HIGH-RESOLUTION ANORECTAL MANOMETRY: A COMPARISON OF SOLID-STATE AND WATER-PERFUSED CATHETERS

Running title:

Solid-state vs water-perfused HR-ARM

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Abstract:

Background

Anorectal manometry is the most commonly performed investigation for assessment of anorectal dysfunction. Findings from previous studies comparing water-perfused (WP) and solid-state (SS) techniques in the anorectum are conflicting. We compared anal sphincter pressure at rest and during dynamic maneuvers (squeezing and coughing) in healthy volunteers using SS and WP high-resolution anorectal manometry (HR-ARM) employing equivalent catheter configurations, a standardized protocol, and identical data acquisition and analysis software.

Methods

60 healthy volunteers (40F; median age: 40; range: 18-74) underwent WP and SS HR-ARM in randomized order. Anal resting pressure, and squeeze and cough increments were measured. Median pressure and 5th and 95th percentiles were calculated for each maneuver and compared using Wilcoxon signed rank test. Bland and Altman plots were used to assess agreement between the systems. The impact of gender and parity was also explored.

Key Results

Anal sphincter pressure measurements during squeeze ($P < 0.001$) and cough ($P < 0.001$) were significantly higher using SS HR-ARM than WP HR-ARM. No differences were seen at rest between the two types of catheter (nulliparous: $P = 0.304$; parous: $P = 0.390$; males: $P = 0.167$). Normal ranges for SS and WP manometry from this small group of healthy volunteers are presented.

Conclusions & Inferences

Greater sensitivity to rapid pressure change is one of the advantages associated with SS HR-ARM. This is reflected in the differences observed during dynamic maneuvers performed during this study. Catheter type should be taken into consideration when selecting normal ranges for comparison to disease states.

Keywords: Healthy volunteers, Manometry, Normative data, Solid-state, Water-perfused

Key points:

1. Anorectal manometry is currently performed using both solid-state and water-perfused catheters. This study assesses the agreement between the two methods using high-resolution anorectal manometry (HR-ARM).

2. Solid-state measurements of squeeze and cough pressures were higher compared to water-perfused HR-ARM.

3. Interpretation of pressure against normal ranges should consider the catheter-type used to acquire pressures.

Introduction

Anal sphincter dysfunction is a leading cause of symptom generation in functional anorectal disorders such as fecal incontinence (FI) and constipation[1]. Anorectal manometry (ARM) is the most widely accepted and utilized investigation in such patients, where mechanical activity of the anal sphincters and rectum is quantified via measurement of intra-luminal pressures during voluntary and involuntary maneuvers, designed to interrogate both striated and smooth muscle components, reflex functions, and recto-anal coordination[2].

Measurements of pressure are typically quantified using either water-perfused (WP) or solid-state (SS) catheters attached to a manometry system. WP catheters comprise multi-lumen tubing through which degassed water is perfused at a steady rate via a pneumohydraulic pump. Occlusion of perfusion ports due to increased luminal (sphincter) pressure increases resistance to flow within the system, which is detected by external force transducers. By contrast, solid-state catheters incorporate microtransducers within the catheter assembly for direct measurement of pressure change.

Until recently, the number of sensors within both WP and SS systems has been limited to <10. In 2002, a 'minimum standards' document for performing ARM advocated the use of six sensors[3]. The last decade, however, has seen the development of high-resolution anorectal manometry (HR-ARM), with a key improvement being the ability to incorporate an increased number of closely spaced sensors or recording ports on catheters. Alongside increasing sensor numbers, the incorporation of topographical color-contour plots into analytical software has helped to facilitate depiction (and interpretation) of pressure changes compared to traditional

line tracings. Although data are still emerging, it is believed that the increased spatiotemporal resolution of HR-ARM is likely to provide many advantages including a better appreciation of global anal function, improved diagnostic accuracy, and a reduction in data misinterpretation due to correct identification of movement artefact[4].

