Quantitative EMG of external urethral sphincter in neurologically healthy men with prostate pathology

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Abstract

Introduction: There are no data on quantitative EMG of the external urethral sphincter (EUS) in men. The aim of this study was to obtain reference data from a group of neurologically healthy continent men with prostate pathology using a standardized technique. **Methods:** Sixty-six subjects without neurological disorders were included. Motor unit potential (MUP) and interference pattern (IP) analysis were performed using multi-MUP and turns/amplitude (T/A) techniques, respectively. **Results:** Of 66 patients, 51 (mean age: 65.17, SD: 6.70) had localized prostate cancer (PCa), and 15 (mean age 61.67, SD 6.25) had benign prostate hyperplasia (BPH). Descriptive MUP parameters and IP-clouds were obtained, respectively in the BPH and PCa groups. No group differences were found. **Discussion:** This study provides quantitative EMG measures of EUS functionality in continent men with prostate pathology. The data could be used as reference values for patients undergoing prostate surgery to identify post-operative changes in EUS function possibly influencing continence.

Key words: external urethral sphincter, quantitative EMG, urinary incontinence, prostatectomy, motor unit potentials

Introduction

Urinary incontinence is one of the most disabling complication of radical prostatectomy (RP), with rates ranging from 0,8% to 87% [1–4]. Internal urethral sphincter (IUS) deficiency is the most frequent cause of stress urinary incontinence after prostate surgery (60-100%) [5]; however the role of external urethral sphincter (EUS) incompetence [6] as a determining factor for postoperative stress incontinence should not be excluded[7].

Concentric needle EMG is a useful technique to evaluate EUS functional integrity. In particular, quantitative template-based motor unit potential (MUP) analysis (multi-MUP) and interference pattern (IP) analysis have been shown to be useful for study of the pelvic floor muscles [8,9]. Multi-MUP analysis allows collection of a large number of MUPs, even in small muscles such as sphincters [10–12]. Although the sensitivity of quantitative IP analysis in detecting neuropathic changes is lower than multi-MUP and qualitative IP analysis [13], a quantitative evaluation of IP could be useful in pelvic floor muscles, where voluntary recruitment of MUPs is very difficult [9]. Multi-MUP and automatic IP analysis are recommended tools for examination of the external anal sphincter (EAS), [14] and reference data for this muscle have been published [14,15]. Moreover, urethral sphincter normative values recorded in a group of continent women using quantitative EMG have been recently reported in a single study [16]. In contrast, reference parameters obtained from a large group of normal men have not been reported [9].

The aim of this study was to collect MUP and IP parameters of the EUS in a cohort of continent men with prostate pathology and without neurological disorders, in order to create a preoperative reference pool of data. These reference parameters should allow detection of preoperative subclinical alterations or post-operative changes in the EUS of patients who undergo radical prostatectomy for prostate cancer (PCa) and develop post-surgical urinary incontinence.

Materials and methods

From July 2012 to April 2013, 81 consecutive men who were referred to the Urology clinic at the Cantonal Hospital of Lucerne (Switzerland) for prostate biopsy (PB) for suspected PCa, defined as elevated PSA levels

(≥ 4.0 ng/ml) and/or suspicious digital rectal examination, were recruited. Inclusion criteria were: 1) the presence of urinary continence status, defined using the short form of the International Continence Society Questionnaire (ICS-male SF) [17]; 2) negative history of neurological and other pelvic disorders; and 3) normal neurological examination. The study was approved by the local Ethics Committee, and all patients provided informed consent. Of all eligible 81 patients, 66 agreed to EMG analysis of the EUS immediately before PB. Depending on the results of PB, patients were assigned to the following groups: benign prostate hyperplasia (BPH) and PCa. Patients with malignant disease were subjected to robot-assisted radical prostatectomy (RARP). Continence status of all operated patients was evaluated with the 24-hr Pad-test [18] 3 months after surgery. The range of incontinence was defined as: "mild incontinence" (1.3-20 g/24h), "moderate incontinence" (21-74 g/24h), and "severe incontinence" (more than 75 g/24h). An EMG analysis was repeated in incontinent patients at 3 months follow-up after surgery.

