more detailed quantitative characterization, preserving the distinct rhythmic patterns of varying frequencies rather than combining them into a single measure. In cardiac literature, root mean square of successive differences (RMSSD) is used as a measure of heart rate variability (HRV), which is widely accepted as a reflection of autonomic influence (34, 35). We adapted this concept. Within the rhythmic bursts, we calculated RMSSD to measure variability in time between contractions [RMSSD time (RMSSDt)] and variability in contraction amplitude [RMSSD amplitude (RMSSDa)] as defined in Table 1. We reported RMSSDt separately for slow, medium, and fast rhythmic bursts because RMSSDt is expected to differ based on contraction rate (with greater time variability between contractions at slower contraction rates). Conversely, RMSSDa was reported across all time intervals.

Statistical Considerations

All analyses were performed using customized R (28) and python (36) scripts. The source code for this study is available at github. Descriptive statistics were performed for demographic, GI, and autonomic variables. Plots were created to visualize the distribution throughout the small bowel of slow, medium, and fast rhythmic bursts (Fig. 2). For the purpose of these plots only, we created a new standardized time variable "fractional SBTT," which ranged from 0 to 1; thus, for each patient, zero corresponded to their gastric emptying time (GET) and 1 corresponded to passage through the ileocecal junction (ICJ).

Statistical significance was assessed at an $\alpha = 0.05$ level for all inferential statistics. In the primary analyses, all the GI contractility metrics (Table 1) were calculated for all participants, and median values were compared between healthy controls ($n = 98$) and PWH ($n = 71$) using the Mann–Whitney U and Chi-square tests. Given the imbalances in sex and age between the groups (PWH were older and had a higher proportion of men), we performed multivariable analyses adjusting for age and sex using negative binomial, quasibinomial regression, or analysis of covariance (ANCOVA) models (as appropriate to the data type). We used a threshold of a 10% change in regression coefficients to assess for the presence of confounding. In secondary analyses, the GI contractility metrics were compared across four groups (healthy

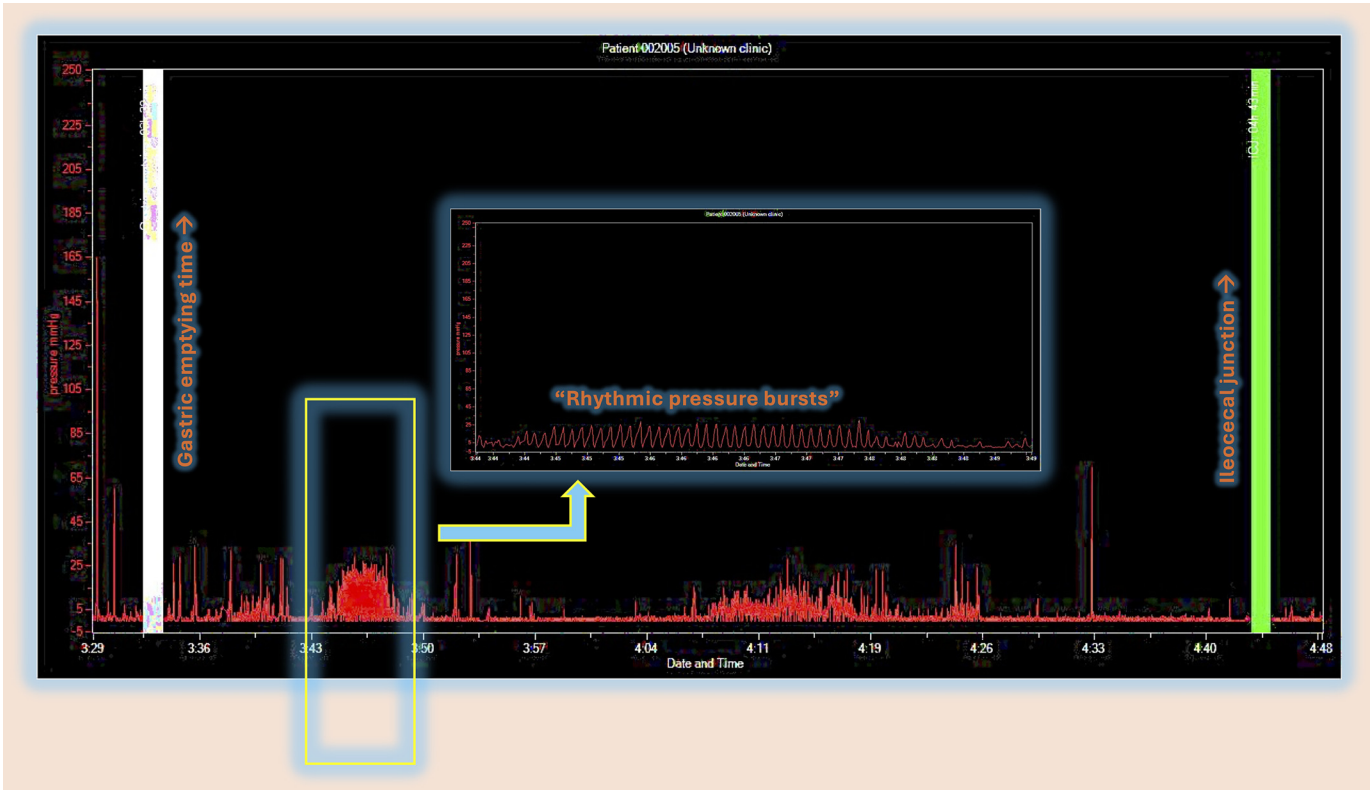

Figure 1. Rhythmic pressure bursts observed in wireless motility capsule (WMC)-derived pressure data, used to define and quantify rhythmic bursts and associated measures.

