Original Article

Airway resistance in children measured using the interrupter technique: reference values*

Resistência de vias aéreas em crianças medida pela técnica do interruptor: valores de referência

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Abstract

Objective: The interrupter technique is used for determining interrupter resistance (Rint) during quiet breathing. This noninvasive method requires minimal cooperation and can therefore be useful in evaluating airway obstruction in uncooperative children. To date, no reference values have been determined for Rint in a Brazilian population. The objective of this study was to define a prediction equation for airway resistance using the interrupter technique for healthy children aged 3-13 years. **Methods:** This was a prospective, cross-sectional study involving preschool and school children in Porto Alegre, Brazil, in whom Rint was measured during peak expiratory flow. **Results:** One-hundred and ninety-three children were evaluated. Univariate analysis using linear regression showed that height, weight and age correlated significantly and independently with Rint. Multiple regression with height, weight, age and gender as variables resulted in a model in which only height and weight were significant, independent predictors of Rint. Collinearity was identified among height, weight and age. **Conclusions:** Reference values and an equation for calculating Rint in healthy children were obtained and are adjusted for height.

Keywords: Respiratory function tests; Airway resistance; Diagnostic techniques, respiratory system; Airway obstruction/diagnosis; Reference values.

Resumo

Objetivo: A técnica do interruptor é usada para determinar *interrupter resistance* (Rint, medida de resistência das vias aéreas através da técnica do interruptor) durante respiração tranqüila. Este método não-invasivo requer mínima cooperação e, por isso, pode ser útil para avaliar obstrução de vias aéreas em crianças não-colaborativas. Não existem dados publicados de valores de referência para Rint na população brasileira até o momento. O objetivo deste estudo foi definir uma equação para prever a resistência das vias aéreas pela técnica do interruptor em crianças saudáveis de 3 a 13 anos de idade. **Métodos:** Este estudo transversal prospectivo com crianças pré-escolares e escolares em Porto Alegre, Brasil, mensurou Rint durante pico de fluxo expiratório no volume corrente. **Resultados:** Cento e noventa e três crianças completaram as medidas. Estatura, peso corporal e idade mostraram correlação significante e independente com Rint na análise univariada usando regressão linear. A regressão múltipla com estatura, peso corporal, idade e gênero como variáveis resultou em um modelo no qual somente estatura e peso corporal foram significativos e independentes para predizer Rint. Colinearidade foi identificada entre estatura, peso corporal e idade. **Conclusões:** Valores e equação de referência para Rint em crianças saudáveis foram obtidos e são relacionados a estatura.

Descritores: Testes de função respiratória; Resistência das vias respiratórias; Técnicas de diagnóstico do sistema respiratório; Obstrução das vias respiratórias/diagnóstico; Valores de referência.

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Introduction

Pulmonary function tests permit ventilatory disorders to be evaluated and the severity of respiratory diseases to be estimated. In addition, among other objectives, such tests allow the monitoring of patient progress and of individual responses to interventions.[1,2]

The evaluation of respiratory disorders in adults is generally performed through forced expiratory maneuvers (spirometry). In special cases, volume measurements are taken using plethysmography.[3]

The proper performance of spirometry requires instruction of the individual being tested, as well as cooperation on the part of that individual. In children under the age of 7 years, even when equipment with animated stimulus and qualified evaluators is used, the results are rarely reliable and reproducible.[2-4]

Plethysmography appears to be a sensitive and reproducible method of estimating changes in bronchial diameter. However, the equipment is costly, demands more from the operator and requires the child to perform a series of respiratory maneuvers that are not always executed correctly.[3]

In contrast with the spirometry and plethysmography, using the interrupter technique to determine interrupter resistance (Rint) can provide useful information on pulmonary function and requires, on the part of the subject, minimal comprehension and active coordination.[5,6]

The interrupter technique of determining Rint is a noninvasive test used to estimate airway resistance (a measure of airway diameter), which is important in the determination of pulmonary function.[7,8]

The measurement is based on the principle that the airflow is interrupted for a brief period, during which there is rapid equalization between mouth pressure and alveolar pressure. Based on the Rint, we register the expiratory flow immediately prior to occlusion by the sealer clip and the mouth pressure immediately after occlusion. Airway resistance is calculated by dividing the change in mouth pressure by the expiratory flow.[9-11] In Figure 1, we present a simplified diagram of the function of Rint, together with an analysis of the pressure and flow data obtained during the maneuver. In healthy lungs, equilibrium between mouth pressures and alveolar pressure is reached almost instantaneously. When there is increase in airflow resistance and upper