Quantitative EMG of the EUS, consisting of MUP analysis, performed using a template-based technique (multi-MUP), and IP analysis, was carried out. The EMG signal was acquired by a disposable concentric needle electrode (TECA Medelec, 50 mm x 26G) connected to an EMG system (NeuroMep Micro, Neurosoft, Russia), with standard settings (amplifier filters 5 Hz-10 KHz, gain 200 µV/div, sweep speed 10 ms/div). Patients were examined in the lithotomy position. Using a transperineal approach, the needle was inserted in the midline, 2 cm anterior to the anus at the base of the penis and advanced toward the apex of the prostate under transrectal ultrasound guidance. The needle tip was inserted at the 3 and 9 o'clock positions into the EUS just beneath or at the level of the levator ani.

Multi-MUP analysis

Multi-MUP analysis was performed as described by Stalberg et al. [12]. The needle electrode position was adjusted under auditory and oscilloscope guidance in order to find a crisp EMG signal. With an empty bladder, at slight to moderate voluntary and reflex (Valsalva) activation, several MUP classes, each containing MUPs matching the same template, were automatically stored. MUPs containing rough artifacts (such as unstable baseline) were discarded by the operator, and classes considered to represent the same MUP were merged into a single class[14]. As previously described by Podnar et al. [14] only muscles with 15 or more MUPs were included in the multi-MUP analysis. The following MUP parameters were automatically measured: amplitude (voltage difference between maximum negative-positive peak within the duration), duration (time between starting-point and end-point), area (calculated over the duration), number of phases (a phase is part of a MUP included between 2 baseline crossings), and turns (peak in the MUP waveform that exceeded both the preceding and succeeding turn of 100 µV). Mean values and standard deviations for each MUP parameter were calculated.

IP analysis

For IP analysis, several 500 ms-epochs of EMG signal (IP samples) were recorded automatically from different sites in both parts of the EUS, at different levels of voluntary and reflex muscle activation. Only samples with a sufficiently crisp EMG signal were included in the analysis [14,19], corresponding to positive values for all IP parameters. Furthermore patients with less than 15 samples were excluded. The automatic turns/amplitude (T/A) analysis of the interference pattern was used to assess the characteristics of the recruitment pattern, and the following T/A parameters were measured: number of turns per second (turns/s) and mean change in amplitude per turn (amplitude/turn). To perform the T/A analysis without contraction force monitoring, the concepts developed by Stalberg et al [20] were used, and a cloud of points obtained plotting amplitude/turn against turns/s at varying levels of contraction was obtained. The procedure is illustrated in figure 1. A scatterplot of all IP samples was drawn. Univariate linear regression analysis was then performed on log-transformed data to calculate the regression line and the corresponding 95% confidence interval (±2 SD from the regression line). The lines limiting the upper and lower confidence interval were then back-transformed into the original coordinate system and drawn on the original plot with a linear scale. The upper limit for turn values was defined by a vertical line including at least 99% of all points, whereas for amplitudes it was set slightly higher than the maximum amplitude observed.

Statistical analysis

Multi-MUP parameters were compared between groups using the Student *t*-test, with Bonferroni correction for multiple comparisons. To analyze the relation of MUP and IP data with age and BMI, the correlation indexes (Pearson r) were evaluated. Single patient values were compared with group values using z-scores.

The regression lines obtained from IP analysis within the 2 groups were compared using the Student *t*-test assessing the equality of slopes and intercepts, as explained in the supplementary materials. The Levene test was used to test the equality of standard deviations.

Results

All of the 66 patients (mean age: 64.38, SD: 6.73, range 51-86) enrolled in the study and undergoing EMG tolerated the procedure. Of these patients, 51 (mean age: 65.17, SD: 6.70, range: 52-86) had positive histology for localized PCa, whereas the remaining 15 (mean age 61.67, SD 6.25, range 51-71) were diagnosed with BPH. No significant age difference was found between groups.