controls and the three PWH groups: dSBTT, AN, and normal PWH) using the Kruskal–Wallis test. For contractility metrics displaying an overall significant difference across the four groups, we also performed post hoc pairwise comparisons (Dunn's test with Bonferroni correction) to determine which groups were the primary drivers of the observed differences.

Healthy controls did not undergo autonomic testing, so correlation analyses for GI metrics and ANS variables could only be performed among PWH. Spearman rank correlations were performed for each of the GI metrics and the MCASS, its three subscores, and BRSA.

Finally, we used a K-means clustering algorithm to determine the extent to which our contractility metrics could distinguish between our four groups. To maximize data retention, missing values were addressed systematically. Categorical variables (e.g., sex) were imputed using the most frequent category, whereas continuous variables underwent multivariate iterative imputation with tree-based regressors. To minimize demographic confounding, key GI metrics were residualized with respect to age and sex. Continuous features were then transformed using a monotonic Yeo–Johnson power transformation to approximate normality and stabilize variance, followed by z-score standardization to place all variables on a common scale and prevent dominance by features with larger numeric ranges. Clustering using k-means was performed on the transformed feature matrix. Model selection for the number of clusters used a hybrid criterion: *1*) internal validity via silhouette coefficients computed for $k \in \{2, ., 8\}$ and *2*) external, clinically driven interpretability. After clustering, we mapped our four participant groups onto the clusters to assess stratification by group membership status. To visualize the cluster separation, we used two-dimensional principal component analysis (PCA) on the standardized features. Finally, to facilitate clinical interpretation, we identified the top five discriminative features for each cluster based on standardized effect size of the feature comparing participants in a given cluster to those outside of it.

RESULTS

Participant Characteristics

Cohort characteristics are described in Table 2. There were notable demographic differences between PWH and healthy controls. Reflective of the overall population of PWH, our sample of PWH had a majority of men (74.6%) as compared with the control group, where sex was balanced. Controls were also relatively younger (med = 42 yr) compared with PWH, where the median age was 55 yr.

Comparison between Healthy Controls and PWH

Compared with controls, PWH demonstrated higher contractility metrics in univariate analyses across all total and time-adjusted contractility metrics (Table 2). In contrast, PWH experienced fewer rhythmic bursts ($P = 0.008$, Fig. 2) and within the rhythmic bursts the RMSSD variables tended to be larger for PWH, indicating greater variability in the rate and amplitude of contractions. In addition to demonstrating fewer rhythmic bursts overall among PWH, Fig. 2 also suggests an alteration in the distribution of rhythmic bursts throughout the small bowel transit. In healthy controls, a clear pattern emerged: fast intervals (≥8 contractions/min)

Table 2. *Participant demographics and WMC-derived gastrointestinal motility parameters**

