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REVIEW ARTICLE

Normative values in esophageal high-resolution manometry

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Key Messages

- This study aimed to provide a complete set of the currently known normative thresholds for the available HRM systems, and to evaluate which factors influence them.
- Numerous factors influence the normative data: type of HRM system, demographic factors, catheter diameter, body position during testing, consistency of bolus swallows, and esophageal length.
- It would be ideal to have different sets of normal values for each of the factors which influence them.
- Broadening the normal range for parameters would allow abnormal values to be of greater significance.

Abstract

Background *Esophageal high-resolution manometry (HRM) has rapidly gained much popularity worldwide. The Chicago Classification for esophageal motility disorders is based on a set of normative values for key metrics that was obtained using one of the commercially available HRM systems. Thus, it is of great importance to evaluate whether these normative values can be used for other HRM systems as well.* ***Purpose*** *In this review, we describe the presently available HRM systems, the currently known normative thresholds and the factors that influence them, and assess the use of these thresholds. Numerous factors including the type of HRM system, demographic factors, catheter diameter, body position during testing, consistency of bolus swallows, and esophageal length have an influence on the normative data. It would thus be ideal to have different sets of normal values for each of these factors, yet at the moment the amount of normative data is limited. We suggest broadening the normal range for parameters, as this would allow abnormal values to be of more significance. In addition, we suggest conducting studies to assess the physiological relevance of abnormal values and stress that for each system different normative thresholds may apply.*

Keywords *high-resolution manometry, normal values, reproducibility, solid-state manometry, technical aspects, water-perfused manometry.*

Abbreviations: DCI, Distal Contractile Integral.

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INTRODUCTION

In the 1940s, the first clinical application of esophageal manometry began with rudimentary set-ups of water-filled balloons. Since then, the technique has evolved via systems that used either water-perfused or solid-state catheters with relatively low spatial resolution (now labeled conventional manometry), to systems with closely spaced recording sites, known as high-resolution manometry (HRM).[1] Currently, several different HRM systems are commercially available and in addition new types of catheters are being developed as the clinical importance of esophageal manometry grows. In this issue of Neurogastroenterology and Motility, the third version of the Chicago Classification will be published, which is of great importance as this classification of esophageal motility disorders has gained acceptance worldwide.

THE SPECTRUM OF AVAILABLE HRM SYSTEMS

The development of HRM systems has led to multiple advantages in comparison to the use of conventional manometry, such as the establishment of an objective measurement of the gastro-esophageal junction (EGJ) relaxation, namely the integrated relaxation pressure (IRP),[2] and a more detailed characterization of esophageal body motor response.[3,4] As in conventional manometry, two types of manometric catheters can be used in HRM: water-perfused and solid-state. A variety of materials are used to make the catheters (most frequently polyvinyl chloride or silicone), their diameter ranges from 2.7 to 4.7 mm, and up to 36 measurement sites are present.[1]

The water-perfused catheters contain multiple small-caliber lumina terminating in side-holes oriented radially to the catheter. These orifices can vary in location and number depending on the catheter type and manufacturer. The proximal ends of the catheter lumina are connected to external transducers which in turn are connected, via a capillary, to a water-perfusion pump. Thus, pressure changes in the esophagus or its sphincters are transferred to the external transducers via the water in the catheter,[1] after which the analog electrical signals are converted to a digital signal and fed into a digital data recorder or computer. To obtain reliable pressure measurements, the perfusion system must be minimally compliant, which is achieved by the interposition of capillaries between the pump and the transducers.[5]

The solid-state catheters contain microtransducers which convert intraesophageal pressure into an analog electrical signal. These are fed into an electronic device that stores the data in digital format (after analog-to-digital conversion).[1] Solid-state catheters have either unidirectional transducers, which can only measure pressure from one direction, or 'circumferential' transducers, capable of measuring pressure from different sides and averaging the values.[1]

High-resolution manometry systems are produced by a number of manufacturers, of which the most globally represented are summarized in Table 1. Whereas in the United States an almost exclusive use of the 36-channel solid-state catheter is found, in emerging economies and the Asian Pacific region the majority of systems are water perfused.

LIMITATIONS AND ADVANTAGES OF SOLID-STATE AND WATER-PERFUSED HRM SYSTEMS

The most important pros and cons of solid-state and water-perfused HRM techniques are summarized in Table 2. Solid-state systems tend to be relatively simple to set up, preparation is not time-consuming and the pressure response rates are fast. The latter is of relevance when high-pressure contractions and rapidly changing pressures must be measured (e.g. in the pharynx and upper esophageal sphincter [UES]). Water perfusion manometry requires more technical skill and training as the performance of this system is dependent on factors such as perfusion rate, presence of bubbles in the capillaries and because it must be adjusted for hydrostatic pressures and for the offset pressure required to perfuse the water through the catheter. Some solid-state catheters also allow circumferential pressure measurement, which is assumed to have advantages in asymmetrical regions such as the esophageal sphincters, yet the clinical significance of this has not been determined. However, solid-state catheters are more vulnerable, much more expensive, and