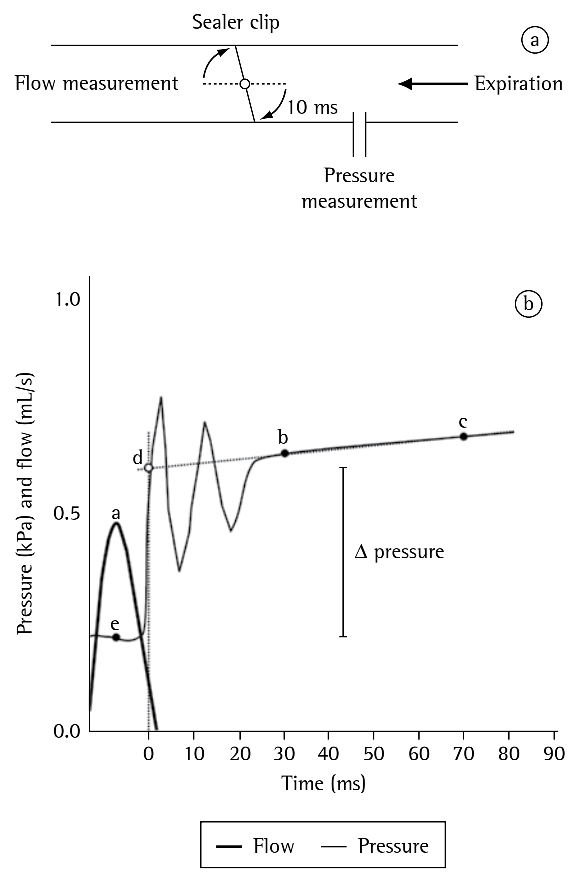

Figure 1 - Diagram of the equipment and the data analysis. 1A. Schematic diagram of the equipment. The sealer clip is closed for approximately 10 ms; the flow (immediately before the onset of closing) is registered, as is the pressure (when occlusion is complete). 1B. Linear back-extrapolation during 100 ms of occlusion. Following the onset of occlusion (point a, shown in the expiratory curve) a rapid reduction in the expiratory flow and an abrupt elevation in mouth pressure are observed, followed by a series of high frequency oscillations. These oscillations occur due to inertia and to the compressibility of the air column in the airways, making the direct measurement of pressure at the precise moment of occlusion difficult. At the moment of complete occlusion (point d), which occurs approximately 10 ms after the onset of closing (point a), the mouth pressure is estimated through linear back-extrapolation, using the pressure measured at 30 and 70 ms after closing (points b and c), when there are no longer any rapid oscillations in pressure, as points of reference. Airway resistance measured using the interrupter technique is calculated based on the ratio between the flow measured at point a and the difference (delta pressure) between the pre-occlusion pressure (point e) and post-occlusion pressure (point d).

airway compliance, the time to pressure equalization, following interruption, can be prolonged.[9,12]

Reference values in healthy children, determined using the interrupter technique, have been developed with the use of equipment commercially available for Rint determination. The use of the Micro Medical device (Micro Medical Inc., Rochester, Kent, UK) has been referred to in publications by groups in Holland,[8-11,13] Italy[5] and England.[14] Reference equations devised using the Jaeger apparatus (Jaeger, Würzburg, Germany) have been published in Holland.[3,15] In France, reference values for Caucasian children have been determined using a commercially unavailable tool (Spiroteq apparatus; Dyn'R Ltd, Toulouse, France).[16]

There is evidence that, even with the same equipment, duly calibrated and used under carefully controlled conditions, pulmonary function test results can vary. The hypothesis that the populations really are different from each other, genetically or regarding general health, has been discussed.[17] These differences observed among results reinforce the importance of using local equations, generated based on healthy controls, in the analysis of clinical studies.

A reference equation for Rint in Brazilian children has yet to be generated. Once such an equation, consisting of predicted values and respective confidence intervals, has been devised, it will be possible to apply it in clinical practice and in research. Therefore, the purpose of this study was to establish an equation to predict airway resistance in children aged 3 to 13 years, in Porto Alegre, Brazil, using the interrupter technique.