	Healthy Controls (n = 98)	PWH Overall (n = 71)	PWH with Delayed SBTT (n = 16)	Normal PWH (n = 30)	PWH with AN (n = 24)	P Value (for Controls vs. PWH)	P Value (for 4 Groups)
Age	41.0 (30.0–65.0)	55.0 (44.0–62.5)	47.0 (40.0–63.0)	53.0 (46.3–60.0)	57.0 (48.3–64.0)	0.004	0.028
Sex, No. (%)							
Men	50 (51.0)	53 (74.6)	13 (81.2)	23 (76.7)	17 (70.8)	0.002	0.012
Women	48 (49.0)	18 (25.4)	3 (18.8)	7 (23.3)	7 (29.2)		
Delayed SBTT No. (%)	4 (4.1)	16 (22.9)	16 (100.0)	0 (0.0)	0 (0.0)	<0.001	<0.001
Meets criteria for AN (CASS ≥ 3), No. (%)	N/A	31 (43.7)	7 (43.8)	0 (0.0)	24 (100.0)		
Total contractility metrics							
Sum of amplitudes ($\times 10^5$)	1.03 (0.79–1.29)	1.58 (1.16–2.00)	2.08 (1.69–3.26)	1.40 (1.10–1.93)	1.50 (1.18–1.77)	<0.001	<0.001
Motility index	18.09 (17.52–18.62)	18.40 (17.83–19.06)	19.02 (18.02–19.29)	17.92 (17.57–18.90)	18.50 (17.86–18.82)	0.023	0.015
Time-adjusted contractility metrics							
Contractions per hour	218.81 (160.09–272.26)	285.28 (224.77–367.89)	231.71 (183.64–355.17)	272.25 (211.17–326.46)	334.50 (280.66–373.35)	<0.001	<0.001
High amplitude contractions per hour	20.88 (11.76–37.63)	38.17 (20.02–59.23)	30.68 (16.34–49.15)	25.46 (18.51–63.39)	48.20 (29.56–61.08)	<0.001	<0.001
Percent of time spent rapidly contracting	6.7	10.6	6.0	7.8	15.1	0.010	0.002
Rhythmic bursts metrics							
Total rhythmic bursts per hour	3.43 (2.16–4.99)	2.51 (1.69–3.86)	1.51 (1.14–2.30)	3.08 (1.77–3.96)	3.14 (2.12–4.32)	0.008	<0.001
RMSSDa	47.95 (37.71–59.30)	55.44 (45.39–71.45)	55.91 (39.05–67.17)	52.05 (42.01–66.66)	57.24 (49.21–75.71)	0.010	0.054
RMSSDt for fast rhythmic bursts	49.28 (47.43–53.17)	52.54 (48.16–57.18)	53.62 (48.52–57.06)	52.53 (47.04–57.32)	51.37 (48.32–56.22)	0.012	0.11
RMSSDt for medium rhythmic bursts	61.95 (58.10–65.89)	65.59 (60.89–70.89)	64.43 (60.54–68.96)	64.80 (60.70–69.29)	68.79 (64.31–71.42)	0.005	0.018
RMSSDt for slow rhythmic bursts	77.98 (71.35–84.54)	80.72 (73.76–89.06)	77.40 (73.42–84.98)	82.92 (73.54–95.79)	80.19 (76.07–88.49)	0.042	0.22

AN, autonomic neuropathy; PWH, people living with human immunodeficiency virus; RMSSDt, root mean square of successive differences for time; RMSSDa, Root mean square of successive differences for amplitude; SBTT, small bowel transit time; WMC, wireless motility capsule. *Values are presented as median (IQR) unless indicated as a percentage.