At 3 months follow-up after RARP, only 2 of the operated patients (4%) reported urinary incontinence (mild and moderate grade): one did not agree to undergo a new EMG examination since his continence was spontaneously improving.

Multi-MUP analysis

Fifty-nine patients out of 66 (11 with BPH and 48 in the PCa group) had recordings that included more than 15 MUPs and were included in this analysis. A mean of 22 different MUPs was collected from each muscle (range: 15-40), for a total of 1290. No statistical differences were found between the 2 groups for each of the MUP parameters, therefore BPH and PCa values were combined to obtain a single group. Data are reported in Table 1.

No correlations were found between age, BMI, or MUP parameters ($|r|<0.3$ for all MUP parameters).

An additional statistical comparison (z-score) was carried out between the MUP values of the 2 patients who reported post-operative urinary incontinence and the BPH group values: no differences were found for each parameter ($z<1.12$).

MUP parameters of the only incontinent patient evaluated 3 months after surgery showed a significant reduction of amplitude, area, and duration ($P<0.0001$) compared to pre-operative values.

IP analysis

Recordings from 62 patients out of 66 (13 with BPH and 49 in the PCa group) had more than 15 IP samples and were included in this analysis. A mean of 33 different IP samples were obtained from each patient (range: 15-50), for a total of 2086.

T/A values were plotted for the BPH group, and confidence curves were calculated. T/A values of PCa patients were then plotted, and points exceeding the BPH confidence curves were counted; no patients, including the 2 who reported post-operative incontinence, had more than 10% of points outside this area.

The regression analysis on log-transformed turns/s and amplitude/turn values was performed separately for the 2 groups. In BPH patients the regression line slope was $b_{BPH}=0.234$, and the intercept was $a_{BPH}=1.962$, with standard deviation $DS_{BPH}=0.151$. In the PCa patients the regression parameters were $b_{PCa}=0.233$, $a_{PCa}=1.956$, and $DS_{PCa}=0.154$, respectively. Since the 2 regression lines were not significantly different with regard to slope ($t=1.24$; $P>0.2$) and elevation ($t=1.47$; $P>0.05$), and standard deviations were almost identical ($F=0.003$; $P=0.954$), these data were considered to belong to the same population.

A new cloud, formed by BPH and PCa T/A values, was plotted, and the relative confidence curves were calculated (Figure 2).

No correlations were found between age, BMI, or IP parameters ($|r|<0.3$ for both turns/s and amplitude/turn IP parameters).

The post-operative IP scatterplot of the patient who developed incontinence showed 4 points (14.8%) below the inferior boundary of the confidence area (Figure 3).

Discussion

The use of robot technology allows surgeons to preserve the key anatomic structures for urinary continence. However the prevalence of urinary incontinence after RARP still varies from 4% to 31% [21]. Different factors can influence the prevalence of post-RARP urinary incontinence, such as preoperative patient characteristics, surgeon experience, surgical techniques, and other methodological aspects [21]. Between potential clinical predictors, patient age [22–25], body mass index [26,27], comorbidity index [22], lower urinary tract symptoms [23,26], and prostate volume could be relevant factors influencing recovery of urinary continence [28–30].

Post-prostatectomy incontinence may be attributed to sphincter incompetence and/or bladder dysfunction [5]. Bladder dysfunction, which includes involuntary detrusor contractions and/or decreased bladder compliance, is associated classically with urge incontinence [31–33]. However, the majority of patients with post-prostatectomy incontinence develop stress incontinence, characterized by involuntary urinary leakage on effort or exertion, or on sneezing or coughing [34]. Stress incontinence may be due to damage of the urethral closure mechanism, through denervation and/or ischemic changes [35]. In most patients (60-100%) it is the result of IUS sphincter deficiency [5], followed by direct muscle injury or neurogenic impairment [36]; however stress incontinence might also be caused by EUS deficiency [32,37] or its inability to compensate for IUS dysfunction [7]. As the striated sphincter is close to the prostate apex, this structure can be injured during surgical dissection either by myogenic damage or by denervation [6].

Furthermore, it has been shown that radical transabdominal surgery for lower urinary tract pathology may produce significant EMG changes in the EUS that may potentially affect continence [38].

