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Comparison of mathematical methods for calculating colonic compliance in humans: power exponential, computer-based and manual linear interpolation models

B. N. I. FLOYD*, M. CAMILLERI*, V. ANDRESEN*, T. ESFANDYARI*, I. BUSCIGLIO*, and A. R. ZINSMEISTER†

*Clinical Enteric Neuroscience Translational and Epidemiological Research, Mayo Clinic College of Medicine, Rochester, MN, USA

†Department of Health Sciences Research, Division of Biostatistics, Mayo Clinic College of Medicine, Rochester, MN, USA

Abstract

Measuring compliance allows differentiation of sensory changes from changes in thresholds because of altered compliance. As compliance of the colorectum is sigmoidal, a power exponential analysis was recommended. We aimed to develop and validate simpler measurements of compliance. Forty subjects (23 female, 17 male) underwent colonic barostat procedures comparing dronabinol vs placebo. Results of the effects on compliance were reported elsewhere. Compliance was determined as volume response to pressures ranging from 0 to 36 mmHg. Pressures corresponding to 10%, 50% and 90% (Pr10, Pr50 and Pr90) of maximum volume at 36 mmHg were estimated using a power exponential model, computer-based and manual linear interpolation. Data were compared and concordance evaluated. Pr50 and Pr90 were not significantly different by all methods for baseline and post-treatment. Respectively, concordance correlation coefficients were: pretreatment, 0.879, 0.464 and post-treatment, 0.879, 0.623. There is larger variation in Pr10 comparing all methods and manual calculations allow for the closest fit to the data. Concordance correlation coefficients were pre-treatment = 0.189 and post-treatment = 0.322. There were no gender differences in compliance measurements. Results of compliance are highly concordant amongst all models. However, computer-based or manual interpolations appear superior to power exponential models for estimating Pr10.

Keywords

pressure; volume; tone; viscus; gastrointestinal; rectal

BACKGROUND

Standardized distensions of viscera utilizing a barostat have been used over the last 2 decades to evaluate colorectal sensorimotor function in health and disease. Compliance of hollow viscera can be described as the ability of the organ to expand (volume change) in response to pressure. In distension studies, compliance is described using the pressure–volume relationship. This is typically achieved using a barostat, which is able to maintain a

constant pressure within an airfilled bag that is placed with the lumen and is distended to maintain apposition between the bag and the mucosa of the viscus.¹

The barostat is designed to maintain a constant pressure within the bag when the organ contracts or relaxes. To maintain a constant pressure, the volume entering the bag is altered by a servomechanism in the barostat, and the volume is indirectly associated with the tone of the colon or with phasic contractions superimposed on the baseline tone, as observed in health or disease or in response to pharmacological modulation.^{2–4} A plot of volume against pressure (the fixed parameter on the x -axis) reflects viscus compliance, and is measured by the slope of the pressure volume curve.⁵ In barostat studies of viscus sensorimotor function, it is essential to know whether there is a difference in compliance to interpret whether a difference in sensation results from an alteration in the viscoelastic or motor properties of the viscus, or a change in afferent function.⁶ One of the currently accepted methods to measure compliance uses a power exponential model of the volume response to imposed pressure.⁷ The rationale for using a power exponential model is that pressure–volume relationships in the colorectum are sigmoidal. This estimate of compliance is summarized as the pressure observed at half the maximum observed volume ($Pr^{1/2}$) where a smaller $Pr^{1/2}$ corresponds to a higher compliance. However, given the complexity of the calculation, few centres have adopted the method.

Therefore, our aim was to develop and validate alternative, simpler mathematical measurements of colonic compliance.

MATERIALS AND METHODS

Study design

The data used to develop these simpler mathematical models were obtained as part of a double-blind, randomized, placebo-controlled, parallel-group study of the effects of dronabinol on colonic compliance in healthy human volunteers. The results of the study have been published.⁸ The study was approved by the Mayo Clinic Institutional Review Board prior to initiation.

Participants and study protocol

The details of the experimental protocol are published in detail elsewhere.⁸ Briefly, 40 (23 female, 17 male) healthy human volunteers between the ages of 18 and 65 years attended the Clinical Research Unit at Mayo Clinic in Rochester, Minnesota. They underwent colonic barostat procedures during a randomized comparison of the non-selective cannabinoid agonist, dronabinol vs placebo. After overnight bowel cleansing with an oral colonic lavage solution, a multilumen assembly that included a polyethylene balloon was positioned in the descending colon using flexible endoscopy and fluoroscopy. Premedication was not given. Colonic compliance was measured prior to and after medication to which they were randomly assigned in a double blind manner; allocation was concealed. Results of the effects of dronabinol have been reported elsewhere.⁸ Colonic compliance was measured as the volume response to 4 mmHg increments in intra-balloon pressures at 60-s intervals from 0 to 48 mmHg.