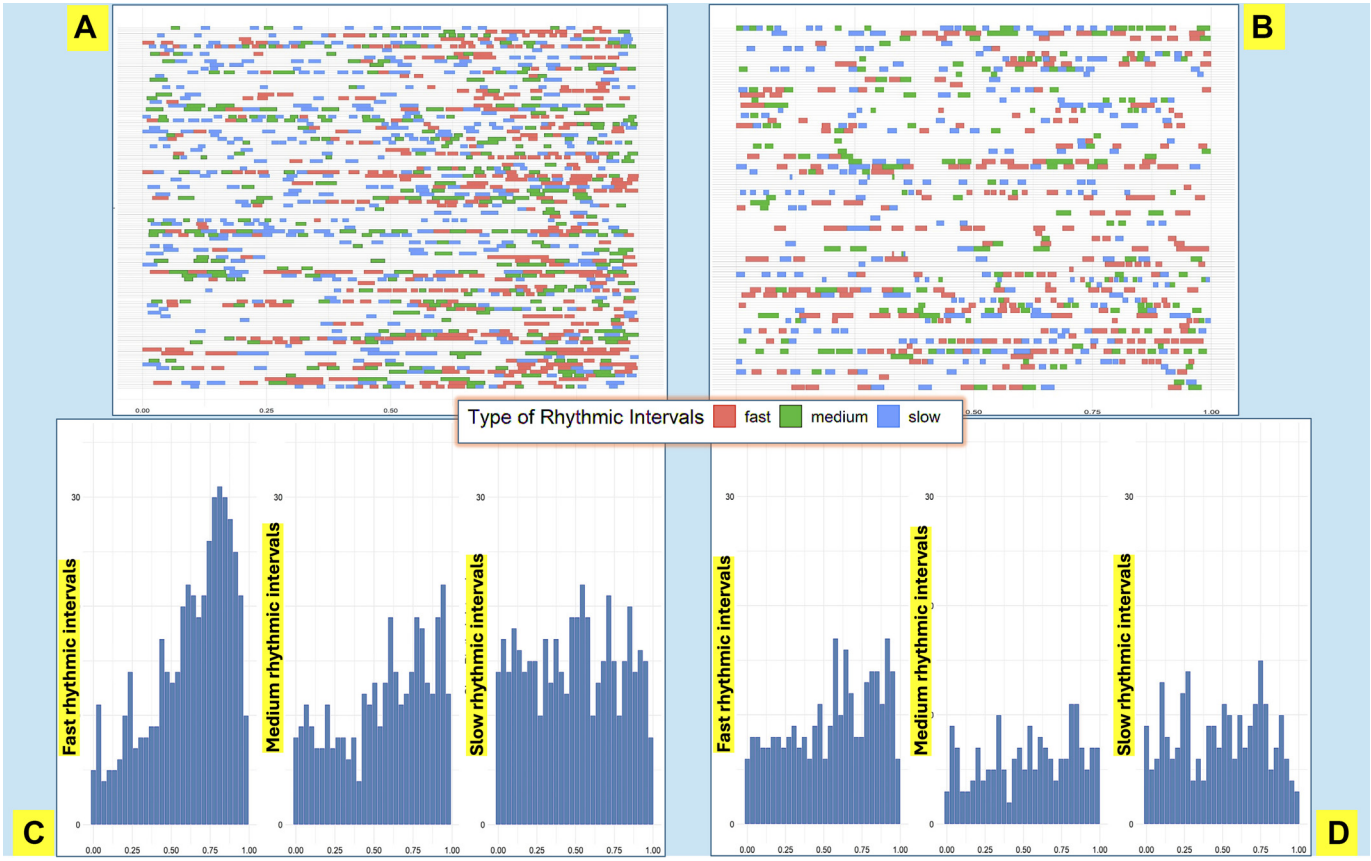

Figure 2. Distribution of rhythmic bursts across small bowel regions. The *x*-axis in all panels represents the total time spent by the wireless motility capsule (WMC) in the small intestine, where zero represents passage of the WMC from the stomach into the small intestine and one represents passage of the WMC into the colon. For *A* and *B* (controls and PWH, respectively), each row is an individual participant. Fast intervals are shown in pink, medium in green, and slow in blue. *C* and *D*: histograms showing the distribution of fast, medium, and slow rhythmic bursts over time in the small bowel for controls (*C*) vs. PWH (*D*). PWH, people living with human immunodeficiency virus.

were more frequent later in the recording; medium intervals (6–8/min) showed a biphasic distribution with peaks early and late; and slow intervals (4–6/min) appeared diffusely. In contrast, rhythmic bursts in PWH were less frequent overall and lacked temporal organization, appearing scattered throughout the recording.

Multivariable analyses to assess for confounding effects of age and gender differences between the groups showed no confounding effect for sum of the amplitudes, contractions per hour, high-amplitude contractions per hour, and total rhythmic bursts per hour. A modest confounding effect (slightly above the 10% threshold) was observed for motility index (MI) and fraction of time spent rapidly contracting. The RMSSD metrics showed varying sensitivity to covariate adjustment: RMSSDt for fast and medium intervals and RMSSDa exhibited confounding, whereas RMSSDt for slow intervals was unaffected.

Properties of WMC Metrics within Subgroups of PWH

As described earlier, overall, PWH demonstrated significant differences across multiple contractility metrics when compared with healthy controls, differences that generally persisted after accounting for age and sex. To understand the relationship between contractility metrics, we next performed comparisons across four groups (Table 2): healthy controls, dSBTT, AN, and normal PWH.

Most of the total and time-adjusted contractility metrics (sum of amplitudes, MI, contractions per hour, high amplitude contractions per hour, and fraction of time spent rapidly contracting) and the total rhythmic bursts per hour remained highly significant across four-group analyses ($P \leq 0.009$ for all). Post hoc pairwise comparisons revealed these findings were largely, though not exclusively, driven by differences between the healthy controls and the AN group (Fig. 3).

Correlating Specific Features of the ANS Data with Novel GI Motility Metrics

In exploratory analyses, we assessed correlations between our ANS variables and GI metrics among PWH ($n = 71$). We found that the time-adjusted contractility metrics were modestly correlated with the total MCASS score: contractions per hour ($r = 0.25$, $P = 0.035$), high-amplitude contractions per hour ($r = 0.24$, $P = 0.044$), fraction of time spent rapidly contracting ($r = 0.31$, $P = 0.008$). Of the three MCASS subscores, the cardiovagal subscore appeared to be primarily responsible for these correlations ($P < 0.05$ for correlations between the cardiovagal subscore and two of the three contractility metrics). In addition to the correlation with MCASS, contractions per hour and high amplitude contractions per hour were inversely associated with BRSA ($P < 0.03$ for both).