Table 1 Commercially available HRM systems

Company	System	Catheter type	Channels
Medical Measurements Systems (MMS)	Solar GI HRM (HRM and high-resolution impedance manometry (HRIM))	Solid-state (Unisensor AG) and water-perfused (Dentsleeve)	Up to 36 pressure channels and 16 impedance channels
Sandhill Scientific	InSIGHT G3	Solid-state (Unisensor AG)	32 pressure/16 impedance
Sierra Scientific/Given Imaging	ManoScan	Solid-state (Sierra)	36 pressure channels ± impedance
Star Medical, Inc	Starlet HRM system	Solid-state (Unisensor AG)	36 pressure channels

Table 2 Characteristics of solid-state and water-perfused catheters

Characteristic	Solid-state catheter	Water-perfused catheter
System setup	Simple	Complex, more time consuming
Durability	Less durable	More durable
Cost of catheter	High	Low
Catheter flexibility	Relatively stiff	Flexible
Pressure rise rate/ dynamic performance	High	Lower: may not be adequate in the pharynx
Orientation of sensor	Circumferential or unidirectional	Unidirectional
Transducer site	In catheter	External, in perfusion pump
Channel spacing	7.5–10 mm (in newer designs)	Any
Catheter construction	Metal/plastic/silicone	Plastic/silicone
Channel number	36	Up to 36
Reprocessing	Chemical/none*	Chemical/autoclave

*No reprocessing is necessary with use of a protective sheath.

tend to be less comfortable as they are less flexible and have a larger diameter than most water-perfused catheters. The performance of the transducers of solid-state catheters is also temperature-dependent and may therefore require temperature compensation to normalize the pressures.[6]

In a prospective, randomized, double blind, cross-over study, Capovilla *et al.* compared the tolerability, procedure duration and costs of a 36-channel solid-state system (Given Imaging, Los Angeles, CA, USA) with that of a 24-channel water-perfused system (EB Neuro, Firenze, Italy).[7] In this study, 20 healthy control subjects and 20 patients with esophageal symptoms (i.e. reflux symptoms, chest pain or dysphagia) were enrolled. The tolerability of the two systems was assessed by a dedicated questionnaire investigating the occurrence of symptoms, and the presence and location of discomfort. No difference in tolerability between the two systems was noted by the healthy volunteers, whereas surprisingly patients better tolerated the solid-state procedure. They also observed that the water-perfused procedure required a significantly higher set-up and analysis time compared to the solid-state HRM, while no difference between the two was observed in terms of tracing acquisition time. The total procedure time for the water-perfused system was 26.4 ± 2.8 min and 20.3 ± 2.7 min for the solid-state system.[7] In addition, they noted a higher cost of a single procedure for the solid-state system, which was mainly due to the higher price of the solid-state catheter in comparison to the water-perfused catheter.[7] This study therefore concludes that water-perfused systems are cheaper, but less comfortable than the solid-state systems. It is, however, important to note that prices may vary between different centers.

One other study, conducted by Kessing *et al.*, directly compared a solid-state to a water-perfused HRM system.[8] In this study only small differences in outcome measures, such as the Chicago Classification metrics, were found. An exception is the basal pressure of the EGJ and UES, of which the relevance can be argued.

EFFECT OF SPATIAL RESOLUTION ON THE CHICAGO METRICS AND DIAGNOSIS

Even though water-perfused catheters with 36 channels exist, many motility laboratories use catheters with a lower number of recording orifices. De Schepper *et al.* conducted a study[9] in which they investigated the effect of spatial resolution on the Chicago metrics and diagnosis. HRM recordings obtained from 20 healthy controls and 47 random patients were retrospectively reanalyzed by off-line reduction in the original 1-cm spacing to 2-, 3- and 4-cm spacing in segments outside the esophagogastric junction region. The healthy subjects underwent HRM using a 36-channel water-perfused catheter (Dentsleeve, Mississauga, ON, Canada), while HRM in the patients was carried out with a solid-state assembly with 36 circumferential pressure sensors (Given Imaging). They concluded that there was a very strong correlation between the 1- and 2-cm analysis in the normal values for all parameters in the healthy volunteers and in the diagnosis of the patients. For most parameters this was even the case for 3- and 4-cm spacings. Therefore, when a sensor interval greater than 1 cm in segments outside the esophagogastric junction region is used, the normal values and the Chicago Classification for esophageal motility disorders are still applicable. As spacing increased to 3 and 4 cm, the correlation was less solid for contractile front velocity (CFV) and break size and therefore an interval spacing above 2 cm may require adjustment of some of the normal values.[9] It should be borne in mind, however, that this study was performed investigating sensor intervals outside the esophagogastric junction and that at the LES the spacing was always kept at 1 cm.