Analysis of compliance curves

Three approaches were used to analyse the compliance curves. Firstly, compliance was summarized using the power exponential model recommended in the literature.⁸ As in the previous study⁷, plotting the proportionate volume at each pressure (i.e. the observed volume divided by the maximum observed volume) as a function of $1/\text{pressure}$ yields a curve that can be approximated by the following nonlinear (power exponential) model: $\text{Vol}/$

$Vol_{max}=r+\exp[-(\kappa*1/Pr)^\beta]$, where Vol is the actual volume, Vol_{max} is the maximum volume, r is the observed value of proportional volume at the initial pressure step, Pr is pressure and κ and β are constants that are estimated for each compliance curve. The pressures corresponding to 10%, 50% and 90% (Pr_{10} , Pr_{50} , Pr_{90} , respectively) of maximum volume were then calculated for each compliance curve using the estimated constants from the power exponential model.

Secondly, a computer program to linearly interpolate between the pressure data points on either side of the 10%, 50% and 90% of maximum volume values was used to obtain 'empirical' estimates of the pressures corresponding to these (proportionate) volume levels for each compliance curve.

Finally, a manual linear interpolation (see Fig. 1A, for example) was performed by a single observer (BF) who was blinded to the results of the other two methods. In this approach, a slope was drawn at the 10%, 50% and 90% of maximum volume points of the (proportionate) volume vs pressure compliance curve. A ruler was then used to identify the intersection of the horizontal line at each (proportionate) volume with the corresponding slope. A vertical line at this intersection was drawn to the x-axis to obtain the interpolated pressure value. During the manual linear and computer-based linear interpolations, the Pr_{10} was determined by extrapolating the slope line back from the observed data to the point that traversed the line of the 10% maximum volume (see Fig. 1B).

Analysis

The three sets of calculated pressure values were summarized for pretreatment and post-treatment compliance curves separately. The agreement of the three methods was assessed using a measure of concordance for quantitative response values⁹ separately for each (proportionate) volume level in the pre- and post-treatment data sets.

RESULTS

The results of all three methods of calculation of compliance pre- and post-treatment are presented in Table 1. Data are presented for the entire group ($n = 40$) and separately for females ($n = 23$) and males ($n = 17$). There are no differences in colonic compliance by gender. Concordance correlation coefficients (CCC; with 95% confidence intervals) pretreatment amongst all three models Pr_{10} , Pr_{50} and Pr_{90} , respectively, were 0.189 (0.098, 0.278), 0.879 (0.815, 0.922) and 0.464 (0.320, 0.586). The overall CCC (with confidence intervals) post-treatment amongst all three models Pr_{10} , Pr_{50} and Pr_{90} , respectively, were 0.322 (0.188, 0.444), 0.879 (0.815, 0.922) and 0.623 (0.489, 0.729).

Concordance correlation coefficients between two models are each listed in Table 2. Note that Pr_{50} and Pr_{90} values are very similar by all methods of analysis at baseline and post-treatment (R_x) for all three methods. However, there is larger variation in estimates of Pr_{10} . Whereas the computer-based linear interpolation and manual linear interpolation model were highly concordant, both had substantially worse concordance with the power exponential model estimates of Pr_{10} . Moreover, as illustrated in Fig. 2, the fit of the power exponential curve to the actual data in the part of the compliance curve corresponding to low imposed pressures was suboptimal.

DISCUSSION

In this study, we wished to validate two easier methods of calculating compliance (computer-based linear interpolation and manual linear interpolation) by comparing the results with these approaches to those determined with the power exponential model

(standard approach used in our laboratory to date). We have been able to demonstrate that the Pr50 and Pr90 are very similar for all models. We also determined that the manual approach is as accurate as the more sophisticated models for estimating Pr50 and Pr90. In addition, the Pr10, Pr50 and Pr90 values are very similar for the computer-based linear interpolation and manual linear interpolation. Differences observed in estimates of Pr10 between these two linear (computer and manual) models and the power exponential model may reflect the poor fit of the more sophisticated power exponential model to the actual data, as illustrated in Fig. 2. The approach using power exponential analysis provides estimates of the whole compliance curve from the data available for each subject, thereby allowing derivation of an average curve for each treatment or group (based on the constants β and κ of individual curves). Thus, one can estimate differences on the whole curve for different groups or treatments. Linear interpolation approach does not allow the whole curve to be evaluated, but it may allow more accurate estimates of discrete points on the curves.