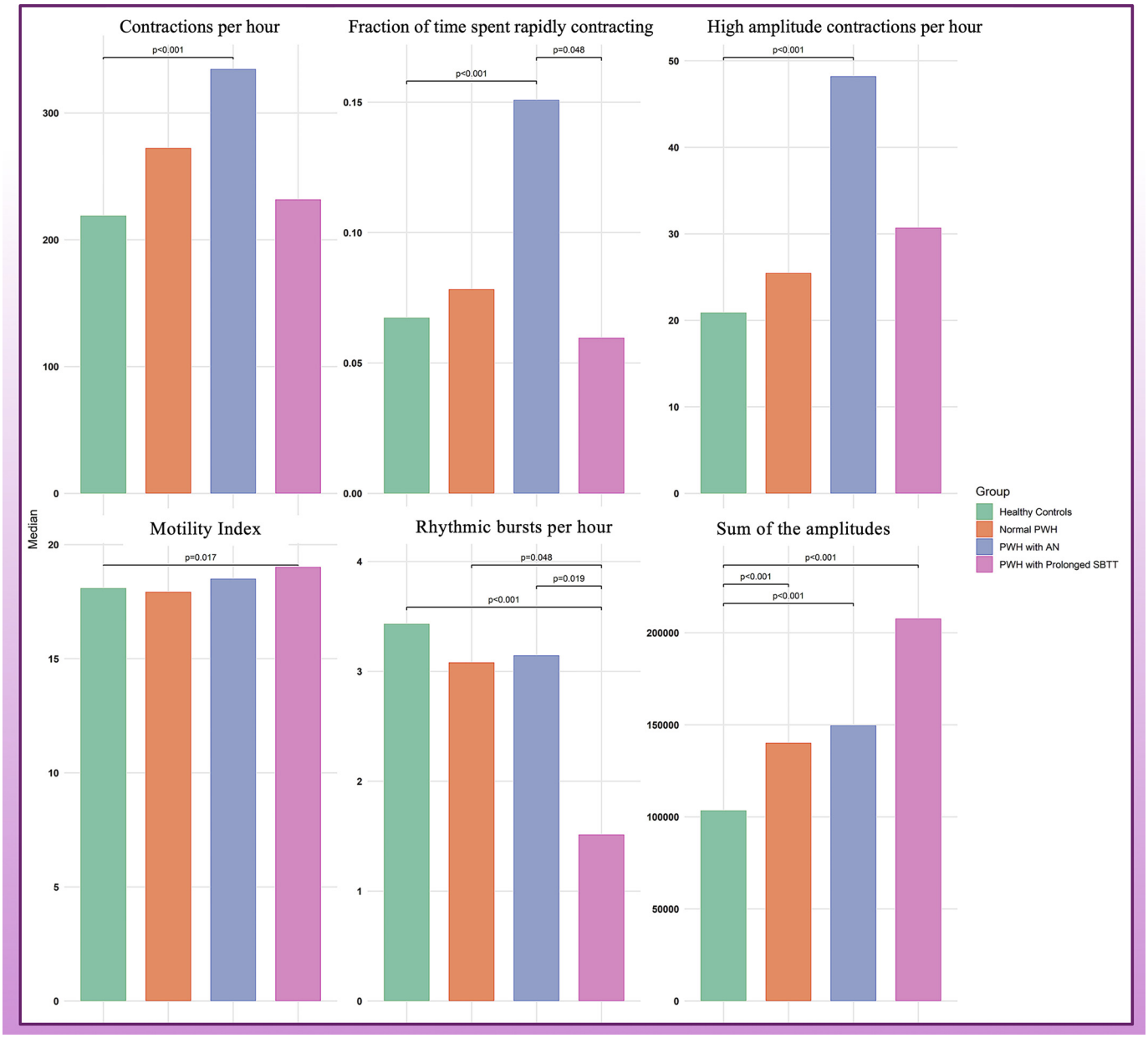

Figure 3. Group comparisons of contractility measures. Panels show median values for significant pairwise differences (with Dunn's post hoc test and Bonferroni's correction) for 6 motility metrics across all 4 groups.

Cluster Analysis

The silhouette score was highest for k = 2 (0.18), followed by k = 3 (0.15), with k = 4 producing a slightly lower score (0.14). Despite this, k = 4 was selected because it provided the most clinically meaningful separation as seen in Fig. 4.

Cluster 1 had the highest proportion of healthy controls and was defined primarily by lower values of the time-adjusted contractility variables. *Cluster 2* was also comprised predominantly of healthy controls and several normal PWH and was defined primarily by lower RMSSD values, representing less variability in contractility during rhythmic bursts. *Cluster 3* was defined by higher GI contractility metrics. This cluster contained substantial numbers of participants from all groups except the dSBTT group.

PWH from the AN and dSBTT groups were disproportionately represented in *cluster 4*, which was primarily defined by higher RMSSDs.

DISCUSSION

Manometry studies, performed mostly in the 1980s and 1990s, provided sufficient data to characterize normal small bowel motility patterns in humans (37, 38) and confirm their similarity to more extensive animal studies (39). However, efforts to extend this foundational work to comprehensively describe the changes in contractility that occur due to ENS and/or ANS dysfunction were only partially successful. Relevant studies in people with diabetes illustrate the