Methods

This study had a cross-sectional, analytical, prospective design. Reference values for airway resistance measured using the interrupter technique were obtained from a convenience sample of healthy children, selected consecutively at four elementary schools and two junior high schools in Porto Alegre, Brazil, (89.7% of the children being from public schools and 10.3% being from private schools).

Children with chronic pulmonary diseases (asthma or recurrent wheezing), acute diseases or respiratory diseases reported or observed during Rint measurement, skeletal abnormalities or neuromuscular abnormalities were excluded, as were those born prior to week 37 of gestation.

Parents or legal guardians gave written informed consent, after which they completed a questionnaire for respiratory diseases recommended by the American Thoracic Society Division of Lung Diseases and designated ATS-DLD-78-C, which has been adapted and validated for use in Brazil.[18] Perinatal data and data on smoking were also collected. Data were collected between April of 2005 and February of 2006.

This study was approved by the Ethics in Research Committee of the São Lucas Hospital, under the auspices of the Pontifical Catholic University of Rio Grande do Sul.

Measurements to determine Rint were taken with a portable device (MicroRint®; Micro Medical Inc, Rochester, Kent, UK).

Using the MicroRint®, the flow is measured immediately prior to valve closure. During respiration in tidal volume, the sealer clip closes automatically 10 ms after the peak expiratory flow is reached and remains closed for up to 100 ms. The pressure is measured using two points by linear back-extrapolation.[5,14,15]

Flow and pressure calibration of the MicroRint®, accurate to within 1%, was carried out every 50 measurements, using a manometer and a 3-L syringe.

For hygiene purposes and in order to avoid alterations in the pneumotachograph due to saliva, measurements were taken with a commercial Rint filter (changed every two measurements).[13]

For the purposes of undergoing the procedures and measurements used in the study, all of the children were classified as healthy based on the answers their parents had given on the questionnaire. Measurements were taken in school classrooms.

Body weight was measured using a personal digital scale (EB710; Glicomed, Rio de Janeiro, Brazil), and height was determined with a stadiometer, accurate to within 1 mm, supplied by the Pontifical Catholic University of Rio Grande do Sul.

The Rint measurement was taken with the child sitting comfortably and voluntarily, during quiet spontaneous respiration, using a disposable mouthpiece with a 2.5-cm diameter. The child was instructed to put the nasal clip in place, closing the lips around the mouthpiece and placing the tongue under the mouthpiece. The researcher supported the face and chin of the child in order to avoid energy loss and reduce the effect of upper airway compliance. The head was held in a neutral position (neck slightly extended).[8,16,19] Researchers trained in the method performed the measurements.

The evaluator first demonstrated the maneuver in order to familiarize the child with the closing action (sound) during the valve interruption.[12] The subjects listened to a children's story during the test. This was done in an attempt to reduce anxiety and avoid abnormal respiration.[20]

Ten airflow interruptions were performed sequentially at the peak flow of an unforced expiration, in ten consecutive respiratory cycles, and obtained during a technically satisfactory measurement session.[20,21] Interruptions occurred at an automatically-determined random frequency (regardless of the investigator); the child was unable to predict the moment of measurement but was able to hear the sealer clip closing.[14,22] Using the Rint values obtained, the median was calculated and was considered the measurement of the individual.[14,16] The process was considered successful if at least five satisfactory measurements were obtained and the coefficient of variation was ≤ 20%.[16,23,24]

In carrying out the measurement, the following were avoided: leaks around the mouthpiece; extreme extension or flexion of the neck; closing of the vocal chords; irregular respiratory pattern; movements during the closing of the sealer clip; respiration that was not completely quiet; cough; swallowing; and sneezing (excessive flow due to the forced expiration). If any of these occurred, the measurement was rejected.[8,19]

In the data analysis, linear correlations among continuous variables were evaluated and sample size was calculated with the objective of obtaining a correlation coefficient appropriate to a cross-sectional study. Since we intended to determine whether the correlation coefficient was different from zero (expected correlation coefficient of 0.25), the calculated sample size for a bidirectional α of 0.05 and a β of 0.10 was 164 children.[25] Nominal data are presented as absolute frequencies and percentages, whereas continuous data are presented as arithmetic means and standard deviations or standard errors.