The current study demonstrates that it is possible to calculate compliance by plotting volume against pressure and manually calculating the slope or more simply estimating the pressures corresponding to specified volumes, such as those at 10%, 50% and 90% of maximum. If this simpler method is adopted more broadly, we believe that this will facilitate reporting of compliance and standardize the observations on viscus compliance across centres. If the manual linear interpolation or computer-based linear interpolation are not used to calculate Pr10, our data suggest that further revision of the power exponential model would be necessary to enhance the 'fit' of the exponential curve to the actual data.

A weakness in the study is the inability to determine which model most accurately characterizes Pr10. There are very few actual volume data at the lower levels of imposed pressures. During the manual linear and computer-based linear interpolations, the Pr10 was determined by extrapolating the slope line back from the observed data to the point that traversed the line of the 10% maximum volume (see Fig. 1B). Hence, there may be a potential for minor error. However, as was mentioned previously, the power exponential curve does not exactly fit the data well either, so it is unclear whether the Pr10 value obtained using this model is also inaccurate. It appears that the goodness-of-fit of the curve drawn by the power exponential model shows the worst fit in this part of the curve. It is very relevant to define this part of the compliance curve as accurately as possible, because many drugs such as clonidine¹⁰ and pregabalin¹¹ have a significant effect on this section of the compliance curve. This pressure-volume relationship is shifted to the left, whereas the slope of the linear part of the curve is unaffected by the drug being studied, e.g. clonidine.¹⁰

It is also important to emphasize that our analysis to date has been based on results in healthy volunteers and further validation in patients would be valuable. This is especially relevant for conditions like irritable bowel syndrome in which hypersensitivity may lead to the participant signalling a level of pain that precludes completion of the planned ascending method of limits to 48 mmHg. The plateau phase of the sigmoidal P : V curve may not be reached in a hypersensitive or hypervigilant patient. Thus, using the 10th, 50th and 90th percentiles of the maximum volume to estimate compliance may present a significant problem in patients who have visceral sensitivity, as in irritable bowel syndrome. In these cases, volume determinations at specific pressures may be a better approach (which has been termed static compliance in prior reports), at least for the pressures that can be achieved during the distensions. It may be argued that, in the absence of a change in the slope of the compliance curve, such a shift in the volume at specific pressures may represent a change in compliance. Such a measurement may also serve as the primary end point in the comparisons of the effects of disease or perturbations such as medications.

However, this concern regarding the pressures achievable during a sequence of distensions is a general criticism for any estimation of compliance: for example, the less steep, uppermost part of the sigmoidal curve may be excluded from the approach that uses a 'tangent' or linear interpolation of the plot if the higher pressures are not assessed. In such cases where the compliance curve would be incomplete, the Pr10 becomes a more useful measurement than the Pr50 or Pr90 or of the slope calculation, as it would be able to reflect a shift of the compliance curve to the left or right (Fig. 3). Further validation studies comparing these approaches are required to determine which approach (static compliance or volume at specified pressure vs Pr10 and Pr50) best identify the effects of disease or pharmacological perturbations.

In conclusion, our data suggest that, if it is to be used, the power exponential model needs to estimate Pr10 more accurately. On the other hand, we confirm that the power exponential model provides a good summary for the whole curve. The linear interpolation models yield accurate estimates of pressures at specific percentiles of the maximum volumes observed. We conclude that the manual approach is sufficiently accurate, and would be enhanced by having more data plotted at low pressures. We recommend using pressure increments of 2 mmHg between 0 and 12 mmHg, followed by 4 mmHg increments between 12 and 36 mmHg. This will increase the accuracy for estimating Pr10. The remainder of the compliance calculation is virtually equal using the power exponential, computer-based or manual linear interpolation of the data. Nevertheless, it is important to continue validating these approaches and estimates of static compliance in patients with hypersensitivity or hypervigilance in whom it may not be possible to obtain a full, sigmoidal compliance curve.

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Figure 1.

(A) Example of manual linear interpolation for Pr50. In this approach, a slope was drawn at the 50% of maximum volume points of the (proportionate) volume vs pressure compliance curve. A ruler was then used to identify the intersection of the horizontal line at each (proportionate) volume with the corresponding slope. A vertical line at this intersection was drawn to the x -axis to obtain the interpolated pressure value. (B) Example of manual linear interpolation for Pr10. During the manual linear and computer-based linear interpolations, the Pr10 was determined by extrapolating the slope line back from the observed data to the point that traversed the line of the 10% maximum volume using a ruler.

Figure 2.