REPRODUCIBILITY AND VARIABILITY IN HRM SYSTEMS

Multiple studies have assessed the reproducibility and variability in HRM systems. Bogte *et al.* tested the reproducibility of HRM parameters in twenty healthy volunteers who underwent HRM on two separate days. A 36-channel solid-state catheter (Unisensor AG, Attikon, Switzerland) was used. The authors illustrated that day-to-day variability may occur but that this does not frequently alter the final conclusion of the test. It was concluded that HRM yields reproducible results, mainly in parameters representing anatomic structures and less in contraction wave parameters.[10]

Singh *et al.* looked at interobserver variability in esophageal body measurements among four novice physician users with a Sandhill Scientific Inc. HRM probe with 32 circumferential pressure sensors and 16 impedance channels. This study was conducted in 20 patients who were retrospectively selected for reanalysis. After a thorough instruction session the HRM-naïve physicians were able to score the recordings with good to excellent agreement for both parameters tested (CFV and DCI).[11]

Hernandez *et al.*[12] assessed interrater and intrarater agreement of achalasia subtyping according to the Chicago Classification, using a solid-state HRM catheter with 36 sensors (Sierra Scientific Instruments, Los Angeles, CA, USA). Five gastroenterologists (three motility staff and 2 trainees) first received training on the classification criteria after which they classified 20 achalasia and 10 non-achalasia cases on two different occasions. In addition, two senior investigators (who did not receive training) classified all 101 available achalasia HRMs. Intra-rater and inter-rater agreement was very good for type III achalasia, yet agreement was weaker for types I and II. Moreover, there was an excellent interobserver and intraobserver agreement for differentiating achalasia from non-achalasia patients and the agreement of the two senior investigators over all available cases was very good.[12]

HOW TO DEFINE NORMALITY?

In medicine there are several ways to define normality. One method is to determine thresholds on the basis of percentiles in a healthy population. An example is to define a range of normality with an upper limit of 95% and a lower limit of 5% in a healthy population. An alternative method is to define normality by determining the threshold for pathological changes. For example, it has been shown that a BMI above and below 19–25 kg/m^2 increases the risk of adverse health effects. Whereas the 95th percentile for BMI of young males in the USA is approximately 32 kg/m^2, acceptance of this value as a 'normal value' would not provide a medically useful separation between healthy and unhealthy.

In the studies reported in this review normality tends to be defined by the upper limit of 95% measured in a population of asymptomatic subjects. There are multiple problems with this approach. As these values were obtained in a population of healthy volunteers, the use of an upper limit of 95% to define normality means that 5% of the healthy volunteers who underwent an HRM had a value which will be considered abnormal even though they do not have any symptoms. If in addition to this a lower limit of 5% is used (as is the case in DCI), then 10% of healthy volunteers will have deviant results. Additionally, when one starts looking at multiple tests with multiple parameters such as is the case in the Chicago Classification, each parameter has 5% (or 10%) chance of being abnormal purely by chance. As a result, many patients will have a result judged to be abnormal, while this is not pathological. This has been confirmed in a study conducted by our own research group, in which unpublished data by Weijenborg *et al.*[13] was analyzed and revealed that 24/50 normal subjects who underwent HRM had one or more abnormal values, therefore illustrating a high false-positive rate for disease. Broadening the normal range would cause an increase in specificity and thus an abnormal value will be of greater significance. This would, however, be at the cost of missing out on a diagnosis in a slightly larger amount of patients due to the lower sensitivity. At the end, the physician has the role to interpret the data in the context of the clinical picture.

ESTABLISHED NORMATIVE VALUES FOR HRM SYSTEMS

Multiple studies have established normal values for HRM systems. These values are summarized in Table 3. The first sets of normal values were established in 2006 by Ghosh *et al.* (esophageal body) and Pandolfino *et al.* (EGJ). The normative values (5th and 95th percentiles) were obtained by studying 75 healthy volunteers in supine position using a solid-state manometric assembly with 36 circumferential sensors spaced at 1-cm intervals (4.2-mm outer diameter) from Sierra Scientific Instruments and 10 5-mL water swallows in each subject. Esophageal peristalsis was divided into a proximal contraction, a distal contraction and a transition zone (TZ) separating the two. Each of these segments was quantified in length and normalized among subjects.[14] The normal range (5th–95th percentile) of basal EGJ pressure during 5-mL water swallows was 5.0–31.6 mmHg.[2] Additionally, pressure profiles across the UES were analyzed using customized computational algorithms that measured