Multiple linear regression analysis was used for the development of the prediction equation, which allows airway resistance to be calculated based on the independent variables age, weight, gender and height.

The distribution of data was evaluated as for the normality and homoscedasticity, and the linear trend was determined. Collinearity analysis was also carried out. The regression line was estimated and the 95% confidence interval for prediction was determined.[26]

Data were analyzed using the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Between April of 2005 and February of 2006, we obtained questionnaires containing the respiratory history data of 349 children aged 3 to 13 years. Of those 349 children, 152 (43.6%) had a history of premature birth or wheezing and were excluded from the study.

Of the 197 children considered healthy from a respiratory point of view, 4 (2%) were unable to perform the Rint maneuver properly or refused to participate. Acceptable Rint measurements were obtained in 193 children, 86 (44.6%) of whom were boys. Of the 193 parents or guardians, 11 (5.7%) provided no response to the question related to smoking in the home, 84 (43.5%) declared that both parental figures were nonsmokers, and 98 (50.8%) stated that they themselves were smokers. In the study sample as a whole, 50 fathers (25.9%) smoked, 48 mothers (24.9%) smoked, and only 21 couples (11.54%) smoked. Another 43 family members or guardians (22.3%) also smoked in the home. Demographic characteristics and the Rint data in the population studied are presented in Table 1.

In Table 2, the results of the multiple linear regression of Rint (as a dependent variable) are presented for *height, age, weight* and *gender*.

The collinearity analysis was performed based on these results (only the variables *height* and *weight* correlated significantly with Rint). The variance inflation factor was greater than 10 for the variable *height*, and the mean of the variance inflation factors was substantially greater than 1, the tolerance being less than 0.2 for *age* and less than 0.1 for *height*. These aspects confirm the collinearity between variables in the model.[27]

Table 1 – Demographic characteristics and airway resistance measured using the interrupter technique in the reference population.

Age (n)	Gender, M:F	Height,[a] cm	Body weight,[a] kg	Rint,[a] kPa . L^{-1} . s^{-1}
3 ├ 5 (15)	4:11	105.05 ± 6.14	17.25 ± 3.15	0.88 ± 0.15
5 ├ 7 (44)	25:19	119.12 ± 6.88	23.88 ± 4.81	0.77 ± 0.17
7 ├ 9 (52)	21:31	128.81 ± 6.20	29.89 ± 7.32	0.64 ± 0.16
9 ├ 11 (62)	26:36	141.24 ± 8.26	38.70 ± 10.88	0.57 ± 0.13
11 ├ 13 (20)	10:10	152.91 ± 6.62	49.66 ± 10.99	0.52 ± 0.15

[a]Data presented as mean ± standard deviation. Rint: airway resistance measured using the interrupter technique.

The variable *age* presented a strong correlation (r = 0.92) with *height*, which could be the cause of collinearity. In addition, since *age* and *gender* did not reach statistical relevance in the multivariate regression model = (Table 2), these variables were excluded, and another regression analysis was performed. Using only *height* and *weight* as independent variables to predict Rint, a coefficient of determination (R^2) of 0.41 was obtained and collinearity was again checked.

Therefore, a simplified model was developed, in which the only independent variable was *height*. In the simple linear regression analysis of the correlation between Rint (as a dependent variable) and *height*, the intercept presented a regression coefficient of 1.613 and a standard error of 0.095. The regression coefficient for *height* was −0.0073, with a standard error of 0.001 and a standardized regression coefficient of −0.593.

In this model mentioned above and presented in Figure 2, we observed a statistically significant correlation between lower Rint and greater growth ($p < 0.0001$). *Height*, in itself, explains 35% of the variance of Rint.

An analysis using only *weight* as a variable was also performed. However, without the adjustment for *height*, Rint (dependent variable) was inversely correlated with *weight*, explaining only 15% of the variance.

Table 2 – Multiple linear regression analysis of the physical characteristics and of airway resistance measured using the interrupter technique.

Variable	b	Standard error	β
Intercept	1.877	0.197	–
Height (cm)	−0.01032	0.002	−0.838*
Age (years)	−0.01432	0.012	−0.176
Body weight (kg)	0.00705	0.002	0.473*
Gender (M = 0; F = 1)	0.01495	0.020	0.041

*$p < 0.0001$. R^2 = 0.42; residual standard deviation = 0.14; n = 193. R^2: determination coefficient; b: regression coefficient; and β: standardized regression coefficient.

