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High-Resolution Manometry Thresholds and Motor Patterns Among Asymptomatic Individuals

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OBJECTIVE: **High-resolution manometry (HRM) is the current standard for characterization of esophageal body and esophagogastric junction (EGJ) function. We aimed to examine the prevalence of abnormal esophageal motor patterns in health, and to determine optimal thresholds for software metrics across HRM systems.**

DESIGN: **Manometry studies from asymptomatic adults were solicited from motility centers worldwide, and were manually analyzed using integrated relaxation pressure (IRP), distal latency (DL), and distal contractile integral (DCI) in standardized fashion. Normative thresholds were assessed using fifth and/or 95th percentile values. Chicago Classification v3.0 criteria were applied to determine motor patterns across HRM systems, study positions (upright vs supine), ages, and genders.**

RESULTS: **Of 469 unique HRM studies (median age 28.0, range 18–79 years). 74.6% had a normal HRM pattern; none had achalasia. Ineffective esophageal motility (IEM) was the most frequent motor pattern identified (15.1% overall), followed by EGJ outflow obstruction (5.3%). Proportions with IEM were lower using stringent criteria (10.0%), especially in supine studies (7.1%–8.5%). Other motor patterns were rare (0.2%–4.1% overall) and did not vary by age or gender. DL**

Abbreviations used in this paper: CCv3.0, Chicago Classification version 3.0; DCI, distal contractile integral; DES, diffuse esophageal spasm; DL, distal latency; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; UES, upper esophageal sphincter.

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thresholds were close to current norms across HRM systems, while IRP thresholds varied by HRM system and study position. Both fifth and 95th percentile DCI values were lower than current thresholds, both in upright and supine positions.

CONCLUSIONS: Motor abnormalities are infrequent in healthy individuals and consist mainly of IEM, proportions of which are lower when using stringent criteria in the supine position. Thresholds for HRM metrics vary by HRM system and study position.

Key words: High-Resolution Manometry; Integrated Relaxation Pressure; Distal Latency; Distal Contractile Integral.

High-resolution manometry (HRM) is recognized as the standard for assessment of esophageal peristalsis and lower esophageal sphincter (LES) function.[1,2] Using pressure data acquired from a catheter with circumferential pressure sensors 1 cm apart, a 3-dimensional topographical image of esophageal motor function is generated that incorporates time along the x-axis, distance along the esophagus on the y-axis, and pressure in the form of color-coded isobars. This image is termed a Clouse plot, in honor of the technology's pioneer, Ray Clouse (Figure 1).[1]

Pressure phenomena following a 5-mL test swallow can be visualized on an HRM Clouse plot as a chain of relaxing sphincters and contracting segments. Starting with upper esophageal sphincter (UES) relaxation and initiation of peristalsis in the skeletal muscle esophagus, smooth muscle peristalsis propagates through the esophageal body and LES. HRM assesses esophageal smooth muscle function and LES relaxation using intuitive tools embedded into HRM interpretation software (Figure 1).[3] Adequacy of LES relaxation is assessed by nadir residual pressure over 4 seconds during swallow induced LES relaxation, using the integrated relaxation pressure (IRP) (normal varies with HRM system).[3,4] The distal contractile integral (DCI) (normal 450–8000 mm Hg•cm•s) assesses esophageal body contraction vigor, distal latency (DL) (normal >4.5 seconds) evaluates peristaltic timing, and a 20-mm Hg isobaric contour tool determines peristaltic integrity (normal when breaks <5 cm).[3,4]

Normative thresholds for HRM software metrics were based on small, single-center studies of asymptomatic patients and are used for formulating motor diagnoses as part of the Chicago Classification version 3.0 (CCv.3.0).[4] However, a large-scale effort in systematically evaluating normative data across regions, countries, and HRM systems has not been performed. We aimed to define normative esophageal body and LES physiology by analyzing HRM studies from asymptomatic volunteers across multiple world regions.

Materials and Methods

Cohort Characteristics

HRM studies performed on healthy, asymptomatic adult volunteers were solicited from motility centers worldwide. Exclusion criteria consisted of prior foregut surgery, use of medications affecting esophageal motility and intragastric acidity, and history of diabetes mellitus, neurologic disorders, or chronic gastrointestinal disease. Solid-state HRM catheters were used (Medtronic, Duluth, GA; Laborie, Enchede, the Netherlands; Diversatek, Boulder, CO), with catheter diameters of 4.2 mm, 4.2 mm, and 3.6 mm, respectively, in either supine (semi-recumbent) or upright (sitting) positions. Raw HRM studies, including those obtained using earlier software versions, were de-identified, encrypted, and uploaded into a secure Web-based storage system (Tresorit, Zürich, Switzerland) by the collaborators. Given known inaccuracies, automated software interpretation was not utilized. Instead, de novo analysis was performed using current software specific to each HRM manufacturer by 2 study investigators (A.R., B.D.R.), each with primary responsibility for manual extraction of esophageal body and esophagogastric junction (EGJ) metrics according to CCv3.0, and supervision by the senior investigator (C.P.G.) including resolution of discrepancies. Inadequate (artifacts, poor study quality) and incomplete studies (<10 water swallows) were excluded. Because the present study consisted of post hoc analysis of previously collected de-identified HRM studies with no links to the original study subjects, institutional review board approval was not deemed necessary.