Due to its perceived advantages over 'conventional' ARM, uptake of HR-ARM into clinical practice has been rapid. A recent survey of 107 institutions worldwide has demonstrated that 53% already use HR-ARM as their manometric catheter/system of choice[5]. Of these, 23% use WP catheter systems and the remaining 77% use SS systems for data collection. However, WP catheters remain a convenient and popular choice, especially in the UK and mainland Europe, and have the advantages of being single-use, less costly, and more robust[6].

A number of studies have explored differences between WP and SS manometry systems in the esophagus[7-15], colon[16], and anorectum[17-23] and also *ex-vivo*[24]. Whilst the correlation between WP and SS measurements of pressure is good[9, 10, 14, 18, 19, 21-24], some authors have noted significant differences in absolute pressures acquired using each system[8-10, 12, 13, 15, 17, 19-21, 23]. Consequently, individuals studied using WP systems may be considered 'abnormal' when compared to normative data-set cut-offs based on SS measurements[15, 25, 26]. The need for system specific normative values has already been recognized in the esophageal literature[14, 27].

This study aims to explore the influence of recording method in the anorectum. Hence, the specific aims are to compare anal sphincter pressure measurements at rest and during dynamic maneuvers (squeezing and coughing) in healthy volunteers using WP and SS HR-ARM to further inform normative data needs.

Materials and Methods

Subjects

Healthy, asymptomatic volunteers were recruited from Hull and East Yorkshire Hospitals NHS Trust, Cottingham, UK. Exclusion criteria were: symptoms of fecal incontinence and/or constipation (modified Vaizey score >4 and/or Cleveland Clinic Constipation score >6), active local anorectal complaints (hemorrhoids, anal fissure, or fistula), previous anal surgery, and history of inflammatory bowel disease. A general and focused history was obtained via questionnaire. Written informed consent for the study was obtained from all volunteers; permission for the study was granted locally (Research and Development, Castle Hill Hospital, Cottingham, UK).

Equipment

SS HR-ARM

A SS catheter (UniTip: UniSensor AG, Switzerland), with an external diameter of 12 Fr (~16 Fr at sensors) was used to perform studies. The catheter incorporates 8 micro-transducers placed 0.8 cm apart, with a total measurement distance of 5.6 cm. Pressure is measured circumferentially at each sensor by means of a unidirectional pressure sensor embedded within silicone gel. An additional, single microtransducer was located within a non-latex balloon with a maximum capacity of 600 ml (Mui Scientific, Ontario, Canada). Prior to each study, the balloon was attached to a groove cut into a metal ring 3 cm from the catheter tip using suture thread. Sensors were soaked in tepid water for at least 3 minutes prior to zeroing to atmosphere under 1 cm of water. The catheter was inserted into the anorectum such that the distal two microtransducers were visible, with the more proximal one situated at the anal verge.

WP HR-ARM

Customized, single-use anorectal catheters with 10 channels and an external diameter of 14 Fr were used for WP measurements (Mui Scientific, Ontario, Canada). Perfusion ports were spaced 0.8 cm apart, spanning a total measurement distance of 7.2 cm; the unidirectional ports were arranged in a spiral formation relative to each other. A premounted non-latex balloon with maximum capacity of 400 ml was incorporated at the catheter tip. Sterile water (containing 5 ml L^{-1} of 6% Oxygenal) was perfused at a rate of 4.2 ml min^{-1} using an external pressure pump set to 1000 mmHg. Prior to each study, the catheter channels were filled with fluid, and any air in the capillary tubing, transducers or catheter was expelled to prevent artefacts. The catheter was zeroed to atmosphere in a horizontal position and level with the anal canal. Calibration and quality of the recording were then checked by raising the catheter to a height of 60 cm. Pressures were recorded by external pressure transducers (Argon, Texas, USA) incorporating 0.6 ml min^{-1} flow restrictors. On intubation, the channels were positioned such that at least two ports remained exposed to atmospheric pressure (as above).

Data acquisition

Data acquisition (sampling rate: 10Hz), online visualization and signal processing for both catheters were performed using a commercially available manometric system (Solar GI HRM v9.1, Medical Measurement Systems (MMS), Enschede, The Netherlands).