As for the variable *age*, when a univariate analysis was carried out in order to determine the dependence of Rint, a statistically significant correlation was observed among the variables, and the explained variance was 35%.

The most economical linear regression equation (multiple analysis) to predict Rint in the population of these study was as follows:

Rint (kPa . L^{-1} . s^{-1}) = 1.613 + (−0.0073·*height* [in cm])

R2 = 0.35; residual standard deviation = 0.15

Discussion

This study is the first to consider Rint values and devise a reference equation for Rint in the Brazilian population. In addition, the results of other studies were confirmed. First, we confirmed that the interrupter technique can be easily performed in preschool and school age children, since the acceptability was excellent (failure = 2%). This point has been raised in many studies using Rint as a measure of pulmonary function; therefore, there is great interest in its use in clinical and epidemiological research in children.[5,8] Second, Rint is significantly and independently associated with *height*, *age* and *weight*. Somatic growth reduces airway resistance, which therefore correlates inversely with *age*, whereas *weight*, adjusted for *height*, correlates directly with airway resistance. This observation is in accordance with data presented in recent publications on the association between obstructive lung disease and obesity.[28,29]

As for the subjects who participated in this investigation, the exclusion of children born prematurely

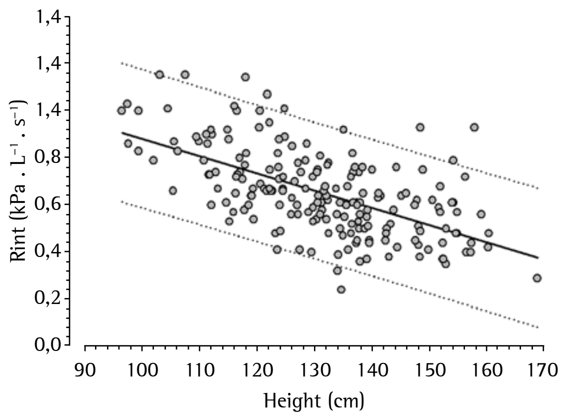

Figure 2 - Linear regression of airway resistance measured using the interrupter technique (Rint) versus height. The continuous line indicates linear regression, and the dotted lines indicate the 95% confidence interval for prediction.

was necessary due to abnormalities in growth and to the airway dynamics referred to in the literature.[16]

In relation to the reference values for Rint *per se*, in accordance with most studies,[5,13,15,16] the linear model, when tested, was considered better than the exponential model at describing the relationships between *height* and Rint.[8,14]

In our results, Rint presented a significant inverse correlation with *height*, a finding consistent with previously published reference values for Rint, as well as with the findings of studies on airway resistance measured by plethysmography. The physiological argument for the use of *height* as the independent variable is that Rint reflects the increase in the dimensions of the airways during growth.[13,15]

We also observed an association between *weight* and Rint. After the multivariate regression analysis had been adjusted for *height*, *weight* presented a statistically significant association with airway resistance. Recently, there has been scientific interest in the association between asthma and obesity, a relationship that was unknown prior to the recent increase in the prevalence of obesity but has now been documented the large population-based studies.[28] Studies on the subject are still limited, and no causal relationship between obesity and asthma has been established.[29]

The independent variable *age* has also been used and is considered an appropriate predictor of Rint.[14] In the present study, *age* showed no statistical significance in the multiple regression analysis for Rint after the adjustment for *height*. In isolation, *age* showed good explained variance to predict Rint; however, due to high collinearity with *height*, it adds no power to the model.

In addition, collinearity can also bring problems to the model, such as difficulty in the evaluation of the importance of each variable in the estimation of and increase in the variance in the regression coefficient. This alteration in variance of this coefficient can generate an unstable prediction equation, that is, one which estimates values of regression coefficient that will vary for each sample.[27]

In Figure 3, we present six previously published reference equations, together with the equation generated in the present study. Good concordance was observed among most equations, which presented small differences in the intercept and in the slope.

In most analyses, the relationship between Rint and *height* has been described linearly, except in one study carried out in England,[14] in which that relationship is described using an exponential model.