CC Definitions

Within each HRM study, each swallow was categorized using CCv3.0 criteria[4] into the following: (1) intact swallow (DCI >450 mm Hg•cm•s), (2) fragmented swallow (DCI >450mm Hg•cm•s with >5-cm break), (3) premature swallow (DCI >450mm Hg•cm•s with distal latency <4.5 seconds), (4) hypercontractile swallow (DCI >8000 mm Hg•cm•s), (5) weak swallow (DCI 100–450 mm Hg•cm•s), and (6) failed swallow (DCI <100 mm Hg•cm•s). Both weak and failed swallows were included under the umbrella of ineffective swallows. For assessment of swallow-induced LES relaxation, IRP was measured for each individual swallow, and the median IRP was determined for each subject.[4]

Motor diagnoses were based on individual swallow designations using the CCv.3.0 criteria.[4] IRP normative thresholds consisted of 15 mm Hg for Medtronic,[4]

28 mm Hg for Laborie,[5] and 21 mm Hg for Diversatek.[6] Standard DCI and DL thresholds were utilized across the 3 systems. Motor diagnoses consisted of (A) EGJ outflow obstruction (median IRP ≥upper limit of normal depending on HRM system), (B) absent contractility (100% failed swallows), (C) ineffective esophageal motility (IEM) (≥50% of any combination of weak or failed swallows), (4) fragmented peristalsis (≥50% fragmented swallows), (5) diffuse esophageal spasm (DES) (≥20% premature swallows), (6) hypercontractile esophagus (≥20% hypercontractile swallows), and (7) normal (those that did not meet any of the above criteria).[4]

Recent data suggest that stratification of IEM into mild and severe categories may have clinical relevance.[7,8] For this reason, additional analyses were performed using the following definitions: mild IEM (50%–70% of weak, failed, or fragmented swallows) and severe IEM (80%–100% of weak, failed, or fragmented swallows, or 60%–90% failed swallows).[7]

Data Analysis

Data are reported as median, with either interquartile range and fifth to 95th percentile range. Categorical data were compared using the chi-square test with Yates correction, and continuous data using the Student's *t* test, Kruskal-Wallis test, or analysis of variance, with Bonferroni correction for multiple comparisons when appropriate. Lower threshold of normal was defined as the fifth percentile of normal values, and the upper limit of normal was the 95th percentile. In all instances, $P < .05$ denoted statistical significance. All statistical and plots were performed using Microsoft Excel (Microsoft, Redmond, WA), RStudio version 2.11 (RStudio, Boston, MA), or SPSS version 26 (IBM, Armonk, NY).

> **What You Need to Know**
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> **Background**
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> High-resolution manometry (HRM) is the current standard for assessment of esophageal motor phenomena and lower esophageal sphincter function. Three software metrics, integrated relaxation pressure, distal contractile integral, and distal latency, are used for formulating Chicago Classification diagnoses. Normative thresholds for these metrics in current use are based on small, single-center studies of asymptomatic patients.
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> **Findings**
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> Major motor disorders are infrequently encountered in asymptomatic individuals, and no achalasia was identified. Ineffective esophageal motility was the most frequent abnormal pattern identified, and proportions with ineffective esophageal motility were lower with use of stringent criteria in the supine position. Important differences in thresholds for HRM metrics exist between HRM systems and study position, but proportions of motor abnormalities seen in health are similar worldwide and across sexes.
>
> **Implications for patient care**
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> Interpretation of HRM studies requires understanding of differences between HRM systems and study position.