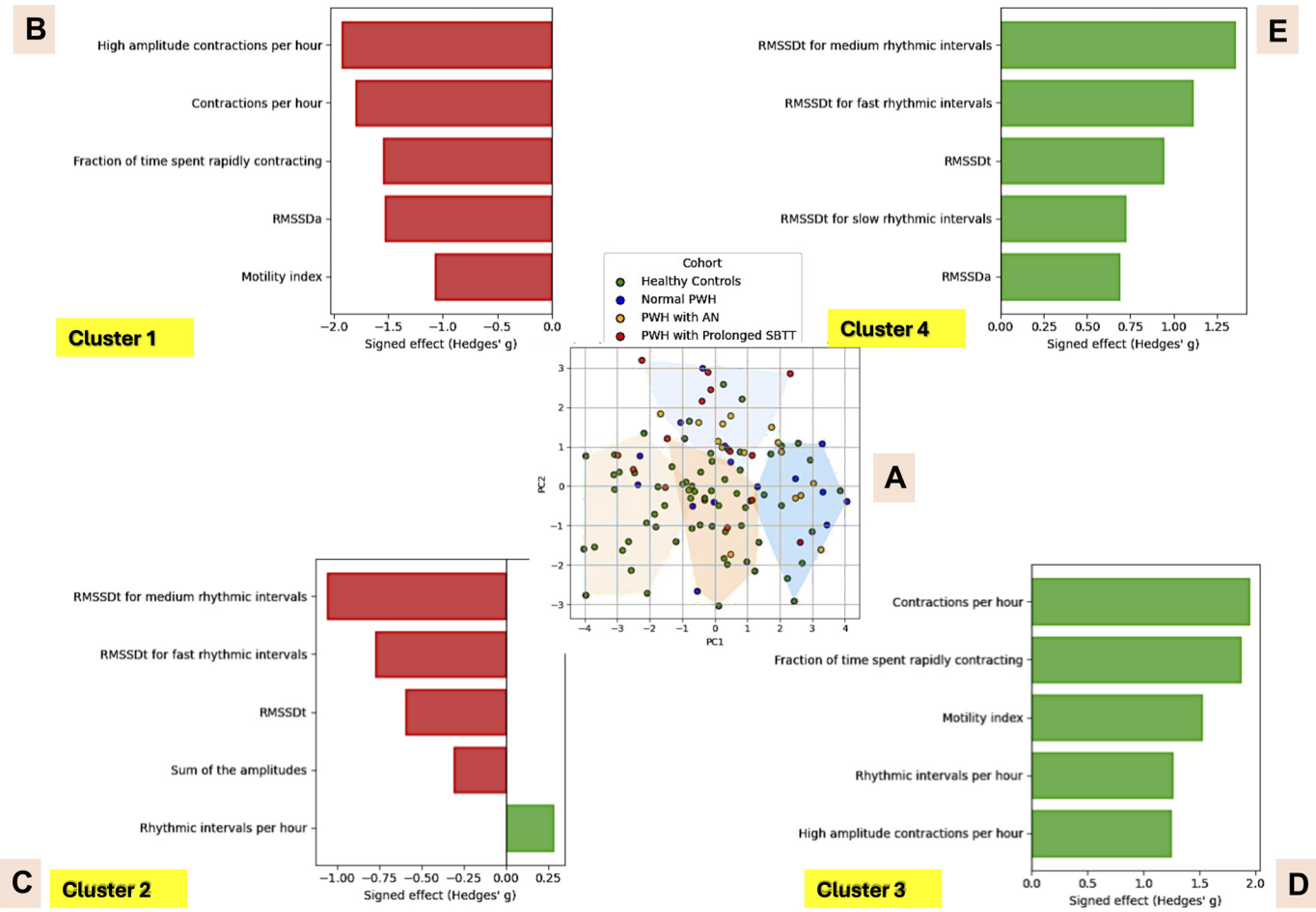

Figure 4. Cluster analysis. *A*: the distribution of individual participants in a two-dimensional principal components analysis. *B–E*: the top 5 factors defining each cluster; red indicates a lower value and green a higher value.

challenges (40–44). Studies were small due to the intensive nature of manometry. The observed pathophysiology was variable, some patients had high amplitude bursts of activity, others had reduced frequency and amplitude of contractions, whereas others had a composite of both. This diversity makes sense neuroanatomically; given the layered neural feedback loops influencing GI muscle, alterations in contractility would be expected to vary based on the extent of underlying pathology. A final challenge is that it is not possible to directly measure damage to the ENS in humans, and measurement of damage to the extrinsic ANS, even using gold-standard AFTs, is inherently indirect. Considering the expected diversity of the outcomes and the measurement imprecision, large sample sizes are needed, and capsule-based methods are a logical choice given their relative ease of administration.

In the present study, we sought proof-of-concept that WMC-derived small intestinal pressure data could provide physiologically meaningful contractility metrics despite the obvious challenge of the WMC's mobility, which precludes knowledge of precise localization within the gut and observation of wave propagation. We then sought to demonstrate how such metrics might be altered in a patient population known to have a high prevalence of both ENS and extrinsic ANS dysfunction, namely PWH. We examined a total of 10 candidate contractility metrics in three categories: *1*) two traditional total contractility metrics (sum of amplitudes and motility index); *2*) three time-adjusted contractility metrics (contractions per hour, high amplitude contractions per hour, and fraction of time spent rapidly contracting); and *3*) five novel rhythmic bursts metrics (total rhythmic bursts per hour, RMSSDa, RMSSDt for fast rhythmic bursts, RMSSDt for medium rhythmic bursts, and RMSSDt for slow rhythmic bursts). Our main findings were as follows:

- All 10-contractility metrics were significantly different between healthy controls and PWH.
- When the small intestine was considered as a whole, PWH showed greater (i.e., more frequent, high amplitude, rapid) contractility despite slower SBTT.
- Among controls, periods of rhythmic contraction tended to be more clustered, especially toward the later portion of the small bowel recording. In contrast, contractility was more dispersed and irregularly distributed throughout the transit recording among PWH.
- Within periods of rhythmic contraction, variability in the amplitude and timing of the contractions was greater in PWH than controls.