To obtain descriptive parameters of EUS functional integrity we used multi-MUP and IP T/A analysis, which are fast and simple techniques that provide objective and reproducible EMG data [39]. The use of such a standardized technique allows comparison of individual findings with common reference values that could be used in different laboratories [8,10]. Furthermore, multi-MUP analysis has several advantages: automatization of MUP extraction enabling rapid sampling of a large number of MUPs in a short time; simultaneous sampling of many MUPs at 1 investigation site; lower bias in MUP selection; and the possibility to manually discard MUPs containing too many artifacts [10]. As reported in the literature [40–42], IP analysis is a practical technique to study the neuromuscular function of the striated muscles of the pelvic floor [19]. The well-established technique of "cloud analysis" can be used to evaluate muscle interference patterns, independently from the force of contraction [20].

In the absence of urinary incontinence and neurological and pelvic floor muscle disorders in our patients, we considered patients with benign pathology to be a control group for PCa patients. Moreover, Abe et al. [43] analyzed the action potentials of the EUS in patients with BPH and in a group of subjects without urinary disorders; no differences related to prostate pathology were found between the 2 groups.

Although urethral sphincter normative values obtained using quantitative EMG in men are still lacking, Kenton and collaborators recently used an automatic EMG analysis to describe urethral neuromuscular function in a cohort of continent women [16], providing female EUS normative data. Furthermore Podnar and co-workers [14], using a standardized technique, provided normative data for MUP and IP parameters of the EAS from a large group of healthy subjects. The mean MUP parameter values found in these studies did not differ from the data in our BPH group, suggesting motor unit functional integrity in the EUS of these patients.

When we compared the multi-MUP parameters of our 2 groups, no differences were found, so the values were joined to form a larger reference pool of data. Similarly, the analysis of IP was performed separately in BPH and PCa groups, and 2 separate clouds were obtained. IP samples of each PCa patient were plotted over the BPH confidence area, verifying that less than 10% of IP values were outside the boundaries of the control cloud. Moreover the regression lines and the confidence intervals of the 2 groups did not differ significantly, therefore the IP data were also merged into a unique pool. As we did not detect any difference between BPH and PCa patients at baseline in either the multi-MUP or T/A analysis, we can conclude that the EUS is functionally normal in PCa patients.

Although post-RP neuropathic changes in EMG of the EUS have been reported [44], the relationship between these alterations and continence has not been clarified completely. Aanestad et al. analyzed 10 patients before and 25-32 months after surgical procedures using quantitative EMG (IP analysis and fiber density)[45]. A tendency towards post-operative changes in IP and an increase in fiber density were found after retropubic-RP, suggesting a partial nerve lesion that could contribute to the pathogenesis of urinary stress incontinence. Liu and collaborators performed a urethral sphincter EMG study in 20 men undergoing prostate surgery with nerve-sparing and non-nerve sparing techniques to determine whether the cavernous nerves carried fibers to the EUS [46]. The authors found a significantly prolonged MUP duration in patients compared with controls, whereas there was no difference related to nerve-sparing and non-nerve-sparing techniques. They concluded that damage of the neurovascular bundle in the prostate capsule did not compromise EUS function, whereas lower urinary tract surgery may induce significant EMG changes which may not be clinically evident.

In our study postoperative continence status was evaluated at 3 months after surgery, and only 2 patients reported mild to moderate incontinence. To investigate a possible role of EUS disorders in post-RARP urinary incontinence we compared pre-surgical EMG data of the incontinent patients with those of the continent ones. As no differences were found, we can confirm that there are no predictive factors for post-surgical continence outcome. However, the small number of patients who developed incontinence does not allow one to draw definitive conclusions.

The only incontinent patient examined with EMG 3 months after surgery showed significant changes in MUP parameters (shorter duration and lower area and amplitude) compared to his baseline values, and more than 10% of IP values were outside the lower edge of the confidence area. Even though these alterations could lead one to suspect myopathic change, early reinnervation cannot be excluded. However, from a single case we cannot draw any conclusion about a causal relationship between EMG parameter modifications and continence outcome.