Results

Of 478 studies acquired from 15 countries across 4 continents, 9 studies were excluded because of artifacts or incomplete swallow complements (Medtronic: 4

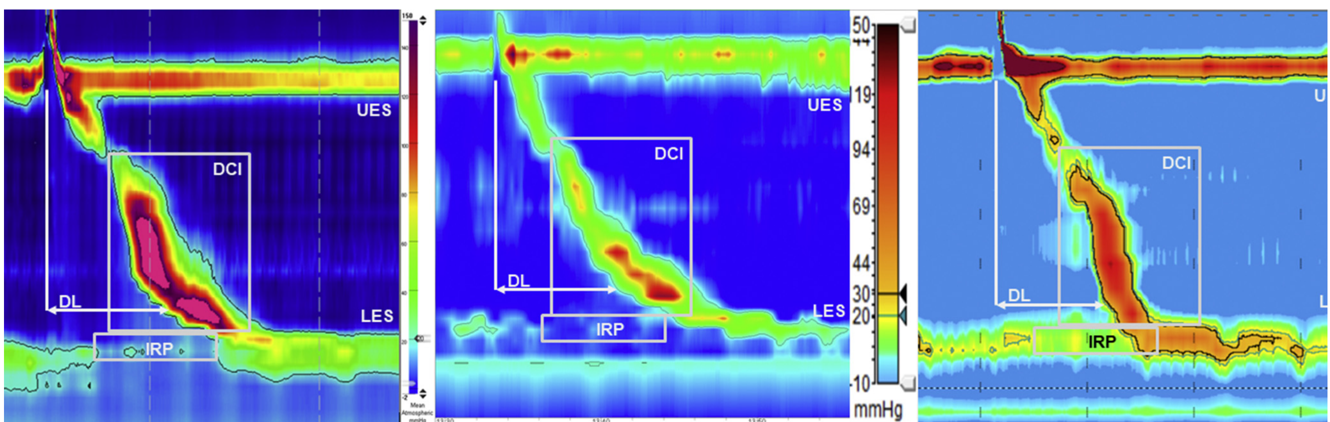


Figure 1. Examples of Clouse plots following 5-mL supine water swallows—(*A*) Medtronic, (*B*) Laborie, (*C*) Diversatek—anchored by the UES and LES with contraction progressing from proximal skeletal muscle to the distal smooth muscle. The UES relaxes upon swallowing, followed by LES relaxation to allow bolus passage and re-establishment of resting sphincter pressures. Adequacy of LES relaxation is assessed using IRP. Esophageal body contraction vigor reflects contraction amplitude, contracting segment length, and duration of contraction within the measurement box (DCI). Timing of peristalsis is assessed using DL.

Table 1. Clinical Characteristics by HRM Manufacturer

	Overall (N = 469)	Medtronic (n = 293)	Laborie (n = 117)	Diversatek (n = 59)	*P* value
Age, y	28.0 (24.0–35.4)	27.7 (24.0–35.4)	26.0 (21.0–37.0)	30.0 (28.0–35.0)	.02
Female	259 (55.2)	148 (50.5)	78 (66.7)	33 (55.9)	.01
HRM diagnosis					
EGJOO	25 (5.3)	20 (6.8)	3 (2.6)	2 (3.4)	.173
DES	19 (4.1)	10 (3.4)	1 (0.9)	8 (13.6)	<.001
Hypercontractile	1 (0.2)	1 (0.3)	0 (0.)	0 (0.0)	
Absent contractility	2 (0.4)	1 (0.3)	1 (0.9)	0 (0.0)	
Fragmented	1 (0.2)	0 (0.0)	1 (0.9)	0 (0.0)	
IEM (standard)	71 (15.1)	40 (13.7)	17 (14.5)	14 (23.7)	.14
Severe IEM	47 (10.0)	29 (9.9)	8 (6.8)	10 (16.9)	.107

NOTE. Values are median (interquartile range) or n (%).There were no subjects with achalasia.
DES, diffuse esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IEM, ineffective esophageal motility.

studies; Diversatek: 5 studies; Laborie: 0 studies). Of the remaining 469 unique studies, 62.5% were performed with the Medtronic system, 24.9% with Laborie, and 12.6% with Diversatek. Median age was 28.0 (interquartile range, 18–79) years and was numerically similar between the 3 HRM systems (Table 1). Female subjects were overrepresented, particularly in studies performed using Laborie and Diversatek equipment (Table 1). In comparing 4 world regions (Asia, Europe, North America, Latin America), subjects from Latin America were older (median age 37.0 years, $P \leq .005$ compared with other regions), but subjects from Europe, North America, and Asia were similar in age (median age 28.0, 27.0, and 28.0 years, respectively; $P \geq .46$). There were no differences in sex proportions across world regions ($P = .71$).

Chicago Classification Diagnoses

Using CCv3.0 criteria, three-quarters (n = 350, 74.6%) had a normal manometry. Among the remainder, IEM was diagnosed in 71 (15.1%), and EGJ outflow obstruction (EGJOO) (using HRM system–specific IRP thresholds) in 25 (5.3%) patients. None of the subjects had achalasia.

