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Long-term anorectal function in rectal cancer patients treated with chemoradiotherapy and endorectal brachytherapy

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The study was conducted in conformity with the Declaration of Helsinki after the Regional Committees granted ethical approval on Health Research Ethics for Southern Denmark (ID S-20150050).

Patient consent statement:

All participants gave written informed consent before inclusion.

Author contribution:

Study design: All authors**; Data collection:** SH, PF; **Data analysis:** PF, LD, HG, KK; **Interpretation of results:** All authors. **Manuscript preparation:** All authors. **Anophysiological expertise:** KK, LL, SL; **Biomechanical expertise:** LD, HG; **Critical revision of the manuscript:** All authors.

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Structured Abstract:

Aim: To study anorectal function in long-term survivors after combined, curatively intended, chemoradiotherapy and endorectal brachytherapy for low rectal cancer.

Methods: case-control design. We compared anorectal function by anal manometry, anal EndoFLIP and rectal bag distension in rectal cancer patients (RCP) and healthy, normal subjects (NS). Symptoms by the Low Anterior Resection Syndrome (LARS) and Wexner faecal incontinence scores.

Results: Thirteen RCP (12 men, median age 68 years (range: 52-92)) after 60 Gy radiotherapy, 5 Gy endorectal brachytherapy and oral tegafur-uracil with complete clinical response (median time since treatment 2.8 years (range: 2.2-5.6)) were compared to 15 NS (14 men, median age 64 years (range: 47-75)). RCPs had lower than normal anal resting 38.6 (range: 8.8-67.7) versus 58.8 mmHg (25.7-105.2)($p<0.003$) and squeeze pressures 117 (55.2-203) versus 188 mmHg (103-248)($p<0.01$). Squeeze-induced pressure increase recorded by EndoFLIP was also lower in RCP ($q>7.56$, $p<0.001$) as was the anal canal resistance to increasing distension ($q = 3.13$, $p<0.05$). No differences in median rectal volume at first sensation (72 (22-158) versus 82 (36-190) ml, $p=0.4$) or at urge to defaecate (107 (42-227) versus 132 (59-334) ml, $p=0.2$) were found. However, maximum tolerable rectal volume was lower in RCPs (145 (59-319) versus 222 (106-447) ml, $p<0.02$). The median (range) LARS score was 27 (0-39) for RCP and 7 (0-23) for NS ($p<0.001$), while the Wexner score was 0 (0-5) versus 0 (0-4) ($p=0.56$).

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Conclusion: Radiotherapy combined with endorectal brachytherapy for rectal cancer causes long-term anorectal symptoms, impaired anal sphincter function, and reduced rectal capacity.

What does this paper add to the literature?

Organ preservation in rectal cancer patients is presumed to have better functional results than surgical treatment. This paper provides novel data on long-term anorectal function after curatively intended chemoradiotherapy for rectal cancer. Patients had anorectal symptoms, impaired anal sphincter function and reduced rectal capacity.

Introduction:

The standard treatment for cancer of the rectum (adenocarcinoma) is surgery with or without (neo)adjuvant chemoradiotherapy. Unfortunately, this treatment leads to long-term bowel dysfunction in a large proportion of patients (1). Symptoms of low anterior resection syndrome (LARS) mainly include frequent or fragmented defaecation, urge to defaecate, and incontinence to faeces or flatus (2). Risk factors for a poor functional outcome are low-situated tumours, neoadjuvant radiotherapy, and surgical complications such as anastomotic leakage (2). The exact mechanism behind LARS is not fully understood.

In recent years, organ-preserving and stoma-free treatments have been introduced (3–7). Non-surgical treatment seems to be safe in selected patients with no distal lymph node involvement or metastasis at the time of diagnosis (7–9). Complete clinical and pathological response to chemoradiotherapy has been reported in up to 65 % of patients (6,10–14) and should be followed by close surveillance in a "watch and wait" approach (6–8,15) on the premise that avoidance of surgery improves the functional outcome. Unfortunately, studies on anorectal physiology and functional outcomes in a "watch and wait" cohort remain scarce (12). Previous data suggest that patients treated with "watch and wait" have better anorectal function than those receiving the same chemoradiotherapy regimen followed by total mesorectal excision (11,16).