- The subgroup of PWH with AN and normal SBTT showed the highest time-adjusted contractility metrics overall. Healthy controls showed the lowest.
- Although MI showed statistically significant differences ($P \leq 0.01$), there was substantial overlap between controls and PWH (and subgroups; Fig. 3). This aligns with prior work (45), showing limited utility of MI in differentiating pressure profiles, underscoring the need for novel variables beyond standard indices.
- Higher MCASS scores, indicating greater dysfunction of the extrinsic ANS, were associated with greater time-adjusted contractility metrics; this appeared to be mostly driven by the cardiovagal subscore, indicating that AN and especially AN involving cardiovagal (i.e., parasympathetic) dysfunction is associated with more active GI contractility.
- A measure of sympathetic reflex reactivity, BRSA, was inversely correlated with two of the three time-adjusted contractility metrics, suggesting that greater sympathetic reactivity was associated with less GI contractility.
- Unsupervised cluster analysis using the 10 contractility metrics showed significant overlap between healthy controls and the three PWH subgroups but did identify low time-adjusted contractility metrics and low RMSSD metrics as being most characteristic of healthy controls and normal PWH.

Our findings should be contextualized within existing knowledge of normal MMC propagation and HIV-related neuromuscular pathology. Under normal fasting conditions, the ICCs and ENS are primarily responsible for the basic form of the MMC (8, 46). The ANS (via parasympathetic/vagal activity) triggers MMC onset in the stomach and duodenum contributing to orderly propagation from proximal to distal small bowel (47, 48). Meanwhile, the sympathetic branch of the ANS contributes by suppressing contractions during MMC *phases 1* and *2*, allowing for organized, energy-efficient motility. Thus, the primary expected effect of ICC/ENS damage would be a degradation in basic MMC structure. ANS parasympathetic dysfunction might cause a greater proportion of MMCs to arise in more distal parts of the small bowel (48), whereas ANS sympathetic dysfunction might allow more breakthrough contractions. Acute HIV infection profoundly disrupts the GI mucosa as viral reservoirs are established in the gut-associated lymphoid tissue. The ENS suffers collateral damage as demonstrated in early biopsy studies (12); longitudinal studies are not available to document the degree of recovery, but given the limited ability of neurons to regenerate, it seems likely that some ENS damage persists in most if not all PWH. Autonomic neuropathy is also known to be common in PWH. Thus, people with chronic well-controlled HIV, such as those included in this study, are expected to have varying degrees of both ENS and ANS dysfunction, and this dysfunction is expected to manifest as a degradation of MMC structure.

Our novel contractility metrics capture several aspects of disrupted fasting motility including breakthrough contractility, disorganized distribution of rhythmic bursts throughout the small bowel recording, and loss of organization within rhythmic bursts. Breakthrough contractility (i.e., contractions in excess of those displayed by healthy controls) was reflected by our time-adjusted contractility metrics (contractions per hour, high amplitude contractions per hour, and fraction of time spent rapidly contracting), which were lowest in the healthy controls and highest in the group of PWH with AN and normal SBTT. Among PWH with dSBTT (with and without AN), time-adjusted contractility metrics tended to be lower (although still higher than healthy controls). These findings could indicate a spectrum of GI neuromuscular dysfunction. With milder ENS/ANS dysfunction, the MMC becomes disorganized, but higher contraction rates and high amplitude contractions might maintain normal transit time, albeit at the expense of functional performance and efficiency. This stage may correspond with previous manometry studies linking hypercontractility in neuropathic disorders (e.g., bursts and sustained uncoordinated pressure activity) with vagal dysfunction and abnormal propagation of MMCs, though WMC cannot confirm classic MMC phases (49). With more severe ENS/ANS dysfunction, contractility declines, resulting in dSBTT (50).