When EGJOO was diagnosed, median IRP values (Medtronic: 17.2 mm Hg; Laborie: 30.5 mm Hg; Diversatek: 26.0 mm Hg) were only marginally above the system-specific thresholds for each HRM system, and distal esophageal pressure compartmentalization was noted in only 6 of 25 patients (median 5 swallows with compartmentalization [range, 3–10 swallows]). When both supine and upright IRP values were available (11 patients studied using the Medtronic system), median IRP decreased from 17.4 mm Hg while supine to 12.5 mm Hg while upright ($P = .002$), with only 3 of 11 upright median IRP values measuring >15 mm Hg.

DES was identified in 19 (4.1%) individuals with a median of 3 (interquartile range, 2–4) premature sequences; only 2 subjects had >5 premature sequences. One subject had borderline hypercontractile esophagus (2 hypercontractile sequences [0.2%]). Among other hypomotility disorders, only 2 (0.4%) had absent contractility, and 1 subject had fragmented peristalsis with 6 (0.2%) fragmented sequences. The diagnosis of DES was more frequent, with Diversatek equipment accounting for 8 out of the 19 DES diagnoses, but 6 subjects had only 2–3 premature sequences. Proportions of CCv3.0 diagnoses in the supine position were similar across 4 world regions overall ($P = .11$), as well as within Medtronic ($P = .44$), Laborie ($P = .88$), and Diversatek systems ($P = .07$).

Normative Thresholds for Supine HRM Metrics

Median supine IRP values were significantly different between the 3 HRM systems ($P < .001$) (Figure 2*A*). The supine 95th percentile IRP values also differed between the systems (Medtronic: 15.9 mm Hg, Laborie: 24.6 mm Hg, Diversatek: 18.5 mm Hg). The fifth percentile supine DL values were 4.7 seconds and 4.8 seconds for Medtronic and Diversatek systems, respectively ($P = .4$ across medians), and significantly longer, at 5.3 seconds, for Laborie ($P < .001$ across medians, compared with other 2 groups) (Figure 2*B*). Supine fifth percentile (178–319 mm Hg•cm•s) and 95th percentile (3378–4269 mm Hg•cm•s) DCI values were lower than currently utilized DCI thresholds across all 3 HRM systems. Median DCI values were significantly different between HRM systems collectively ($P < .001$) as well as between individual systems ($P \leq .02$) (Figure 2*C*).

HRM Metrics and Diagnoses in the Upright Position

Median IRP was similar between supine vs upright test position within each of the Medtronic and Laborie systems ($P \geq .34$) (Figure 2*A*); there were no upright test