Table 3 Normal values for high-resolution manometry systems

	Sierra/Given							MMS		Sandhill		Starlet	EB Neuro
	Sweis *et al.*[22]	Niebisch *et al.*[21]	Weijenborg *et al.*[13]	Xiao *et al.*[23]	Kuribayashi *et al.*[20]	Capovilla *et al.*[19]	Chicago Classification	Bogte *et al.*[31]	Kessing *et al.*[8]	Shi *et al.*[35]	Gao *et al.*[36]	Kuribayashi *et al.*[20]	Capovilla *et al.*[19]
Catheter type	36 circumferential solid-state sensors (Sierra)	36 circumferential solid-state sensors (Sierra)	36 circumferential solid-state sensors (Sierra)	36 circumferential solid-state sensors (Sierra)	36 circumferential solid-state sensors (Sierra)	36-channel solid-state sensors (Sierra)		36 solid-state unidirectional sensors (Unisensor AG)	36-channel water-perfused catheter (Dentsleeve)	32 solid state and 5 dual impedance sensors (Unisensor AG)	32 solid state and 4 pairs of impedance sensors (Custom-designed)	36 solid-state Unisensor Catheter (Starlet)	24-channel water-perfused sensors (EB Neuro)
DCI (mmHg ·s·cm)	197–2433	420–4236	178–2828	448–4721	144–2489	400–2417	<5000	186–3408	142–3674	3195	4365	1413–6844	557–1725
Peristaltic break (cm)	6.5	NA	8.2	NA	NA	NA	<2.0	5.63	9.5	NA	NA	NA	NA
DL (s)	NA	5.4	5.4	4.3	5.0	4.6	>4.5	5.0	6.2	NA	4.5	5.8	7.0
CFV (cm/s)	4.8	7.5	5.9	8.9	6.2	7.2	<9.0	6.5	6.6	6.9	5.0	5.8	7.2
IRP4 (mmHg)	8.7	16.7	15.5	14.6	10.4	12.6	<15.0	28.28	18.8	20.5	19.8	26.1	8.8
IBP (avg max, mmHg)	16.0	14.6	19.5	NA	13.1	NA	NA	19	12	NA	NA	29.2	NA
Expiratory EGJ pressure median (mmHg)	38.4	30.8	31.2	NA	NA	NA	NA	51.4	29.8	NA	NA	NA	NA
UES basal pressure (mmHg)	NA	NA	137.7	NA	NA	NA	NA	165.1	199.3	NA	NA	NA	NA

This table uses water swallows. 5th percentile is shown for DL, 5th–95th percentile if possible for DCI and 95th percentile for the rest. All are supine position except Niebisch *et al.* who is semi-supine.

the relaxation interval and the deglutitive sphincter resistance. UES relaxation and intrabolus pressure characteristics were also studied.[15]

Following this, in 2007, Ghosh *et al.* conducted a study with 473 subjects of which 73 were controls. This study aimed to determine the optimal method for discriminating normal from abnormal deglutitive EGJ relaxation by using a solid-state HRM (Sierra Scientific Instruments) with 36 sensors spaced at 1-cm intervals and an outer diameter of 4.2 mm. Subjects were tested in supine position and used 10 5-mL water swallows. After applying automated analysis, the optimal 4-s IRP (IRP4) was calculated. When using a cutoff value of 15 mmHg, the IRP4, performed optimally with 98% sensitivity and 96% specificity in the detection of achalasia.[16] They calculated a 95th percentile cutoff for the IRP4 of 14.7 mmHg.[16]

Using the above information, Pandolfino *et al.* produced a systematic approach to classify esophageal motility using HRM and pressure topography plots.[17] This has led to the establishment of the Chicago Classification criteria for esophageal motility disorders. Since then, an iteration of the Chicago Classification has been published in 2012 after the HRM Working Group meeting in Ascona, Switzerland[18] and the third version is published in this issue. In Table 4 the esophageal pressure topography metrics utilized in the Chicago Classification are shown. These are the definitions that will be used throughout this review unless stated otherwise. The IRP is referenced to gastric pressure, while all other metrics are referenced to the atmospheric pressure.

ARE CURRENTLY USED NORMATIVE SIERRA VALUES REPRODUCIBLE?

As summarized in Table 3, most studies researching normal values have used the Sierra Scientific Instruments/Given Imaging HRM system using a 36-channel circumferential solid-state catheter with a diameter of 4.2 mm.[13,16,19–23] These studies tested patients in the supine position and used 10 5-mL water swallows to evaluate the normative thresholds. As illustrated in Table 3, the values obtained in some of these studies differ from the suggested Chicago Classification thresholds. For instance, in the study by Sweis *et al.*[22] a lower cutoff for the upper limit of normal for DCI, CFV and IRP4 and a higher cutoff for the TZ were found. Some methodological differences may explain the observed discrepancies as Sweis *et al.* used a 30-mmHg isobaric contour when evaluating the TZ rather than a 20-mmHg isobaric contour which is used in the Chicago Classification. In addition, they took the first effective peristaltic contraction after each bolus administration during the evaluation instead of the first peristaltic contraction, which is not standard. Other reasons for the discrepancy in the results can be demographic factors between the population studies such as age, obesity and racial background which have been shown to have an effect on esophageal parameters.[24–26] This suggests the need for different normative thresholds for different populations.