Study Protocol

WP HR-ARM and SS HR-ARM were performed consecutively in a randomized order.

A predetermined, alternating schedule between SS and WP was created prior to study commencement for males, parous-, and nulliparous females. As such, the first participant in each gender/parity group had SS followed by WP, the second participant had WP followed by SS, and the third started with SS etc. All studies were performed and analyzed by one of two experienced practitioners (AR/MW); the same practitioner performed WP and SS HR-ARM for each individual participant to ensure instructions were given in a consistent manner for each catheter. The time interval between WP and SS manometry, regardless of the order in which studies were performed, was approximately 5 minutes to allow perfusion of WP tubing or soaking of SS sensors.

The manometry protocol was identical for each study. Subjects were encouraged to empty their bowel prior to the investigations, but no bowel preparation was given. Studies were conducted with the subject in left-lateral position with knees and hips flexed. After a 3-minute familiarization period, test maneuvers were performed as previously described[4]. To summarize, the following maneuvers were performed: (1) rest: with the subject relaxed and lying still, anorectal pressures were measured for 1 minute, (2) cough: the subject was asked to cough once maximally, and (3) squeeze: the subject was asked to squeeze maximally for 5 sec. Cough and squeeze maneuvers were both repeated. Each maneuver was followed by a 30-second period of rest.

Data analysis

Data from both catheters were analyzed using the same automated software. Pressure regions delineating rest and squeeze areas of interest on the topographic color-contour plot were reviewed, adjusting the e-sleeve box manually where

required. The anal canal was identified as a band of color that was visually distinguishable from the color above and below as previously described[4]. Visualization was made relative to atmospheric pressure and with the color scale set from 0-150 mmHg. Resting pressure was defined as the mean maximal pressure recorded by channels within the anal canal e-sleeve during the 60-second rest period. Maximum squeeze increment was defined as the highest pressure difference relative to baseline pressure (at rest) achieved during a 5-second period of voluntary squeeze; baseline pressure was defined as the mean maximum pressure recorded across all channels during the 10 seconds immediately preceding the squeeze maneuver. Similarly, the maximum cough increment was taken as the highest pressure difference recorded during a single cough relative to baseline pressure measured in the 10 seconds preceding cough. As squeeze and cough were performed twice, the greater of the two pressure increments achieved was used for analysis.

Statistical analysis

Data are presented as median, 5th and 95th percentiles. Student's t-test was used to compare demographic data between groups. Wilcoxon signed rank test or Sign Test was used to compare WP and SS outcomes. Bland-Altman plots[28] with 95% limits of agreement were created to assess agreement between the measurements. Statistical analyses were performed using a commercially available software package (SPSS Statistics Version 24: IBM, New York, USA). A P value of <0.05 was considered statistically significant.

Results

Subjects

Sixty healthy volunteers were recruited to the study. Subject demographics are shown in Table 1. No significant difference in age was observed between males and females (P >0.05). However, nulliparous females were significantly younger than parous females (P <0.001). The median number of births within the parous group was 2 (range: 1-4). Of 44 births, 22 were reported as normal vaginal deliveries, 12 were considered traumatic involving a tear (7) or an episiotomy (5), and 4 were reported as involving forceps. Six deliveries occurred by caesarean-section. One woman had only ever given birth by caesarean-section. Median constipation and incontinence scores for the total population were 2 (range 0-5) and 0 (range 0-4), respectively. The procedures were tolerated well and without complications by all subjects.

Comparison between WP and SS measurements and normal ranges

The distribution of data obtained using WP and SS catheters is shown in Figure 1. In women, Wilcoxon signed-rank test showed that catheter type did not affect measured anal canal resting pressure (nulliparous: Z= -1.027, P = 0.304; parous: Z= -0.860, P = 0.390). Similarly in males, median resting pressure as recorded using the SS catheter was not significantly different compared to WP (P = 0.167). There was a significant difference in the pressures measured by SS and WP catheters during squeeze (nulliparous: Z= -3.846, P <0.001; parous: Z= -3.603, P <0.001; males: Z= -3.920, P <0.001) and during cough (nulliparous: Z= -3.696, P <0.001; parous: Z= -3.584, P <0.001; males: median increase compared to WP= 66mmHg, P <0.001). Numerically, the median squeeze pressure was higher using a SS than WP catheter