Therefore, in the reference equation for Rint, published in Holland in 2001, greater slope (b = −0.0160) results in greater influence of individual growth (*height*) on the drop in airway resistance.[13] At the opposite end of the spectrum, in a study carried out in Denmark, the slope of the line was lower and, therefore, *height* had less influence on the model of regression.[15] In the present study, another algorithm was used in the calculation of the Rint measurements, using the opening interrupter method. Therefore, the pressure measured (immediately before the valve was reopened) is higher than that calculated using devices that employ two previously measured points in order to extrapolate the value.[14-16] In addition, a mask with an adapted mouthpiece was used. As the respiratory occlusion was programmed to occur at 50 mL over the functional residual capacity, with the increase in height, the interruptions could have occurred in levels of inflation gradually lower. That would explain the lower slope of the reference equation.[8]

As for the explained variance (R^2), a study carried out in Italy has a lower explained variance through the regression analysis carried out (14%),[5] followed

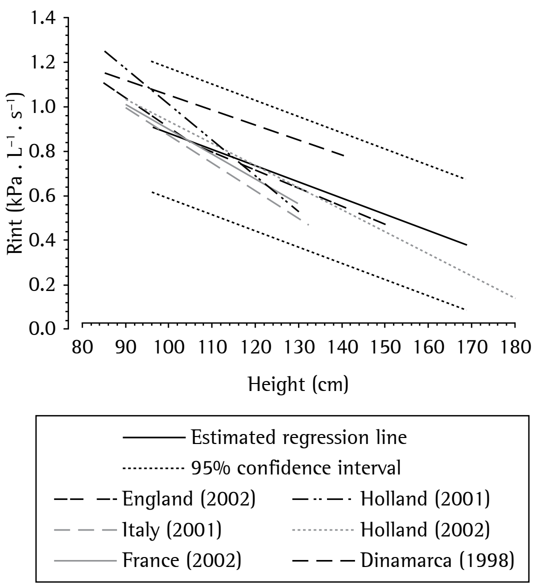

Figure 3 - Linear regression equations for airway resistance measured using the interrupter technique (Rint) versus height. Comparison of linear regression equations for Rint versus height. The continuous line indicates linear regression, and the dotted lines indicate the 95% confidence interval for prediction of the equation generated in this study.

by the study in Denmark (21%),[15] by our study (35%) and by the two studies carried out in Holland[8,13] in 2001 and 2002 (40% and 59%, respectively).

In the study in Italy,[5] the low explained variance by the reference equation can be justified by the difference in the standardization of the technique—there was no facial support.

The standard of measurement, as well as the equipment used, in our study, was similar to that used in the investigations carried out in Holland.[8,13]

The discrepancies among studies can represent differences in equipment, algorithms, diverse genetic composition or simply the health of the populations studied, that is, real differences in the populations.

In a publication comparing the study conducted in France and the study conducted in Italy, no significant differences were observed in the regression coefficient of the equations.[16] In the study carried out in Holland, the regression coefficient variability was not reported, and therefore no comparisons could be made with other models. Apparently, the intercept and the slope are greater than in the other studies.

Among the limitations of these studies, we can highlight the following: the healthy children were identified based on the questionnaire completed by the parents, and children with respiratory symptoms that are unrecognized or unperceived by their parents might not have been identified; the sample was heterogeneously distributed in terms of age and gender; exposure to smoking (passive smoking during pregnancy) and history of respiratory infection were not used as exclusion criteria[8,13,15,16]; and convenience sampling was used. In this fourth aspect, to minimize possible selection bias, all children who met the selection criteria were consecutively included in the study for 10 months (ensuring seasonal variations during collection).

It is also worthy of note that in the interrupter technique, in the presence of severe airway obstruction, the balancing between mouth pressures and alveolar pressures might not be completed in time for the closing of the valve, generating difficulties in the interpretation of Rint.[12] The estimate of resistive pressure through the airways can be underestimated in case the balancing of pressures continues beyond the time of valve closure.[30]

We concluded that, in the multivariate regression analysis, the relevant factors for the determination of the Rint value were *height* and *weight*. *Gender* and *age*, when considered as independent values (to the exclusion of *height* and *weight*), presented no statistically significant relationships that would make them predictive of Rint. However, since relevant collinearity was observed (among *height*, *weight* and *age*), the linear regression equation is presented using only the variable *height* to predict Rint.

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