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Our group has previously applied state-of-art technology to examine anorectal function in patients suffering from LARS and patients treated for anal cancer. We found that pelvic radiotherapy significantly affected the neorectum's sensory function (17). Furthermore, radiotherapy for anal cancer caused weakening of the anal sphincter complex (18) as well as abnormal cerebral processing of anorectal sensory stimuli (19). In the present study, we aimed to study long-term (mean 3.2 years) anorectal function both by standard anorectal manometry and in terms of distensibility and flow resistance. Clinical function was assessed by the LARS and the Wexner scores. Thus, we compared a group of patients treated with chemoradiotherapy for rectal cancer to a group of comparable healthy subjects.

Methods:

Subjects

The "watch and wait" protocol, patient selection, and two-year follow-up have been described in detail previously (6). Their long-term patient-reported outcomes (PROMs) are reported in a recent paper (9). Between 2009 and 2013, 55 (40 male and 15 female) patients with a primary and resectable T2-T3a, N0-N1 adenocarcinoma in the lower 6 cm of the rectum, not involving the anal sphincters, and with no nodal or distant metastasis at CT or MRI scan were screened. Among these, 50 patients were included in the "watch and wait" protocol. Patients were given chemoradiotherapy (including 60 Gy in 30 fractions to the tumour, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil 300 mg/m2) every weekday for six weeks. Patients with a complete clinical response and negative tumour site biopsy six weeks after neoadjuvant treatment were allocated to the observational group with no surgery (n = 41). The remaining patients were treated surgically as per standard protocol. We invited all patients in the observational group by spring 2016 to participate in the present study. Healthy colleagues and relatives were invited as an age- and gender-matched group of normal subjects (NS) examined by the same methods as the patients. Exclusion criteria for NS were faecal incontinence defined by the Wexner faecal incontinence questionnaire (20)

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(flatus incontinence was accepted), prior colorectal or pelvic surgery or disease, and use of medication known to interfere with gastrointestinal function.

The present study reports questionnaire data and data from anorectal physiology tests (21), including anorectal manometry, 3D endoanal ultrasound and examination with the Functional Lumen Imaging Probe (EndoFLIP) (22). The study was conducted in conformity with the Declaration of Helsinki after the Regional Committees granted ethical approval on Health Research Ethics for Southern Denmark (ID S-20150050). All participants gave written informed consent before inclusion.

Questionnaires

All subjects included, completed the LARS (2) and the Wexner faecal incontinence questionnaires (20). The LARS score is a symptom-based scoring system for bowel dysfunction after low anterior resection with or without preoperative radiotherapy for rectum cancer (23). The score consists of five independent questions characterizing frequency, urgency, incontinence, and clustering that are weighted and added up to a total score between 0 and 42 points. The LARS score allows the categorization of patients into three groups: `no LARS` (0–20 points), `minor LARS` (21–29 points), and `major LARS` (30–42 points). The Wexner score consists of five questions: incontinence for either solid stool, liquid stool, or flatus, pad usage, and lifestyle impact. Each item is assigned 0-4 points depending on frequency (never to daily). Hence, the global score ranges from 0-20.

Standard anorectal physiological tests and 3D endoanal ultrasound

Anorectal physiology tests were conducted under standardized conditions by a specialist anal physiology nurse with the patient in the left lateral position. All participants had fasted for two hours and had an empty bladder. If the lower rectum was not empty at the digital examination or if participants felt that the rectum was not evacuated, a rectal enema (Microlax®, McNeil, Birkeroed, Denmark) was administrated. A detailed description of equipment and procedures for anorectal physiology tests conducted at our laboratory have been published earlier (21,24).

Standard anal manometry (Menuet, Dantec Medicals, Bristol, UK) was performed by the pull-through technique and reported as the mean of three consecutive recordings: anal

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resting and squeeze pressures and rectal volumes at first sensation, urge to defaecate, and maximum tolerable volume. Rectal compliance during balloon distension was the slope of the volume–pressure curve. 3D endoanal ultrasound scans (BK Medical, Herlev, Denmark) were done to ensure that no structural abnormalities were present.