in nulliparous females (SS: 182 vs WP: 109 mmHg), parous females (SS: 149 vs 98 mmHg), and in men (SS: 322 vs WP: 177 mmHg). Similarly, median cough increment was higher using a SS than a WP catheter (nulliparous: 136 vs 82 mmHg; parous: 120 vs 78 mmHg; males: 157 vs 91 mmHg). Normative ranges for each catheter type are shown in Table 2.

Agreement between SS HR-ARM and WP HR-ARM

Bland and Altman plots are presented in Figure 2a-c. At rest, the mean difference is -0.7 mmHg with a 95% confidence interval for bias -4.8 to 3.4 mmHg. However, the mean difference in squeeze increment was 85 mmHg (95% confidence interval for bias: 67 to 102 mmHg) i.e. the mean pressure difference recorded by using SS would likely be between 67 and 102 mmHg above WP if the study was repeated. Similarly, the mean difference in cough increment was 62 mmHg (95% confidence interval for bias: 48 to 77 mmHg).

Further exploration of squeeze and cough plots revealed proportional disagreement between the catheters (i.e there was a greater magnitude in the differences seen at higher pressures/with stronger contractions). To illustrate this further, Bland & Altman plots were regenerated for using a mean pressure of 150 mmHg as the cutoff. For values <150 mmHg, the mean difference during squeeze (n=29) was 43 mmHg (95% limits of agreement -17.1 to 103.1 mmHg) and the mean difference during cough (n=46) was 43 mmHg (95% limits of agreement -31.5 to 118.8 mmHg). For values >150 mmHg, the mean difference during squeeze (n=31) was 124 mmHg (95% limits of agreement -12.2 to 259.9 mmHg) and the mean difference during cough (n= 14) was 123 mmHg (95% limits of agreement -6 to 252 mmHg).

Discussion

This study compared commonly utilized functional anal canal parameters using WP HR-ARM and SS HR-ARM in 60 healthy volunteers. We evaluated the level of agreement between measurements made using two methods of pressure detection at rest, during squeeze and during cough. At rest, no clinically significant difference or systematic bias between the catheters was found. This is consistent with results from esophageal studies, in which lower esophageal sphincter (LES) resting pressures generally show good agreement between catheter types,[14, 29] and also from studies in the anorectum, where measured pressure did not differ between SS and WP HR-ARM catheters[18, 20, 22, 23]. Regarding peak cough and squeeze pressures, however, the results of this study showed significant differences between measures recorded by WP and SS HR-ARM catheters.

Comparable literature in the anorectum is limited and results are conflicting at times (see Table 3). Simpson et al[18] found no differences at rest or during squeeze between end-hole WP, side-hole WP and SS manometry using a conventional, station pull-through technique in patients and healthy volunteers. On the contrary, simultaneous pressure measurements performed in patients with constipation or FI, resulted in significantly higher resting and squeeze pressures using SS HR-ARM compared to a WP sleeve assembly[19]. Kang et al[22] compared WP station pull-through manometry with SS HR-ARM in a mixed patient group. No significant differences in resting and squeeze pressures were found. Most recently, Wu et al[23] reported no differences in WP and SS measurements at sphincter level (rectal pressure at rest was higher with SS), however no figures are provided and SS measurements were transmitted via a wireless device. Comparisons within and between studies are confounded by the variety of techniques (conventional vs high

resolution), catheter configurations (end-hole, side-hole, sleeve sensor, etc.), and study populations (patients with constipation and/or FI vs healthy volunteers) used. Furthermore, clinical interpretation of pressures is hindered by lack of normative data from substantive datasets; these data are only available for SS systems[4, 30-32] and not WP.