In a study by Weijenborg *et al.*,[13] carried out with Sierra equipment in a European population, most parameters were in line with the Chicago Classification and substantial differences were only observed in the upper limits of normal of DCI, TZ length and the UES resting pressure. The DCI was markedly lower than in other studies which is possibly due to a low BMI in the study population (23.4 kg/m^2 compared to 28.7 kg/m^2 in the average population in the United States). Other studies, such as the study by Kuribayashi *et al.*, conducted in a Japanese population,[20] and Capovilla *et al.*, conducted in an Italian population,[19] also obtained significantly lower values for the upper limit of normal for DCI. This suggests that demo-

Table 4 Esophageal pressure topography metrics utilized in the Chicago Classification

Metric	Description
Integrated relaxation pressure (IRP) (mmHg)	Mean EGJ pressure measured with an electronic equivalent of a sleeve sensor for four contiguous or non-contiguous seconds of relaxation in the 10-s window following deglutitive UES relaxation
Distal contractile integral (DCI) (mmHg·s·cm)	Amplitude × duration × length (mmHg·s·cm) of the distal esophageal contraction >20 mmHg between the proximal and distal pressure troughs
Contractile deceleration point (CDP) (time, position)	The inflection point along the 30-mmHg isobaric contour where propagation velocity slowsdemarcating the tubular esophagus from the phrenic ampulla
Contractile front velocity (CFV) (cm/s)	Slope of the tangent approximating the 30-mmHg isobaric contour between the proximal trough and the CDP
Distal latency (DL) (s)	Interval between UES relaxation and the CDP
Peristaltic breaks (cm)	Gaps in the 20-mmHg isobaric contour of the peristaltic contraction between the UES and EGJ, measured in axial length

graphic factors could possibly play a vital role in this lower DCI. This is further supported by the study by Niebisch *et al.* who recruited 68 normal volunteers in the United States to produce a second set of normative thresholds for HRM under standardized protocol[21] and showed strikingly similar results to the study by Ghosh *et al.*, not having a significantly lower DCI. It is, however, important to note that Niebisch *et al.* conducted their study in a semi-supine position (approximately 30-degree elevation), which could influence their results.

EVALUATION OF THE CHICAGO CLASSIFICATION

According to the 2012 version of the Chicago Classification, hypercontractility was defined as a DCI >8000 mmHg·s·cm in a single swallow, which was based on the highest DCI value observed in asymptomatic healthy subjects. However, in the study by Weijenborg *et al.*[13] a highest value of 9005 mmHg·s·cm was observed and in the study by Niebisch *et al.*[21] two subjects had a DCI up to 9000 mmHg·s·cm. As DCI >8000 mmHg·s·cm is considered pathological this is an inconsistency as there have been subjects with higher values yet without symptoms. This problem has been addressed in the third version of the Chicago Classification by requiring ≥20% of contractions with a DCI >8000 mmHg·s·cm for the diagnosis of Jackhammer esophagus.

Multiple studies have shown that peristaltic breaks occur frequently in healthy subjects.[13,20,21,27,28] In a study by Kumar *et al.*,[27] 199 participants (110 had gastroesophageal reflux disease (GERD), 74 were symptomatic without GERD and 15 were healthy controls), underwent HRM to evaluate the intersegmental troughs. They observed that extended intersegmental troughs (defined as troughs exceeding 20% of the esophageal length in ≥30% of swallows) were present in 26.7% of healthy controls, suggesting that extended intersegmental troughs are physiological. This is supported by Niebisch *et al.*[21] who concluded that up to 26% of swallows with small breaks are present in normal subjects. According to the 2012 version of the Chicago Classification, both peristaltic breaks of 2–5 cm (small breaks) and breaks larger than 5 cm (large breaks) were used to classify peristaltic dysfunction. In the most recent version of the Chicago classification (3.0), only breaks of more than 5 cm will be taken into account. This 5 cm cutoff is in part derived from a study by Roman *et al.*[28] where they used HRIM to show that a break of >5 cm in the 20-mmHg isobaric contour was associated with incomplete bolus transit (IBT) in 100% of swallows while small peristaltic breaks (2–5 cm) were associated with incomplete bolus clearance in only 16% and thus breaks of 2–5 cm seem to lack importance.

However, even IBT can lack relevance. A study by Bogte *et al.* looked at the relation between failed bolus transport and abnormal esophageal motility and found that impaired bolus clearance for solids, and to some degree for liquids, is common in both patients and controls.[29] They also showed that even in the healthy volunteers there was stasis of liquid boluses in 41% and stasis of solid boluses in 82%, illustrating that this occurs frequently in both patients and in controls[30] and thus IBT is not necessarily pathological. Hopefully future studies will allow more insight into the relevance of IBT.