Functional Lumen Imaging Probe (EndoFLIP)

The EndoFLIP procedure was initiated after 15 minutes of rest following the standard anorectal physiology tests. The EndoFLIP® System (Crospon Ltd, Galway, UK), protocol and data analysis have previously been described in detail (18,22,25,26). Thus, diameters along the length of the anal canal were shown as colour-coded topographies by interpolation between adjacent channels over time (27,28). The diameters were shown as single pixels by spatial orientation (y-axis) and time (x-axis). Finally, the bag pressure and volume were overlaid on the diameter map to ease data interpretation.

The pressure and the diameters along specific locations in the anal canal were analyzed at: a) the initial state, b) during rest, c) during squeeze, and d) during filling of the bag (27). The diameters at the proximal, middle and distal sections of the anal canal were used for further analysis. The distensibility of the anal canal was determined as the pressure strain elastic modulus (Ep) from the pressure-diameter diagrams in the narrowest part as previously described (29). The yield pressure was defined as the pressure when the narrowest part of the anal canal dilated 110% of the initial diameter (27). The flow resistance of the anal canal was computed according to previously published principles (29).

Statistical analysis

Data analysis was done with the STATA/IC 10 software for Windows (StataCorp, College Station, TX, USA), and SigmaPlot for Windows Version 11.0 (Systat Software, Inc). Two-way repeated-measures ANOVA analysis was used to compare the diameter and pressure changes. The Tukey test was used for post hoc analysis. Squeezing and resting-state pressure changes, as well as the resistance ratio at the resting state, were compared with factor 1: patients versus normal subjects, and factor 2: volumes. Student t-test was used for comparisons of the yield pressure, and Ep. As the physiological data deviated from the normal distribution (determined by normal

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probability plots), the nonparametric Wilcoxon's signed-rank test was used for comparisons. Correlations between questionnaires and FLIP data were performed with the Pearson Product Moment Correlation. Descriptive statistics were used for the background data. P <0.05 was considered statistically significant.

Results:

Subjects

From our original cohort of 41 patients, 12 had local recurrence followed by secondary surgery, including three who later died from metastatic disease, and three did not respond to the study participation invitation. Among the remaining 26 (21 male/4 female) patients, 13 (12 male/1 female, median age 68 years (range: 52-92)) accepted to participate. The median time since treatment was 2.8 years (range: 2.2-5.6). Data from patients were compared to data from 15 age- and gender-matched normal subjects (14 men/ 1 female, median age 64 years (range: 47-75)). Demographic data are presented in Table 1.

Bowel symptoms

Data on bowel symptoms are presented in table 2. The high LARS score in RCPs was mainly due to ”clustering” and ”urgency” for which the patients scored significantly higher than NS, p<0.003. No RCP reported incontinence to solid stools. Four RCP reported incontinence to liquid stools using the LARS score and another two reported incontinence using the Wexner score (i.e. incontinence for liquid stools at least monthly). Seven RCP reported incontinence for flatus using the LARS score, including two who reported incontinence to flatus when using the Wexner score.

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Standard anorectal physiology tests

The RCP had low anal resting pressure, low anal squeeze pressure, and low maximum tolerable rectal volume compared to NS (Table 3). No structural abnormalities were detected by anal ultrasound.

Functional lumen imaging probe data

The diameter of the proximal anal canal was the largest, followed by the distal and then the middle anal canal ($F=113.6$, $p<0.001$). No statistically significant difference in diameters of the anal canal ($F=0.00134$, $p=0.97$, figure 1A) or anal pressures during distension ($F=0.331$ $p=0.57$, figure 1B) was found between RCP and NS. The anal squeeze pressure and the squeeze-induced pressure increase during FLIP were lower in RCP than in NS ($q>7.56$, $p<0.001$, figure 1C and 1D). The pressure-diameter curve for the narrowest and middle anal canal in RCP was located to the right of that for the NS. This indicates that the anal canal was less resistant in RCP than NS (figure 2).