In conclusion, our patients with PCa did not show any differences compared to those with BPH. Since the overall data did not differ from findings reported in the literature for the anal sphincter [14] or EUS in women [16], we can assume that EUS function is normal in the whole population studied here. Our data could be used as reference values for evaluation of MUPs and IP samples of patients who undergo RP and develop post-surgery urinary incontinence in order to investigate the possible role of EUS damage.

Tables

Table 1: MUP Parameters*

Group	Duration [ms]		Amplitude [µV]		Area [µV×ms]		Phases		Turns	
BPH	7.07	±2.49	449.51	±201.30	362.80	±190.19	3.85	±1.75	2.33	±1.55
PCa	6.77	±2.02	411.72	±281.13	339.18	±260.52	3.67	±1.60	2.09	±1.40
Total	6.81	±2.09	417.11	±271.44	342.55	±251.77	3.70	±1.62	2.13	±1.42

* MUP parameters (duration, amplitude, area, phases, and turns) are reported as mean ± S.D. for BPH, PCa and Total groups.

Abbreviations

BPH	benign prostate hyperplasia
EAS	external anal sphincter
EUS	external urethral sphincter
IP	interference pattern
IUS	internal urethral sphincter
MUP	motor unit potential
PCa	prostate cancer
PB	prostate biopsy
RP	radical prostatectomy
RARP	robot assisted radical prostatectomy
T/A	turns/amplitude

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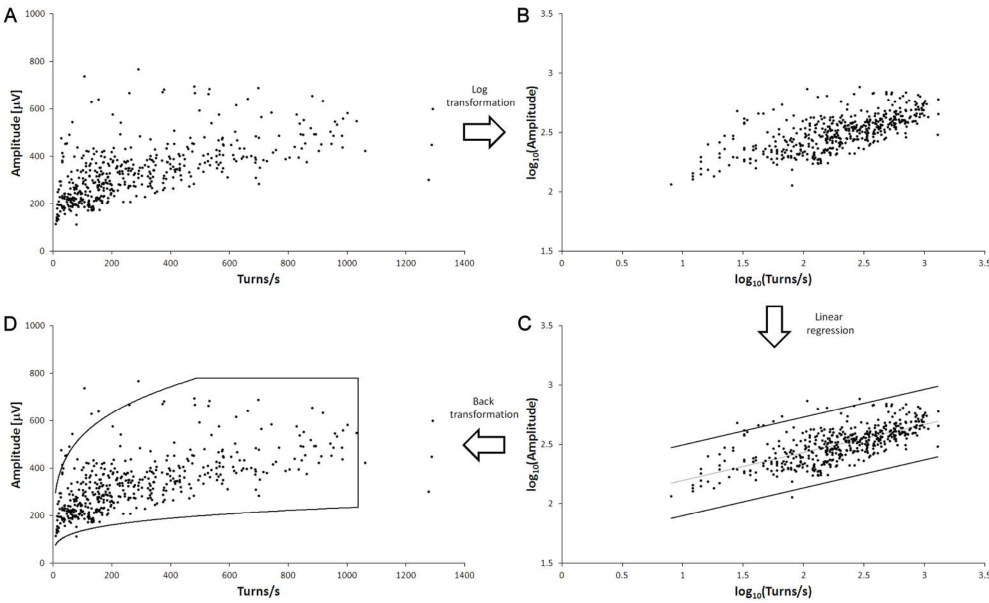
Figure legends

Figure 1. The procedure to calculate the confidence lines in T/A analysis is illustrated. A) the T/A values are plotted in a scatter diagram. B) after log transformation, the cloud seems to be arranged in a linear way. C) the regression line and corresponding confidence lines are obtained. D) after back transformation, the confidence lines take a logarithmic shape. The upper amplitude limit is represented by a horizontal line set a little higher than the maximum observed amplitude, while the upper turn limit corresponds to a vertical line leaving to the left of 99% of turn values.

Figure 2. The cloud obtained from combining the BPH (filled circles) and PCa (empty circles) T/A values is plotted in a scatter diagram together with the resulting confidence area.