DIFFERENCES BETWEEN HRM SYSTEMS AFFECT NORMAL VALUES

Recent published studies have shown that the normative thresholds vary with different HRM systems.[8,19,20,31,32] In a study in 50 healthy volunteers carried out by Kessing *et al.*,[8] a water-perfused HRM catheter with 36 unidirectional pressure channels (Dentsleeve) and a diameter of 4.7 mm was compared to a solid-state HRM with 36 circumferentially measuring sensors (Given Imaging). The authors observed a moderate to good agreement between the two systems, producing only small differences in most outcome measures (CFV, DL, DCI and IRP4s). In contrast, basal pressure of the EGJ and UES were markedly different between the two systems. The relevance of this observation for clinical practice is limited as these two parameters do not form part of the Chicago Classification. The substantial difference may be explained by the unidirectional *vs* circumferential pressure measurement. Additional reasons for differences in normal values measured in this study could be intraindividual variability, catheter diameter, the pressure response rate of water-perfused systems and the pharyngo-UES reflex. The pharyngo-UES reflex, that can be generated by stimulation of the pharynx by perfusion of water, can cause an increase in UES pressure[33] and as a result influence the normative data.

Other studies using 22-channel water-perfused catheters have shown a larger difference in normative thresholds.[32,34] In the study by Ortiz *et al.*[34] 695 controls without achalasia and 47 patients with untreated achalasia were evaluated. They concluded that for their system the cutoff value of 15 mmHg for IRP4 was not adequate for diagnosing esophageal achalasia as 23 of the 47 achalasia patients had an IRP4 less than 15 mmHg. In the study by Zavala-

Solares *et al.*[32] a 22-channel water-perfused catheter was also used. They found a significantly lower UESp, DCI, CFV, LESp and IRP when using the water-perfused catheter in comparison to the use of a solid-state catheter (Given Imaging). This decrease in measurement values is further supported by a study by Capovilla *et al.*,[19] who also showed significantly lower values of 4s-IRP, DCI, CFV and UESp when using a 24-channel water-perfused catheter (EB Neuro, Firenze, Italy) in comparison to a 36-channel solid-state catheter (Given Imaging). These studies therefore indicate that, when using water-perfused catheters, caution is required when normative values are used that were established with solid-state catheters.

As shown in Table 3, studies have also been performed using 36-channel solid-state catheters using systems other than the Given Imaging HRM system. The values obtained in these studies also tend to differ from the normative values used by the Chicago Classification. To our knowledge, only two studies have been published using the Sandhill high-resolution impedance manometry (HRiM) system to establish normal values. In one study, Shi *et al.*[35] found a lower DCI and a lower CFV in comparison to the Chicago Classification. This study did, however, have a small sample size which could have played part in finding a lower upper limit. They also noted a higher limit of normality for IRP4 of 20.5 mmHg which would cause a proportion of individuals to be misclassified as having EGJ outflow obstruction when using the reference value of 15 mmHg obtained using the Sierra system. Another study, by Gao *et al.*, which has been accepted for publication in Diseases of the Esophagus, also evaluated normative thresholds for the Sandhill system.[36] They confirmed the results by Shi *et al.* as they also found a lower DCI, lower CFV and a higher IRP4. In a study by Kuribayashi *et al.*[20] a 36-channel solid-state Unisensor catheter with the Starlet system was compared with the ManoScan system. They noted a significantly higher DCI, DL and IRP4 and a lower CFV. Additionally it was illustrated that values differed between the ManoScan and the Starlet system using the same subjects, thus ruling out demographic factors as a possible cause for the different values obtained. In a study by Bogte *et al.*,[31] normal values for HRM, performed with a 36-channel solid-state unidirectional Unisensor AG catheter and the MMS perfusion and acquisition system, were calculated. As shown in the table, significantly higher upper limits of normal were found for IRP, EGJ resting pressure, UES resting pressure and TZ length, with the difference being most pronounced for the IRP. These discrepancies in normal values could in part be explained by factors such as a smaller catheter diameter of 3.3 mm and a unidirectional sensor orientation instead of circumferential sensor orientation. Additionally, in this study, subjects who had hypotensive peristalsis were included in the measurement of the TZ, which is a possible explanation for the higher TZ length.

These studies illustrate that caution is needed when using normal values of the Sierra system if another manometric system is used as the normative thresholds tend to differ between systems. There are multiple factors influencing the results obtained such as technical differences in equipment and differences in studied populations, however, we suggest acquiring normative thresholds for each manometric system using adequately sized groups of control subjects.

EFFECT OF BODY POSITION

Another factor influencing normative values is the body position of the subject during HRM evaluation. Values from relevant studies are shown in Table 5. Esophageal manometry is usually performed in supine position which allows the testing of peristaltic function without having an effect of gravity on bolus transit. Some authors argue that a seated position is more physiologic and have proposed to perform studies in this upright position. Bernhard *et al.*[37] noted a higher proportion of patients with ineffective esophageal motility and a lower proportion with normal manometry when testing in the upright position than in the recumbent position. Similarly, the study by Xiao *et al.*[38] concluded that a change in position elicited a significant change in diagnosis in approximately 10% of cases. Additionally, they illustrated that positional changes helped to remove a vascular artifact that would have led to an inaccurate diagnosis of EGJ outflow obstruction in three patients.