The yield pressure of the anal canal tended to be lower in RCP (32.6±3.5 mmHg) compared to NS (43.5±6.3 mmHg) ($p=0.11$). The pressure strain elastic modulus showed no difference between RCP (3.65±0.40 kPa) and NS (3.84 ±0.90 kPa) ($p=0.83$). At distension volumes of 10, 20, 30 and 40 ml, the flow resistance of the anal canal was smaller in RCP than in NS ($q=3.13$, $p=0.03$, Figure 3). The flow resistance showed a borderline significant association to the LARS score ($r = -0.55$, $p=0.05$) but no association to the Wexner score.

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Discussion and conclusions:

The present study is the first to examine changes in anorectal physiology in rectal cancer patients treated with curatively intended chemoradiotherapy alone. Our main findings were that RCP treated with combined chemoradiotherapy and endorectal brachytherapy had faecal clustering and urgency for defecation, impaired anal sphincter function, lower flow resistance of the anal canal, and reduced rectal capacity.

Patients included in the present study

Most RCP (12/13) in our cohort suffered symptoms resembling LARS with urgency and clustering being the most severe symptoms. However, only two patients reported major LARS. In studies among patients undergoing surgery for rectum cancer, 60% of patients have LARS (minor or major LARS). This number increases to 93 % in patients who have had adjuvant RT (30). Others have presented normative data for the LARS score in healthy subjects. Approximately 10% of healthy males and 20% of healthy females have symptoms corresponding to major LARS (31,32). This is close to the prevalence of symptoms found among patients in the present study. No RCP reported incontinence to solid stool while six had incontinence for liquid or loose stools. It is noteworthy that there was was no overlap between patients reporting incontinence to liquid or

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loose stools by the LARS and the Wexner scores. The inconsistency between the two scores highlights the lack of a validated instrument to assess dysfunction following non-surgical treatment of rectal cancer.

All patients included were at least 2.2 years after end of treatment. Late anorectal toxicity is a dynamic process, and symptoms may alter over time (33). The "watch and wait" cohort from Vejle Hospital, Denmark reported more rectal bleeding after five years of follow-up (9). The severity of LARS seems to plateau approximately two years after surgery for rectum cancer (30). An ongoing prospective study will determine how the functional consequences of chemoradiotherapy for rectum cancer develop over time. We speculate whether the boost with endorectal brachytherapy may cause worse symptoms than external radiotherapy alone. Results from patients treated with high dose radiotherapy for anal cancer (18) could indicate that this is the case.

Anal sphincter function

We have previously shown that radiotherapy for anal cancer weakens the anal sphincter complex (18). The same was true for RCP treated with radiotherapy in the present study. The EndoFLIP is a promising method primarily used to evaluate lower oesophagus function (22,34,35). Only a few EndoFLIP studies have evaluated anal sphincter function (26–28,36–38). However, the EndoFLIP adds information on the function of the anal canal as data allow computation of biomechanical parameters along the length of the anal canal. We found no difference in the distensibility of the anal canal in patients and NS. However, the flow resistance of the anal canal was significantly lower among patients.

The anal flow resistance showed borderline association with the LARS score. Larger studies are needed to determine potential associations between biomechanical properties of the anal canal and anorectal symptoms in patients treated for anorectal cancer. An intact and functional sphincter complex, normal anorectal sensibility and normal wall properties of the rectal wall are all necessary to prevent faecal incontinence. Our findings suggest that RCP with anorectal toxicity after CRT suffer a generalized degeneration of pelvic floor tissue (muscle and nerves). In previous studies, we found increased anal distensibility in patients with atrophy of the

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internal anal sphincter caused by systemic scleroderma (28), patients with idiopathic faecal incontinence (28), and patients treated with radiotherapy for anal cancer (18).

Anorectal sensation

Radiotherapy may cause fibrosis and increased tone of the muscle cells in the rectal wall (30,33,39). This can lead to lower rectal capacity, as found in the present study. Our group has previously shown that patients treated with low anterior resection and neoadjuvant chemoradiotherapy have severely impaired neorectal sensibility, likely caused by neuropathy (29). We also found that adjuvant pelvic radiotherapy for rectum cancer significantly affects the neorectum's sensory function (17) and the cerebral processing of stimuli from the anorectum (19). Likewise, newly published data from the present watch and wait cohort indicate that the chemoradiotherapy may induce injury of afferent nerve fibres in pelvic and anal structures, causing cortical awareness changes due to the disintegration of consciously perceived stimuli (40).