Our data suggest that two forms of MMC organization may be observable with the WMC. First, as shown in Fig. 2, our control group exhibited distinct rhythmic bursts, with fast rhythmic bursts ($\geq$8 contractions/min) occurring more frequently later during small bowel transit recording. However, in PWH, rhythmic bursts were fewer and more scattered, lacking clear predominance at any particular time during transit. Our novel approach to isolating rhythmic bursts (i.e., defining 5-min intervals meeting-specific contractility thresholds) was key to identifying this difference, which cannot be detected with simpler metrics such as overall contraction rates. Second, within those rhythmic bursts, our RMSSD variables, which quantify variability in contraction size and timing, tended to be larger in PWH. This is in contrast to what we expected based on the cardiac literature, where higher RMSSD often indicates health (51). These differences likely reflect both the organizational structure and physiological roles of the heart and gut. The ENS is a diffuse network of neurons that operates semiautonomously, coordinating complex local reflexes and integrating gut activity as a continuous, distributed process. In contrast, the sinoatrial (SA) node is a compact, specialized pacemaker that generates a regular intrinsic rhythm, ensuring precise sequential contractions of the atria and ventricles. Its rate is tightly controlled and modulated by the ANS, providing fine temporal control of heart rhythm (52) In the gut, well-coordinated peristalsis is critical for efficient GI transit, and excessive variability may disrupt this process, whereas heart rate variability (HRV) is necessary to meet dynamic metabolic needs. The cluster analysis reinforces the other findings by confirming that normal participants tend to exhibit lower time-adjusted contractility metrics and RMSSDs.

An aspirational goal of this work is to develop a more nuanced understanding of how the extrinsic ANS interacts with the ENS in health and disease to influence GI function and ultimately GI symptoms. Such information could be of critical importance for advancing the understanding of disorders of the gut-brain-axis (GBA), which are currently often dismissed as lacking a demonstrable physiological cause. This is a complex undertaking, given the hierarchical and likely nonlinear relationships between the structures of the GBA including the gut itself, ICCs, ENS, peripheral and central ANS, and higher control centers within the brain. As a first

pass at this complex system, herein we demonstrated that among PWH, higher (i.e., worse) MCASS scores, especially cardiovagal (i.e., parasympathetic) subscores, were associated with greater time-adjusted contractility metrics. This is superficially counterintuitive, given that, grossly, parasympathetic input to the gut is supposed to promote motility (as per the famous "rest and digest" pneumonic). However, a potential explanation might be that in the absence of parasympathetic direction to begin the MMC cycle in the stomach or duodenum, local feedback loops seek to compensate with increased contractility (2, 53). This effect might be augmented by a decline in sympathetic inhibition, which can act both on the ENS and directly on muscle (54) and is supported by the finding of an inverse correlation between a measure of sympathetic reflex reactivity, BRSA, and two of the three time-adjusted contractility metrics.

Our study has several limitations. This is a secondary data analysis combining data from multiple studies. The studies from which healthy controls were drawn lacked autonomic testing data, precluding direct correlations between ANS function and GI motility in this group. The specific WMC that was used in this study (Medtronic) has been discontinued. Of the two new WMCs, MotiliCap records pressure, but it is unclear whether the indices described herein would transfer to that platform. The Atmo capsule (Atmo Biosciences) does not measure intraluminal pressure. However, its accelerometry and orientation sensors may enhance detection of contractile dynamics (e.g., frequency and amplitude), capsule motion, and rhythmicity, thereby allowing differentiation between normal and pathological motor patterns. Adaption and/or revalidation of the novel contractility indices developed here should therefore use this or equivalent next-generation platforms. WMCs in general cannot detect MMC propagation or definitively isolate *phase 3*; thus, these metrics quantify and characterize rhythmic contractile patterns rather than serving as direct *phase 3* surrogates. Moreover, its free-floating nature may potentially lead to over- or underestimation of contraction amplitudes, limiting the clinical applicability of these contractility metrics. The cross-sectional, observational study design precludes causal inferences, and temporal asynchrony between ANS and WMC assessments may weaken observed associations (55, 56); these factors are not considered here. Finally, small subgroup sizes constrained statistical power.

In summary, this study showcases the use of WMC technology to provide a detailed noninvasive, ambulatory assessment of small bowel motility, capturing detailed pressure recordings that are critical for understanding motility disorders. This study is the first to leverage WMC-derived pressure data to develop these novel indices, offering a granular view of dysmotility that surpasses traditional parameters. Although colonic motility has been extensively studied, research on small bowel motility remains comparatively limited, highlighting the distinctiveness of our study. These findings bolster prior expert opinion and consensus statements that anecdotally described neurogenic small bowel dysmotility as hypercontractile and disorganized (49, 57). They also extend the literature into a previously unstudied neuropathic condition with a uniquely relevant pathophysiology and establish for the first time that this kind of detailed contractility analysis is feasible with WMCs and linkable to extrinsic ANS biomarkers. Future studies should validate these indices in larger, more diverse cohorts, integrating them with autonomic and/or microbiome data to elucidate mechanistic drivers and enhance physiological understanding of motility disorders and disorders of the GBA more broadly.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.R.-P. conceived and designed research; M.M., N.N., K.C., and G.C. performed experiments; Z.Z. and A.E. analyzed data; M.M., Z.Z., A.E., J.S., and J.R.-P. interpreted results of experiments; M.M., Z.Z., A.E., and J.R.-P. prepared figures; M.M. and J.R.-P. drafted manuscript; M.M., Z.Z., A.E., J.S., B.R.M., and J.R.-P. edited and revised manuscript; M.M., Z.Z., A.E., J.S., N.N., B.R.M., K.C., G.C., and J.R.-P. approved final version of manuscript.

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