Figure 3. Pre- and post-surgery IP scattergrams of the patient who developed urinary incontinence is plotted on the control confidence area of figure 2. More than 90% of pre-surgery values (filled circles) are inside the confidence area. Post-surgery values (empty circles) tended to shift toward the lower boundary, and 4 (more than 10%) are outside it.



The procedure to calculate the confidence lines in T/A analysis is here illustrated. A: the T/A values are plotted in a scatter diagram. B: after log transformation, the cloud seems arranged in a linear way. C: the regression line and the corresponding confidence lines are obtained. D: after back transformation, the confidence lines take a logarithmic shape. The upper amplitude limit is represented by a horizontal line set a little higher than the maximal observed amplitude, while the upper turn limit corresponds to a vertical line leaving on the left the 99% of turn values.
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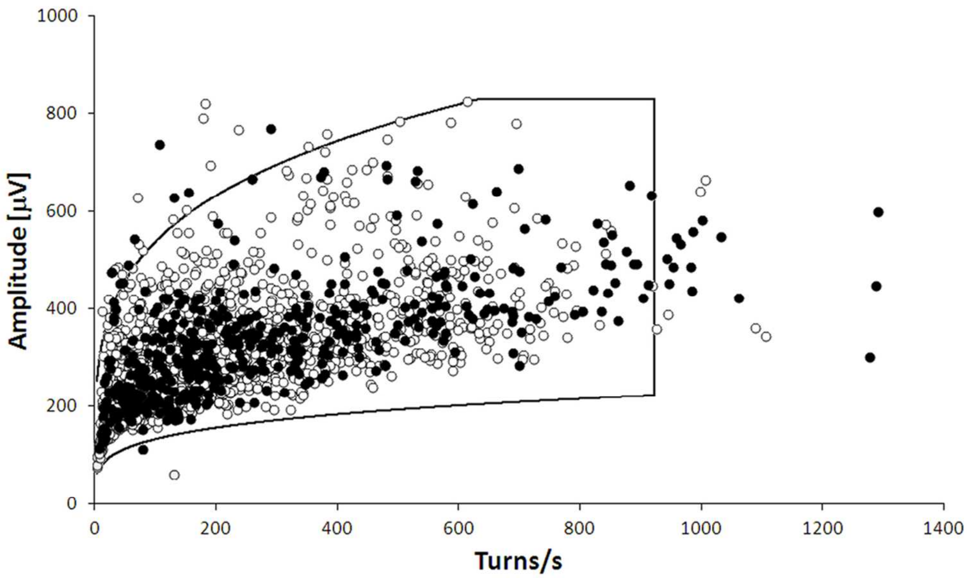
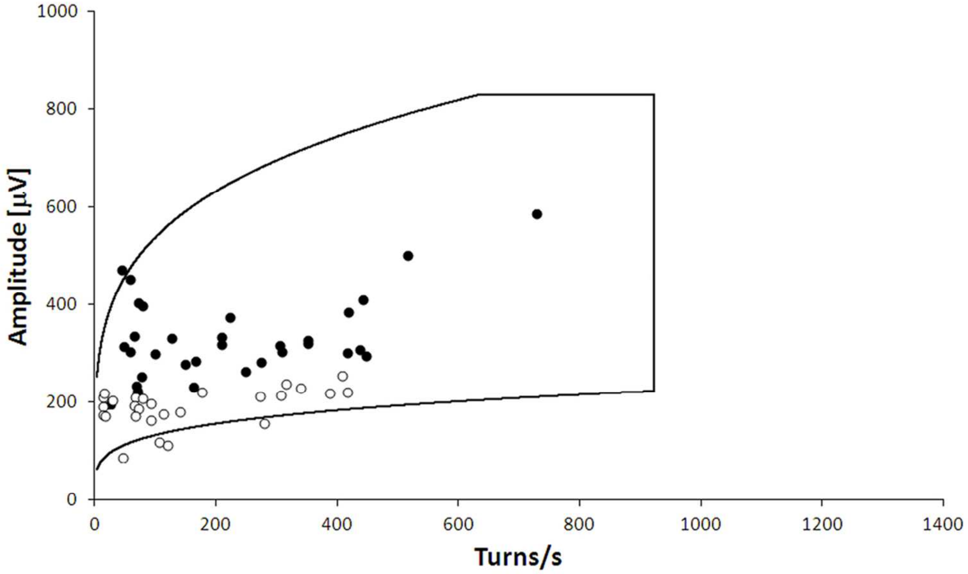