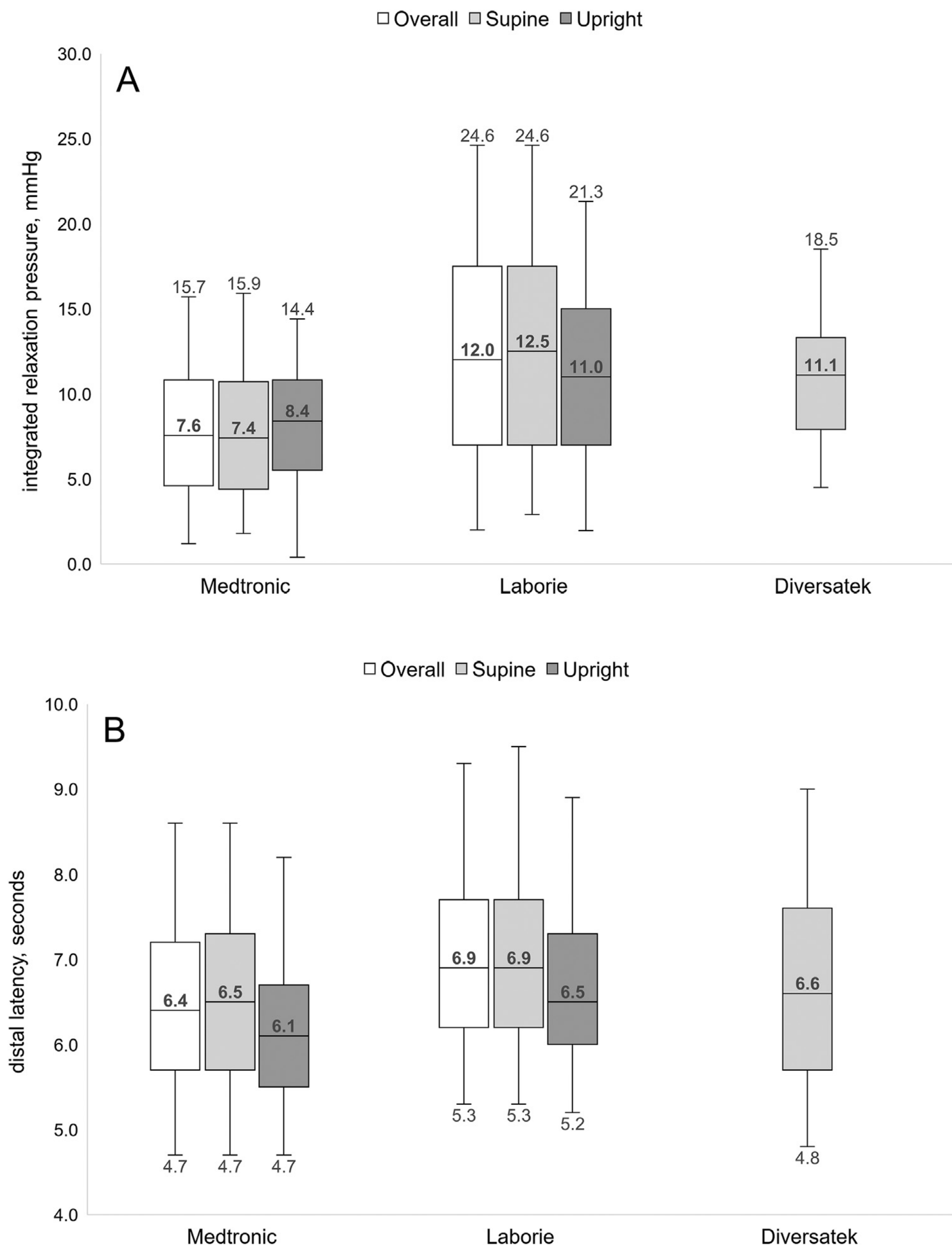
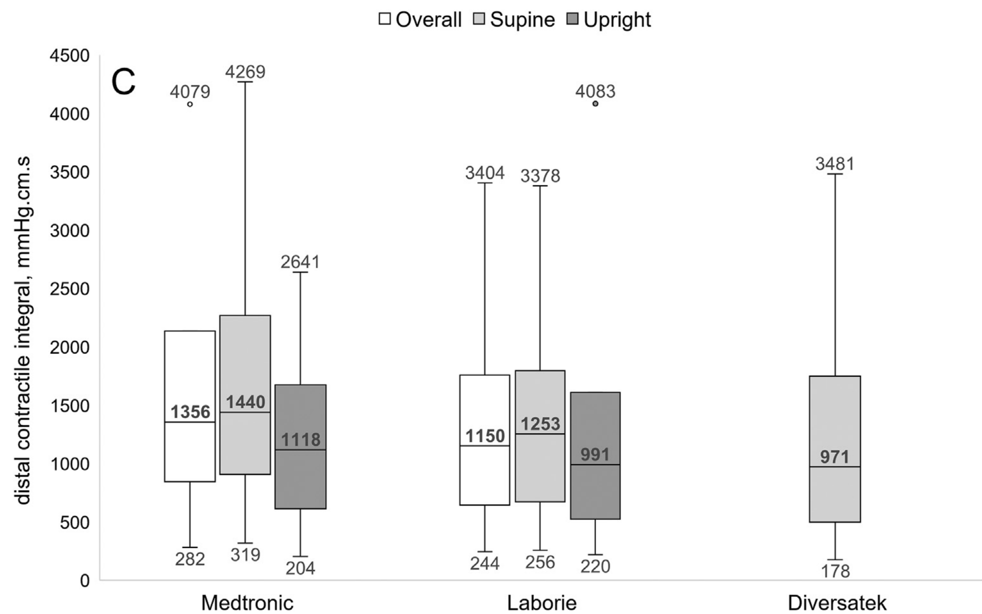


Figure 2. Normative HRM findings across 3 HRM systems (Medtronic, Laborie, and Diversatek) in both supine and upright positions, when available. The 95th percentile values are reported at the top ends of the box-and-whisker plots, with fifth percentile values at the bottom ends. The horizontal line within each box represents the median value. (*A*) Normative IRP (mm Hg) values. Both 95th percentile and median values were different between systems ($P < .001$) but were similar within systems between supine and upright position, where available (Medtronic and Laborie). (*B*) DL (seconds) values. The fifth percentile and median values were similar between Medtronic and Diversatek systems but both were shorter compared with Laborie ($P < .001$ for each comparison). (*C*) DCI (mm Hg•cm•s) values. The fifth percentile, 95th percentile, and median values were significantly different across the 3 systems ($P < .001$).

position studies with Diversatek. However, median IRP values were significantly different between Medtronic and Laborie systems in the upright position ($P = .04$) (Figure 2*A*); 95th percentile upright IRP values were 14.4 mm Hg and 24.3 mm Hg, respectively.