Limitations of the study

The study is limited by the small number of patients and the fact that less than half of the potentially eligible patients agreed to participate. Furthermore, almost all patients were men. This does not reflect the population of Danish patients with rectum cancer, where approximately 3 in 5 patients are male. We decided to compare RCP to NS, as this may provide information about the expected added burden of bowel dysfunction caused by the disease and its treatment. When patients are diagnosed with rectal cancer, they face treatment decisions in a "shared decision making" process. The information we present can help guide in this. Despite the small cohort, we found significant differences between RCP and NS. The highly selected group of patients does not allow us to conclude about the prevalence of functional problems in a "watch and wait" cohort after chemoradiotherapy for rectum cancer. Nevertheless, our study points towards damage to the rectal wall, the anal canal and the sensory nerves as the main causes of poor functional outcome, but the results cannot be generalized without reservations. The LARS score was developed to assess the severity of bowel symptoms after surgery for rectum cancer

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(23). To what degree the LARS score applies to patients having undergone chemoradiotherapy without surgery remains undetermined.

Treatment of anorectal dysfunction after rectal chemoradiotherapy

Treatment algorithms for late anorectal toxicity remain to be established. Management of bowel disorders and rectal hypersensitivity include psyllium, loperamide and biofeedback. Small enemas and transanal irrigation may help relieve LARS symptoms via better emptying of the rectum diminishing the fragmented defaecation. These treatments should be tested before considering highly specialized treatment such as sacral nerve modulation (39).

In conclusion, our study indicates that patients treated with CRT for low rectal cancer have significant anorectal dysfunction, including impaired anal sphincter function and reduced rectal capacity.

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Table 1:

	Rectal cancer patients	**Normal subjects**	**P value**
Number (males)	13(12)	15(14)	0.3
Age (median(range)), years	68 (52-92)	64 (47-75)	0.4

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Height (median(range)), cm	178 (170-194)	179 (170-198)	0.9
Weight (median(range)), kg	82(71-130)	85 (65-92)	0.3
Smokers (cigarettes)	0	1 (2 former)	0.08
> 15 units of alcohol/week	0	2	0.16
Time since diagnose (median(range)), years	2.8 (2.2-5.6)		
TNM classification:			
-T2N0M0	7		
-T2N1M0	2		
-T3N0M0	1		
-T3N1M0	3		

Table 2:

	Rectum cancer patients	**Normal subjects**	**p value**

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LARS score, Median (range)	27 (0-39)	7 (0-23)	0.001
LARS score divided into groups, N			
- "no LARS", N	1	13	
- "Minor LARS", N	10	2	0.001
- "Major LARS", N	2	0	
The Wexner score	0 (0-5)	0 (0-4)	0.56

Table 3:

	Rectum cancer patients	**Normal subjects Median (range)**	**p value**

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	Median (range)		
Anal manometry			
Anal resting pressure (mmHg)	38.6 (8.8-67.7)	58.8 (25.7-105.2)	0.003
Anal squeeze pressure (mmHg)	117.3 (55.2-203)	188.3 (103-248)	0.01
Rectal sensation			
First sensation (ml)	72 (22-158)	82 (36-190)	0.4
Urge to defaecate (ml)	107 (42-227)	132 (68-334)	0.2
Maximum tolerable volume (ml)	145 (58-319)	222 (106-447)	0.01

Legends to figures:

Figure 1. Diameters and pressure of the anal canal in rectal cancer patients treated with chemoradiation (RCP) and normal subjects (NS). A) The diameter change of the middle (MP), proximal (PPC) and distal (DPC) anal canal during distension; B & C), the anal canal pressure during resting and squeeze states; D) The squeeze-induced pressure increase to the resting pressure. Data are given as mean±SEM.