Example of a compliance curve (the volume response to an imposed pressure) in the colon. The 'ideal' curve is generated using this power exponential model. Overall, it has a sigmoidal shape. Note the initial flattening of the line in which an increase in pressure does not cause any change in volume, in contrast to the actual data curve. The second part of the curve is more linear and reflects the elasticity of the colon.

Figure 3.

Hypothetical compliance curves associated with an incomplete analysis due to patient intolerance of pain during ascending method of limits. Note that the Pr10 still appraises the shift of the curve and is less inaccurate than Pr50 when the compliance curve is incomplete. Note also that, in all situations, the slope is similar, but it fails to identify the curve's shift to the right.

Table 1

Comparison of compliance using power exponential, computer-based linear interpolation and manual linear interpolation models

	Exponential model Baseline	Post-Rx	Computer interpolation Baseline	Post-Rx	Manual interpolation Baseline	Post-Rx
Pr10 *	8.0 and 12.6 [10.2 (1.9)]	6.1 and 12.3 [8.9 (2.4)]	4.9 and 9.2 [6.5 (1.3)]	4.3 and 8.0 [5.9 (1.4)]	4.9 and 7.9 [6.1 (1.4)]	1.3 and 8.0 [5.3 (2.3)]
Pr50 *	15.0 and 22.1 [18.5 (3.1)]	11.4 and 20.4 [16.2 (3.5)]	15.0 and 25.4 [20.6 (4.3)]	11.7 and 23.1 [18.0 (4.4)]	15.3 and 25.3 [20.3 (4.0)]	11.7 and 22.2 [17.6 (4.3)]
Pr90 *	35.2 and 57.0 [47.7 (10.9)]	27.7 and 50.9 [42.0 (9.3)]	27.9 and 41.8 [37.3 (5.7)]	25.0 and 39.7 [34.8 (5.9)]	27.3 and 41.3 [36.9 (5.8)]	23.7 and 39.4 [34.1 (5.9)]
Females [n = 23; mean (SD)]						
Pr10	9.6 (1.7)	8.2 (2.3)	6.2 (1.4)	5.5 (1.4)	6.0 (1.4)	4.7 (2.5)
Pr50	17.7 (3.2)	15.4 (3.9)	19.6 (4.4)	17.1 (5.1)	19.2 (4.2)	16.8 (5.0)
Pr90	46.9 (12.9)	41.8 (10.9)	36.7 (6.4)	34.3 (6.8)	36.3 (6.5)	33.5 (6.9)
Males [n = 17; mean (SD)]						
Pr10	10.9 (2.0)	9.8 (1.9)	7.1 (1.0)	6.4 (1.3)	6.2 (1.3)	6.0 (2.0)
Pr50	19.5 (2.8)	17.3 (2.6)	21.9 (3.8)	19.1 (3.0)	21.8 (3.4)	18.8 (2.7)
Pr90	48.9 (7.7)	42.2 (6.8)	38.1 (4.7)	35.4 (4.6)	37.7 (4.7)	34.9 (4.9)

* Values are expressed as 10th and 90th percentiles [mean (SD)] in each cell.

Table 2

Concordance correlation coefficients (CCC) comparing power exponential, computer-based linear interpolation and manual linear interpolation models

	Power exponential model	Computer-based linear interpolation	Manual linear interpolation
Pr10			
Power exponential model	–	Post-Rx – 0.297 (0.159–0.424)	Post-Rx – 0.251 (0.107–0.384)
Computer-based linear interpolation	Pre-Rx – 0.178 (0.080–0.274)	–	Post-Rx – 0.583 (0.349–0.749)
Manual linear interpolation	Pre-Rx – 0.108 (0.024–0.191)	Pre-Rx – 0.707 (0.522–0.828)	–
Pr50			
Power exponential model	–	Post-Rx – 0.866 (0.783–0.918)	Post-Rx – 0.892 (0.820–0.937)
Computer-based linear interpolation	Pre-Rx – 0.808 (0.702–0.879)	–	Post-Rx – 0.989 (0.980, 0.994)
Manual linear interpolation	Pre-Rx – 0.835 (0.741–0.898)	Pre-Rx – 0.983 (0.968–0.994)	–
Pr90			
Power exponential model	–	Post-Rx – 0.579 (0.416–0.707)	Post-Rx – 0.527 (0.361–0.660)
Computer-based linear interpolation	Pre-Rx – 0.405 (0.236–0.550)	–	Post-Rx – 0.978 (0.960–0.988)
Manual linear interpolation	Pre-Rx – 0.391 (0.225–0.535)	Pre-Rx – 0.991 (0.984–0.995)	–

Values are expressed as CCC (95% confidence interval).