Median supine DL was prolonged compared with the upright position for both Medtronic and Laborie systems ($P < .001$ for each comparison) (Figure 2*B*), but fifth percentile values were similar within each system between the 2 positions. Median upright DL was more prolonged with the Laborie system compared with the Medtronic system ($P < .001$), and fifth percentile values were correspondingly prolonged (Figure 2*B*). Median DCI values were also higher in the supine position compared with upright swallows for both the Medtronic ($P < .001$) and Laborie ($P = .03$) systems (Figure 2*C*). Upright DCI values were similar between the Medtronic and Laborie systems ($P = .51$) (Figure 2*C*). Upright fifth percentile values ranged from 204 to 220 mm Hg•cm•s and 95th percentile values from ranged from 2641 to 4083 mm Hg•cm•s between the Medtronic and Laborie systems.

Despite differences in HRM metrics, among motor diagnoses, only the overall proportions of IEM significantly differed between supine and upright positions (11.7% in supine studies compared with 23.7% in upright studies; $P = .01$). This difference was most marked in studies performed using the Medtronic system (Table 2). Although overall EGJOO prevalence was



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numerically higher while supine (6.3%) compared with upright (2.6%), this difference was not statistically significant ($P = .33$). All other motor diagnoses were similar in proportion between supine and upright positions, overall, and for each of the Medtronic and Laborie systems.

Chicago Classification Diagnoses and HRM Metrics by Age and Sex

There were no statistically significant differences in HRM motor diagnoses in the supine position between subjects over 50 years of age compared with those <50 years of age ($P = .76$) (Table 3). There was only 1 subject over 50 years of age who underwent HRM in the upright position. The CCv3.0 diagnoses were similar between genders in the supine position ($P = .85$ across groups), regardless of HRM system ($P \geq .06$ for each comparison). In the upright position, male subjects trended toward higher proportions of IEM (33.3%) compared with female subjects (13.5%; $P = .08$) but not of severe IEM (17.9% vs 8.1%; $P = .33$) or other motor diagnoses, which were of similar proportions ($P = .25$). There were no differences in proportions of subjects with motor diagnoses in the supine or upright position between sexes across world regions ($P \geq .08$ and $P = .54$, respectively).

In Medtronic studies, there was no difference in median supine or upright IRP values between sexes ($P \geq .68$

Table 2. Comparison of HRM Diagnoses in Supine vs Upright Position

	Medtronic		Laborie	
HRM Diagnosis	Supine (n = 236)	Upright (n = 57)	Supine (n = 98)	Upright (n = 19)
EGJOO	18 (7.6)	2 (3.5)	3 (3.1)	0 (0.0)
DES	8 (3.4)	2 (3.5)	1 (1.0)	0 (0.0)
Hypercontractile	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Absent contractility	1 (0.4)	0 (0.0)	1 (1.0)	0 (0.0)
Fragmented	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
IEM (standard)	26 (11.0)	14 (24.6)[a]	13 (13.3)	4 (21.1)
Severe IEM	20 (8.5)	9 (15.8)	7 (7.1)	1 (5.3)

NOTE. Values are n (%).
DES, diffuse esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IEM, ineffective esophageal motility.
[a]$P = .01$ compared with supine

Table 3. Variation in Supine HRM Diagnoses by Age and Sex

	Age		Sex	
Supine HRM Diagnosis	<50 y (n = 300)	≥50 y (n = 34)	Male (n = 145)	Female (n = 189)
EGJOO	18 (6.0)	3 (8.8)	10 (6.9)	11 (5.8)
DES	7 (2.3)	2 (5.9)	4 (2.8)	5 (2.6)
Hypercontractile	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)
Absent contractility	2 (0.7)	0 (0.0)	1 (0.7)	1 (0.5)
Fragmented	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)
IEM (standard)	37 (12.3)	2 (5.9)	15 (10.3)	24 (12.7)
Severe IEM	27 (8.1)	0 (0.0)	11 (7.8)	16 (8.5)

NOTE. Values are n (%).
DES, diffuse esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IEM, ineffective esophageal motility.

for each comparison). Female subjects had longer median DL compared with male subjects in both supine (6.6 seconds vs 6.4 seconds) and upright positions (6.4 vs 5.8 seconds) ($P \leq .01$ for each comparison). While supine DCI was higher in female subjects compared with male subjects (1506.3 mm Hg•cm•s vs 1360.7 mm Hg•cm•s), upright DCI was higher in male subjects compared with female subjects (1242.9 mm Hg•cm•s vs 968.4 mm Hg•cm•s) ($P \leq .01$ for each comparison). Sex comparisons could not be performed reliably for the other 2 HRM systems due to smaller sample sizes.