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Figure 2. Three-dimensional configurations and pressure-diameter relationship of the anal canal. Left: A representative three-dimensional configurations at distension volume 20 ml in rectal cancer patient (top panel) and normal subject (bottom panel). The purple lines are locations of the narrowest point (NP), middle (MP), proximal (PPC) and distal (DPC) part of the anal canal, colors from blue to red are the diameter increase of the anal canal. Right: The averaged diameter and pressure relationship of the NP, MP, PPC and DPC part of the anal canal during inflation up to 50ml is shown for rectal cancer patients (RCP, top panel) and for normal subjects (NS, bottom panel). The narrowest point and the middle part of the anal canal is less distensible than the distal and proximal part. The NP and MP curves from patients are located to the right of the corresponding curves from healthy controls, indicating a softer wall in patients. The two black markers indicate the yield pressure needed for opening of the narrowest part of the anal canal.

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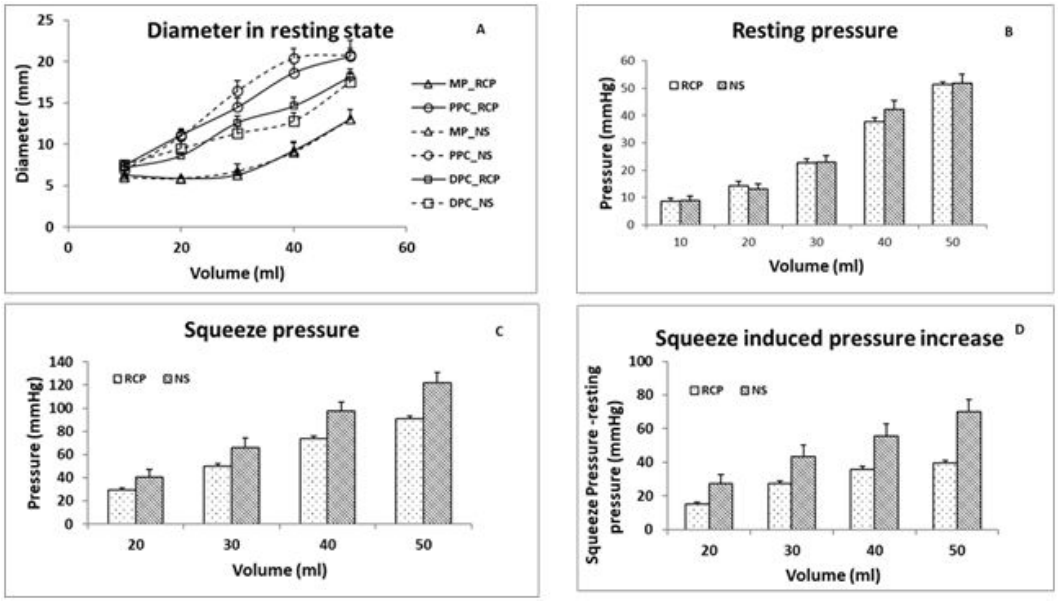