Roman *et al.*[39] also demonstrated that body position can affect the results of esophageal HRM as DCI, wave amplitude and wave duration significantly altered with change in position. In addition, they concluded that the mean resting LES pressure was not significantly changed by body position, nor was the mean residual LES pressure or the CFV. This finding stands in contrast to the results of a previous study[40] using conventional manometry demonstrating a lower LES tone in the upright position. Possibly, the low mean LES resting pressure in the supine position masked the effect of changing to upright in this study. However, Roman *et al.* did note a lower DCI in the sitting position than in the supine position, which could be explained by the lower workload required for bolus transport in the

Table 5 Effect of body position

	Sweis (23 controls) Liquid swallows		Xiao (75 controls) Liquid swallows		Roman (100 patients) Liquid swallows	
	Supine	Upright	Supine	Upright (70–90°)	Supine (mean values)	Upright (mean values)
Integrated relaxation pressure (mmHg)	8.7	15.8	14.6	10.8	NA	NA
Proximal transition zone length (cm) (at 30 mmHg)	6.5	10.9	NA	NA	NA	NA
Contractile front velocity (cm/s)	4.8	5.5	8.9	6.1	7.1	6.1
Distal contractile integral (mmHg·cm·s)	197–2433	181–2444	448–4721	187–1991	1639	1126
Intra-bolus pressure (mmHg)	16.0	17.2	NA	NA	NA	NA
Proximal contractile segment at 30 mmHg (cm)	7.3	6.9	NA	NA	NA	NA
Distal contractile segment at 30 mmHg (cm)	18.1	18.0	NA	NA	NA	NA
Proximal transition zone (PTZ) mean pressure at 30 mmHg (mmHg)	45.4	24.9	NA	NA	NA	NA
Distal Latency (s)	NA	NA	4.3	4.9	NA	NA
Basal LES pressure (mmHg)	NA	NA	NA	NA	8.1	7.1

5th percentile is shown for DL, 5th–95th percentile for DCI and 95th percentile for the rest. All values of Roman *et al.* are mean values.

sitting position, due to gravity. Therefore, if supine normal values were to be used, this could lead to an overdiagnosis of hypotensive peristalsis.[39]

A study by Xiao *et al.*[23] also shows significant alterations when changing posture, with a lower IRP, DCI and CFV in the sitting position than in the supine position. Sweis *et al.* also reported a decrease in DCI in sitting position,[22] but observed an increase in IRP and CFV, which stands in contrast to the study by Xiao *et al.* Further studies will need to be performed to evaluate the effect of body position on IRP and to further assess the benefit of testing in both supine and sitting position, as currently sufficient evidence supporting this is lacking. It is, however, clear that different normative values need to be established for the sitting position. As shown in Table 3, a study by Niebisch *et al.* was performed in a semi-supine position (approximately 30-degree elevation),[21] which could have contributed to the lower DCI and DL found.

BOLUS CONSISTENCY AND VOLUME

Esophageal symptoms mainly tend to arise during and after meals and are rarely triggered by small volumes of water.[41] Therefore, some authors argue that the addition of solid boluses to manometric investigations may increase the sensitivity for clinically relevant dysmotility. However, solid boluses are more difficult to standardize for volume and consistency compared to water. In addition, solids produce more complex pressure activity and are not always transported with a single peristaltic contraction, making it more difficult to analyze and impairing inter-investigator agreement. The results of studies comparing liquid to solids are shown in Table 6. In a study by Sweis *et al.*,[22] conducted in 23 asymptomatic volunteers, it was shown that using bread compared to liquid swallows led to a lower CFV and greater DCI. Additionally it was found that the IRP and intra-bolus pressure were increased when solids were used instead of liquids. This increase in DCI and IRP could perhaps be explained by an increased workload and increased friction between the bolus and the luminal wall at the sphincter level. These results are supported by the study by Shi *et al.*[35] in which there was an increase in the IRP threshold and a decrease in CFV when viscous swallows were used instead of water swallows. They did, however, show an unchanged DCI and a decrease in the median IRP. The study by Gao *et al.* also found a lower CFV, yet in contrary to the aforementioned studies, they found a lower IRP.[36] These studies illustrate the need for separate normative values for bolus swallows of different consistency as this has a clear impact on obtained results. Xiao *et al.*[38] reported that the use of high-volume (10 and 20-mL) water swallows did not change the diagnosis. However, the use of viscous liquids and marshmallows increased the detection of EGJ outflow obstruction. These results are consistent with results from Blonski *et al.*[42] who reported a 10% increase in the detection of impaired

Table 6 Effect of bolus consistency

	Sweis (23 controls) Supine position		Shi (42 controls) Supine position		Gao (62 controls) Supine position	
	Liquid	Solid	Liquid	Viscous (yogurt)	Liquid	Viscous (gel)
Integrated relaxation pressure (mmHg)	8.7	12.8	20.5	23.2	19.8	19.7
Proximal transition zone length (cm) (at 30 mmHg)	6.5	5.0	NA	NA	NA	NA
Contractile front velocity (cm/s)	4.8	4.4	6.9	6.2	5.0	4.4
Distal contractile integral (mmHg·cm·s)	197–2433	330–4041	3195	3198	4365	4696
Intra-bolus pressure (mmHg)	16.0	19.9	NA	NA	NA	NA
Proximal contractile segment at 30 mmHg (cm)	7.3	7.5	NA	NA	NA	NA
Distal contractile segment at 30 mmHg (cm)	18.1	20.7	NA	NA	NA	NA
PTZ mean pressure at 30 mmHg (mmHg)	45.4	58.0	NA	NA	NA	NA