Differences between WP and SS pressure measurements in the esophagus have been noted during LES relaxation and esophageal body contraction[13, 14, 33], which can impact clinical diagnosis[26, 27]. These autonomic functions are assessed using derived metrics: integrated relaxation pressure (IRP) for the LES relaxation, and distal contractile integral (DCI) for esophageal contraction. Both IRP and DCI are affected by the type of pressure recording technology used, with differences being attributed to the greater sensitivity and higher 'rise rate' of SS catheters allowing greater ability to register transient peak and nadir pressures[6, 16, 17, 27].

Measurement of anal squeeze increment primarily reflects external anal sphincter function (EAS), which may be compromised as a result of sphincter injury or damage to the motor component of the pudendal nerve[2]. As such, classification of squeeze pressures into normal or abnormal can have a direct influence on clinical diagnosis and decision making. We also present normal values for cough increment in HV using WP and SS catheters. Again, differences in the absolute values recorded during this rapid response were noted. At present, there is no consensus on the appropriate method for performing or analyzing the cough maneuver, despite some indication that absence of sphincter contraction in response to a rapid rise in abdominal pressure is reflective of compromised integrity of the sacral reflex arc[2, 3, 34, 35]. The clinical significance of the magnitude of the difference in measurements between WP and SS during cough remains to be explored.

To date, the differences between WP and SS systems have only been recognized to any meaningful effect in esophageal literature. Unlike in the esophagus, where diagnostically important pressure changes occur in smooth muscle, rapid pressure changes in the anorectum occur in response to reflex behavior and somatic skeletal muscle contraction, which are both preceded by voluntary actions (coughing and squeezing respectively)[36]. One limitation within our study design was that individual understanding and ability to perform test maneuvers was not verified during a clinical examination prior to performing anorectal manometry. A recent study from Belgium showed that despite good theoretical knowledge of pelvic floor muscle contraction among young, nulliparous women, only a minority had experience of pelvic floor muscle training[37]. Furthermore, it has been demonstrated that enhanced instruction and reinforcement during manometry maneuvers has a direct and positive impact on recorded measures[38]. Nevertheless, we mitigated against this by having only one investigator perform both SS and WP HR-ARM in any individual volunteer to ensure consistent instruction was given during each manometry procedure. Although we did not evaluate observer variability, this, and the use of a standardized protocol and randomization of catheter order aimed to reduce investigator bias. Moderate to high repeatability of stationary perfusion manometry using a multi-channel assembly at rest (intraindividual correlation coefficient (ICC) between 0.6-0.7) and during squeeze (ICC: 0.75-0.79) has been shown previously in 30 healthy volunteers[39]. However, repeatability data for SS HR-ARM is still lacking and data using pull-through/ conventional techniques are conflicting[40]. Other limitations include the relatively small sample size.

To illustrate potential clinical impact of these study results, when WP catheter measurements were compared against the SS normal ranges, 20 WP measurements

were below the lower limit of normal, and would have been defined as hypotensive (1/60 at rest, 5/60 during squeeze, and 14/60 during cough; data not shown). Clinically, this falsely low interpretation of squeeze could lead a clinician to consider therapies unsuitable for (supposed) sphincter dysfunction. Using the *appropriate* normal range (i.e. derived from WP catheters in this instance) would have revealed normal squeeze pressure, highlighting the need to consider alternative causes for incontinence such as anorectal sensory deficiency, overflow secondary to poor emptying etc.[41]

In summary, the findings from this study, illustrating differences in measurements between SS and WP manometry, support the need for catheter-specific normal ranges. Fundamentally, normal values should not be used interchangeably between catheter types for clinical decision making. However, we recognize that currently available normal data sets for WP (including ours), have limited application due to the small numbers of individuals studied. Further development of normative ranges, based on large data sets stratified by sex, age, and parity (and perhaps other factors such as body mass index (BMI) and ethnicity using a repeatable and standardized methodology as called for previously[3, 42] and demonstrated herein.

Author contributions: AMPR & MW performed the research. AMPR analyzed the data and wrote the paper. AMPR, JB, MW, & WJ designed the research study. JB, MW, & WJ recruited study participants. WJ acquired R&D approval and funding; SMS provided critical commentary and editing, and helped finalize the paper.