Discussion

In this post hoc analysis of HRM studies performed in asymptomatic volunteers from 15 countries and 4 continents, we report no cases of achalasia, and very low incidence of major motor disorders. The most frequent motor pattern identified was IEM, with reduced proportions when stringent criteria were applied, especially in studies performed in the supine position. While IRP threshold values varied between HRM manufacturers, DL and DCI threshold values were similar across systems. When EGJOO was diagnosed based on IRP >upper limit of normal, IRP values were only marginally elevated, and were significantly lower with upright swallows when available. We report that currently utilized thresholds for IRP and DL are appropriate, based on 95th percentile and fifth percentile values, respectively. In contrast, DCI has a broader range at the low end of the spectrum, and 95th percentile values are much lower than the currently utilized threshold.

An hierarchical algorithm is utilized for CCv3.0, starting with determination of adequacy of EGJ relaxation using IRP. Our study supports the well-known fact that IRP thresholds vary between HRM systems, potentially related to differences in hardware configuration including catheter diameter, pressure sensors, and pressure recording mechanisms. We also demonstrate variation in IRP based on patient position, including a significant reduction in upright IRP values when EGJOO was diagnosed while supine. This highlights the need for use of both system-specific and position-specific thresholds for IRP. Our findings show that 95th percentile values vary minimally from established normative values for all 3 HRM systems. Our 95th percentile upright value was 15.9 mm Hg for Medtronic, indicating that EGJOO will be infrequently overdiagnosed if the 15-mm Hg Medtronic threshold is strictly applied, especially if upright swallows are also performed. This might explain the fact that 20%–50% of patients diagnosed with EGJOO based on IRP values alone spontaneously improve with nonspecific approaches or no treatment,[9–11] and as many as a third may not have obstructive symptoms in some studies.[12] The normative supine IRP thresholds for Diversatek and Laborie systems were modestly lower than published thresholds. However, changing normative IRP thresholds will not be clinically meaningful, as true achalasia can exist with significantly lower IRP values than the current upper limit of normal.[13]

Thresholds for DL based on 95th percentile values were not significantly different from established norms. When DL is abnormally low, DES is diagnosed based on proportions with ≥20% premature sequences, rather than on the averaged DL threshold. There were disproportionately higher numbers of subjects who fulfilled DES criteria using the Diversatek system (13.6%) compared with Medtronic or Laborie systems (3.4% and 0.9%, respectively) (Table 1). Most subjects fulfilling DES criteria had only 2–3 premature sequences (median 2 sequences), suggesting that a higher threshold of premature sequences could improve specificity of a DES diagnosis. Our fifth percentile DL values (4.7–5.3 seconds in both upright and supine positions) indicate that premature sequences will not be overdiagnosed using the currently established threshold of 4.5 seconds, regardless of patient position or HRM system. However, fifth percentile DL values using the Laborie system were ∼0.5–0.6 seconds longer than the other 2 systems. The exact reason for this difference is not apparent from review of the studies; we speculate differences in software algorithms between HRM systems, possibly involving the threshold of the pressure ramp-up embedded in the software algorithm for identification of the contraction front and the contraction deceleration point for DL calculation. Although a full understanding of the underlying mechanism for this discrepancy will require internal investigations by HRM manufacturers, clinicians interpreting HRM studies will need to be aware of these differences. Interrogation of software algorithms is beyond the scope of this work.

Vigor of esophageal body contraction varied widely in normal volunteers, with wider variation at the low end of the DCI spectrum across the 3 HRM systems. This might indicate that the CCv3.0 threshold of 450 mm Hg•cm•s may be too high; 3.7%–15.3% supine swallows and 11.4%–14.4% upright swallows will be designated within the ineffective category if the CCv3.0 threshold is used instead of the fifth percentile values from this study. The higher CCv3.0 threshold might explain why IEM is frequently encountered even in healthy cohorts, and why the IEM pattern does not correlate well with symptoms.[14] We recommend studying a lower DCI threshold between 200 and 300 mm Hg•cm•s to determine if this relates better to symptoms or esophageal reflux burden. Our findings support tightening the CCv3.0 IEM diagnostic criteria, as reducing proportions of motor abnormalities occurring "by chance" in the healthy asymptomatic population increases the predictive power of the DCI metric. At the high end of the spectrum, 95th percentile values were within 5000 mm Hg•cm•s, and only 1 subject fulfilled current criteria for hypercontractile esophagus (with only 2 sequences with

DCI >8000 mm Hg•cm•s). Older versions of the CC utilized a DCI threshold of 5000 mm Hg•cm•s as the upper limit of normal,[15] and further research may be needed, perhaps utilizing complementary testing modalities like functional lumen imaging probe, barium esophagography, and ambulatory reflux monitoring to determine if DCI values between 5000 and 8000 mm Hg•cm•s are clinically relevant in symptomatic patients.