5th–95th percentile is shown for DCI if possible, and 95th percentile for the rest.

esophageal function when using viscous swallows. Additionally, Bernhard et al.[37] concluded that the use of both water and bread swallows identifies subtle differences between patients with chest pain, dysphagia, and GERD symptoms that are not revealed by water swallows alone. These studies therefore illustrate that additional testing with boluses of different consistency can result in a diagnosis that would otherwise have been missed. However, it is important to note that the observed increase in sensitivity almost certainly leads to a decrease in specificity and that 'abnormal' motility responses to solid bolus swallows are frequently seen in healthy subjects.[30]

CATHETER DIAMETER

Xiang et al. describes the effect of catheter diameter by comparing two 36-channel solid-state high-resolution catheters (Sierra Scientific Instruments), with outer diameters of 2.7 and 4.2 mm, in 9 asymptomatic volunteers and 18 patients with GERD.[43] They concluded that the 2.7-mm catheter in comparison to the 4.2-mm catheter yielded a higher LES pressure, a lower UES resting pressure, a lower mean DCI and a higher IRP4. This could affect the final diagnosis of esophageal dysmotility. Another study, performed by Lu et al., also compared the aforementioned catheters.[44] They concluded that the 2.7-mm catheter provided similar results to the 4.2-mm catheter. However, they also noted deviating values for UES pressure and IRP. Thus, it is recommended to have normative values for differences in catheter diameters used.

ESOPHAGEAL LENGTH

Another factor influencing HRM values is the esophageal length. In a study by Singendonk et al.,[45] the effect of age and size on the Chicago classification metrics was assessed. 76 HRM solid-state impedance manometry recordings in children and 25 recordings from healthy adult subjects were evaluated in the upright position and with a bolus volume ranging from 3 to 10 mL. They concluded that younger patient age and a shorter esophageal length correlates significantly with an increase of IRP4, a shorter DL and a smaller break size. This then leads to an over-diagnosis of EGJ outflow obstruction or diffuse esophageal spasm. This could in part clarify why in the studies by Shi et al. and Kuribayashi et al. higher cutoff levels were found for the IRP4 as the average height in the Chinese and Japanese population is lower, and the esophagus is shorter. In another pediatric study, the authors advocated to adapt the metrics of DCI to the length of the esophagus[46] thus again suggesting that esophageal length influences normative values.

DISCUSSION

Several different HRM systems are used around the globe. It is therefore of great importance for the dissemination of HRM to evaluate whether the currently used normative values in the Chicago Classification (obtained using a solid-state HRM from Sierra Scientific Instruments) can be used in other HRM systems as well, as this is a necessity for the global comparison of studies and techniques.

It is of considerable importance to know which factors influence normative values. The factor with the greatest influence is the type of HRM system used. Other factors influencing results are demographic factors such as age, obesity, and racial background.[24–26] Additionally, factors such as catheter diameter,[43] body position during testing,[22,23,37–39] consistency of bolus swallows,[22,35,37,38,42] and esophageal length[45] have an impact on normative values obtained. It would therefore be ideal to have different sets of normal values for each of the aforementioned factors. Moreover, some authors concluded that a change in position during HRM testing,[37,38] or the addition of boluses with different consistency,[37,38,42] was beneficial in leading to a correct diagnosis. We caution the addition of a change in posture or consistency to standardized protocol as it is more than likely that the increase in sensitivity would come at the cost of a decrease in specificity, and thus cause the frequency of false-positive diagnoses to increase even further.

Despite multiple factors influencing normative values, the Chicago Classification is still applicable in most situations. This is even the case when using a higher sensor interval of 2 cm in segments outside the esophagogastric junction,[9] or to some degree when using a type of water-perfused catheter.[8] However, there were certain flaws in the criteria for hypercontractility and the criteria looking at break size in the 2012 version of the Chicago classification, which have now been addressed in the third version.

In conclusion, the available information clearly shows that for each HRM system a different set of normal values should be used. Cutoff values based on the 95th percentile of normal carry the risk of erroneously labeling esophageal motility as abnormal and there is thus a need for meaningful cutoffs that separate patients with and without well-defined symptoms. In addition, the available data lends support to the notion that the criteria for weak peristalsis and frequent failed peristalsis should be adjusted.

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AUTHOR CONTRIBUTION

TH designed the review, drafted the manuscript, revised the article critically for important intellectual content, and approved the final submitted draft; AJB and AS designed the review, critically revised the manuscript for important intellectual content, and approved the final submitted draft; PJK and SR critically revised the manuscript for important intellectual content, and approved the final submitted draft.

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