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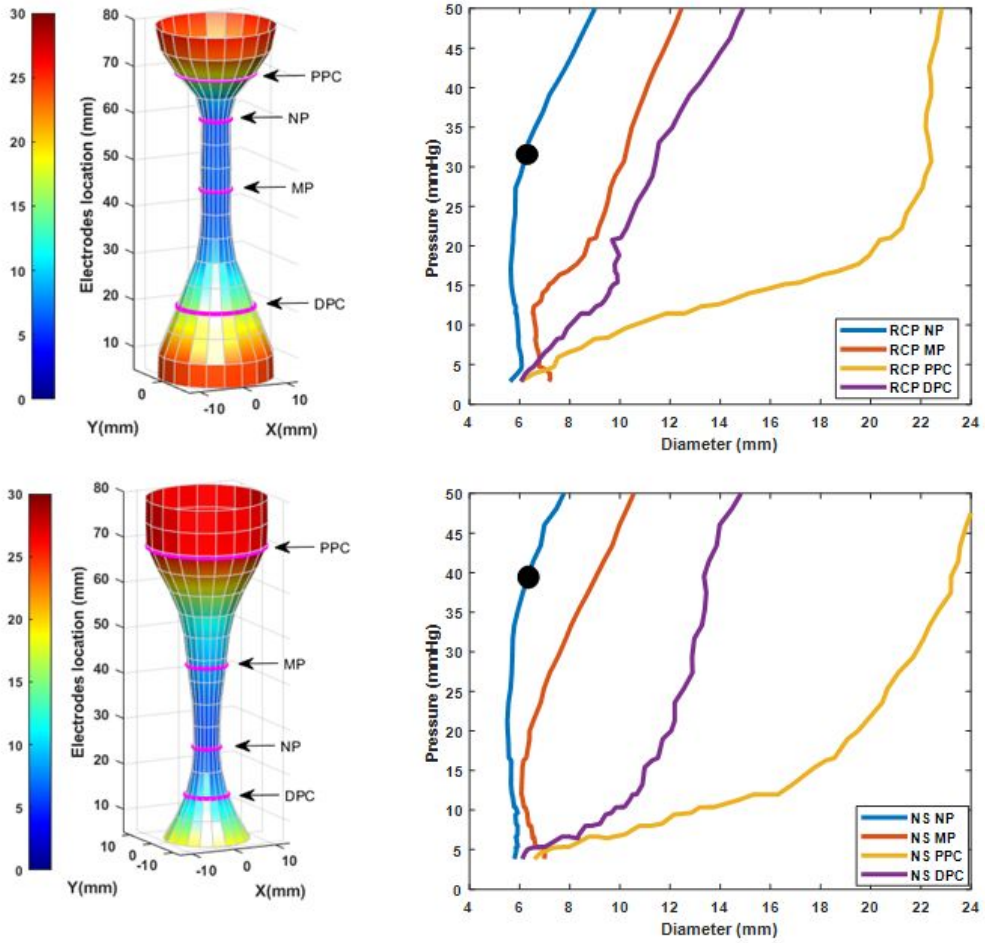

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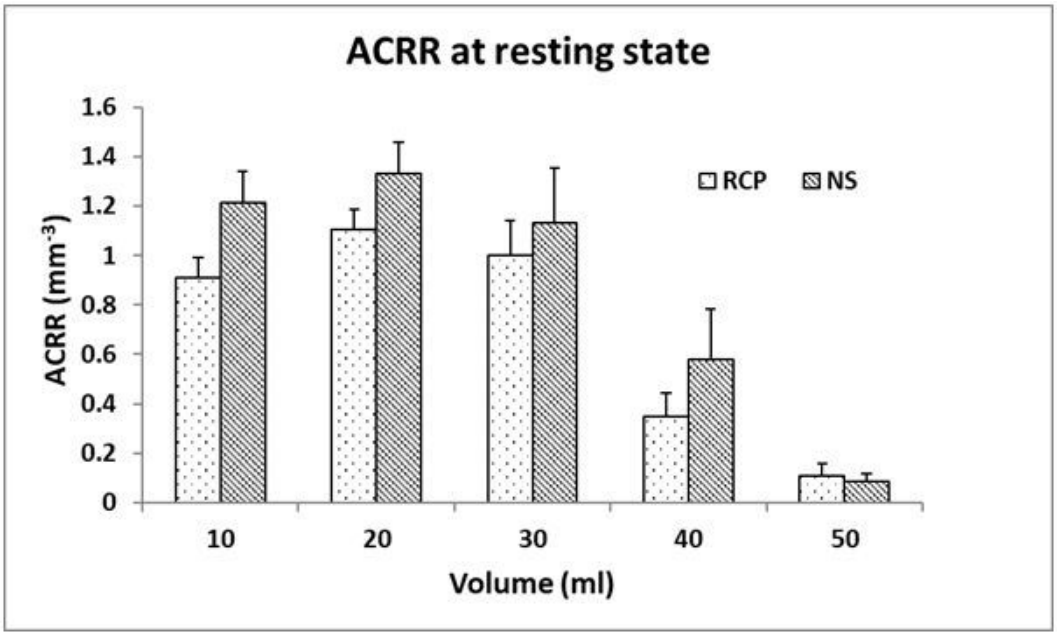

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