Only 2 subjects fulfilled criteria for absent contractility, and 1 subject had fragmented peristalsis, indicating that these patterns are rare in health. In contrast, IEM was diagnosed in 15.1% using conventional criteria (≥50% of swallows with DCI <450 mm Hg•cm•s). A confounder in IEM diagnosis is study position, as the likelihood of IEM was higher among studies performed in the upright position (21.1%–24.6%) compared with the supine position (11.0%–13.3%) when both positions were available within the same HRM system (Medtronic and Laborie). Recent studies have suggested further stratification of IEM, with ≥80% ineffective swallows and ≥50% failed swallows having clinical relevance in predicting abnormal reflux burden.[7,8] Using these stringent criteria in studies performed using Medtronic and Laborie equipment, the proportion with "severe" IEM decreased to 10.0% overall, 7.1%–8.5% in supine HRM studies and 5.3%–15.8% in upright studies.

Although there were differences in median DL and DCI values between sexes on a swallow-by-swallow analysis, no significant difference was found in median IRP values. The clinical significance of these variations is unclear, as proportions of motor diagnoses were not different between sexes. Future investigations should focus on sex differences, particularly using Laborie and Diversatek systems with adequate sample sizes.

This investigation has several strengths. It represents the largest collection of HRM studies from asymptomatic volunteers, representing 4 continents and 3 HRM systems. Given the large sample size, power was >0.9 for most comparisons, with very low probability of a type II error. We attempted to mitigate variability between motility laboratories and investigators by de novo analysis of raw studies by the same 2 investigators using HRM system-specific software tools, thus providing a more complete perspective of normative thresholds and motor diagnoses in healthy individuals than has been previously possible. Based on our findings, the definition of major motor disorders may need to be changed from "not encountered in healthy individuals" to "encountered very infrequently in healthy individuals." However, our study is not without limitations. Our dataset was overrepresented by studies performed using the Medtronic system; hence, data are more robust for this system. We relied on individual motility laboratories and investigators to ensure asymptomatic status of the subjects; therefore, enrollment criteria were not protocolized, and relevant patient factors including body mass index were not available. While substantial efforts were made to determine HRM study position and catheter type, variations in technique could not be uniformly ascertained. The role of impedance measurements and intrabolus pressure could not be determined, which we hope to study in the future using HRM studies incorporating impedance. We were unable to obtain follow-up information from asymptomatic individuals with motor abnormalities. Future normative projects will benefit from inclusion of studies from the African continent, which was not represented here. Nevertheless, our report contributes to normative assessments of esophageal motor function worldwide, and provides insight into prevalence of abnormal motor patterns in healthy individuals.

In conclusion, we report normative values for HRM metrics and prevalence of abnormal motor patterns in a large worldwide cohort of healthy volunteers. We describe prominent differences between HRM systems, particularly in IRP thresholds. We demonstrate the relatively high prevalence of IEM patterns in healthy volunteers, although proportions were lower with the use of stringent criteria, especially in studies performed while supine. Nevertheless, we demonstrate that using specific thresholds for different HRM systems, the relative prevalence of motor diagnoses is similar among different centers around the globe, reinforcing the appropriateness of universal use of CCv3.0. These normative metrics will provide a standard for comparing future studies performed on symptomatic individuals, and may provide perspective to updating the Chicago Classification of motor disorders.

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Reprint Requests

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Conflicts of Interest

These authors disclose the following DAC has served as a teacher and as a consultant and has a licensing agreement with Medtronic. Jose M. Remes-Troche has served as a consultant for Medtronic, Takeda, and Asofarma; and received lecture fees Medtronic, Takeda, Asofarma, Janssen, and Sanfer. Sabine Roman has served as a consultant for Medtronic and received research support from Diversatek Healthcare and Medtronic. Edoardo Savarino has received lecture fees from Medtronic, Takeda, Janssen, MSD, AbbVie, and Malesci; and served as a consultant for Medtronic, Takeda, Janssen, MSD, Reckitt Benckiser, Sofar, Unifarco, SILA, and Oftagest. Jordi Serra received research grants or acted as consulter/speaker for AB-biotics, Allergan, Bayer, Cassen-Recordati, Norgine, Reckitt Benckiser, Salvat, and Zespri; Daniel Sifrim has received research grants from Reckitt Benckiser UK, Jinshan Technology China, and Alfa Sigma Italy. John Pandolfino has served as a consultant for Medtronic, Diversatek, Torax, Ironwood, Takeda, and AstraZeneca; received research funding from Impleo; and owns stock options in Crospon. C. Prakash Gyawali has served as a consultant for Medtronic, Diversatek, Isothrive, Ironwood, and Quintiles. The remaining authors disclose no conflicts.