The cloud obtained from joined BPH (filled circles) and PCa (empty circles) T/A values is plotted in a scatter diagram together with the resulting confidence area.
49x29mm (600 x 600 DPI)



Pre- and post-surgery IP scattergrams of the patient who developed urinary incontinence is plotted on the control confidence area of figure 2. More than 90% of pre-surgery values (filled circles) are inside the confidence area. Post-surgery values (empty circles) tended to shift toward the lower boundary, and 4 (more than 10%) are outside it.
49x29mm (600 x 600 DPI)

Supplementary material

COMPARISON OF TWO REGRESSION LINES USING THE T-TEST

The comparison between two different regression lines, estimated on n_1 and n_2 coordinate sets (x_{1i},y_{1i}) and (x_{2i},y_{2i}) respectively, may be carried out by two Student's t-tests.
The first one, with $n_1 + n_2 - 4$ degrees of freedom, is used to check the slopes.
The *t* value is given by:

$$t_{(N-4)} = \frac{b_1 - b_2}{se_{(b_1-b_2)}}$$

where b_1 and b_2 represent the slopes of the two regression lines, $N = n_1+n_2$, and $se_{(b1-b2)}$ is the standard error of the difference b_1-b_2:

$$se_{(b_1-b_2)} = \sqrt{s^2_{(b_1-b_2)}\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}$$

and

$$s^2_{(b_1-b_2)} = \frac{\sum_{i=1}^{n_1}(y_{1i}-\overline{y_1})^2 + \sum_{i=1}^{n_2}(y_{2i}-\overline{y_2})^2}{n_1 - 2 + n_2 - 2} \cdot \left(\frac{1}{\sum_{i=1}^{n_1}(x_{1i}-\overline{x_1})^2} + \frac{1}{\sum_{i=1}^{n_2}(x_{2i}-\overline{x_2})^2}\right)$$

If $t_{(N-4)}$ is lower then $t_{critical}$ (α=0.05) then the null hypothesis $b_1 = b_2$ is accepted, and we can say that the two regression lines have the same slope.
The second t-test, with $n_1 + n_2 - 3$ degrees of freedom, is used to check the elevations.
The *t* value is given by:

$$t_{(N-3)} = \frac{(\overline{y_1}-\overline{y_2}) - b_c(\overline{x_1}-\overline{x_2})}{\sqrt{s^2_{y(C)}\left(\frac{1}{n_1}+\frac{1}{n_2}+\frac{(\overline{x_1}-\overline{x_2})^2}{A_c}\right)}}$$

Given:

$$A_C = \sum_{i=1}^{n_1}(x_{1i}-\overline{x_1})^2 + \sum_{i=1}^{n_2}(x_{2i}-\overline{x_2})^2$$

$$B_C = \sum_{i=1}^{n_1}(x_{1i}-\overline{x_1})(y_{1i}-\overline{y_1}) + \sum_{i=1}^{n_2}(x_{2i}-\overline{x_2})(y_{2i}-\overline{y_2})$$

$$C_C = \sum_{i=1}^{n_1}(y_{1i}-\overline{y_1})^2 + \sum_{i=1}^{n_2}(y_{2i}-\overline{y_2})^2$$

we can then compute:

$$b_c = \frac{B_C}{A_C}$$

and

$$s^2_{y(C)} = \frac{1}{n_1+n_2-3}\left(C_C - \frac{B_C^2}{A_C}\right)$$

If $t_{(N-3)}$ is lower then $t_{critical}$ (α=0.05) then the two regression lines have the same elevation.
If the two regression lines are not significantly different regarding slope and elevation, we can conclude that they belong to the same population.