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Table 1- Participant demographics

	n	Median age (years)	Minimum age	Maximum age
Females	40	39	18	63
Nulliparous	20	26*	18	60
Parous	20	48	27	63
Males	20	43	23	74
All	60	40	18	74

* *P* <0.001 vs parous females

Table 2- Normal ranges for SS and WP HR-ARM

	n	Resting pressure (5th-95th percentile)		Squeeze pressure* (5th-95th percentile)		Cough pressure* (5th-95th percentile)	
		SS	WP	SS	WP	SS	WP
Females	40	57 (26-94)	64 (34-101)	172 (35-329)	105† (27-188)	128 (43-259)	79† (28-136)
Nulliparous	20	55 (20-111)	62 (19-120)	182 (36-381)	109† (52-173)	136 (45-287)	82† (22-136)
Parous	20	58 (26-86)	65 (34-82)	149 (35-254)	98† (27-210)	120 (42-257)	78† (35-146)
Males	20	71 (49-117)	67 (40-116)	322 (63-538)	177† (36-305)	157 (63-425)	91† (29-152
All	60	60 (40-111)	65 (36-101)	183 (37-433)	111† (28-142)	136 (45-288)	81† (29-142)

*maximum increment relative to resting pressure

† P <0.001 vs SS

Table 3- Catheter configurations and reported differences between WP and SS ARM / HR-ARM in previous studies

Author (year)	Water-perfused				Solid-state			
	Ө (mm)	Port #	Orientation and spacing	HR-ARM	Ө (mm)	Sensor #	Orientation and spacing	HR-ARM
Johnson (1990)	12	4	Radial; 14 mm side openings 90° apart	No	15	4	Radial; 4mm sensors 90° apart	No
Simpson (2006)	5	5	Radial and end-hole	No	n.r	1	n/a	No
Jones (2007)	n.r	n.r	Side-holes 'above, below, and along the 6 cm body of the sleeve' at 2 cm intervals	No	4.2	36	Circumferential 12 radially dispersed sectors at 1 cm intervals	Yes
Nguyen (2010)	n.r	n.r	n.r	No	n.r	n.r	n.r	Yes
Vitton (2013)	201	4	Side opening ports	No	10.75	256	Circumferential 16 rows or 16 sensors	Yes
Kang (2015)	n.r	'multi'	Radial catheter circumferential sensors	No	n.r	10	Circumferential 0.7 cm intervals	Yes
Wu (2016)	4.7	8	Longitudinal and staggered 1 cm intervals	No	n.r	8	6+2 Longitudinal sensors at 1 cm intervals with 2 cm gap	Yes

Author (year)	n	Rest			Squeeze		
		Absolute values	Correlation	ICC	Absolute values	Correlation	ICC
Johnson (1990)	27	WP higher in proximal anal canal only, $P <0.05$	n.r	n.r	SS higher, $P < 0.05$	n.r	n.r
Simpson (2006)	21	'not significantly different'	'satisfactory'	n.r	'not significantly different'	'satisfactory'	n.r
Jones (2007)	29	SS higher, $P =0.003$	r=0.52 $P =0.004$	0.51 $P =0.004$	SS higher, $P <0.003$	r=0.81, $P <0.001$	0.776, $P <0.001$
Nguyen (2010)	30	$P =$ n.s	n.r	0.74 CI: 0.53-0.87	SS higher, $P <0.03$	n.r	0.83 CI: 0.67-0.92
Vitton (2013)	201	SS higher, $P <0.001$	r=0.593 $P <0.001$	0.415, $P <0.001$	SS higher, $P <0.001$	r=0.703, $P <0.001$	0.481, $P <0.001$
Kang (2015)	14	$P =$ n.s	$P =0.002$	n.r	$P =$ n.s	$P<0.001$	n.r
Wu (2016)	78	Sphincters: n.s Rectum: SS higher, $P <0.001$	r=0.81 $P <0.001$	n.r	$P =$ n.s	r=0.91, $P <0.001$	n.r

n.r= not reported; n.s= non-significant; n/a= not applicable; Ө= catheter diameter